Perioperative Pain Management

✓ 2026 Edition

From Preoperative Optimization to Transitional Postoperative Care

Padma Gulur
Hesham Elsharkawy
Rene Przkora
Editors

Springer

Perioperative Pain Management

✓ 2026 Edition

✓ 2026 Edition

Padma Gulur
Hesham Elsharkawy • Rene Przkora
Editors

Perioperative Pain Management

From Preoperative Optimization to Transitional Postoperative Care

✓ 2026 Edition

Springer

Editors
Padma Gulur
Anesthesiology
Duke University Health System
Durham, NC, USA

Rene Przkora
Anesthesiology
University of Florida Health
Gainesville, FL, USA

Hesham Elsharkawy
Anesthesiology, Pain Center,
MetroHealth
Case Western Reserve University
Cleveland, OH, USA

ISBN 978-3-032-11483-9 ISBN 978-3-032-11484-6 (eBook)
https://doi.org/10.1007/978-3-032-11484-6

This Springer imprint is published by the registered company Springer Nature Switzerland AG
The registered company address is: A L E F B A 1 4 0 5

2026 Edition

Preface

The journey of a surgical patient does not begin in the operating room, nor does it end upon discharge. Pain management before, during, and after surgery is central to that journey. It shapes not only recovery and rehabilitation but also the patient's overall experience, safety, and quality of life. As our understanding of pain mechanisms has advanced and new modalities have emerged, the need for a comprehensive and coordinated approach to perioperative pain care has become increasingly clear.

This book was conceived to meet that need. *Perioperative Pain Management: From Preoperative Optimization to Transitional Postoperative Care* presents a unified, multidisciplinary framework that extends across the entire continuum of care, from preoperative assessment and optimization through intraoperative management, early recovery, and the transition to long-term outcomes. The goal is to provide readers with both a foundation of scientific knowledge and a practical guide to clinical decision-making in the complex environment of perioperative care.

Each chapter has been written by experts who represent the many disciplines that intersect in the field of pain management. Their contributions reflect the shared commitment of anesthesiologists, surgeons, nurses, pharmacists, psychologists, and rehabilitation specialists to improving patient outcomes through collaboration, innovation, and compassion. The text emphasizes multimodal strategies, individualized care, and the integration of emerging technologies, while addressing challenges such as opioid stewardship, prevention of chronic post-surgical pain, and equitable access to effective pain management.

This book was created with the hope that it will serve both as a guide for clinicians and as an inspiration for continued advancement in the field. The work of caring for patients in pain is at once scientific and deeply human. It demands precision, empathy, and the constant pursuit of better solutions. We dedicate this text to all who share that pursuit.

Durham, NC, USA — Padma Gulur
Cleveland, OH, USA — Hesham Elsharkawy
Gainesville, FL, USA — Rene Przkora

Contents

Part I

Introduction to Perioperative Pain

1 The Importance of Pain Management in Surgery

Lady Christine Ong Sio, Cameron Schmutz, and Tyler Burkhart

Introduction

Recognizing noxious stimuli is essential for survival, making pain an unavoidable part of daily life. While pain serves as a protective mechanism, it is often accompanied by maladaptive changes in the nervous system. Pain management, especially in the perioperative setting, is a frequent topic in the medical field, with a focus on enhancing surgical outcomes and patient recovery. In today's healthcare environment, which prioritizes patient satisfaction, providing effective analgesia is crucial for ensuring patient comfort. Addressing and treating acute post-surgical pain effectively not only improves recovery times but also helps prevent the development of chronic pain.

Background and Current Understanding

Acute pain is a physiological response to noxious stimuli that can become pathological. It typically has a sudden onset, is time-limited, and motivates behaviors to avoid potential or actual tissue injuries [1]. This definition encompasses an inciting event, sudden onset, a limited timeframe, and potential pathological development. Acute pain often lasts less than seven days but can extend up to three months [2].

Effective management of postoperative pain is crucial for increasing patient comfort and satisfaction. Persistent, intractable pain can lead to avoidance behaviors, resulting in detrimental changes in mobility, mood, and social function [3]. Surgery, trauma, or acute injury can cause neuroplastic changes in the peripheral and central nervous systems, potentially leading to chronic pain [4]. Inadequate postoperative pain control is associated with a higher likelihood of developing chronic postoperative pain (CPP), defined as pain lasting more than three months after surgery [4, 5].

Managing acute post-surgical pain involves prevention and treatment using conventional medical, psychiatric, complementary, integrative, and alternative modalities, all aimed at pain relief, improved function, enhanced quality of life, expedited recovery, and reduced morbidity and mortality. Notably, the reduction of physiological pain is just one target among these goals [2, 6].

The central nervous system (CNS) and peripheral nervous system (PNS) are integral to the mechanisms and pathways of pain perception. Nociceptive signals from the site of surgery are transmitted to the CNS primarily by small myelinated (A-delta) and unmyelinated (C) sen-

L. C. O. Sio (✉) · C. Schmutz · T. Burkhart
Department of Anesthesiology and Perioperative Medicine, University of Louisville, Louisville, KY, USA
e-mail: leydikris@yahoo.com

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_1

sory afferent fibers [7]. Mechanical, thermal, and chemical stimuli are received by free nerve endings of various primary afferent neurons in the periphery. These neurons transduce stimuli to secondary neurons in the dorsal horn of the spinal cord or the medulla oblongata of the brainstem if from the head [8, 9]. The dorsal horn integrates input from multiple peripheral afferent neurons [10]. Secondary neurons transmit signals up the lateral (pain, temperature) or anterior (crude touch, pressure) spinothalamic tract and spinoreticular tract to the thalamus, which processes and relays somatosensory information to various brain regions, including the primary and secondary somatosensory cortices, insula, anterior cingulate cortex, and prefrontal cortex for interpretation and further physiological response [9]. Multiple brain areas, such as the periaqueductal gray, rostral ventral medulla, amygdala, and parabrachial nucleus, are involved in pain pathway modulation and emotional processing [10]. This complex process, occurring in nanoseconds, is modulated by factors such as segmental inhibition, descending inhibition, and endogenous opioids, ultimately contributing to pain perception.

Acute pain induces a stress response within the body, releasing catecholamines, cortisol, and glucagon, which can be maladaptive in certain sustained settings [11]. Catecholamine release often manifests as tachycardia and hypertension, increasing myocardial oxygen consumption. Stress hormones like cortisol and glucagon cause insulin resistance, hyperglycemia, and alterations in protein and fat metabolism. In the perioperative setting, these changes can lead to severe complications, including myocardial infarction, venous thromboembolism, and postoperative infection [12]. Without prevention or treatment, sustained pain can increase sensitivity and response, even without a stimulus, leading to chronic pain development [12].

Importance and Significance of Pain Control in Surgery

Considering the negative effects of perioperative pain on patient morbidity and mortality, it is imperative to establish effective pain management methods in the preoperative setting. Providers should consider all patient aspects, including age, comorbidities, drug interactions, frailty, allergies, pain history, individual perception, type and urgency of surgery, and discharge plans.

Clinical Applications and Techniques

Multimodal analgesia, introduced in 1993, leverages the additive and/or synergistic effects of different analgesic classes. It involves diverse analgesic medications and techniques targeting various receptors and mechanisms within the peripheral and central nervous systems to enhance analgesia while mitigating individual class-related side effects [13–15]. Research shows that multimodal analgesia is more effective in pain management than singular interventions and significantly reduces opioid consumption [14–17]. This approach is routinely integrated into Enhanced Recovery After Surgery (ERAS) protocols to optimize postoperative outcomes, enabling better anesthesia with fewer side effects and quicker recovery [15]. Recognized as the gold standard for perioperative pain control, multimodal analgesia encompasses systemic pharmacological therapy, regional anesthesia, neuraxial anesthesia, and nonpharmacological modalities [14].

Systemic Pharmacological Therapy

Common medications used in systemic pharmacological therapy include opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), cyclooxygenase-2 (COX-2) inhibitors, acetaminophen, gabapentinoids, N-Methyl-D-aspartate (NMDA) receptor antagonists (intravenous ketamine and magnesium), and intravenous lidocaine. Oral opioids are recommended over intravenous opioids for postoperative pain control [14]. Preoperative use of opioids is not recommended [14]. NSAIDs, including COX-2 inhibitors like celecoxib, are a mainstay of any multimodal

analgesic plan and can be as effective as opioids in relieving pain [18, 19]. Small doses of these medications can significantly reduce postoperative pain levels and opioid consumption [16, 19, 20]. However, their usage is accompanied by potential side effects, including heightened risks of gastrointestinal bleeding, wound bleeding, diminished kidney function, and concerns regarding cardiovascular complications [18].

Acetaminophen is less potent than NSAIDs, however, when combined, they provide effective analgesia and are associated with less postoperative pain and opioid consumption than with opioids alone [14, 16, 18, 21]. Preoperative administration of acetaminophen and gabapentinoids has been demonstrated to decrease postoperative pain, hospital stay duration, and opioid-related side effects [18]. Giving gabapentin and pregabalin prior to surgery can lower pain scores and opioid consumption up to 24 h postoperatively [18, 22]. Most studies find IV ketamine as an effective adjunct for pain control, showing a decrease in pain, nausea, vomiting, and opioid consumption postoperatively [14, 23, 24]. Some recommend IV ketamine be reserved for use only in major surgeries and caution its use in the elderly and cognitively impaired due to increased risk of postoperative delirium, nightmares, and hallucinations [14, 23, 24]. Alpha-2 agonists, including dexmedetomidine and clonidine, have shown promise in reducing postoperative pain and opioid consumption when given in both the preoperative setting and intraoperatively [25–28]. These medications have the added benefit of decreasing postoperative delirium but can cause bradycardia [25–28]. IV lidocaine has been most thoroughly studied in open laparoscopic abdominal procedures and has shown promise in decreasing pain after surgery and can shorten the duration of surgical related ileus [29].

Regional and Neuraxial Anesthesia

Nerve blocks can be categorized into regional and neuraxial. The anesthesia provider performs a nerve block by injecting anesthetic around specific nerves or nerve bundles using landmarks and/or ultrasonography. Nerve blocks can offer targeted analgesia with fewer systemic side effects, and research consistently shows a reduction in opioid consumption and pain scores. This can lead to shorter hospital stays and enhanced patient satisfaction [14, 30, 31]. Regional nerve blocks are often used in surgeries involving extremities, in thoracotomies, abdominal procedures, breast procedures, and circumcisions. Despite the potential advantages of peripheral nerve blocks, there are inherent complications such as infection, hematoma, and nerve damage, although these are rare [14, 30, 31]. Overall, the benefits of regional anesthesia outweigh safety concerns in most major surgeries, highlighting their pivotal role in modern pain management strategies. Moreover, for patients who have multiple co-morbidities and who will not tolerate general anesthesia, this technique can prove to be invaluable.

Adjuvant Therapies

Preoperative rehabilitation or "prehabilitation" is a term used to describe the practice of enhancing a patient's functional capacity before surgery. It comprises multidisciplinary interventions, including exercise, nutritional optimization, and psychological preparation, designed to dampen the metabolic response to surgery, shorten the period of recovery, reduce complications, and improve the quality of recovery and quality of life [32]. Psychological interventions that may aid prehabilitation include cognitive-behavioral therapies, relaxation techniques, mindfulness-based interventions, coping strategies, hypnosis, and narrative medicine [32]. Music therapy is a safe, inexpensive, simple tool that can be used for postoperative pain from different types of surgeries [33–41] as well as relaxation techniques [42–45].

Challenges and Considerations

Achieving successful treatment of postoperative pain remains a challenge. Effective postoperative

pain control starts with risk assessment and preoperative education, followed by a multimodal intraoperative plan, and extends through postoperative management, education, and appropriate discharge information.

Certain patient groups pose challenges in pain management despite well-planned strategies. These groups include pediatric and geriatric patients, pregnant patients, opioid-tolerant patients, patients with active substance use, and those with kidney or liver disease. A multidisciplinary approach involving anesthesiology, surgery, and acute pain services is essential for achieving optimal postoperative pain control for these patients.

High-risk patients should be screened preoperatively for potential pain management challenges. Those with active substance use disorders undergoing surgery should be referred to mental health, rehabilitation, or addiction specialists as needed. Educating patients about expectations before surgery is standard in every preoperative surgical evaluation [46].

Chronic pain patients on buprenorphine, methadone, or naltrexone also present challenges, especially in ambulatory surgery settings, due to their increased postoperative opioid requirements. Guidelines exist for managing perioperative pain in these patients [47].

Whenever possible, surgeons should opt for minimally invasive surgeries using nerve-sparing techniques. Anesthesiologists should employ regional anesthesia and deliver effective multimodal postoperative analgesia.

Future Directions and Research

Several risk factors for developing acute and chronic postoperative pain have been identified. Ongoing studies aim to determine potential genetic, demographic, and clinical risk factors for constructing prediction models. The goal is to better stratify patients at risk for post-surgical pain [48].

Oliceridine, a novel mu-opioid receptor agonist and part of a new class of biased ligands, preferentially activates one intracellular signaling pathway over another, potentially limiting opioid-related adverse events [49, 50]. In vivo studies show Oliceridine is 4–10 times more potent than morphine in achieving analgesia in rats [49]. A Phase IV study is currently underway.

Sublingual sufentanil, a thienyl derivative of fentanyl, delivered via a patient-controlled handheld system, has shown promise. It is provided as a 30-microgram sublingual tablet in a disposable applicator for placement under the tongue [51, 52]. The sufentanil sublingual tablet system (SSTS) has been approved for postoperative pain management, offering good bioavailability, rapid equilibrium attainment, elimination without metabolites, rapid onset, and effective pain reduction [53, 54].

Virtual reality (VR), an immersive three-dimensional experience, offers distraction from pain through a multisensory environment of auditory, visual, and proprioceptive stimuli [55]. A systematic review and meta-analysis of eight randomized controlled trials showed significant improvements in postoperative satisfaction in two studies, though it did not affect physiological parameters related to pain in minor surgery [56].

Conclusion

Postoperative pain management is a persistent challenge in modern medicine. Effective acute pain treatment improves recovery times and prevents chronic pain. Acute pain triggers a stress response, releasing maladaptive hormones. Multimodal analgesia, using various medications and techniques, targets different receptors to enhance pain relief while minimizing side effects. Comprehensive pain control involves risk assessment, preoperative education, a multimodal intraoperative plan, and thorough postoperative management and discharge education. This holistic approach enhances patient outcomes and satisfaction.

Key Takeaways

1. Postoperative pain management remains a challenge in modern day medicine.
2. Addressing and treating acute post-surgical pain improves recovery times and mitigates the development of chronic pain.
3. Acute pain induces a stress response that release catecholamines, cortisol, and glucagon, which can all be maladaptive in certain settings.
4. Multimodal analgesia utilizes multiple analgesic medications and techniques to target various receptors and mechanisms of action within the peripheral and/or central nervous system to enhance analgesia while mitigating side effects.
5. Postoperative pain control begins with risk assessment, followed by perioperative education, then implementing a multimodal intraoperative plan. Postoperative management, education, and appropriate discharge information is important as well.

References

1. Tighe P, Buckenmaier CC 3rd, Boezaart AP, Carr DB, Clark LL, Herring AA, et al. Acute pain medicine in the United States: a status report. Pain Med. 2015;16(9):1806–26.
2. Chou R, Hartung D, Turner J, Blazina I, Chan B, Levander X, et al. Evidence summary. Opioid Treatments for Chronic Pain [Internet] 2020.
3. Liu S, Kelliher L. Physiology of pain—a narrative review on the pain pathway and its application in the pain management. Dig Med Res. 2022;5:56.
4. McGreevy K, Bottros MM, Raja SN. Preventing chronic pain following acute pain: risk factors, preventive strategies, and their efficacy. Eur J Pain Suppl. 2011;5(2):365–72.
5. Fregoso G, Wang A, Tseng K, Wang J. Transition from acute to chronic pain: evaluating risk for chronic postsurgical pain. Pain Physician. 2019;22(5):479.
6. Le-Wendling L, Glick W, Tighe P. Goals and objectives to optimize the value of an acute pain service in perioperative pain management. Tech Orthop. 2017;32(4):200–8.
7. Kehlet H. Surgical stress: the role of pain and analgesia. BJA. 1989;63(2):189–95.
8. Kuner R, Kuner T. Cellular circuits in the brain and their modulation in acute and chronic pain. Physiol Rev 2020.
9. Lee GI, Neumeister MW. Pain: pathways and physiology. Clin Plast Surg. 2020;47(2):173–80.
10. Yam MF, Loh YC, Tan CS, Khadijah Adam S, Abdul Manan N, Basir R. General pathways of pain sensation and the major neurotransmitters involved in pain regulation. Int J Mol Sci. 2018;19(8):2164.
11. Reardon DP, Anger KE, Szumita PM. Pathophysiology, assessment, and management of pain in critically ill adults. Am J Health Syst Pharm. 2015;72(18):1531–43.
12. Dunwoody CJ, Krenzischek DA, Pasero C, Rathmell JP, Polomano RC. Assessment, physiological monitoring, and consequences of inadequately treated acute pain. J Perianesth Nurs. 2008;23(1 Suppl):S15–27.
13. Goldberg SF, Pozek J-PJ, Schwenk ES, Baratta JL, Beausang DH, Wong AK. Practical management of a regional anesthesia-driven acute pain service. Adv Anesth. 2017;35(1):191–211.
14. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. 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. J Pain. 2016;17(2):131–57.
15. Gelman D, Gelmanas A, Urbanaitė D, Tamošiūnas R, Sadauskas S, Bilskienė D, et al. Role of multimodal analgesia in the evolving enhanced recovery after surgery pathways. Medicina (B Aires). 2018;54(2):20.
16. Elia N, Lysakowski C, Tramer MR. Does multimodal analgesia with acetaminophen, nonsteroidal antiinflammatory drugs, or selective cyclooxygenase-2 inhibitors and patient-controlled analgesia morphine offer advantages over morphine alone? Meta-analyses of randomized trials. J Am Soc Anesthesiol. 2005;103(6):1296–304.
17. Geng Z, Bi H, Zhang D, Xiao C, Song H, Feng Y, et al. The impact of multimodal analgesia based enhanced recovery protocol on quality of recovery after laparoscopic gynecological surgery: a randomized controlled trial. BMC Anesthesiol. 2021;21:1–8.
18. Decker H, Wu CL, Wick E. Multimodal pain control in surgery 2020. Adv Surg. 2021;55:147–57.
19. Gimbel JS, Brugger A, Zhao W, Verburg KM, Geis GS. Efficacy and tolerability of celecoxib versus hydrocodone/acetaminophen in the treatment of pain after ambulatory orthopedic surgery in adults. Clin Ther. 2001;23(2):228–41.
20. Matsota P, Nakou M, Kalimeris K, Batistaki C, Pandazi A, Kostopanagiotou G. A single dose of celecoxib 200 mg improves postoperative analgesia provided via patient-controlled epidural technique after caesarean section. Arch Med Sci. 2013;9(5):877–82.
21. Maund E, McDaid C, Rice S, Wright K, Jenkins B, Woolacott N. Paracetamol and selective and non-selective non-steroidal anti-inflammatory drugs for the reduction in morphine-related side-effects after

major surgery: a systematic review. Br J Anaesth. 2011;106(3):292–7.
22. Hurley RW, Cohen SP, Williams KA, Rowlingson AJ, Wu CL. The analgesic effects of perioperative gabapentin on postoperative pain: a meta-analysis. Reg Anesth Pain Med. 2006;31(3):237–47.
23. Zhou L, Yang H, Hai Y, Cheng Y. Perioperative low-dose ketamine for postoperative pain management in spine surgery: a systematic review and meta-analysis of randomized controlled trials. Pain Res Manag. 2022;2022:1.
24. Hannon CP, Fillingham YA, Gililland JM, Sporer SM, Casambre FD, Verity TJ, et al. A systematic review of the efficacy and safety of ketamine in Total joint arthroplasty. J Arthroplast. 2023;38(4):763–8. e2.
25. Unlugenc H, Gunduz M, Guler T, Yagmur O, Isik G. The effect of pre-anaesthetic administration of intravenous dexmedetomidine on postoperative pain in patients receiving patient-controlled morphine. Eur J Anaesthesiol. 2005;22(5):386–91.
26. Schnabel A, Meyer-Frießem C, Reichl S, Zahn P, Pogatzki-Zahn E. Is intraoperative dexmedetomidine a new option for postoperative pain treatment? A meta-analysis of randomized controlled trials. Pain. 2013;154(7):1140–9.
27. Tian C, Malhan RS, Deng SX, Lee Y, Peachey J, Singh M, et al. Benefits of dexmedetomidine on postoperative analgesia after bariatric surgery. Minerva Anestesiol. 2021;88(3):173–83.
28. Ju JY, Kim K-M, Lee S. Effect of preoperative administration of systemic alpha-2 agonists on postoperative pain: a systematic review and meta-analysis. Anesth Pain Med. 2020;15(2):157.
29. Rimbäck G, Cassuto J, Tollesson P-O. Treatment of postoperative paralytic ileus by intravenous lidocaine infusion. Anesth Analg. 1990;70(4):414–9.
30. Jogie J, Jogie JA. A comprehensive review on the efficacy of nerve blocks in reducing postoperative anesthetic and analgesic requirements. Cureus. 2023;15(5)
31. Kianian S, Bansal J, Lee C, Zhang K, Bergese SD. Perioperative multimodal analgesia: a review of efficacy and safety of the treatment options. Anesthesiol Perioperative Sci. 2024;2(1):1–16.
32. Lobo DN, Pavel S, Gomez D, Greenhaff PL. Prehabilitation: high-quality evidence is still required. Br J Anaesth. 2023;130(1):9–14.
33. Choi EK, Baek J, Lee D, Kim DY. Effect on music therapy on quality of recovery and postoperative pain after gynecological laparoscopy. Medicine (Baltimore). 2023;102(9):e33071.
34. Grafton-Clarke C, Grace L, Harky A. Music therapy following cardiac surgery—is it an effective method to reduce pain and anxiety? Interact Cardiovasc Thorac Surg. 2019;28(5):722–7.
35. Bagle A, Phansalkar S, Gaur S. The effect of music therapy on hemodynamic parameter and pain score in patients under going abdominal and lower limb surgeries under spinal anaesthesia. Med J Dr DY Patil Vidyapeeth. 2023;16(2):232–6.
36. Zhang Q-L, Xu N, Huang S-T, Lin Z-W, Chen L-W, Cao H, et al. Music therapy for early postoperative pain, anxiety, and sleep in patients after mitral valve replacement. Thorac Cardiovasc Surg. 2020;68(6):498–502.
37. Nelson K, Adamek M, Kleiber C. Relaxation training and postoperative music therapy for adolescents undergoing spinal fusion surgery. Pain Manag Nurs. 2017;18(1):16–23.
38. Jing L, Xiaofeng T, Wei Y. Application of music therapy in general surgical treatment. Biomed Res Int. 2021;2021
39. Sin WM, Chow KM. Effect of music therapy on postoperative pain Management in Gynecological Patients: a literature review. Pain Manag Nurs. 2015;16(6):978–87.
40. Lin C-L, Hwang S-L, Jiang P, Hsiung N-H. Effect of music therapy on pain after orthopedic surgery-a systematic review and meta-analysis. Pain Prac. 2020;20(4):422–36.
41. Gogoularadja A, Bakshi SS. A randomized study on the efficacy of music therapy on pain and anxiety in nasal septal surgery. Int Archiv Otorhinolaryngol. 2020;24(02):e232–e6.
42. Pishgooie SAH, Akbari F, Keyvanloo Shahrestanaki S, Rezaei M, Nasiri M, Momen R. Effects of relaxation techniques on acute postlaminectomy pain: a three-arm randomized controlled clinical trial. J Perianesthesia Nurs. 2020;35(5):533–8.
43. Merz AE, Campus G, Abrahamsen R, Wolf TG. Hypnosis on acute dental and maxillofacial pain relief: a systematic review and meta-analysis. J Dent. 2022;123
44. Weekes DG, Wicks ED, Campbell RE, Hadley C, Carter A, Chaudhry Z, et al. Do relaxation exercises decrease postoperative pain after rotator cuff repair? A randomized controlled trial. Orthop J Sports Med. 2019;7
45. Szeverenyi C, Kekecs Z, Johnson A, Elkins G, Csernatony Z, Varga K. The use of adjunct psychosocial interventions can decrease postoperative pain and improve the quality of clinical care in orthopedic surgery: a systematic review and meta-analysis of randomized controlled trials. J Pain. 2018;19(11):1231–52.
46. Paladini A, Rawal N, Coca Martinez M, Trifa M, Montero A, Pergolizzi J Jr, et al. Advances in the management of acute postsurgical pain: a review. Cureus. 2023;15(8):e42974.
47. Kohan L, Potru S, Barreveld AM, Sprintz M, Lane O, Aryal A, et al. Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel. Reg Anesth Pain Med [Internet]. 2021;46(10):840–59. https://doi.org/10.1136/rapm-2021-103007.
48. Li S, van Boekel RLM, van den Heuvel SAS, Coenen MJH, Vissers KCP. Pain predict genetics: protocol for a prospective observational study of clinical and genetic factors to predict the development of post-

operative pain. BMJ Open [Internet]. 2022;12(11) https://doi.org/10.1136/bmjopen-2022-066134.
49. Daksla N, Wang A, Jin Z, Gupta A, Bergese SD. Oliceridine for the management of moderate to severe acute postoperative pain: a narrative review. Drug Des Devel Ther. 2023;17:875–86.
50. Liu Y, Hu Q, Yang J. Oliceridine for the management of acute postoperative pain. Ann Pharmacother. 2021;55(10):1283–9.
51. Van de Donk T, Ward S, Langford R, Dahan A. Pharmacokinetics and pharmacodynamics of sublingual sufentanil for postoperative pain management. Anaesthesia. 2018;73(2):231–7.
52. Reardon CE, Kane-Gill SL, Smithburger PL, Dasta JF. Sufentanil sublingual tablet: a new option for acute pain management. Ann Pharmacother. 2019;53(12):1220–6.
53. Thangaraju P, Varthya SB, Venkatesan S, Tamilselvan T, Singh S. Efficacy and safety of sufentanil sublingual tablet system in postoperative pain management: a systematic review and meta-analysis. BMJ Supportive & Palliative Care [Internet]. 2023;13(e1):e20–e9. https://doi.org/10.1136/bmjspcare-2020-002693.
54. Giaccari LG, Coppolino F, Aurilio C, Esposito V, Pace MC, Paladini A, et al. Sufentanil sublingual for acute post-operative pain: a systematic literature review focused on pain intensity, adverse events, and patient satisfaction. Pain Ther. 2020;9(1):217–30.
55. Pandrangi VC, Shah SN, Bruening JD, Wax MK, Clayburgh D, Andersen PE, et al. Effect of virtual reality on pain management and opioid use among hospitalized patients after head and neck surgery. JAMA Otolaryngol Head Neck Surg. 2022;148(8):724–30.
56. Ding L, Hua H, Zhu H, Zhu S, Lu J, Zhao K, et al. Effects of virtual reality on relieving postoperative pain in surgical patients: a systematic review and meta-analysis. Int J Surg. 2020;82:87–94.

2 Understanding Pain Pathways: Exploring the Biological and Neurological Mechanisms of Pain, Essential for Pain Management

Andrew Sobczak and Yasmin Sritapan

Introduction

Pain is one of the most common reasons to seek medical attention. It is described as an unpleasant sensory and emotional experience associated with, or resembling actual or potential tissue damage ("IASP Announces Revised Definition of Pain," [5]). The experience of pain is variable, making it challenging to objectively measure and treat. Chronic pain can significantly impact a person's quality of life. It can profoundly affect a person's mental health and well-being, often leading to anxiety, depression, and a sense of despair.

Pain signaling involves neurotransmitters, receptors, and ion channels that are essential for transmitting and modulating pain signals and perception. Understanding these pain pathways is crucial for effective pain management, enabling physicians to address the root cause of pain and provide personalized treatment.

Neuroanatomy of Pain

The perception of pain involves interaction between neural pathways and structures within the nervous system. The nervous system is split into two parts: the Central Nervous System (CNS) and the Peripheral Nervous System (PNS). The CNS comprises the brain and spinal cord for processing and integrating information. The PNS includes nerves extending from the CNS to parts of the body providing sensory information to the CNS.

The pain signaling pathway consists of four elements: transduction, transmission, modulation, and perception [2, 6].

Nociceptors: Primary Receptors for Pain

Nociceptors serve as primary detectors of a variety of noxious stimuli and are located throughout the body, from skin to viscera and dura. Nociceptors can be categorized into two types based on their response characteristics: A-delta fibers and C fibers. A-delta fibers are myelinated and transmit sharp, well-localized pain signals, while C fibers are unmyelinated and transmit dull, poorly localized pain signals [16].

Transduction occurs when a nociceptor is activated by a noxious stimulus. When activated, the nociceptor produces electrical signals which are transmitted to the CNS through nerve fibers. This process is called transmission [2].

A. Sobczak · Y. Sritapan (✉)
University of Louisville, Louisville, KY, USA
e-mail: yasmin.sritapan@uoflhealth.org

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_2

Pathway for Signaling Pain

A receptor potential is generated when a nociceptor is activated by a stimulus. If the receptor potential is strong enough, it triggers the opening of voltage-gated sodium channels, leading to the generation of an action potential. Action potentials then travel to second-order neurons in the dorsal horn of the spinal cord. From the spinal cord, the pain signal is transmitted to the thalamus and cerebral cortex for processing and perception. The frequency and pattern of action potentials generated provide information about the intensity, duration, and location of the noxious stimulus, which is part of the modulation of pain signaling [4].

The spinothalamic tract is the main ascending pathway responsible for transmitting pain signals to the brain. The thalamus transmits the pain signals to the somatosensory cortex. The limbic system, which deals with emotions and memories, also influences how we emotionally perceive pain [12].

In addition, there are descending pathways that originate from the brainstem and release neurotransmitters such as serotonin and norepinephrine, which modify the transmission of pain signals in the spinal cord. This descending modulation plays a crucial role in the perception of pain [12].

Neurotransmitters in Transmitting Pain Signals

Neurotransmitters act as messengers that convey signals between neurons and other cells in the body. With regard to pain, neurotransmitters regulate pain signals traveling from areas of injury or inflammation to the CNS. Various neurotransmitters participate in transmitting pain signals within the PNS and CNS. Any imbalance in their activity can contribute to the onset and persistence of pain conditions.

Glutamate serves as the main excitatory neurotransmitter in the CNS by activating receptors on second-order neurons in the spinal cord, leading to the transmission of pain signals to higher brain regions. Disruption in glutamate signaling has been linked to neuropathic pain.

Substance P is released by nociceptors when exposed to stimuli and conveys pain messages by activating receptors on second-order neurons within the spinal cord. Elevated levels of substance P have been associated with inflammatory pain.

Serotonin and norepinephrine play a role in reducing pain signals by inhibiting their transmission in the spinal cord. Medications like tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors are prescribed for pain management, as they boost these neurotransmitters in the body.

Endorphins are the body's natural pain-relieving substances. They block pain signals in the nervous system. They are produced in response to stress or pain and bind to receptors in the brain and spinal cord to alleviate pain. Opioids, which mimic endorphin effects, are commonly used to treat pain [16].

Drugs that target neurotransmitter systems involved in pain signaling, such as glutamate antagonists, substance P antagonists, and serotonin-norepinephrine reuptake inhibitors, can help reduce pain sensitivity and improve pain management in chronic pain conditions. Additionally, nonpharmacological interventions, including cognitive-behavioral therapy and acupuncture, can modulate neurotransmitter signaling.

Inflammation and Pain

Inflammation is a process that helps the body defend against injury and infection. One of the significant aspects of the inflammatory response is the release of inflammatory mediators such as cytokines, chemokines, and prostaglandins, which coordinate the immune response and promote tissue repair. Inflammation increases blood flow to the region, bringing cells and inflammatory substances. While inflammation is a part of healing, it can also contribute to pain development [10].

Inflammation can influence pain perception by sensitizing nociceptors. Inflammatory mediators, such as prostaglandins and bradykinin, decrease the threshold for activating pain receptors, leading to heightened sensitivity to pain. Prostaglandins can also enhance the effects of other inflammatory mediators, such as bradykinin and histamine, further intensifying the inflammatory response and pain perception [10].

Histamine is released by mast cells in response to injury or allergens. Histamine plays a role in promoting blood vessel dilation and increasing permeability, contributing to inflammation symptoms such as redness and swelling and conveys the sensation of pain to the brain [10].

Inflammation can also trigger the release of neuropeptides, like substance P and calcitonin gene-related peptide (CGRP) from nociceptors. These neuropeptides contribute to inflammation leading to increased vasodilation and vascular permeability, which intensify the response and perception of pain [10].

Recognizing how inflammation influences pain is crucial for managing pain. Medications that target inflammation, such as nonsteroidal anti-inflammatory drugs (NSAIDs) and corticosteroids, can help reduce inflammation and relieve pain. NSAIDs work by blocking cyclooxygenase, which is responsible for the production of prostaglandins. By lowering prostaglandin levels, NSAIDs decrease both inflammation and pain.

Antihistamines function by counteracting the effects of histamines, thereby reducing inflammation and easing symptoms like itching and swelling. While antihistamines are not typically used as pain relievers, they can be beneficial in inflammatory conditions with significant histamine release.

Aside from medication, physical therapy, acupuncture, and other complementary therapies may help decrease inflammation and enhance pain relief. Lifestyle modifications, such as maintaining a healthy weight and avoiding inflammatory foods, can help reduce inflammation and pain.

Sensitization

Sensitization of nociceptors is a process in which responsiveness to stimuli is enhanced, which can lead to increased pain perception even in the absence of ongoing tissue damage. Nociceptor sensitization can occur through peripheral sensitization and central sensitization.

Peripheral Sensitization

Peripheral sensitization refers to the increased sensitivity of nociceptors in the PNS, causing an intensification of pain signals. This phenomenon plays a role in the onset and persistence of pain; therefore, it is a focus for pain management strategies [13].

The interplay of molecular mechanisms within nociceptors and surrounding tissues is involved in peripheral sensitization. This can occur through the release of inflammatory substances like prostaglandins and bradykinin that lower the activation threshold of nociceptors. Further, alterations in ion channel expression or function on nociceptors may occur, leading to heightened excitability and increased sensitivity to stimuli [15].

Targeting the pathways involved in sensitization, such as inflammatory agents or neuropeptides, can help reduce sensitivity to pain and alleviate symptoms. For example, NSAIDs can decrease inflammation and the release of inflammatory agents, and medications focusing on neuropeptides like CGRP antagonists can help lessen neurogenic inflammation.

Central Sensitization

Central sensitization refers to an intensification of pain signals within the central nervous system (CNS). This occurs when neurons in the spinal cord and brainstem become hyperexcitable, altering the transmission of pain signals between synapses. Hyperalgesia, an increased sensitivity to

painful stimuli, and allodynia, the perception of pain in response to non-painful stimuli, are characteristic features of this phenomenon [13].

Central sensitization can lead to a decreased pain threshold and an escalation in the intensity and duration of pain. A significant factor behind sensitization is the activation of N-methyl-D-aspartate (NMDA) receptors within the spinal cord. These glutamate receptors play a critical role in transmitting pain signals. Intense nociceptive input can result in prolonged NMDA receptor activation, increasing neuronal excitability in the spinal cord and amplifying pain signaling [9].

Another component of sensitization involves the activation of glial cells, specifically microglia and astrocytes, within the CNS. These glial cells, which are involved in immune responses in the CNS, can release inflammatory mediators and neurotrophic factors that contribute to neuronal sensitization and enhanced pain signaling.

Central sensitization plays a significant role in the transition from acute to chronic pain. Acute pain is a response to tissue damage or inflammation and is usually self-resolving. However, persistent or intense nociceptive input associated with acute pain can lead to sensitization and the development of chronic pain [3].

By targeting the molecules and pathways involved in nociceptor sensitization, such as inflammatory mediators and ion channels, it is possible to reduce sensitivity to pain and alleviate symptoms. Pharmaceutical interventions such as NSAIDs, TRPV1 antagonists, and opioids are used to target nociceptor sensitization. Additionally, medications that modulate sensitization, such as gabapentinoids or NMDA antagonists, are effective in managing chronic pain conditions. Non-pharmaceutical methods, like acupuncture and cognitive-behavioral therapy, are also beneficial for managing pain by regulating central pain processing.

Neuroplasticity and Neuronal Hyperexcitability

Neuroplasticity is the brain's ability to reorganize itself by forming connections in response to learning, experiences, or injury [4]. Neuroplasticity also plays a role in the development and persistence of pain conditions. For example, increased expression of receptors and ion channels on neurons involved in transmitting pain signals leads to sensitization. In chronic pain, there may be an elevation in NMDA receptor levels leading to central sensitization and amplification of pain [11].

Additionally, neuroplasticity can alter synaptic transmission. Synaptic plasticity refers to changes in the effectiveness of connections between neurons. There may be enhanced excitatory synapse strength or reduced inhibitory synapse strength, leading to heightened neuronal excitability and amplified pain [8].

Pain Modulation

Pain modulation refers to how the nervous system regulates and controls the intensity and perception of pain via excitatory and inhibitory mechanisms. Descending pathways from the brainstem release neurotransmitters that either inhibit or facilitate pain signal transmission in the spinal cord. The periaqueductal gray (PAG) and rostral ventromedial medulla (RVM) descending spinal cord pathway is an essential pathway for pain modulation. The PAG is part of the opioid system, which blocks pain signals by releasing endorphins and enkephalins. The RVM can block or enhance pain signals based on the neurotransmitters released. For instance, serotonin and norepinephrine release inhibits pain signals, while glutamate release enhances them [17].

Gate Control Theory of Pain

Gate control theory proposes that pain is not a direct response to nociceptive input but rather a complex interplay involving sensory, emotional, and cognitive factors. This theory postulates that a "gate" within the spinal cord controls the flow of pain signals to the brain. This system can open up, allowing pain signals to reach the brain, or close off, blocking the transmission of pain signals. The operation of this gate is regulated by a network of excitatory and inhibitory neurons in the spinal cord [4].

According to the theory, factors like heightened activity due to anxiety, stress, or inflammation can open up the gate, resulting in increased sensitivity to pain. Conversely, non-nociceptive inputs can trigger neurons that shut down the gate, limiting pain signal transmission. This implies that non-pharmacological methods such as relaxation techniques, behavioral therapy, and physical therapy can effectively influence pain perception by closing off the gate and decreasing pain signal transmission.

The gate control theory emphasizes the importance of an individual's psychological state and surroundings. Creating a supportive atmosphere may help alleviate stress and anxiety, ultimately closing off the gate and reducing perceived pain levels.

New Treatment Approaches

Recent methods for treating long-term pain are aimed at pain pathways for efficient relief.

One method targets inflammatory pain pathways. Monoclonal antibodies that target pro-inflammatory cytokines like tumor necrosis factor alpha or interleukin-6 have proven effective in alleviating inflammation in conditions such as arthritis and inflammatory bowel disease [7].

Neuromodulation treatments use magnetic stimulation to regulate specific neural pathways associated with transmitting pain. Spinal cord stimulation entails placing electrodes along the spinal cord to send electrical pulses that disrupt pain signals. Similarly, transcranial magnetic stimulation focuses on brain regions involved in processing pain. These show potential in easing neuropathic pain and complex regional pain syndrome [1].

Progress in comprehending the role of ion channels and receptors in transmitting pain has led to the creation of treatments that target these channels and receptors. For example, there are promising results for drugs targeting subtypes of voltage-gated sodium channels, such as Nav1.7. New drugs that focus on types of opioid receptors offer more precise pain relief and fewer side effects compared to traditional opioids [14].

Another novel method is gene therapy, which targets the production of opioid peptides or anti-inflammatory cytokines and has demonstrated potential in initial studies. Gene therapy may deliver lasting pain relief through a single treatment.

Novel treatments concentrating on pain pathways have the potential to transform pain management by offering more precise and efficient therapies with reduced side effects. More research is necessary for increased understanding and application of these therapies.

Challenges and Future Directions

Present Challenges in Unraveling Pain Pathways

Despite advancements in understanding the mechanisms behind pain, significant hurdles and gaps remain in our comprehension of pain pathways.

One major obstacle is the inherent subjectivity of pain. Pain perception is influenced by factors such as genetics, past experiences, cultural background, and emotional well-being, making it difficult to quantify and study pain objectively.

Furthermore, the intricate nature of pain pathways, which involves multiple layers of processing, adds to the complexity. Pain signals travel from the periphery to the spinal cord and then to the brain for further processing. This complexity makes it challenging to pinpoint specific mechanisms involved in pain transmission and modulation.

Future Prospects

Progress on brain imaging methods, such as functional magnetic resonance imaging (fMRI) and positron emission tomography (PET), can aid in understanding the specific brain areas responsible for processing pain. Further, research on micro-RNAs can offer information on molecules and genetic elements that impact pain sensitivity, potentially offering clues for treatment.

Key Takeaways

1. Pain signaling consists of neurotransmitters, receptors and ion channels that play roles in pain signal transmission and perception.
2. Pain signaling pathway consists of four elements: transduction, transmission, modulation, and perception.
3. Nociceptors serve as primary detectors of a variety of noxious stimuli and are located throughout the body, from skin to viscera to dura.
4. Transmission is the process in which the electrical signals from the nociceptors are transmitted to the central nervous system.
5. The frequency and pattern of action potentials generated provides information about the intensity, duration, and location of the noxious stimulus, which is part of the modulation and perception of the pain signaling.
6. The spinothalamic tract is the main ascending pathway responsible for transmitting pain signals to the brain.
7. Sensitization of nociceptors is a process in which responsiveness to stimuli is enhanced, which can lead to increased pain perception even in the absence of ongoing tissue damage.

References

1. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. Lancet. 2021;397(10289):2082–97. https://doi.org/10.1016/S0140-6736(21)00393-7.
2. Gould HJ, Kaye AD. The anatomy of pain. In: Kaye AD, Urman RD, Vadivelu N, editors. Essentials of regional anesthesia. Springer New York; 2012. p. 83–119. https://doi.org/10.1007/978-1-4614-1013-3_4.
3. van Griensven H, Schmid A, Trendafilova T, Low M. Central sensitization in musculoskeletal pain: lost in translation? J Orthop Sports Phys Ther. 2020; https://doi.org/10.2519/jospt.2020.0610.
4. Hall JE, Guyton AC. Guyton and Hall textbook of medical physiology. 12th ed. Saunders/Elsevier; 2011.
5. IASP Announces Revised Definition of Pain. (n.d.). International Association for the Study of Pain (IASP). Retrieved June 30, 2024, from https://www.iasp-pain.org/publications/iasp-news/iasp-announces-revised-definition-of-pain/
6. Institute of Medicine (US) Committee on Pain, D, Osterweis M, Kleinman A, Mechanic D. The anatomy and physiology of pain. In: Pain and disability: clinical, behavioral, and public policy perspectives. National Academies Press (US); 1987. https://www.ncbi.nlm.nih.gov/books/NBK219252/.
7. Knezevic NN, Mandalia S, Raasch J, Knezevic I, Candido KD. Treatment of chronic low back pain—new approaches on the horizon. J Pain Res. 2017;10:1111–23. https://doi.org/10.2147/JPR.S132769.
8. Kuner R, Flor H. Structural plasticity and reorganisation in chronic pain. Nat Rev Neurosci. 2016;18(1):20–30. https://doi.org/10.1038/nrn.2016.162.
9. Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. J Pain. 2009;10(9):895–926. https://doi.org/10.1016/j.jpain.2009.06.012.
10. Matsuda M, Huh Y, Ji R-R. Roles of inflammation, neurogenic inflammation, and neuroinflammation in pain. J Anesth. 2019;33(1):131–9. https://doi.org/10.1007/s00540-018-2579-4.
11. McCarberg B, Peppin J. Pain pathways and nervous system plasticity: learning and memory in pain. Pain Medicine (Malden, Mass). 2019;20(12):2421–37. https://doi.org/10.1093/pm/pnz017.
12. Purves D, Augustine GJ, Fitzpatrick D, Katz LC, LaMantia A-S, McNamara JO, Williams SM. The physiological basis of pain modulation. In: Neuroscience. 2nd ed. Sinauer Associates; 2001. https://www.ncbi.nlm.nih.gov/books/NBK10985/.
13. Toth C. Peripheral and central sensitization. In: Toth C, Moulin DE, editors. Neuropathic pain: causes, management and understanding. Cambridge University Press; 2013. p. 51–64. https://doi.org/10.1017/CBO9781139152211.006.
14. Waxman SG, Dib-Hajj SD. NaV1.7: a central role in pain. Neuron. 2023;111(17):2615–7. https://doi.org/10.1016/j.neuron.2023.08.011.
15. Wei S-Q, Tao Z-Y, Xue Y, Cao D-Y, Wei S-Q, Tao Z-Y, Xue Y, Cao D-Y. Peripheral sensitization. In: Peripheral nerve disorders and treatment. IntechOpen; 2019. https://doi.org/10.5772/intechopen.90319.
16. Yam MF, Loh YC, Tan CS, Khadijah Adam S, Abdul Manan N, Basir R. General pathways of pain sensation and the major neurotransmitters involved in pain regulation. Int J Mol Sci. 2018;19(8):2164. https://doi.org/10.3390/ijms19082164.
17. Yao D, Chen Y, Chen G. The role of pain modulation pathway and related brain regions in pain. Rev Neurosci. 2023;34(8):899–914. https://doi.org/10.1515/revneuro-2023-0037.

Part II

Preoperative Optimization

3 Patient Assessment and Risk Stratification: Methods for Evaluating Patient's Pain Risks Before Surgery

Channing C. Twyner and Kevin Vorenkamp

Introduction

The perioperative assessment of pain trajectory should be considered in the prevention of severe acute pain and the transition to chronic post-surgical pain (CPSP). Acute post-surgical pain is a normal physiological response to the tissue injury caused by surgery. In general, this pain is expected to last about seven days and, at most, 2–4 weeks [1–3]. When acute pain lasts for more than a month after surgery, there is a concern that acute post-surgical pain may transition to CPSP [4, 5]. Although the definition of CPSP has become more elaborate over the past two decades, the most current definition states: "Chronic post-surgical pain is pain developing after a surgical procedure and persisting beyond the healing process, i.e., at least 3 months after surgery. The pain is either localized to the surgical field, projected to the innervation territory of a nerve situated in this area, or referred to a dermatome (after surgery/injury to deep somatic or visceral tissues). Other causes of pain including infection, malignancy, etc. need to be excluded as well as pain continuing from a preexisting pain problem" [5].

CPSP may account for one-fifth of the prevalence of chronic in the community [6]. Considering the volume of surgical procedures across the globe, CPSP represents a real public health issue with significant social and economic consequences [7]. Thus, proper utilization of pain assessment tools and risk stratification plays a critical role in the preoperative optimization and comprehensive approach to perioperative pain management. Table 3.1 shows the incidence of CPSP in common surgeries performed across the globe [8, 9].

C. C. Twyner
Department of Anesthesiology, University of Mississippi, Jackson, MS, USA

K. Vorenkamp (✉)
Department of Anesthesiology and Pain Medicine, Duke University School of Medicine, Durham, NC, USA
e-mail: kevin.vorenkamp@duke.edu

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_3

Table 3.1 Incidence of CPSP based on surgery type

Surgery type	Incidence of CPSP	Incidence of severe CPSP	Percentage of Neuropathic CPSP
Amputation	30–85%	5–10%	80%
Caesarean delivery	6–55%	5–10%	50%
Inguinal hernia repair	5–63%	2–4%	80%
Total knee arthroplasty	13–44%	15%	6%
Total hip arthroplasty	7–23%	6%	1–2%
Mastectomy	11–57%	5–10%	65%
Thoracotomy	5–65%	10%	10%

Adapted from [8, 9]

Fundamentals of Pain Assessment

It is necessary to gather baseline information about the timing, location, intensity, quality, aggravating factors, alleviating factors, and prior treatments for the pain, as well as to perform a focused physical examination. In addition, it is important to ascertain the psychological (i.e., mood disorders, substance abuse disorders, posttraumatic stress disorder, and other psychiatric domains) and the social contexts (i.e., poverty, education, culture, support, and other social domains) in which the pain occurs. Lastly, it is critical to assess patient expectations, pain experience, the severity of preexisting pain at the surgical site, the presence of pain problems elsewhere, and the presence of disability due to pain.

Pain Quality

Surgical patients often present with preexisting pain at the surgical site and chronic pain problems elsewhere in the preoperative period. Identifying a baseline of nociceptive and neuropathic pain characteristics allows for surveillance of pain syndromes as they evolve in the perioperative period. Nociceptive pain represents a predictable response to tissue injury and is characterized by aching and/or sharp pain. If the pain is in the immediate vicinity of an injury to a musculoskeletal component or the skin, it is defined as somatic nociceptive pain. If the injury involves a visceral organ and is poorly localized from the injury, it is termed visceral nociceptive pain. Neuropathic pain, in contrast, represents an unpredictable response to tissue injury. Neuropathic pain is characterized by burning, tingling, electrical shocks, sensory loss, and spontaneous pain, often evoked by normal stimuli (i.e., allodynia) or enhanced by painful stimuli (i.e., hyperalgesia) [10]. Acute pain can be a mixture of somatic, visceral, and neuropathic pain.

Unidimensional Tools

Pain intensity is the most commonly assessed component of pain in the clinical setting, with the numerical rating scale (NRS), verbal rating scale (VRS), and visual analog scale (VAS) being the most prominently used self-reported pain tools [11]. The ease of administration is the greatest strength of these unidimensional tools of pain intensity. However, because these unidimensional pain assessment tools only measure pain intensity, they have been shown to be limited in the ability to predict how patients do clinically as it relates to response to therapy and function [12–14].

Multidimensional Pain Assessment Tools

Multidimensional pain assessment tools were created in response to the limitations of unidimensional pain assessment tools. The most validated multidimensional pain tools used in the perioperative setting include the McGill Pain Questionnaire (MPQ) and the Brief Pain Inventory (BPI). Short forms of both MPQ and BPI were developed to ease administration in the

clinical setting [15, 16]. The MPQ assesses sensory, emotional, and cognitive components of pain experience, and has been shown to be responsive to therapeutic interventions in many different pain populations [15, 17–22]. The BPI assesses pain severity and its impact on functioning and sleep and has also been shown to be useful for evaluating pain in many different types of post-surgical and other chronic pain populations [23–27].

Most patients are willing to accept pain, but the acceptability of pain and how it affects physical function in the immediate postoperative period needs emphasis during preop assessment. Setting reasonable expectations or goals is important to individualize treatment [34]. To improve perioperative outcomes, it is important to optimize patients early and continue to assess pain trajectory in the postoperative period [35]. The Patient-Reported Outcome Measurement Information Scores (PROMIS) are relatively new multidimensional pain tools that assess pain in the context of physical function, sleep, mental health, social health, pain interference, and other domains [28]. PROMIS scores have been proven to be valuable in predicting post operative pain and other pain-related outcomes, particularly in both spine and joint replacement surgery [29–33].

Tools Assessing Psychiatric Comorbidity

Several psychological factors have been consistently associated with pain-related outcomes, including those related to CPSP. The Pain Catastrophizing Scale (PCS), the Multidimensional Affect Pain Survey (MAPS), the Hospital Anxiety and Depression Scale (HADS), and the State-Trait Anxiety Inventory are commonly used tools clinically and for clinical research. Pain catastrophizing results in negative emotional and cognitive responses to actual or potential pain, resulting in unrealistic expectations. Scores on the PCS have been shown to predict CPSP across many different surgeries, including mastectomy, cesarean delivery, abdominal surgery, spine surgery, orthopedic surgery, and cardiac surgery [36–44]. The MAPS, which evaluates both somatosensory and affective components of pain, has been shown to predict post operative opioid requirement after colectomy when administered preoperatively [45]. Lastly, anxiety-targeted assessment tools, such as the HADS and the State Trait Anxiety Inventory, have been shown to predict the severity of acute post operative pain and CPSP [40, 44, 46, 47].

Challenges with Assessment Tools

Pain, by definition, is very much a subjective experience, which makes objectively measuring and assessing pain difficult. Easy-to-administer unidimensional tools have essentially tried to objectify the subjective pain experience, with little ability to impact pain-related outcomes. Although more difficult to administer, multidimensional tools include subjective components in the assessment of perioperative pain, the complex interactions between biological, psychological, and social factors have unmasked even more challenges in choosing which determinants require the most resources and interventions. Unfortunately, the use of these tools preoperatively has done little to reduce the burden of CPSP in the population [48].

Risk Stratification

Biopsychosocial Model of CPSP

The newest International Association for the Study of Pain (IASP) definition of pain demonstrates a commitment to the biopsychosocial model [49]. The biopsychosocial model of chronic pain acknowledges that the pain experience is influenced by biological, psychological, and social factors. Table 3.2 shows a non-exhaustive list of known and suspected biological, psychological, and social determinants of CPSP. Biological, psychological, and social determinants are inextricably linked to the incidence of CPSP (Fig. 3.1).

Table 3.2 Biological, Psychological, and Social determinants of CPSP

Biological	Psychological	Social
Age < 50	Anxiety	Education
Female sex	Depression	Socioeconomic status
Surgery (i.e., type, revision)	Pain catastrophizing	Race/ethnicity
Trauma	Coping skills	Culture
Cancer	Personality	Health policy
Preoperative pain	Attitudes	Solicitous response to pain
Poorly controlled acute pain	Expectations	Stigma
Medications	Emotions	Secondary gain
Genetics	Learning	Support/relationships
Infection	Substance use disorder and dependence	Insurance
Radiation	Post-traumatic stress disorder	Built environment

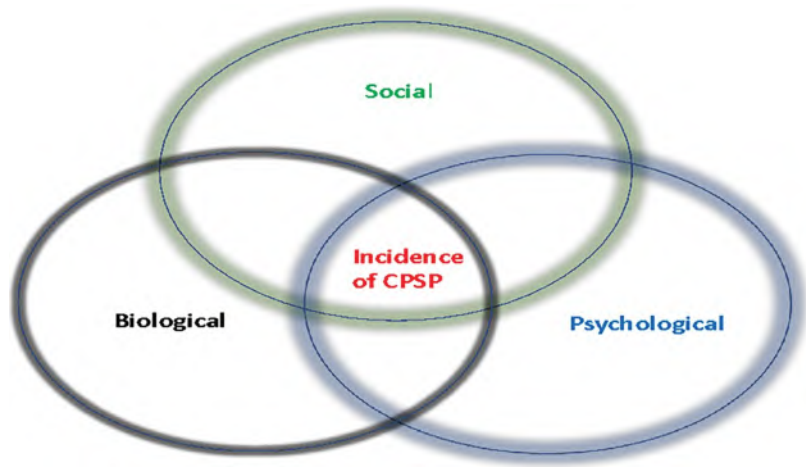


Fig. 3.1 Biopsychosocial Model of CPSP

Age and Gender

Across many different surgical populations, including abdominal, gynecological, orthopedic, and cardiothoracic surgeries, age and gender have been associated with an increased risk for developing CPSP [8, 9, 50–56]. The reasons behind older age being a protective factor as it relates to chronic post-surgical pain are not known, but it may be related to an aging nociceptive system. The reasons behind female sex being more prone to developing CPSP are also not well understood but may be a combination of biological, psychological, and social factors that are more prevalent in women than men.

Type of Surgery

The incidence of CPSP varies across many surgical types, with those surgeries with known or highly suspected direct nerve trauma (i.e., amputation, mastectomy, thoracotomy, and joint replacement) being shown to have the greatest incidence of both CPSP and the greatest incidence of CPSP with a strong neuropathic component [9]. In addition, longer surgeries and revision surgeries not only predict a greater incidence of CPSP but also a propensity for neuropathic pain (Table 3.1) [9].

Perioperative Pain and Opioid Use

Preoperative pain at the surgical site and/or other locations is associated with severe acute pain and/or CPSP [52, 54, 57–62]. Preoperative opioid use may be more or less a confounding factor as it relates to predicting severe acute pain and/or CPSP [63]. The severity of post operative pain, both acute (i.e., less than 2 weeks) and subacute (i.e., between 2 and 12 weeks, postoperatively), has been shown to predict the development of CPSP [57, 64–68]. Nevertheless, preoperative pain, whether at the surgical site or elsewhere, postoperative pain, and preoperative opioid use may represent altered pain processing in the form of peripheral and/or central sentisitzation [69, 70].

Genetic Factors

Despite many publications, the impact of identifying genetic risk factors preoperatively to prevent severe acute pain or the development of CPSP is not well known [71].

Psychological Risk Factors

Preoperative psychiatric comorbidity has been associated with both severe acute pain and the development of CPSP. Preoperative anxiety, depression, and pain catastrophizing have been consistently associated with the development of CPSP across many types of surgeries [36–44, 72–76].

Social Risk Factors

The investigation of social factors on severe acute postoperative pain and CPSP has lagged the search for biological and psychological factors. In fact, prediction models for CPSP tended not to include social factors. Nevertheless, low socioeconomic status, nonwhite race, and lower educational status have been associated with preoperative opioid use, longer opioid use after surgery, and high impact chronic pain after surgery [77–80].

Challenges with Risk Factors and Predictions Tools

Many of the challenges with preoperative assessment and risk stratification for post operative pain stems from methodological issues in clinical research in this domain. For instance, there have been 3 iterations of the definition of CPSP over the past decade, which could impact the prevalence of CPSP over time [4, 5, 81]. In addition, much of this is probably related to most studies using prediction tools that have had small sample sizes, lacked external validity, and had inconsistent definitions of psychological determinants [48]. Yet another example has been the use of c-statistics in predictive models, which predict the outcomes in individuals, not in populatons [52, 57, 82]. In other words, it may be more fruitful to predict outcomes by determining the causes of incidence in CPSP populations (i.e., population health science approach) versus the cause of individual cases of CPSP [83].

Clinical Scenario

A 48-year-old woman is referred by her orthopedic surgeon for perioperative optimization before right knee revision arthroplasty. She reports 9/10 pain at rest and 10/10 pain with activity, which is limited. Her medications include gabapentin 600 mg every 8 hours and oxycodone 10 mg every 6 hours. Intake questionnaires reveal 10/10 points on the function domains of the BPI short form (i.e., severe functional impairment) and a pain catastrophizing score (PCS) of 39. Her exam is significant for a BMI of 37, allodynia over the prior surgical incision, and limited range of motion (ROM) with knee flexion and extension due to pain and fear of pain (kinesiophobia). There is atrophy of the right thigh and calf compared with the left. She ambulates with the use of a cane. She continues to smoke ½ pack per day of cigarettes but is trying to quit. She is very ner-

vous about the upcoming surgery and has been delaying it for years.

You note many concerns for the worsening of her chronic pain and difficulty controlling acute postoperative pain. After discussion with the patient and her surgeon, you agree to delay surgery to improve her baseline condition prior to surgery. You refer her to pain psychology for cognitive behavioral therapy (CBT), biofeedback, and pain coping skills after noting her elevated PCS score and kinesiophobia. You also refer her to the tobacco cessation program, and the surgeon reinforces that they will not operate until the patient has demonstrated evidence of smoking cessation. Additionally, the patient is reporting a loss of benefit from the gabapentin, and you rotate to pregabalin and add a topical lidocaine cream and encourage regular use and massaging of her incision area for desensitization. You also refer to physical therapy, starting with a water-based regimen and a progressive increase in her home exercise program to regain strength and ROM.

After 3 months of ongoing treatment, the patient is reporting improvement. Her pain score at rest is now 7/10, but it is still 10/10 with activity. However, she is now ambulating without the use of a cane and can walk 500 yards without stopping. She has not had a cigarette or nicotine-containing product in 6 weeks and has lost 7 pounds. She continues to do a directed home exercise program for 10 min, twice daily, 5 days/week, and meets weekly with her physical therapist. Her ODI has reduced to 22 (moderate disability), and her PCS has reduced to 25. Her allodynia has improved, and she feels prepared to schedule her surgery in 2–3 months.

Areas of Future Research

Prediction tools for CPSP need further study, and inclusion of social factors as well as population health science research methodologies may be of some benefit. In addition, studies assessing risk stratification and response to treating or removing that risk factor must occur.

Key Takeaways

1. CPSP is a real public health problem, accounting for at least 20% of chronic pain in most communities.
2. A biopsychosocial approach to preoperative assessment and risk stratification is critical for allocating resources to determinants of CPSP that can be treated or removed in the perioperative period.
3. Preoperative pain at the surgical site, preoperative pain elsewhere, young age, female gender, poorly controlled acute pain, and type of surgery represent the most studied biological determinants for CPSP.
4. Pain catastrophizing and anxiety are the most potent psychological determinants of CPSP.
5. Although less well studied, socioeconomic status, education, and race have been associated with disabling CPSP. Prediction models may benefit from including social determinants as well as a population health science approach.

References

1. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet. 2019;393(10180):1537–46. https://doi.org/10.1016/S0140-6736(19)30352-6.
2. Brennan TJ. Pathophysiology of postoperative pain. Pain. 2011;152(3 Suppl):S33–40. https://doi.org/10.1016/j.pain.2010.11.005.
3. B R. Subacute pain as a predictor of long-term pain following orthopedic surgery: an Australian prospective 12 month observational cohort study. Medicine (Baltimore). 2015;94(36) https://doi.org/10.1097/MD.0000000000001498.
4. Werner MU, Kongsgaard UE. I. Defining persistent post-surgical pain: is an update required? Br J Anaesth 2014;113(1):1–4. doi:https://doi.org/10.1093/bja/aeu012.
5. Schug SA, Lavand'homme P, Barke A, et al. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. Pain. 2019;160(1):45–52. https://doi.org/10.1097/j.pain.0000000000001413.
6. Crombie IK, Davies HT, Macrae WA. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. Pain. 1998;76(1–2):167–71.

7. Weiser TG, Haynes AB, Molina G, et al. Size and distribution of the global volume of surgery in 2012. Bull World Health Organ. 2016;94(3):201–209F. https://doi.org/10.2471/BLT.15.159293.
8. Rosenberger DC, Pogatzki-Zahn EM. Chronic post-surgical pain—update on incidence, risk factors and preventive treatment options. BJA Educ. 2022;22(5):190–6. https://doi.org/10.1016/j.bjae.2021.11.008.
9. Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. Pain Rep. 2017;2(6):e627. https://doi.org/10.1097/PR9.0000000000000627.
10. Scholz J, Finnerup NB, Attal N, et al. The IASP classification of chronic pain for ICD-11: chronic neuropathic pain. Pain. 2019;160(1):53–9. https://doi.org/10.1097/j.pain.0000000000001365.
11. Fillingim RB, Loeser JD, Baron R, Edwards RR. Assessment of chronic pain: domains, methods, and mechanisms. J Pain. 2016;17(9 Suppl):T10–20. https://doi.org/10.1016/j.jpain.2015.08.010.
12. Mularski RA, White-Chu F, Overbay D, Miller L, Asch SM, Ganzini L. Measuring pain as the 5th vital sign does not improve quality of pain management. J Gen Intern Med. 2006;21(6):607–12. https://doi.org/10.1111/j.1525-1497.2006.00415.x.
13. Krebs EE, Carey TS, Weinberger M. Accuracy of the pain numeric rating scale as a screening test in primary care. J Gen Intern Med. 2007;22(10):1453–8. https://doi.org/10.1007/s11606-007-0321-2.
14. Baamer RM, Iqbal A, Lobo DN, Knaggs RD, Levy NA, Toh LS. Utility of unidimensional and functional pain assessment tools in adult postoperative patients: a systematic review. Br J Anaesth. 2022;128(5):874–88. https://doi.org/10.1016/j.bja.2021.11.032.
15. Melzack R. The short-form McGill pain questionnaire. Pain. 1987;30(2):191–7. https://doi.org/10.1016/0304-3959(87)91074-8.
16. U Jumbo S, C MacDermid J, E Kalu M, L Packham T, S Athwal G, J Faber K. Measurement properties of the brief pain inventory-short form (BPI-SF) and the revised short McGill pain questionnaire-Version-2 (SF-MPQ-2) in pain-related musculoskeletal conditions: a systematic review protocol. Arch Bone Jt Surg. 2020;8(2):131–41. https://doi.org/10.22038/abjs.2020.36779.1973.
17. Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). Arthritis Care Res. 2011;63(Suppl 11):S240–52. https://doi.org/10.1002/acr.20543.
18. Lowe NK, Walker SN, MacCallum RC. Confirming the theoretical structure of the McGill Pain Questionnaire in acute clinical pain. Pain. 1991;46(1):53–60. https://doi.org/10.1016/0304-3959(91)90033-T.
19. Dworkin RH, Turk DC, Revicki DA, et al. Development and initial validation of an expanded and revised version of the short-form McGill Pain Questionnaire (SF-MPQ-2). Pain. 2009;144(1–2):35–42. https://doi.org/10.1016/j.pain.2009.02.007.
20. Melzack R, Raja SN. The McGill Pain Questionnaire. Anesthesiology. 2005;103(1):199–202. https://doi.org/10.1097/00000542-200507000-00028.
21. Gauthier LR, Young A, Dworkin RH, et al. Validation of the short-form McGill pain questionnaire-2 in younger and older people with cancer pain. J Pain. 2014;15(7):756–70. https://doi.org/10.1016/j.jpain.2014.04.004.
22. Ngamkham S, Vincent C, Finnegan L, Holden JE, Wang ZJ, Wilkie DJ. The McGill Pain Questionnaire as a multidimensional measure in people with cancer: an integrative review. Pain Manag Nurs Off J Am Soc Pain Manag Nurses. 2012;13(1):27–51. https://doi.org/10.1016/j.pmn.2010.12.003.
23. Wang S, Yao S, Wei J, Shang L, Xu C, Ma J. Psychometric properties of the brief pain inventory among patients with osteoarthritis undergoing total knee arthroplasty surgery. J Arthroplast. 2024;39(3):672–6. https://doi.org/10.1016/j.arth.2023.08.072.
24. Cleeland CS, Ryan KM. Pain assessment: global use of the brief pain inventory. Ann Acad Med Singap. 1994;23(2):129–38.
25. Mendoza TR, Chen C, Brugger A, et al. The utility and validity of the modified brief pain inventory in a multiple-dose postoperative analgesic trial. Clin J Pain. 2004;20(5):357–62. https://doi.org/10.1097/00002508-200409000-00011.
26. Stanhope J. Brief pain inventory review. Occup Med. 2016;66(6):496–7. https://doi.org/10.1093/occmed/kqw041.
27. Tittle MB, McMillan SC, Hagan S. Validating the brief pain inventory for use with surgical patients with cancer. Oncol Nurs Forum. 2003;30(2):325–30. https://doi.org/10.1188/03.ONF.325-330.
28. Cella D, Riley W, Stone A, et al. The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005–2008. J Clin Epidemiol. 2010;63(11):1179–94. https://doi.org/10.1016/j.jclinepi.2010.04.011.
29. Penrose CT, George SZ, Bolognesi MP, Bhavsar NA, Horn ME. Do you PROMIS (patient reported outcomes measurement information system)? Physical function and pain interference scores after total knee and hip arthroplasty. Arthroplasty Today. 2023;23:101208. https://doi.org/10.1016/j.artd.2023.101208.
30. Rajan L, Conti MS, Cororaton A, Fuller R, Ellis SJ. Relationship between preoperative PROMIS scores and postoperative outcomes in Hallux Rigidus patients undergoing cheilectomy. Foot Ankle Int. 2022;43(8):1053–61. https://doi.org/10.1177/10711007221088822.

31. Karsalia M, Zhang T, Aneizi A, et al. Predictors of postoperative pain using PROMIS pain interference two-years following knee surgery. J Orthop. 2021;25:271–7. https://doi.org/10.1016/j.jor.2021.05.017.
32. Patel DV, Bawa MS, Haws BE, et al. PROMIS physical function for prediction of postoperative pain, narcotics consumption, and patient-reported outcomes following minimally invasive transforaminal lumbar interbody fusion. J Neurosurg Spine. 2019;30(4):476–82. https://doi.org/10.3171/2018.9.SPINE18863.
33. Parrish JM, Jenkins NW, Hrynewycz NM, Brundage TS, Singh K. The relationship between preoperative PROMIS scores with postoperative improvements in physical function after anterior cervical discectomy and fusion. Neurospine. 2020;17(2):398–406. https://doi.org/10.14245/ns.1938352.176.
34. van Boekel RLM, Vissers KCP, van der Sande R, Bronkhorst E, Lerou JGC, Steegers MAH. Moving beyond pain scores: multidimensional pain assessment is essential for adequate pain management after surgery. PLoS One. 2017;12(5):e0177345. https://doi.org/10.1371/journal.pone.0177345.
35. Walton LL, Duff E, Arora RC, McMillan DE. Surgery patients' perspectives of their role in postoperative pain: a scoping review. Int J Nurs Stud Adv. 2023;5:100124. https://doi.org/10.1016/j.ijnsa.2023.100124.
36. Zinboonyahgoon N, Patton ME, Chen YYK, Edwards RR, Schreiber KL. Persistent post-mastectomy pain: the impact of regional anesthesia among patients with high vs low baseline catastrophizing. Pain Med Off J Am Acad Pain Med. 2021;22(8):1767–75. https://doi.org/10.1093/pm/pnab039.
37. Zinboonyahgoon N, Vlassakov K, Lirk P, et al. Benefit of regional anaesthesia on postoperative pain following mastectomy: the influence of catastrophising. Br J Anaesth. 2019;123(2):e293–302. https://doi.org/10.1016/j.bja.2019.01.041.
38. Ren Y, Guo Y, Tang J, et al. Effect of personality and pain catastrophizing on postoperative analgesia following cesarean section: a prospective cohort study. J Pain Res. 2024;17:11–9. https://doi.org/10.2147/JPR.S443230.
39. Darnall BD. Pain psychology and pain catastrophizing in the perioperative setting: a review of impacts, interventions and unmet needs. Hand Clin. 2016;32(1):33–9. https://doi.org/10.1016/j.hcl.2015.08.005.
40. Granot M, Ferber SG. The roles of pain catastrophizing and anxiety in the prediction of postoperative pain intensity: a prospective study. Clin J Pain. 2005;21(5):439–45. https://doi.org/10.1097/01.ajp.0000135236.12705.2d.
41. Khan RS, Skapinakis P, Ahmed K, et al. The association between preoperative pain catastrophizing and postoperative pain intensity in cardiac surgery patients. Pain Med Malden MA. 2012;13(6):820–7. https://doi.org/10.1111/j.1526-4637.2012.01386.x.
42. Papaioannou M, Skapinakis P, Damigos D, Mavreas V, Broumas G, Palgimesi A. The role of catastrophizing in the prediction of postoperative pain. Pain Med Malden MA. 2009;10(8):1452–9. https://doi.org/10.1111/j.1526-4637.2009.00730.x.
43. Quartana PJ, Campbell CM, Edwards RR. Pain catastrophizing: a critical review. Expert Rev Neurother. 2009;9(5):745–58. https://doi.org/10.1586/ERN.09.34.
44. Theunissen M, Peters ML, Bruce J, Gramke HF, Marcus MA. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. Clin J Pain. 2012;28(9):819–41. https://doi.org/10.1097/AJP.0b013e31824549d6.
45. Yang JC, Clark WC, Tsui SL, Ng KF, Clark SB. Preoperative multidimensional affect and pain survey (MAPS) scores predict postcolectomy analgesia requirement. Clin J Pain. 2000;16(4):314–20. https://doi.org/10.1097/00002508-200012000-00007.
46. Masselin-Dubois A, Attal N, Fletcher D, et al. Are psychological predictors of chronic postsurgical pain dependent on the surgical model? A comparison of total knee arthroplasty and breast surgery for cancer. J Pain. 2013;14(8):854–64. https://doi.org/10.1016/j.jpain.2013.02.013.
47. Fernández-Castro M, Jiménez JM, Martín-Gil B, et al. The influence of preoperative anxiety on postoperative pain in patients undergoing cardiac surgery. Sci Rep. 2022;12(1):16464. https://doi.org/10.1038/s41598-022-20870-9.
48. Wells C, McCormack S. Screening tools for chronic post-surgical pain. Can J Health Technol. 2021;1(1) https://doi.org/10.51731/cjht..27.
49. Raja SN, Carr DB, Cohen M, et al. The revised IASP definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976–82. https://doi.org/10.1097/j.pain.0000000000001939.
50. Holtzman S, Clarke HA, McCluskey SA, Turcotte K, Grant D, Katz J. Acute and chronic postsurgical pain after living liver donation: incidence and predictors. Liver Transpl. 2014;20(11):1336–46. https://doi.org/10.1002/lt.23949.
51. Sex and age differences in chronic postoperative pain among patients undergoing thoracic surgery: a retrospective cohort study—PMC. Accessed 30 June 2024. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10282545/
52. Montes A, Roca G, Sabate S, et al. Genetic and clinical factors associated with chronic postsurgical pain after hernia repair, hysterectomy, and thoracotomy: a two-year multicenter cohort study. Anesthesiology. 2015;122(5):1123–41. https://doi.org/10.1097/ALN.0000000000000611.
53. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother. 2009;9(5):723–44. https://doi.org/10.1586/ern.09.20.
54. Wang L, Guyatt GH, Kennedy SA, et al. Predictors of persistent pain after breast cancer surgery: a system-

atic review and meta-analysis of observational studies. Can Med Assoc J. 2016;188(14):E352–61. https://doi.org/10.1503/cmaj.151276.
55. Schnabel A, Yahiaoui-Doktor M, Meissner W, Zahn PK, Pogatzki-Zahn EM. Predicting poor postoperative acute pain outcome in adults: an international, multicentre database analysis of risk factors in 50,005 patients. PAIN Rep. 2020;5(4):e831. https://doi.org/10.1097/PR9.0000000000000831.
56. Liu J, Wang C, Gao Y, Tian Y, Wang Y, Wang S. Sex-specific associations between preoperative chronic pain and moderate to severe chronic postoperative pain in patients 2 years after cardiac surgery. J Pain Res. 2022;15:4007–15. https://doi.org/10.2147/JPR.S384463.
57. Althaus A, Hinrichs-Rocker A, Chapman R, et al. Development of a risk index for the prediction of chronic post-surgical pain. Eur J Pain Lond Engl. 2012;16(6):901–10. https://doi.org/10.1002/j.1532-2149.2011.00090.x.
58. Pagé MG, Katz J, Romero Escobar EM, et al. Distinguishing problematic from nonproblematic postsurgical pain: a pain trajectory analysis after total knee arthroplasty. Pain. 2015;156(3):460–8. https://doi.org/10.1097/01.j.pain.0000460327.10515.2d.
59. Liu QR, Dai YC, Ji MH, et al. Predictors and predictive effects of acute pain trajectories after gastrointestinal surgery. Sci Rep. 2022;12(1):6530. https://doi.org/10.1038/s41598-022-10504-5.
60. Fletcher D, Stamer UM, Pogatzki-Zahn E, et al. Chronic postsurgical pain in Europe: an observational study. Eur J Anaesthesiol. 2015;32(10):725–34. https://doi.org/10.1097/EJA.0000000000000319.
61. Papadomanolakis-Pakis N, Uhrbrand P, Haroutounian S, Nikolajsen L. Prognostic prediction models for chronic postsurgical pain in adults: a systematic review. Pain. 2021;162(11):2644–57. https://doi.org/10.1097/j.pain.0000000000002261.
62. Lewis GN, Rice DA, McNair PJ, Kluger M. Predictors of persistent pain after total knee arthroplasty: a systematic review and meta-analysis. Br J Anaesth. 2015;114(4):551–61. https://doi.org/10.1093/bja/aeu441.
63. VanDenKerkhof EG, Hopman WM, Goldstein DH, et al. Impact of perioperative pain intensity, pain qualities, and opioid use on chronic pain after surgery: a prospective cohort study. Reg Anesth Pain Med. 2012;37(1):19–27. https://doi.org/10.1097/AAP.0b013e318237516e.
64. Subacute Pain as a Predictor of Long-Term Pain Following... : Medicine. LWW. https://doi.org/10.1097/MD.0000000000001498.
65. Fletcher D, Lavand'homme P. Towards better predictive models of chronic post-surgical pain: fitting to the dynamic nature of the pain itself. Br J Anaesth. 2022;129(3):281–4. https://doi.org/10.1016/j.bja.2022.06.010.
66. van Driel MEC, van Dijk JFM, Baart SJ, Meissner W, Huygen FJPM, Rijsdijk M. Development and validation of a multivariable prediction model for early prediction of chronic postsurgical pain in adults: a prospective cohort study. Br J Anaesth. 2022;129(3):407–15. https://doi.org/10.1016/j.bja.2022.04.030.
67. Aasvang EK, Gmaehle E, Hansen JB, et al. Predictive risk factors for persistent postherniotomy pain. Anesthesiology. 2010;112(4):957–69. https://doi.org/10.1097/ALN.0b013e3181d31ff8.
68. Mathes T, Pape-Köhler C, Moerders L, Lux E, Neugebauer EAM. External validation and update of the RICP-A multivariate model to predict chronic postoperative pain. Pain Med Malden MA. 2018;19(8):1674–82. https://doi.org/10.1093/pm/pnx242.
69. Richebé P, Capdevila X, Rivat C. Persistent postsurgical pain: pathophysiology and preventative pharmacologic considerations. Anesthesiology. 2018;129(3):590–607. https://doi.org/10.1097/ALN.0000000000002238.
70. Fuller AM, Bharde S, Sikandar S. The mechanisms and management of persistent postsurgical pain. Front Pain Res. 2023;4 https://doi.org/10.3389/fpain.2023.1154597.
71. Frangakis SG, MacEachern M, Akbar TA, et al. Association of Genetic Variants with postsurgical pain: a systematic review and meta-analyses. Anesthesiology. 2023;139(6):827–39. https://doi.org/10.1097/ALN.0000000000004677.
72. Tasmuth T, Estlanderb AM, Kalso E. Effect of present pain and mood on the memory of past postoperative pain in women treated surgically for breast cancer. Pain. 1996;68(2–3):343–7. https://doi.org/10.1016/s0304-3959(96)03219-8.
73. Sullivan M, Tanzer M, Stanish W, et al. Psychological determinants of problematic outcomes following Total knee arthroplasty. Pain. 2009;143(1–2):123–9. https://doi.org/10.1016/j.pain.2009.02.011.
74. Hinrichs-Rocker A, Schulz K, Järvinen I, Lefering R, Simanski C, Neugebauer EAM. Psychosocial predictors and correlates for chronic post-surgical pain (CPSP)—a systematic review. Eur J Pain Lond Engl. 2009;13(7):719–30. https://doi.org/10.1016/j.ejpain.2008.07.015.
75. Edwards RR, Mensing G, Cahalan C, et al. Alteration in pain modulation in women with persistent postlumpectomy pain: influence of catastrophizing. J Pain Symptom Manag. 2013;46(1):30–42. https://doi.org/10.1016/j.jpainsymman.2012.06.016.
76. Terradas-Monllor M, Ruiz MA, Ochandorena-Acha M. Postoperative psychological predictors for chronic postsurgical pain after a knee arthroplasty: a prospective observational study. Phys Ther. 2024;104(1):pzad141. https://doi.org/10.1093/ptj/pzad141.
77. George SZ, Bolognesi MP, Bhavsar NA, Penrose CT, Horn ME. Chronic pain prevalence and factors associated with high impact chronic pain following total joint arthroplasty: an observational study. J Pain. 2022;23(3):450–8. https://doi.org/10.1016/j.jpain.2021.09.007.

78. Cook CE, George SZ, Lentz T, et al. High-impact chronic pain transition in lumbar surgery recipients. Pain Med. 2023;24(3):258–68. https://doi.org/10.1093/pm/pnac150.
79. Cook CE, George SZ, Asher AL, et al. High-impact chronic pain transition in surgical recipients with cervical spondylotic myelopathy. Published online January 21. J Neurosurg Spine. 2022; https://doi.org/10.3171/2021.11.SPINE211260.
80. Núñez-Cortés R, Chamorro C, Ortega-Palavecinos M, et al. Social determinants associated to chronic pain after total knee arthroplasty. Int Orthop. 2019;43(12):2767–71. https://doi.org/10.1007/s00264-019-04370-6.
81. Macrae WA. Chronic pain after surgery. Br J Anaesth. 2001;87(1):88–98. https://doi.org/10.1093/bja/87.1.88.
82. Caetano SJ, Sonpavde G, Pond GR. C-statistic: a brief explanation of its construction, interpretation and limitations. Eur J Cancer. 2018;90:130–2. https://doi.org/10.1016/j.ejca.2017.10.027.
83. Rose G. Sick individuals and sick populations. Int J Epidemiol. 2001;30(3):427–32. https://doi.org/10.1093/ije/30.3.427.

4 Medications and Techniques in Preoperative Pain Control: Examines Various Approaches for Managing Pain Prior to Surgery

Bassam Farhat and Lakshmi N. Kurnutala

Introduction

Preoperative pain management and patient education are critical aspects of patient care. Its main goal is to minimize discomfort and improve the overall perioperative experience, enhancing satisfaction and contributing to better postoperative outcomes [1–3]. With recent advances and implementation of multiple enhanced recovery protocols (ERP), optimization of preoperative pain with different approaches (pharmacologic and non-pharmacologic) has became a priority, given the financial burdens, functional impairment, opioid-related adverse events (ORAE) [3–9], and psychological impact on patients.

Background and Current Understanding

Pain is a subjective, complex, multidimensional experience (sensory-discriminative, affective-motivational, and cognitive-evaluative). The interplay among these components was historically described by Melzack and Casey in 1968, highlighting the concept of pain perception, the importance of psychophysiological interactions, and how the patient reflects on it [10].

B. Farhat (✉) · L. N. Kurnutala
Department of Anesthesiology, University of Mississippi Medical Center, Jackson, MS, USA
e-mail: bfarhat@umc.edu; lkurnutala@umc.edu

In the past, pain was highly undertreated (up to 80% in some settings) [11], and its health care, compensation, and litigation costs in the United States of America (USA) have reached more than $100 billion (about $310 per person in the US) each year [3–5]. Pain was officially declared as the "fifth vital sign," emphasizing the importance of adequate pain control [11].

Opioids have been heavily prescribed in the past five decades in response to the challenges mentioned above, hoping to provide a better quality of life. However, it has unfortunately led to an opioid crisis in the USA due to misuse, abuse, and diversion [8, 12, 13].

Poor pain control remains an important and common reason for readmission postoperatively [14, 15], in addition to experiencing the adverse effects of opioids. It leads to central sensitization and plasticity, aggravating the pain experience and making it more challenging to treat.

Keeping up with the advances in technology and surgical approaches, the world has headed towards fast-track surgery [1, 16–18]. The enhanced recovery protocols (ERP), use of multimodal analgesia (MMA), and opioid stewardship became "the new motto" and gold standard for the treatment and prevention of acute postoperative pain [2, 6, 7, 19–22]. This highlights the importance of preemptive analgesia and having a tailored pain management plan that starts preoperatively, continues intraoperatively, and extends to the post-discharge phase, i.e., the EXIT plan [9, 23–27].

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_4

Clinical Applications and Techniques

Preoperative patient education was not emphasized in the past, which led to suboptimal outcomes in terms of satisfaction, pain control, increased rates of readmission, presentation to urgent care clinics at frequent intervals, and increased financial burdens [15].

Starting with the preadmission phase, at the preoperative anesthesia clinic visit, a thorough history should be taken, including:

- Past medical history (PMH), including but not limited to diabetes with long-term complications, arthropathies, spine abnormalities, musculoskeletal disorders, maxillo-fascial disorders, and organic causes related to specific diseases (for example, sickle cell disease with Vaso-occlusive crisis).
- Psychosocial history assessment [28], using standardized tools, highlighting any substance use disorder [12, 13] (SUD—including alcohol, benzodiazepines, opioids, and recreational substances) and poor coping strategies.
- Documentation of previous opioid-related adverse events (ORAE) based on O-NET status (opioid-naïve, exposed vs. tolerant status) [8, 29, 30], prior history of self-harm or suicide attempts is essential. Appropriate referrals to pain psychology or psychiatry specialists should be made when indicated.
- Understanding the patients' support system and access to resources for help.
- Exploration of patients' financial challenges, ability to follow up with providers, commitment to a healthcare plan, and willingness to engage are critical.
- Past surgical history, including but not limited to any residual functional impairment, motor or sensory deficits related to previous spine or joint surgeries.
- Careful and detailed pain assessment should be done preoperatively and on the day of surgery [31, 32].
- Medication reconciliation, including but not limited to psychologic medications, pain medications (opioids and non-opioids), consultation with PDMP (prescription drug monitoring program), hospital pharmacy [27], and prescribing provider for further guidance on patients taking medications for chronic pain (methadone, buprenorphine, suboxone, naloxone) [28, 32].

It could be overwhelming for patients to prepare for surgery [33, 34], and they might not have enough time to ask all the questions. It entails a lot of stress accepting the diagnosis, the need for surgery, the psychological impact, fear of the unknown, and what's coming next. Not to mention the financial aspect and the need to go through the lengthy paperwork process, laboratory testing, and lifestyle changes that will follow.

Providing adequate education to the patient is vital for building a strong rapport based on trust. It is also essential to educate the caretaker during the preoperative anesthesia clinic visit [35]. The most cited reasons for presentation to urgent care or readmission in the postoperative period were related to inadequate knowledge, not providing detailed printout instructions, and not taking medications as prescribed due to misconceptions or fear of addiction [36].

Failure to set expectations is another crucial pitfall that providers often face. After adequate history taking, the preoperative visit to the anesthesia clinic is the best time to familiarize the patient with the current baseline status ("where we are"), what the surgery entails in terms of pain ("what's most likely going to happen"), what we can offer to help ("what could be done" or the PLAN), and how things are expected to play out after ("what's on the horizon"). It's critical to explain that there is no perfect plan and that the plan is fluid and can change depending on the patient's clinical status and response.

Defining the comfort goal comes next. Pain, in some instances, cannot be eliminated or brought down to zero. Our goal is to return to the baseline status before surgery in terms of pain control, where we don't focus on pain assessment as a raw score but on the functional status instead. The patient would resume activities of daily life (compared to baseline) and gradually meet his

recovery goals, as defined by a multidisciplinary team approach. So, patients have different pain tolerance levels and could live a typical day at variable pain scores.

In a culturally sensitive approach, shared decision-making and involvement of the patient and caretaker in the discussion pave the way for more successful preoperative planning, reduce anxiety levels, answer questions, and address concerns [25]. Presenting patients with expert recommendations and choices and explaining the benefits, risks, and alternatives makes them feel they are in safe hands, have control over the process, and can confidently choose the care they are seeking. The use of patient-controlled analgesia (PCA) pumps, when indicated, is one example that improved patients' pain control and satisfaction.

Providers must be mindful of the language barriers and cognitive impairment that might prevent the patient and caretaker from properly understanding or engaging in the discussion [37, 38]. When necessary, it is helpful to use the "repeat-back" strategy to reinforce concepts and avoid miscommunication or misunderstanding.

Thus, careful preoperative risk stratification is vital to formulate a successful, individualized plan using a patient-centered approach. All of this falls under the "prehabilitation" paradigm for surgical readiness [28, 30, 34, 39].

Evidence-Based Practices

Advances in technology have facilitated fast-track surgery [1, 16–18]. The use of minimally invasive approaches (laparoscopy, robotic surgery when deemed appropriate for specific candidates) and increased incorporation of ultrasound (for insertion of lines, nerve blocks, Point of Care (POCUS), Focused Assessment with Sonography in Trauma (FAST), and goal-directed therapy) have revamped the clinical management, providing more suitable, individualized, cost-effective options, and successful perioperative plans. This has resulted in optimizing patient care, minimizing the adverse effects, decreasing opioid burden, reducing financial costs, and length of hospital stay, and increasing efficiency in ambulatory settings.

Some recommendations favor certain practices, but most are institution-specific and could be tailored based on need, patient tolerance, and expectations [7, 29, 40]. The combination that yields the best outcome is yet to be discovered, and what works for a specific patient or surgery might not work for another surgery in the same category (e.g., laminectomy vs. spine fusion) [41]. These could be divided into pharmacologic and non-pharmacologic:

Pharmacologic

ERP pathways (colorectal, spine, cardio-thoracic, etc.)

It encourages the use of MMA [19, 42], starting in the preoperative area (oral paracetamol, NSAIDs, gabapentinoids, etc.). Also, it aims to maintain carbohydrate intake (clear liquids) until 2 hours before surgery and have patients present as euvolemic as possible. Moreover, it embraces the use of regional nerve blocks (single-shot vs. catheter) [31, 43] and opioid-sparing techniques intraoperatively with the incorporation of adjuvants (ketamine, alpha-2 agonists dexmedetomidine, lidocaine infusions, surgical infiltration by the surgeon, and dexamethasone) [16, 23, 44].

An important postoperative educational key involves writing down rescue medications and daily recovery plan goals on a board accessible to the patient, for continued education and reinforcement of the concept.

Besides, it emphasizes continuing home medications after careful reconciliation for possible interactions (including tricyclic anti depressants, serotonin-norepinephrine reuptake inhibitors, muscle relaxants, etc.), while minimizing and limiting opioid use to rescue only [42, 45]. Detailed printout instructions, resources, and necessary prescriptions are provided and explained to the patient and caretaker, including opioid weaning and disposal [30, 46]. The EXIT plan should include follow-up phone calls or virtual appointments in the first postoperative week [23–25].

Non-pharmacologic

It starts with fast-track extubation at the end of surgery or after arrival to a highly monitored care setting. Also, it encourages postoperative incentive spirometer use, early ambulation, and removal of unnecessary lines as soon as possible.

Besides, there is evidence that favors early postoperative oral fluid intake, which decreases nausea, vomiting, and the need for opioids [47]. Many approaches have strongly impacted pain perception and the overall perioperative experience [20, 48]. These include but are not limited to:

- Environmental: sleep hygiene, light, music therapy, comfort items.
- Behavioral: mindfulness meditation, art and music therapy, audio-visual distraction, breathing exercises. It mayt need to be started up to four weeks preoperatively [28, 49].
- Physical: Ice or heat packs, stress ball, repositioning, physical therapy, massage, acupuncture, tai chi, yoga, nutritional counseling, activities (hobbies, leisure, emotional pet visitation).
- Psychological [33, 34, 49–51]: cognitive-behavioral therapy (CBT), acceptance and commitment therapy (ACT).
- Spiritual: religious services and counseling.

The transitional pain service (TPS) plays a vital role in formulating, coordinating, and executing a comprehensive continuum of care that starts in the preoperative phase and extends beyond the discharge phase (i.e., the EXIT plan) [9, 23–27, 52].

Clinical Scenario: Enhanced Recovery Protocol for Breast Reduction Surgery [53, 54]

A 32-year-old obese female (BMI of 42), with no significant past medical history, presents to the preoperative anesthesia clinic for her upcoming bilateral breast reduction surgery. Review of plastic surgery clinic notes reveals complaints regarding "enlarged and heavy breasts" causing back discomfort. She describes bilateral breast pain and recurrent skin infections under the breast folds, 7/10 in intensity using NRS (numerical rating scale). It is constant, localized, exacerbated by prolonged standing and physical activity, and relieved by over-the-counter medications (acetaminophen and ibuprofen).

Symptoms have progressively worsened over the past three years, despite trying various supportive bras and topical treatments, eventually leading to physical limitations and impacting her quality of life.

No family history of breast cancer. Physical examination and ultrasound are negative for any breast lumps. Erythema and irritation were noted under the breast folds, with evidence of recurrent fungal infections.

She reports significant emotional distress due to her condition, including anxiety, decreased self-esteem, and worry about her body image. She is motivated to undergo surgery and improve her quality of life but is afraid of pain postoperatively. She asks about the anesthetic and pain management plan. She's been reading on the internet about nerve blocks and requests a "pain-free" experience.

Challenges and Considerations

There are specific patient populations that present unique challenges to the anesthesiologist. These include patients with a history of chronic pain, opioid dependence, substance use disorder, and extreme psychological disturbances [28, 32, 45, 55–57].

Chronic pain patients have most likely developed central sensitization in response to poorly controlled pain [58], and many depend heavily on opioids to maintain a relatively stable pain control. They are often prescribed long-acting opioid agonists like Buprenorphine (partial agonist), Methadone (full-agonist, high oral bioavailability, once-daily dosing, long half-life up to 3 days) to treat opioid dependence and prevent withdrawal or relapse [56].

Current recommendations are to continue Methadone and Buprenorphine perioperatively

and consult with addiction medicine, pain psychology, or the prescribing provider for further guidance and dose titration in the perioperative period [28, 45, 59–61]. The prolonged blockade of opioid receptors by these medications alters the receptors' sensitivity and number, making pain control more challenging for the anesthesiologist [46]. Education should include following up with the prescribing provider right after discharge.

Gabapentinoids use, initially introduced in the US market in 1993 to treat complex partial seizures, has expanded to many off-label indications, including perioperative pain control as a component of MMA and ERP. There is still a lot of uncertainty regarding the dosing, duration, and timing of administration due to saturable, rate-limiting gut absorption, which could take up to two weeks to reach the peak plasma concentration needed for adequate pain control. Not to mention the extended, unfavorable side-effect profile, increased risk of respiratory adverse events, abuse potential, and interactions in the setting of polypharmacy, renal dysfunction, and advanced age. The French Society of Anesthesia and Intensive Care Medicine's consensus guidelines clearly state that gabapentinoids should not be used routinely for outpatient surgery. Its use in MMA is still questionable given the minimal benefits and high-risk side effect profile, although it might be helpful for neuropathic pain [62].

Post-amputation phantom limb pain is another feared surgical consequence due to violation of neuronal integrity, generation of abnormal impulses, and excessive neuronal firing. A multidisciplinary treatment approach, including regional anesthesia, ketamine, and gabapentinoids, among others, is the mainstay of treatment. Mirror therapy is also vital in prioritizing visual feedback over somatosensory-proprioceptive feedback concerning limb position [58, 63].

Future Directions and Research

Pain management is an evolving practice, and the recommendations provided in this chapter are based on available literature. Considering the level of knowledge and keeping up with the latest evidence-based medicine are vital to maintaining the highest standards of patient care.

Future research will shed light, answer more questions, and hopefully resolve uncertainties:

- Gabapentinoids' role is still questionable, especially regarding optimal dosing, timing of administration, interactions, and use in elderly and outpatient surgery.
- Phantom limb pain is a complex pain experience. There's much more to unveil regarding pathophysiology, and current treatments are not always successful.
- Enhanced recovery protocols are not impeccable; there is always room for improvement. Many are institution-specific and are tailored to the patients' needs. Following up with patients after discharge and tracking the outcomes over years is necessary to continue refining our strategies and protocols.

Key Takeaways

1. Prehabilitation paradigm: careful risk stratification in the preoperative anesthesia clinic visit, education of the patient and caretaker.
2. Setting reasonable expectations.
3. Opioid-stewardship; ERP, MMA.
4. Importance of non-pharmacologic approaches in pain perception and treatment.
5. Challenges requiring a multidisciplinary team approach.

References

1. Abebe MM, et al. Evidence-based perioperative pain management protocol for day case surgery in a resource limited setting: systematic review. Ann Med Surg (Lond). 2022;80:104322.
2. Minnella EM, et al. Multimodal prehabilitation improves functional capacity before and after colorectal surgery for cancer: a five-year research experience. Acta Oncol. 2017;56(2):295–300.
3. Peden CJ, Mythen MG, Vetter TR. Population health management and perioperative medicine: the expanding role of the anesthesiologist. Anesth Analg. 2018;126(2):397–9.

4. Shafi S, et al. Association of opioid-related adverse drug events with clinical and cost outcomes among surgical patients in a large integrated health care delivery system. JAMA Surg. 2018;153(8):757–63.
5. Berwick DM, Nolan TW, Whittington J. The triple aim: care, health, and cost. Health Aff (Millwood). 2008;27(3):759–69.
6. McEvoy MD, et al., American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI). joint consensus statement on optimal analgesia within an enhanced recovery pathway for colorectal surgery: part 1—from the preoperative period to PACU. Perioper Med. 2017;6(1):8.
7. Wu CL, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on perioperative opioid minimization in opioid-naïve patients. Anesth Analg. 2019;129(2):567.
8. Menendez ME, Ring D, Bateman BT. Preoperative opioid misuse is associated with increased morbidity and mortality after elective orthopaedic surgery. Clin Orthop Relat Res. 2015;473(7):2402–12.
9. Mariano ER, et al. A multisociety organizational consensus process to define guiding principles for acute perioperative pain management. Reg Anesth Pain Med. 2022;47(2):118–27.
10. Casey K. Sensory, motivational, and central control determinants of pain. 1968. p. 423–439.
11. Walid MS, et al. The fifth vital sign—what does it mean? Pain Pract. 2008;8(6):417–22.
12. Webster LR. Risk factors for opioid-use disorder and overdose. Anesth Analg. 2017;125(5):1741–8.
13. Akbik H, et al. Validation and clinical application of the screener and opioid assessment for patients with Pain (SOAPP). J Pain Symptom Manag. 2006;32(3):287–93.
14. Bhattacharyya N. Revisits and readmissions following ambulatory uvulopalatopharyngoplasty. Laryngoscope. 2015;125(3):754–7.
15. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. J Pain Res. 2017;10:2287–98.
16. Prabhakar A, et al. Techniques to optimize multimodal analgesia in ambulatory surgery. Curr Pain Headache Rep. 2017;21(5):24.
17. Gustavo R, Emma W, Juliet L. ERAS protocols and multimodal pain management in surgery. In: Pain management, Theodoros A, Christos N (eds), IntechOpen Ch 4: Rijeka. 2023.
18. Bajwa SJS, et al. Anesthesia for day-care surgeries: current perspectives. Medical journal of Dr. D.Y. Patil University. 2017;10(4):327–33.
19. Bhatia A, Buvanendran A. Anesthesia and postoperative pain control-multimodal anesthesia protocol. J Spine Surg. 2019;5(Suppl 2):S160–s165.
20. Hyland SJ, et al. Perioperative pain management and opioid stewardship: a practical guide. Healthcare. 2021;9(3):333.
21. Toby NW, et al. Multimodal analgesic protocol and postanesthesia respiratory depression during phase I recovery after total joint arthroplasty. Regional Anesth Pain Med. 2015;40(4):330.
22. Kaye AD, et al. Non-opioid perioperative pain strategies for the clinician: a narrative review. Pain Ther. 2020;9(1):25–39.
23. Jafra A, Mitra S. Pain relief after ambulatory surgery: progress over the last decade. Saudi J Anaesth. 2018;12(4):618–25.
24. Tharakan L, Faber P. Pain management in day-case surgery. BJA Education. 2015;15(4):180–3.
25. Quemby DJ, Stocker ME. Day surgery development and practice: key factors for a successful pathway. CEACCP. 2014;14(6):256–61.
26. Ong CK-S, et al. The efficacy of preemptive analgesia for acute postoperative pain management: a meta-analysis. Anesth Analg. 2005;100(3):757–73.
27. Genord C, Frost T, Eid D. Opioid exit plan: a pharmacist's role in managing acute postoperative pain. J Am Pharm Assoc (2003). 2017;57(2s):S92–s98.
28. Doan LV, Blitz J. Preoperative assessment and management of patients with pain and anxiety disorders. Curr Anesthesiol Rep. 2020;10(1):28–34.
29. Edwards DA, et al. American Society for enhanced recovery and perioperative quality initiative joint consensus statement on perioperative management of patients on preoperative opioid therapy. Anesth Analg. 2019;129(2):553–66.
30. McAnally H. Rationale for and approach to preoperative opioid weaning: a preoperative optimization protocol. Perioperative Med. 2017;6(1):19.
31. Gramke HF, et al. Predictive factors of postoperative pain after day-case surgery. Clin J Pain. 2009;25(6):455–60.
32. Hilliard PE, et al. Prevalence of preoperative opioid use and characteristics associated with opioid use among patients presenting for surgery. JAMA Surg. 2018;153(10):929–37.
33. Powell R, et al. Psychological preparation and postoperative outcomes for adults undergoing surgery under general anaesthesia. Cochrane Database Syst Rev. 2016;2016(5):Cd008646.
34. Weinrib AZ, et al. The psychology of chronic post-surgical pain: new frontiers in risk factor identification, prevention and management. Br J Pain. 2017;11(4):169–77.
35. Khorfan R, et al. Preoperative patient education and patient preparedness are associated with less postoperative use of opioids. Surgery. 2020;167(5):852–8.
36. Beauregard L, Pomp A, Choinière M. Severity and impact of pain after day-surgery. Can J Anaesth. 1998;45(4):304–11.
37. Núñez-Cortés R, et al. Social determinants associated to chronic pain after total knee arthroplasty. Int Orthop. 2019;43(12):2767–71.
38. Hälleberg Nyman M, et al. Association between functional health literacy and postoperative recovery, health care contacts, and health-related quality of life among patients undergoing day surgery: secondary analysis of a randomized clinical trial. JAMA Surg. 2018;153(8):738–45.

39. Dindo L, et al. Acceptance and commitment therapy for prevention of chronic postsurgical Pain and opioid use in at-risk veterans: a pilot randomized controlled study. J Pain. 2018;19(10):1211–21.
40. Chou R, et al. 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. J Pain. 2016;17(2):131–57.
41. Kurnutala LN, et al. Enhanced recovery after surgery protocol for lumbar spinal surgery with regional anesthesia: a retrospective review. Cureus. 2021;13(9):e18016.
42. Choi GJ, Seong H-K, Kang H. Pharmacological intervention for ambulatory surgery: a protocol for systematic review and network meta-analysis. Medicine. 2020;99(32):e21580.
43. Liu SS, et al. A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. Anesth Analg. 2005;101(6):1634–42.
44. Oliveira D, Gildàsio S, et al. Perioperative single dose systemic dexamethasone for postoperative pain: a meta-analysis of randomized controlled trials. Anesthesiology. 2011;115(3):575–88.
45. Macintyre PE, Roberts LJ, Huxtable CA. Management of opioid-tolerant patients with acute pain: approaching the challenges. Drugs. 2020;80(1):9–21.
46. Huxtable CA, et al. Acute pain management in opioid-tolerant patients: a growing challenge. Anaesth Intensive Care. 2011;39(5):804–23.
47. Chauvin C, et al. Early postoperative oral fluid intake in paediatric day case surgery influences the need for opioids and postoperative vomiting: a controlled randomized trial this article is accompanied by editorial Aew450. Br J Anaesth. 2017;118(3):407–14.
48. Patil JD, Sefen JAN, Fredericks S. Exploring non-pharmacological methods for pre-operative pain management. Front Surg. 2022;9:9.
49. Hadlandsmyth K, et al. Enhancing the biopsychosocial approach to perioperative care: a pilot randomized trial of the perioperative pain self-management (PePS) intervention. Ann Surg. 2022;275(1):e8–e14.
50. Yi JL, et al. The impact of preoperative mindfulness-based stress reduction on postoperative patient-reported pain, disability, quality of life, and prescription opioid use in lumbar spine degenerative disease: a pilot study. World Neurosurg. 2019;121:e786–91.
51. Rolving N, et al. Preoperative cognitive-behavioural intervention improves in-hospital mobilisation and analgesic use for lumbar spinal fusion patients. BMC Musculoskelet Disord. 2016;17:217.
52. Klimke R, et al. Transitional pain service: an update. Curr Pain Headache Rep. 2024;28(6):457–64.
53. Temple-Oberle C, et al. Consensus review of optimal perioperative care in breast reconstruction: enhanced recovery after surgery (ERAS) society recommendations. Plast Reconstr Surg. 2017;139(5):1056e–71e.
54. Offodile AC 2nd, et al. Enhanced recovery after surgery (ERAS) pathways in breast reconstruction: systematic review and meta-analysis of the literature. Breast Cancer Res Treat. 2019;173(1):65–77.
55. Veazie S, et al. Managing acute pain in patients taking medication for opioid use disorder: a rapid review. J Gen Intern Med. 2020;35(Suppl 3):945–53.
56. Ward EN, Quaye AN-A, Wilens TE. Opioid use disorders: perioperative management of a special population. Anesth Analg. 2018;127(2):539–47.
57. Coluzzi F, et al. The challenge of perioperative pain management in opioid-tolerant patients. Ther Clin Risk Manag. 2017;13:1163–73.
58. Dydyk AM, Givler A. Central pain syndrome, in StatPearls. 2024, StatPearls Publishing Copyright © 2024, StatPearls Publishing LLC.: Treasure Island (FL) ineligible companies. Disclosure: Amy Givler declares no relevant financial relationships with ineligible companies
59. Pergolizzi JV, et al. Stopping or decreasing opioid therapy in patients on chronic opioid therapy. Pain Ther. 2019;8(2):163–76.
60. Burns SL, Majdak P, Urman RD. Perioperative and periprocedural anesthetic management of opioid tolerant patients and patients with active and medically treated opioid use disorder. Curr Opin Anaesthesiol. 2022;35(4):514–20.
61. Selvamani BJKL, Swaran Singh T. Perioperative management of patients on buprenorphine for opioid use disorder. ASRA Pain Med News. 2022;47 https://doi.org/10.52211/asra020123.010.
62. Farhat B, I.V., Sondekoppam RV. Curb your enthusiasm: should Gabapentinoids be a routine component of multimodal analgesia? ASRA Pain Med News. 2022;47 https://doi.org/10.52211/asra050122.015.
63. Subedi B, Grossberg GT. Phantom limb pain: mechanisms and treatment approaches. Pain Res Treat. 2011;2011:864605.

5 Psychological Approaches and Patient Education: Emphasizes the Role of Psychological Preparation and Educating Patients About Pain Management

Melvania Williams and Raha F. Sabet

Background and Current Understanding

Psychologists play an integral role in pain management. In fact, most evidence-based approaches include having a psychologist as part of the interdisciplinary team. Relatedly, the biopsychosocial model of pain acutely highlights the importance of focusing on the cognitive, emotional, and behavioral components of pain. In fact, through this conceptual framework, it is clear that a sole biological lens is flawed and insufficient.

In the early 1900s, pain models focused exclusively on the biological underpinnings of pain. Said differently, there was no focus on the mind-body connection. Notably, in 1965, the Gate Control Theory of Pain was introduced by Melzack and Wall. This theory highlighted the role of psychosocial factors for the first time. Put simply, this theory hypothesizes a "gate" that either opens or closes to send or block signals from the central nervous system. They theorized that certain emotional states or behaviors could either "open" or "close" the gate. For example, anger may "open" the gate, whereas diaphragmatic breathing may "close" it. The implications for this seminal article are significant, underscoring the importance of including a behavioral medicine perspective in pain management. As a result, treatments for pain are more cost-effective, more patient-centric, and less invasive.

The evidence-based psychological intervention for pain is Cognitive Behavioral Therapy (CBT) [13]. CBT focuses on restructuring maladaptive thinking as well as changing behaviors to improve overall mood and reduce psychological distress. Common interventions include psychoeducation, maintenance of thought records, and behavioral activation. A recent literature review [8] found that CBT's impact on pain reduction is small, in comparison to no treatment. Compared to a treatment control that is not psychologically based, CBT was found to have a very small impact on ability status/disability. Other psychologically based interventions for pain include Acceptance and Commitment Therapy as well as Mindfulness-Based Stress Reduction.

Whole Health focuses on empowering and equipping individuals to live their best lives. The Whole Health System of Care includes three major components: Pathway, Wellbeing, and Clinical Care [9]. Pathway is focused on empowering Veterans to set goals and engage in Personal Health Planning, as well as engagement with a Health and Wellness Coach and/or Whole Health Partner. Wellbeing programming is focused on equipping Veterans with self-care skills and various Complementary and Integrative Health (CIH) offerings for wellbeing. Finally, Clinical Care is focused on offering traditional, conventional, and

M. Williams (✉) · R. F. Sabet
Durham VA Healthcare System, Durham, NC, USA
e-mail: melvania.williams@va.gov; raha.sabet@va.gov

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_5

excellent evidence-based treatment through a Whole Health paradigm. This includes consideration of the Veteran's Mission, Aspiration, and Purpose, and the provision of CIH treatment offerings (e.g., acupuncture). At the core, Whole Health is Veteran/person centric. Shared decision-making is also emphasized in the clinical care realm. Importantly, another branch of Whole Health includes Employee Whole Health, a proactive model of self-care to promote employee wellness.

Taken together, when addressing pain, regardless of the setting, it is important to adopt a biopsychosocial lens. In addition, integration of a psychologist can enhance the experience for the patient by putting psychosocial factors front and center and by exposing the patient to psychologically oriented, evidence-based interventions. Finally, utilization of a Whole Health model offers an approach for patient care and the provider's experience. Whole Health helps to expose patients to conventional approaches as well as complementary and integrative health approaches, many of which show promising outcomes for pain management. Whole Health also emphasizes the importance of self-care and promoting wellness for providers. In the next sections, we will introduce the concept of compassionate care and review clinical applications.

Compassionate Care

Compassion is a foundational component of patient-centered medicine. There is growing evidence which points to the importance of compassion in driving high-quality, high-value care [3, 10]. Care delivered with compassion and empathy, where patients talk openly about their symptoms and concerns, lends to better assessment of their condition and generates a more accurate diagnosis as it relates to acute and chronic pain management. Research shows that when compassion and respect are deficient in care, patients may avoid necessary treatment and withhold important information from their care providers to the detriment of care [4]. Studies demonstrate that healthcare encounters that exhibit attributes of compassion, empathy, and respect not only make patients "feel good" but, in fact, positively influence health outcomes, including control of chronic conditions, pain control, improved adherence to treatment recommendations, fewer major medical errors, and faster recovery times [4].

Clinical Applications and Techniques

Pain is subjective and reliant on the patient's verbal skills and self-awareness, all of which are influenced by the patient's cultural background. An ethnically and culturally diverse society requires healthcare providers to respect and take into account the particular cultures of their patients [2]. Lack of understanding of the beliefs of patients and families can potentially damage the patient-provider relationship. Further, this lack of trust can act as a significant barrier to appropriate pain management. Health professionals and teams who learn the nuances of culture are rewarded with the knowledge that they have been more effective in managing their patients' pain [4].

Evidence-Based Practices

How can physicians actively demonstrate compassion? Mazzarelli names four behaviors that can be practiced at the patient's bedside: sitting (versus standing) while speaking; face-to-face communication with eye contact; taking an active interest in emotional and psychological well-being; and not interrupting. These exercises, in combination with physical exam skills, are practices vital to improving patient outcomes [10].

To provide compassionate care effectively, providers should also engage in regular self-compassion exercises and promote compassion in the workplace and on the team. This can be done in many ways: (1) modeling self-care (e.g., taking time off, taking a break at work and doing something focused on wellness); (2) modeling self-compassion (e.g., using compassionate self-

talk when a mistake happens); (3) extending compassion to team members; (4) praising team members for use of compassion; and (5) planning team wellness activities and/or ensuring that employees have access to wellness activities. Providers are encouraged to consider resources such as those provided by Dr. Kristen Neff to assess levels of self-compassion and to further build this "muscle" Self-Compassion by Kristin Neff: Join the Community Now [1].

Challenges and Considerations

Compassion fatigue undermines the provider's health and wellbeing. It can also compromise the quality of care at the most basic level. The remedy to compassion fatigue is not clinical detachment. Research supports that connecting with patients on a human level fuels, rather than depletes, provider in their work and is associated with a lower risk of burnout and compassion fatigue. Furthermore, evidence suggests that this restorative ability to connect with patients (i.e., empathy) can be taught and cultivated in those for whom it does not come naturally [5].

Case Studies or Clinical Scenarios

White, heterosexual, cis-male provider meets a "new patient:" a 59-year-old Latina, recently divorced, cis-female with a history of chronic lower back pain following 24 years of service with the United States Air Force. Pain is currently managed with low-dose hydrocodone on and off for 10 years. Patient asks the provider numerous questions at the first meeting: "How long will I have to take pain medication? Are there any other alternatives? I've been under a lot of stress since my divorce and I'm in pain more often. I have a family member with an addiction problem; will I get hooked on pain pills too?" To maintain workflow, the provider stands up to interrupt the patient mid-sentence and deflects any further questions until the next visit, given time limitations.

What Would Be a Compassionate Care Approach?

The provider empathically listens, maintaining eye contact throughout the interview to convey connection and understanding. He then elicits patient questions to avoid fragmenting the conversation. Notably, providers who are responsive to patients' questions may be able to reduce the frequency of fragmented conversations and shorten the overall length of time.

Providers' schedules are often burdened, and some fear that the additional time taken to build meaningful rapport with patients is noble but not feasible. However, providers can be encouraged by a recent study finding that the duration of patient visits increased only minimally when patients asked questions, while patient outcomes improved [12].

Evidence shows that psychological stress and/or trauma is associated with persistent pain and that people with persistent pain are more likely to be exposed to stressful life events such as loss of marriage and employment. It is proposed that unresolved stressors throughout life may be relevant to understanding persistent pain [13]. Taking the time to elicit and respond to patient questions may lead to better-suited non-pharmacological options.

Patient Education

Perioperative patient education programs have superior outcomes in terms of postoperative pain, disability, surgical experience, and health care utilization when compared to usual care [15]. One such example is the Perioperative Pain Neuroscience Education for lumbar radiculopathy [15], in which patients were taught that pain can be normal and expected after surgery. It is postulated that such a reconceptualization of pain is a cornerstone of superior patient outcomes, resulting in a reduction in healthcare utilization despite the presence of pain and disability [11, 13]. Patient education led to a more favorable view of their surgical experience and also used

fewer postoperative healthcare resources. Therefore, taking the time to build rapport and educating patients about the neurophysiology of pain will likely improve patient healthcare experiences.

Recommendations

Looking ahead, we strongly recommend the adoption of a Whole Health approach both for patients treated in perioperative settings and for the staff and providers who treat these Veterans. In addition, we recommend inclusion of a mental health professional in the perioperative setting; this can be a provider with protected time to work with patients in these environments and/or via a consultative service. To help promote compassionate care, teams can consider practicing via role plays. The role of Transitional Pain Service (TPS) with a focus on education and pre-optimization (mental health and opioid intake), protocolized intraoperative care, and follow-up for extended postoperative period cannot be overemphasized in this setting.

Although compassion, even at a rudimentary level, fosters meaningful human connections, cultivating an organizational culture of compassion poses significant challenges. It is an effort that many leaders in healthcare may assume limited utility because of the ambiguous ways to measure "attainment" or the steps necessary to achieve it. Instead, organizations are encouraged to consider converting noble aspirations of cultivating a patient-centered and compassionate culture into real and sustained change by exploring a whole health compassionate care approach. Thus, converting patient-centered care from high aspirations into goals that can be set, measured, and attained.

Key Takeaway Points

1. Compassionate care is an important and frequently overlooked component of patient-centered care. It addresses the emotional and psychosocial aspects of the patient's experience and the patient's innate need for human connections and relationships. At its core, it means recognizing the concerns, distress, and suffering of patients and their families and taking action to relieve them. It is based on active listening, empathy, strong communication and interpersonal skills, knowledge of the patient as a whole person including his or her life context and perspective, and the ability to work together to relieve distress.
2. Pain and psychosocial factors reciprocally influence one another, resulting in chronic and complex pain syndromes.
3. It is imperative that chronic care providers understand, respect, and take into account the particular cultures from which their patients come. Health professionals who learn the nuances of culture are rewarded with the knowledge that they are more effective in managing the pain of their patients.
4. Mental health integration in pain management is a design intervention platform that can address the burden of chronic pain and reduce the risks of overutilization of opioid medications, globally.
5. Empathetic healthcare environments help mitigate burnout among providers treating chronic pain.

References

1. The American Medical Association. What is physician burnout? Available at https://www.ama-assn.org/practice-management/physician-health/what-physician-burnout. Accessed 11 Apr 2024.
2. Givler A, et al. The importance of cultural competence in pain and palliative care. StatPearls, StatPearls Publishing; 22 May 2023.
3. Kohrt BA, et al. Chronic pain and mental health: integrated solutions for global problems. Pain. 2018;159(Suppl 1,Suppl 1):S85–90. https://doi.org/10.1097/j.pain.0000000000001296.
4. Gooding H, et al. All these things don't take the pain away but they do help you to accept it: making the case for compassion-focused therapy in the management of persistent pain. Br J Pain. 2020;14(1):31–41. https://doi.org/10.1177/2049463719857099.
5. Malpus Z, et al. Compassion focused therapy for pain management: '3 systems approach' to understanding why striving and self-criticism are key psychological barriers to regulating activity and

improving self-care for people living with persistent pain. Br J Pain. 2023;17(1):87–102. https://doi.org/10.1177/20494637221133630.
6. Meints SM, Edwards RR. Evaluating psychosocial contributions to chronic pain outcomes. Prog Neuro-Psychopharmacol Biol Psychiatry. 2018;87(Pt B):168–82. https://doi.org/10.1016/j.pnpbp.2018.01.017.
7. Williams ACDC, Eccleston C, Stephen M. Psychological therapies for the management of chronic pain (excluding headaches) in adults (review). Cochrane Database Syst Rev. 2012;11:1–109. PMC—PubMed
8. Williams AC, Fisher E, Hearn L, Eccleston C. Psychological therapies for the management of chronic pain (excluding headache) in adults. Cochrane Database Syst Rev. 2020;8:CD007407.
9. Bokhour BG, Haun JN, Hyde J, Charns M, Kligler B. Transforming the veterans affairs to a whole health system of care: time for action and research. Med Care. 2020;58(4):295–300.
10. Trzeciak S, Roberts BW, Mazzarelli AJ. Compassionomics: hypothesis and experimental approach. Med Hypotheses. 2017;107:92–7. https://doi.org/10.1016/j.mehy.2017.08.015. Epub 2017 Aug 12. PMID: 28915973
11. Squier RW. A model of empathic understanding and adherence to treatment regimens in practitioner-patient relationships. Soc Sci Med. 1990;30(3):325–39. https://doi.org/10.1016/0277-9536(90)90188-x. PMID: 2408150
12. Tai-Seale M, Foo PK, Stults CD. Patients with mental health needs are engaged in asking questions, but physicians' responses vary. Health Aff Millwood. 2013;32(2):259–67. https://doi.org/10.1377/hlthaff.2012.0962. PMID: 23381518; PMCID: PMC5558791
13. Lumley MA, Cohen JL, Borszcz GS, Cano A, Radcliffe AM, Porter LS, Schubiner H, Keefe FJ. Pain and emotion: a biopsychosocial review of recent research. J Clin Psychol. 2011;67(9):942–68. https://doi.org/10.1002/jclp.20816. Epub 2011 Jun 6. PMID: 21647882; PMCID: PMC3152687
14. Urits I, Hubble A, Peterson E, Orhurhu V, Ernst CA, Kaye AD, Viswanath O. An update on cognitive therapy for the management of chronic pain: a comprehensive review. Curr Pain Headache Rep. 2019;23(8):57. https://doi.org/10.1007/s11916-019-0794-9. PMID: 31292747
15. Louw A, Diener I, Landers MR, Puentedura EJ. Preoperative pain neuroscience education for lumbar radiculopathy: a multicenter randomized controlled trial with 1-year follow-up. Spine (Phila Pa 1976). 2014;39(18):1449–57. https://doi.org/10.1097/BRS.0000000000000444. PMID: 24875964.

Part III

Intraoperative Care

6 Anesthesia Considerations and Techniques: Focuses on Anesthesia Methods and Their Role in Pain Management During Surgery

Annie C. H. Fung and Daniel Aviram

Background and Current Understanding

Analgesia is essential in the perioperative period regardless of the chosen anesthetic technique. Anesthetic techniques can be broadly categorized into four main types and may be used alone or in combination:

(a) General anesthesia: inducing a state of reversible unconsciousness, immobilization, and loss of sensation. Typically used for major surgeries, uncooperative patients, or procedures with prolonged surgical times such as intra-abdominal, maxillofacial, cardiothoracic, gynecology, pediatric, trauma, or emergency surgery.
(b) Regional anesthesia: involves the selective infiltration of central or peripheral nerves, also known as neuraxial and peripheral nerve blocks respectively. This is done away from the surgical site, to produce a reversible loss of sensation in a specific area of the body. Typically used for intermediate and major surgeries such as orthopedics, obstetrics, breast, vascular, or ophthalmic surgery, or as an adjunct with general anesthesia in complex major surgeries.
(c) Local anesthesia: involves infiltration beneath the skin around the surgical site to produce a reversible numbing of a small area of the body. Does not affect consciousness and is typically used for minor procedures such as dental or skin operations, cataract removal, or as an adjunct for analgesia.
(d) Monitored anesthetic care (MAC): continuous monitoring and support by an anesthesiologist, with or without administration of sedation, anxiolytics, and analgesics, titrated to preserve spontaneous breathing and airway reflexes while maintaining patient comfort and facilitating surgery. Typically used for day surgeries and a range of diagnostic and therapeutic procedures (e.g., endoscopic procedures, interventional cardiology, otolaryngologic, ophthalmic surgery).

The choice of anesthetic technique depends on surgical, patient, and anesthetic factors (Table 6.1).

Numerous studies show that moderate to severe acute pain is associated with poorer surgical outcomes, an increased likelihood of developing chronic pain syndromes, and higher perioperative complication rates [1–3]. Modern anesthetic techniques are trending toward the use of multimodal analgesia and opioid-sparing anesthesia, aimed to utilize the synergistic effects of individual agents to maximize analgesia while minimizing undesired side effects. Practices for

A. C. H. Fung (✉) · D. Aviram
Department of Anaesthesia and Perioperative Medicine, University College London Hospital, London, UK

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_6

Table 6.1 Factors to consider for choice of anesthetic technique

Patient factors	Surgical factors	Anesthetic factors
Age Comorbidities Cooperability Language barrier Frailty Risk factors for chronic post-surgical pain (CPSP) or difficult pain control	Intended surgical procedure (incision site, extent, complexity, anticipated pain level) Open vs. minimally invasive vs. endoscopic Duration of procedure Position Special considerations (such as requiring awake or neuromonitoring intraoperatively)	Expertise & familiarity of the anesthetist Availability of resources (medications, equipment, staff, logistics) Post-operative monitoring and disposition

pain management vary widely across countries and centers depending on surgical and anesthetic expertise, patient population, medication and equipment availability, etc.

Clinical Applications, Techniques, Challenges, and Considerations

Use of opioid-sparing anesthesia and multimodal analgesia is preferred to provide effective perioperative pain management and minimize opioid-related side effects. Intraoperative and postoperative pain control can be achieved with one or a combination of the following methods:

(a) Systemic analgesia: commonly used intraoperative agents include opioid and non-opioid medications. Also given as premedication and for postoperative pain control.
(b) Central neuraxial block: administration of medications around the nerves of the central nervous system, including spinal, epidural, and caudal blocks.
(c) Peripheral nerve blockade: selective infiltration of medications near the peripheral nervous system but away from the surgical site, including upper limb, lower limb, cervical, and truncal blocks.
(d) Local anesthetic infiltration: infiltration of local anesthetic at the surgical site, typically subcutaneous, intradermal or topical.

Perioperative pain management starts at preassessment from the first point of contact between the patient and anesthetic team. Aside from routine anesthetic history and examination, anesthesiologists are also assessing the patient's risk for acute post-surgical pain, expected level of analgesia required for their intended procedure, and formulating a perioperative analgesic plan. For patients with expected difficult pain control during and after surgery, early input from the acute pain team is beneficial. Patients warranting early referral to the acute pain team in the preoperative stage include: patients with pre-existing chronic pain, current opioid or methadone use, history of drug or alcohol abuse, or history of anxiety or other psychological conditions [4]. Key components of pre-operative counselling include options for analgesia and expectation management for post-operative pain, supplemented by information pamphlets.

Next, we will outline individual agents and techniques commonly used for perioperative pain management.

(a) Systemic analgesia: can be used alone or as a component of multimodal analgesia. Analgesic agents can be classified into opioids and non-opioids. Intraoperatively, this is given via intravenous or per rectal route. Analgesia can also be given as premedication and is commenced immediately postoperatively.

Opioids

Opioids are the traditional choice for analgesia; however, their use is limited by opioid-related side effects including respiratory depression, post-operative nausea and vomiting, ileus, and persistent postoperative opioid use amidst the opioid epidemic [5]. Increasing evidence shows

the benefits of opioid-sparing and multimodal anesthesia; thus, modern anesthetic practices are implementing opioid stewardship and moving away from opioid-based analgesia. Commonly used opioids intraoperatively and their pharmacology are outlined below in Table 6.2.

Non-opioids

Non-opioids exert their analgesic effect through different receptors, which act synergistically with opioids and other analgesic agents. Table 6.3 summarizes commonly used non-opioid analgesics during the intraoperative period and their pharmacological properties.

Paracetamol is an antipyretic, anti-inflammatory medication with weak analgesic effect. It is recommended along with NSAIDs as first line in the WHO analgesic ladder. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a diverse class of medications that inhibit the cyclooxygenase enzyme. They are non-sedative and shown to reduce opioid consumption. Caution must be exercised due to the risk of renal injury, coagulopathy, acute thrombotic events, gastrointestinal bleeding, and impaired bone and wound healing. Selective COX-2 inhibitors were introduced in 1999 and hypothesized to provide a safer alternative to conventional NSAIDs, as GI and bleeding complications are mediated by COX-1 inhibition. However, multiple coxibs were withdrawn from the market due to increased thrombotic events.

Ketamine is an N-methyl-D-aspartate (NMDA) receptor antagonist with multiple mechanisms of action in the peripheral and central pathways of pain. Intraoperative ketamine use has been shown to reduce acute postoperative pain and perioperative opiate consumption for both opioid-naive and opioid-tolerant patients and is particularly effective for complex pain and patients where opioid use should be minimized or avoided [6].

Alpha-2 agonists are centrally acting antihypertensive, anxiolytic, sedative, and analgesic agents. Clonidine is a nonselective agent (alpha-2/alpha-1 = 200:1), and dexmedetomidine is a specific and selective alpha-2 agonist (alpha-2/alpha-1 = 1620:1). These have remained as adjuncts due to the hemodynamic effects of hypotension, bradycardia, and sedative effect limiting their routine use.

Intravenous (IV) lignocaine demonstrates anti-hyperalgesic properties and is efficacious for opioid-sparing analgesia in both acute and chronic pain. Due to the risk of local anesthetic systemic toxicity (LAST), IV lignocaine should not be used in patients with low body weight (< 40 kg), or simultaneously with other local anesthetic interventions including regional or neuraxial blocks.

Dexamethasone and magnesium are safe adjuncts for intraoperative analgesia. Both have weak analgesic effects but are shown to reduce anesthetic requirements, improve postoperative pain levels, and reduce perioperative analgesic consumption.

(b) Neuraxial techniques: can be used alone for regional anesthesia or as a component of multimodal analgesia.

Techniques for neuraxial anesthesia include spinal, epidural, combined spinal epidurals (CSE), and caudal blocks. Neuraxial techniques are invasive procedures and involve administration of medications near the spinal cord to block transmission of autonomic, sensory, and motor nerves. Neuraxial techniques can be used for either anesthesia or analgesia of the lower limbs, abdomen, and pelvis. Indications of each specific technique are discussed below in Table 6.4. Contraindications for neuraxial techniques include patient or parent refusal, coagulopathy, infection at the intended needle insertion site, spinal or neurological disease (such as space-occupying lesions or increased intracranial pressure, spinal bifida, previous spinal instrumentation), and hemodynamic instability. Neuraxial techniques are routinely performed and are a suitable option for effective, safe, and reliable anesthesia and analgesia. Possible serious complications include spinal infections, hematoma, major nerve damage, medication errors involving the wrong route of administration, and cardiovascular collapse. The third National Audit Project conducted in the United Kingdom showed a low incidence (0.012%) of

Table 6.2 Commonly used opioids for intraoperative pain control

	Relative potency (IV)	IV dosage as adjunct to induction	IV dosage for maintenance	Onset time	Duration of action	Alternative routes of administration	Additional comments
Morphine	1	0.1–0.2 mg/kg	0.02–0.05 mg/kg bolus	5–10 minutes	3–5 hours	PO PR Neuraxial Sc IM	Risk of accumulation in renal and liver impairment
Alfentanil	10–20	10–75 mcg/kg	0.1–2 mcg/kg/min infusion	30–60 seconds	5–10 minutes	N/A	Fast and short acting, titratable for intraoperative analgesia
Fentanyl	100	1–5 mcg/kg	0.5–1.5 mcg/kg bolus or 0.01–0.1 mcg/kg/min infusion	1–2 minutes	30–60 minutes	PR Neuraxial IM TD TM IN	Risk of accumulation and long context-sensitive half-time for prolonged infusions ≥2 hours
Remifentanil	100–200	0.5–1 mcg/kg	0.025–1 mcg/kg/min infusion	30–60 seconds	3–10 minutes	N/A	Fast and short acting, titratable for intraoperative analgesia Organ-independent elimination Context-insensitive half-life Risk of chest wall rigidity in high doses
Sufentanil	500–1000	0.1–0.5 mcg/kg	0.002–0.01 mcg/kg/min infusion	1–3 minutes	30 minutes	Neuraxial	Fast and short acting, titratable for intraoperative analgesia Similar profile to fentanyl

PO per oral, *PR* per rectal, *Sc* subcutaneous, *SL* sublingual, *TD* transdermal, *TM* transmucosal, *IM* intramuscular, *IN* intranasal, *IA* intraarticular

Table 6.3 Commonly used non-opioids for intraoperative pain control

	Mechanism of action	IV dosage for analgesia	Onset time	Duration of action	Alternative routes of administration	Comments
Paracetamol	Unknown, inhibition of central prostaglandin synthesis, activation of descending serotoninergic and endocannabinoid pathways	Slow bolus: 15 mg/kg (maximum dose 4 mg/day for adults or 60 mg/kg/day)	5–10 minutes	4–6 hours	PO PR	Risk of toxicity in overdose, hepatic impairment, and glutathione deficiency
Ibuprofen	NSAID Nonselective	Slow bolus: 10 mg/kg (maximum dose: 30 mg/kg/day)	30 minutes	4–6 hours	PO PR IA	
Ketorolac	NSAID Nonselective	Slow bolus: 0.3 mg/kg (maximum dose 120 mg/day for adults with normal renal function, or 60 mg/kg for patients ≥65 years, with renal impairment, or with body weight < 50 kg)	30 minutes	4–6 hours	PO PR IN IM IA	
Diclofenac	NSAID Nonselective	Slow bolus: 0.5–1 mg/kg (maximum dose 2 mg/kg/day)	5–15 minutes	6–8 hours	PO PR IM	
Parecoxib	Selective COX-2 inhibitor	Slow bolus: 0.5 mg/kg (maximum dose 100 mg/day)	10–20 minutes	6–12 hours	IM	Pro-drug of Valdecoxib Only coxib that can be given IV
Ketamine	NMDA receptor antagonist	Loading dose: 0.1–1 mg/kg (adult) or 1–2 mg/kg (children) Low dose infusion for analgesia: 0.1–0.3 mg/kg/hr	15–30 seconds	5–10 minutes	IM PO Neuraxial PR IN TD Sc	Higher dosage for dissociative anesthesia

Table 6.3 (continued)

	Mechanism of action	IV dosage for analgesia	Onset time	Duration of action	Alternative routes of administration	Comments
Clonidine	Nonselective alpha-2 agonist	Loading dose: 0.5–1 mcg/kg Maintenance: 0.2–0.5 mcg/kg/min (maximum dose 1.2 mg/day)	3–5 minutes	3–7 hours	PO Neuraxial TD Topical SL	Dosage adjustment required for renal impairment Monitor for initial hypotension, and rebound hypertension
Demedetomidine	Selective alpha-2 agonist	Loading dose: 0.5–1 mcg/kg Maintenance: 0.2–1.4 mcg/kg/hr	3–5 minutes	11–2 hours	IN	Produces conscious sedation which resembles natural sleep
Lignocaine	Sodium channel blocker	Loading dose: 1–1.5 mg/kg Maintenance: 1–2.5 mg/kg/hr. (maximum dose 5 mg/kg)	45–90 seconds	30–90 minutes	Neuraxial IM Sc Topical	Also anti-arrythmic effect Also used for IV regional anesthesia or bier block
Dexamethasone	Glucocorticoid and anti-inflammatory	Slow bolus: 0.1–0.2 mg/kg	1–2 hours	36–48 hours	PO Neuraxial IA IM	Also has anti-emetic properties
Magnesium	Inhibit calcium influx and antagonist central NMDA receptor signal transmission	Loading dose: 50 mg/kg/hr. Maintenance: 8–15 mg/kg/hr. (maximum infusion rate < 2 g/hr)	15 minutes	4 hours	PO IV	Also muscle relaxation and anti-seizure effect

PO per oral, *PR* per rectal, *Sc* subcutaneous, *SL* sublingual, *TD* transdermal, *TM* transmucosal, *IM* intramuscular, *IN* intranasal, *IA* intraarticular

Table 6.4 Summary of neuraxial anesthesia

	Indications	Commonly used medications	Anatomical landmark	Anesthetic technique	Sensory level
Spinal	Anesthesia Obstetric Lower limb Hernia repair Pelvic, saddle anesthesia Analgesia (intra- & post-operative) Intra-abdominal Gynecology	Intrathecal Bupivacaine (plain or heavy with hyperbaric 0.5% dextrose) Levobupivacaine Fentanyl Morphine Diamorphine	Touffier's line Interspinous space	Midline or paramedian approach One shot technique Reliable, dense anesthesia	Aim for up to T4 level Also accompanied by motor block Block height and laterality can be manipulated by hyperbaric solution
Epidural	Anesthesia Obstetric Analgesia Thoracic UGI Intra-abdominal	Bupivacaine (plain only) Levobupivacaine Ropivacaine lignocaine Fentanyl Morphine Clonidine	Interspinous space	Midline or paramedian approach LOR to saline or air Touhy needle	Level of block can be altered depending on the level of epidural insertion and volume used
Caudal	Anesthesia Anal or saddle anesthesia Analgesia Pediatrics Orchidopexy Hernia repair		Identify the sacral hiatus and sacrococcygeal ligament	One shot technique	Dural sac ends at S4 for infants, S1 for adults

major complications, of which two-thirds of initially disabling injuries fully resolved within 6 months [7].

(c) Peripheral nerve block: can be used alone for regional anesthesia, or as a component of multimodal analgesia. Peripheral nerve blocks can be broadly categorized into upper limb, lower limb, truncal, thoracic, and cervical blocks.

The choice of specific block, choice of medication, dosage and volume is tailored according to the degree of analgesia or anesthesia required for the intended surgery, within safe dosing limits. The clinical effect, including sensory level, degree of motor block and sympatholysis, depends on the nerve signals transmitted by the targeted nerve bundle. Some blocks may be motor sparing, if targeting a purely sensory nerve. Peripheral nerve blocks can be performed by landmark, peripheral nerve stimulator, or ultrasound-guided techniques. Novel techniques for peripheral nerve blocks are being developed with the adoption of ultrasound-guided regional anesthesia, where the nerves and spread of local anesthetic can be visualized in real time and the block performed at any site along its course. This improves analgesic efficacy and safety profile. Regional blocks have the benefit of being opioid-sparing, attenuating of the stress response of surgery, improving recovery time, and reducing postoperative pain levels [8].

(d) Local anesthetic infiltration: used for analgesia for minor, superficial procedures, or in combination with other anesthetic methods as a component of multimodal analgesia.

This involves infiltration of local anesthetics alone or with adjuncts at the surgical site for minor procedures such as minor dermatological procedures, dental procedures, cataract removal, or wound infiltration at the end of intermediate to complex major procedures. This is often performed at the end of surgery by surgeons and is a procedurally simpler option for postoperative analgesia compared to regional anesthesia. The incidence of systemic local anesthetic toxicity (LAST) after wound infiltration is estimated to be around 11%; thus, appropriate dosing is essential, using the lowest concentration and dose necessary for analgesia and employing recommended injection techniques to prevent LAST. There is no increased risk of surgical site infection after wound infiltration. The PROSPECT group from the European Society of Regional Anaesthesia (ESRA) recommends pre- and intraoperative wound infiltration for selected types of surgical procedures such as laparotomies and spinal surgeries [9]. Alternative techniques to single-shot wound infiltration include continuous or patient-controlled wound infiltration, which provides prolonged analgesia. Implementation is limited by the complexity of devices, patient monitoring, and education of patients and healthcare staff.

Evidence-Based Practices

Latest guidelines from the UK, USA, Australia, and New Zealand recommend multimodal techniques, personalized and procedure-specific perioperative pain management to optimize perioperative analgesia [10–12]. The European Society of Regional Anaesthesia & Pain Therapy (ESRA) published the PROSPECT guidelines covering 20 common surgical procedures, offering surgery-specific recommendations according to consensus-based evidence and systematic reviews [13]. Implementation of enhanced recovery after surgery (ERAS) pathways to deliver evidence-based and standardized care, and involvement of acute pain team and anesthesiologists in the immediate postoperative period, demonstrates improved surgical outcomes, faster recovery, and greater patient satisfaction. Perioperative pain control is one of the many multimodal components in ERAS protocols, and the combination of multiple components (such as prehabilitation, smoking and alcohol cessation, patient counselling, early mobilization, feeding, and removal of drains) produces a synergistic benefit [14]. Furthermore, the adoption and availability of ultrasound has transformed the technique and practice for many procedures in anesthesia, including ultrasound-guided regional anesthesia, which is becoming the gold standard for increased block success, greater patient satis-

faction, improved safety profile, ease of training or teaching, and development of novel regional techniques.

Future Directions and Research

Building upon opioid-sparing techniques, multimodal analgesia, and ERAS pathways, further improvements in comprehensive pain control require multidisciplinary perioperative approaches and personalized pain medicine. Future research will focus on capturing of patient-reported postoperative outcomes such as pain scores, function, and satisfaction, instead of conventional surgical outcomes. Implementation of assistive artificial intelligence in ultrasound is a rapidly expanding field for image recognition, optimization, and prediction of needle trajectory. This can improve training in ultrasound-guided regional anesthesia. Ongoing pharmaceutical research and development over the decades has yet to introduce a novel analgesic agent. Agents showing promise include cannabinoids, psychedelics, and VX-548, an experimental non-opioid in Phase 3 clinical trials shown to be effective in moderate to severe acute pain.

Key Takeaways

1. Choice of anesthetic techniques and analgesic methods should be tailored according to patient, surgical, and anesthetic factors.
2. Analgesic techniques for intraoperative pain control include systemic analgesics, neuraxial techniques, peripheral nerve blocks, and wound infiltration.
3. Multimodal analgesia, opioid-sparing techniques, and surgery-specific protocols is recommended for perioperative pain management.

References

1. Santa Cruz Mercado LA, Liu R, Bharadwaj KM, et al. Association of intraoperative opioid administration with postoperative pain and opioid use. JAMA Surg. 2023;158:854–64.
2. Liu Y, Xiao S, Yang H, et al. Postoperative pain-related outcomes and perioperative pain management in China: a population-based study. Lancet Reg Health West Pac. 2023;39:100832–22.
3. Bonnet F, Marret E. Postoperative pain management and outcome after surgery. Best Pract Res Clin Anaesthesiol. 2007;21:99–107.
4. Armstrong AD, Hassenbein SE, Black S, Hollenbeak CS. Risk factors for increased postoperative pain and recommended orderset for postoperative analgesic usage. Clin J Pain. 2020;36:845–51.
5. Hah J, Bateman B, Ratliff J, Curtin C, Sun E. Chronic opioid use after surgery: implications for perioperative management in the face of the opioid epidemic. Anesth Analg. 2017;125:1733–40.
6. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, Beach ML. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic Back pain undergoing back surgery. Anesthesiology. 2010;10:1.
7. Cook TM, Counsell D, Wildsmith JAW. Major complications of central neuraxial block: report on the third National Audit Project of the Royal College of Anaesthetists. Br J Anaesth. 2009;102:179–90.
8. Folino T, Mahboobi S. Regional anesthetic blocks. Treasure Island (FL): StatPearls Publishing [Internet]; 2023.
9. Stamenkovic DM, Bezmarevic M, Bojic S, Unic-Stojanovic D, Stojkovic D, Slavkovic DZ, Bancevic V, Maric N, Karanikolas M. Updates on wound infiltration use for postoperative pain management: a narrative review. J Clin Med. 2021;10:4659.
10. Faculty of Pain Medicine of the Royal College of Anaesthetists (2021) Surgery and Opioids: Best Practice Guidelines 2021.
11. American Society of Anesthesiologists. Practice Guidelines for Acute Pain management in the perioperative setting. Anesthesiology. 2012;116:248–73.
12. Australian and New Zealand College of Anaesthetists and Faculty of Pain Medicine (2020) Acute Pain Management: Scientific Evidence (5th edition). https://www.anzca.edu.au/resources/college-publications/acute-pain-management/apmse5.pdf&ved=2ahUKEwiDr7zXkP2GAxV_XkEAHTkDDUwQFnoECBwQAQ&usg=AOvVaw2jzSM-uFD4qosp6rRy4Rds
13. Joshi GP, Albrecht E, Van de Velde M, Kehlet H, Lobo DN. PROSPECT methodology for developing procedure-specific pain management recommendations: an update. Anaesthesia. 2023;78:1386–92.
14. Jain SN, Lamture Y, Krishna M, Jain SN, Lamture Y, Krishna M. Enhanced recovery after surgery: exploring the advances and strategies. Cureus. 2023; https://doi.org/10.7759/cureus.47237.

7 Monitoring for Adequate Analgesia: Discusses Techniques for Ensuring Effective Pain Relief During Operations

Daniel Aviram and Annie C. H. Fung

Introduction

Analgesia is used intraoperatively to treat any pain arising from the surgical insult.

But why is this important if the patient is already asleep? Will they feel pain or remember it? "If a tree falls in a forest and no one is around to hear it, does it make a sound?"

The simple answer to that philosophical question in this case is "yes". Painful stimulation has a substantial effect on inflammation and chronic pain formation pathways. Nociceptive inputs from surgery induce local molecular changes, such as the release of nerve growth factor (NGF) and cytokines, leading to increased glutamatergic activity in the spinal cord. These changes are responsible for peripheral pain sensitisation, which subsequently influences spinal neuronal activity and results in central pain sensitisation [1–3]. Furthermore, even when ignoring the potential damage of unchecked pain stimulation, analgesics are used as adjuncts to purely hypnotic agents, and achieving sufficient sedation or hypnotic levels with no analgesia during surgical stimulation would require very high amounts of hypnotic agents that could cause haemodynamic instability.

Now that we have established the importance of intraoperative analgesia, the next question is: how can we measure pain in an anaesthetised patient who can't communicate? Pain is defined as an unpleasant sensory and emotional experience associated with actual or potential damage (The International Association for the study of pain definition) [4]. The emotional aspect of pain makes it harder to objectively measure and that is why the term nociception is used. Nociception is the sensory process that provides the signals that lead to the perception of pain. In other words, nociception refers to the painful stimulus, and while pain is multifactorial, nociception has a purer mechanism which is measurable. General anaesthesia provides a special advantage in this regard because when a patient is fully sedated the cognitive emotional aspect of pain is cancelled, making nociception and pain practically identical and therefore, opening the possibility of a more accurate and measurable way of intraoperative analgesia.

This chapter will discuss novel ways of measuring intraoperative pain, the basic physiological concepts behind those methods, their advantages and limitations compared to more traditional methods, review some of the evidence available and discuss the future of intraoperative pain management.

D. Aviram (✉) · A. C. H. Fung
Department of Anaesthesia and Perioperative Medicine, University College London Hospital, London, UK

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_7

Background and Current Understanding

Ideally, all three pillars of anaesthesia, hypnosis-relaxation-analgesia, should be properly monitored intraoperatively. However, while relaxation has been monitored for years using nerve stimulators and the train-of-four method, and consciousness level monitors based on processed EEG, such as Bispectral Index (BIS) monitors, have recently become the standard of care, nociception monitoring is relatively new.

As previously mentioned, sufficient analgesia is critical to avoid unexpected movements, sympathetic reactions followed by cardiocirculatory complications, and the development of pain memory. Using the minimum dose to achieve effective analgesia is desirable to avoid opioid-induced hyperalgesia, drug side effects, and to achieve shorter perioperative treatment periods.

As the quantification of nociception in unconscious subjects is extremely difficult, it is the "reaction" to nociception that is being used for the purpose of monitoring. The most frequently utilised response to "surgical stress" is an increase in sympathetic activity or the corresponding decrease in parasympathetic tone. This assumes that nociception will trigger a shift in the sympatho-vagal balance towards a sympathetic stress response. Changes in cardiac autonomic control, such as increased heart rate, increased peripheral vasoconstriction, pupillary dilatation, and an increase in galvanic skin conductance, offer relatively easy access to the evaluation of such sympathetic responses. Overall, these changes describe common observations in stressed humans: a fast heart rate, dilated pupils, and cold, sweaty hands.

Historically, the administration of analgesic drugs in general anaesthesia was mainly determined by the clinical experience of the anaesthesiologist. Opioid dosage was titrated according to sudden patient movements and other clinical signs of stress-induced activation of the sympathetic system, such as an increase in heart rate, blood pressure, lacrimation, and sweating [5]. However, this traditional method demonstrated limited success in predicting actual pain sensation in anaesthetised patients (Pk- 0.75 in a certain study) [6]. Furthermore, haemodynamic parameters are multifactorial and can be affected by other intraoperative events, such as bleeding, anaphylaxis, sepsis, and drugs.

To measure nociception in an anaesthetised patient, we can try and measure the relation between sympathetic and parasympathetic activity. In addition to simple reactions, sympathetic activation may also influence other physiological parameters that are more subtle and usually hidden from simple observation. The physiology behind these autonomic nervous system parameters will be discussed here, while available commercial devices will be reviewed in the following section.

Heart Rate Variability (HRV) is the subtle, milliseconds, difference between one heartbeat to another. It is a physiological manifestation that is affected by the respiratory cycle via the autonomic nervous system, especially by its parasympathetic branch [7, 8]. During a painful stimulus, distinct changes in HRV are seen. These changes persist when adequate analgesia is administered. The meaning of these findings is that the balance between nociception and analgesia directly affects HRV and therefore can be used as an early marker for insufficient analgesia [9].

Skin Conductance The assessment of electrical skin conductance is a long-known tool for the quantification of stress (for example, as one of the parameters of a polygraph to detect lies) and may represent an additional "vital sign" rather than an actual pain score. With the filling of palmar and plantar sweat glands under sympathetic control, micro-fluctuations in skin conductance caused by rapid changes in the water permeability of the excreting ducts appear to allow an easily accessible insight into rapid changes of sympathetic tone. Skin conductance monitors usually apply a micro-current to the palmar surface of the hand for adults, or the plantar surface of the feet for neonates, and measure the conductance of such current between two electrodes [10, 11].

Pupillometry The autonomic nervous system affects pupil size through its two branches:

Sympathetic activation causes pupil dilation (mydriasis) to enhance vision in low-light conditions and during the fight-or-flight response, while parasympathetic activation leads to pupil constriction (miosis) to protect the eye from bright light and during rest-and-digest states. The balance between these two systems regulates pupil size based on environmental lighting and emotional or physiological states. The assessment of pupillary diameter, its variation, and its unrest in ambient light has been examined for the prediction of pain and intraoperative monitoring of nociception. The use of pupillometry is limited in cases where ocular lesions are present, head access during surgery, and artifacts due to bright environmental lighting limit use. In addition, pupillary diameter cannot be measured continuously.

Photoplethysmographic Amplitude (PPGA) Refers to the magnitude of the pulsatile changes in blood volume detected by a photoplethysmography (pulse-oximeter monitor). It is typically measured as the difference between the peak systolic and trough diastolic levels of the PPG waveform**.** Analgesia can be measured through PPGA via its correlation with changes in sympathetic nervous system activity. A sympathetic nervous system activation causes vasoconstriction and an increase in PPGA due to reduced blood flow and amplitude of the photoplethysmogram. On the other hand, effective analgesia often reduces sympathetic activation, leading to vasodilation and an increase in PPGA as blood flow improves and the amplitude of the photoplethysmogram increases. Overall, PPGA could help in assessing the autonomic response to pain and the effectiveness of analgesic interventions in clinical settings [12].

Clinical Applications and Techniques

Several companies are trying to achieve the "holy grail" of a simple, useful, reliable bedside intraoperative pain monitoring device. Here are some of the commercially available devices, all applying the principle of measuring one or several aspects of the sympathetic-parasympathetic balance using the physiological parameters discussed earlier [13, 14].

AlgiScan (IDMed, Marseille, France)

The infrared video pupillometer is a non-invasive device that measures and identifies nociception in awake and sedated patients. It measures the pupillary dilation response (PDR) and translates it into an index called the Pupillary Pain Index (PPI), which is a score that reflects the patient's level of analgesia. This index was validated by measuring the PDR under increasing nociceptive stimulation between 10 and 60 mA. A higher PPI score (close to 9) indicates uncontrolled nociceptive stimulation and lower analgesia levels, whereas a PPI score close to 1 indicates high analgesia levels.

Surgical Pleth Index (SPI, GE Healthcare)

The SPI (formerly named Stress Surgical Index) is a nociception-monitoring device that measures nociception using photoplethysmographic signals to measure both HRV and PPGA. The information, given by the microvascular wave impulse signal of a finger photoplethysmography, is used to calculate these two parameters. This dimensionless continuous numerical index (from 0 to 100, with 0 = no stress and 100 = high-intensity stress) was previously developed to give a numeric measure of the surgical stress in patients under general anaesthesia. The manufacturer recommends a SPI <50 during surgery. Limitations in the use of SPI include cardiac arrhythmia, cardiac pacing, and peripheral vasoconstriction [15].

Analgesia Nociception Index (ANI, Mdolaris Medical Systems)

ANI is a device used for non-invasive measurements of nociception using an assessment of changes in HRV via an electrocardiographic

measurement. The device rates parasympathetic activity on a scale from 0 to 100, where a painful stimulus causes a relative decrease in parasympathetic activity and, as a result, a decrease in ANI score. ANI was studied and validated in multiple studies and showed a direct correlation between ANI levels lower than 50 and severe pain [6, 16].

Nociception Level Monitor (NOL, Medasense Biometrics Ltd)

The monitor makes use of an algorithm based on advanced statistical and machine learning technologies; it combines multiple autonomic signals (finger photoplethysmogram amplitude, skin conductance, HR, HR variability, and their time derivatives) into a single index, the NOL index. Machine learning was used to create the optimal algorithm to translate input (predictors) into output (NOL index). The index ranges from 0 (absence of nociception) to 100 (extreme nociception) and was validated in multiple studies [17].

Evidence-Based Practices

Being of commercial and financial interest, the medical literature is full of different studies regarding the mentioned devices, the bottom line being that most of them are more sensitive and specific for nociception recognition than the traditional haemodynamic parameters. However, none have shown a significant change in clinical patient outcomes. A comprehensive review published in the British Journal of Anaesthesia in 2019 concluded that although all devices appear to reflect intraoperative stimuli slightly better than traditionally used parameters, such as blood pressure or heart rate, to date, none has shown a convincing and clinically relevant benefit for its routine use [13]. A more recent review published in Anaesthesia and Analgesia in 2024 stated that medical literature indicates that these indexes are more precise in detecting intraoperative nociception under general anaesthesia and that accuracy is translated into lower postoperative pain scores and opioid consumption for several hours after surgery when these monitors are used. As for the impact of nociception monitoring on long-term outcomes such as persistent postsurgical pain or opioid use disorders after major surgery, very few studies evaluated these outcomes and were not robust enough to answer this specific question [14].

Future Directions and Research

The future of intraoperative analgesia monitoring, other than higher accuracy, is the combination of a conclusive closed system, "Anaesthetic monitoring," that could combine the measurement of all three anaesthesia pillars at first and later even "react" by adding the correct anaesthetic agent—hypnotic-muscle relaxant or opioid—to keep the patient as stable and comfortable as possible.

Key Takeaways

1. Pain is a subjective measure and therefore difficult to measure objectively.
2. Nociception is a good surrogate marker for measuring intraoperative pain.
3. Nociception measurement is based on the correlation between nociception and sympathetic activation.
4. Heart rate variability, pupil diameter changes, skin conductance, and photoplethysmographic amplitude are physiologic markers correlated well with autonomic nervous system changes.
5. While commercial devices measure nociception in a more accurate way compared to clinical parameters, it is yet to be determined if this accuracy is translated to better patient care.

References

1. Brennan TJ, Vandermeulen EP, Gebhart GF. Characterization of a rat model of incisional pain. Pain. 1996;64(3):493–502. https://doi.org/10.1016/0304-3959(95)01441-1.
2. Pogatzki-Zahn EM, Zahn PK, Brennan TJ. Postoperative pain—clinical implications of basic research. Best Pract Res Clin Anaesthesiol. 2007;21(1):3–13. https://doi.org/10.1016/J.BPA.2006.11.003.
3. Richebé P, Capdevila X, Rivat C. Persistent postsurgical pain pathophysiology and preventative pharmacologic considerations. Anesthesiology. 2018;129(3):590–607. https://doi.org/10.1097/ALN.0000000000002238.
4. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976–82. https://doi.org/10.1097/J.PAIN.0000000000001939.
5. Best CJ. Monitoring for anaesthesia. Lancet. 1987;330(8566):1033–4. https://doi.org/10.1016/S0140-6736(87)92606-7.
6. Funcke S, Sauerlaender S, Pinnschmidt HO, et al. Validation of innovative techniques for monitoring nociception during general anesthesia: a clinical study using tetanic and intracutaneous electrical stimulation. Anesthesiology. 2017;127(2):272–83. https://doi.org/10.1097/ALN.0000000000001670.
7. Taylor JA, Studinger P. Counterpoint: cardiovascular variability is not an index of autonomic control of the circulation. J Appl Physiol (1985) 2006;101(2):676–682.https://doi.org/10.1152/japplphysiol.00446.2006.
8. Laitio T, Jalonen J, Kuusela T, Scheinin H. The role of heart rate variability in risk stratification for adverse postoperative cardiac events. Anesth Analg. 2007;105(6):1548–60. https://doi.org/10.1213/01.ANE.0000287654.49358.3A.
9. Jeanne M, Logier R, De Jonckheere J, Tavernier B. Heart rate variability during total intravenous anesthesia: effects of nociception and analgesia. Auton Neurosci. 2009;147(1–2):91–6. https://doi.org/10.1016/J.AUTNEU.2009.01.005.
10. Ledowski T, Bromilow J, Wu J, Paech MJ, Storm H, Schug SA. The assessment of postoperative pain by monitoring skin conductance: results of a prospective study. Anaesthesia. 2007;62(10):989–93. https://doi.org/10.1111/J.1365-2044.2007.05191.X.
11. Ledowski T, Bromilow J, Paech MJ, Storm H, Hacking R, Schug SA. Monitoring of skin conductance to assess postoperative pain intensity. Br J Anaesth. 2006;97(6):862–5. https://doi.org/10.1093/BJA/AEL280.
12. Luginbühl M, Reichlin F, Sigurdsson GH, Zbinden AM, Petersen-Felix S. Prediction of the haemodynamic response to tracheal intubation: comparison of laser-Doppler skin vasomotor reflex and pulse wave reflex. Br J Anaesth. 2002;89(3):389–97. https://doi.org/10.1093/BJA/89.3.389.
13. Ledowski T. Objective monitoring of nociception: a review of current commercial solutions. Br J Anaesth. 2019;123(2):e312–21. https://doi.org/10.1016/J.BJA.2019.03.024.
14. Laferrière-Langlois P, Morisson L, Jeffries S, Duclos C, Espitalier F, Richebé P. Depth of anesthesia and nociception monitoring: current state and vision for 2050. Anesth Analg. 2024;138(2):295–307. https://doi.org/10.1213/ANE.0000000000006860.
15. Oh SK, Won YJ, Lim BG. Surgical pleth index monitoring in perioperative pain management: usefulness and limitations. Korean J Anesthesiol. 2024;77(1):31–45. https://doi.org/10.4097/KJA.23158.
16. Upton HD, Ludbrook GL, Wing A, Sleigh JW. Intraoperative "analgesia nociception index"-guided fentanyl administration during Sevoflurane anesthesia in lumbar discectomy and laminectomy: a randomized clinical trial. Anesth Analg. 2017;125(1):81–90. https://doi.org/10.1213/ANE.0000000000001984.
17. Meijer F, Honing M, Roor T, et al. Reduced postoperative pain using nociception level-guided fentanyl dosing during sevoflurane anaesthesia: a randomised controlled trial. Br J Anaesth. 2020;125(6):1070–8. https://doi.org/10.1016/j.bja.2020.07.057.

8 Multimodal Analgesia and Adjunctive Techniques: Explores the Combined Use of Different Analgesic Methods for Optimal Pain Control

Fausto Morell-Ducos

Introduction

The blunting of the autonomic and neurohumoral stress responses to surgical stimulation, caused by the activation of nociceptive pathways due to tissue damage, has historically relied heavily on the intraoperative use of opioids. Increasingly, the use of other analgesic drugs and adjuncts has gained acceptance, spurred by growing interest in opioid-sparing anesthesia as part of perioperative opioid stewardship, as well as greater appreciation of the benefits of multimodal antinociception.

Background and Current Understanding

Before the introduction of opioids to routine anesthetic practice, the main objectives of general anesthesia—unconsciousness, immobility, and the control of the autonomic response to surgical stimulation—were achieved by using high doses of hypnotic agents. This practice was associated with unacceptably high rates of hemodynamic instability and prolonged time to emergence due to the drug concentrations required to achieve satisfactory autonomic blunting [1].

Although often referred to as "intraoperative analgesia," the interruption of nociceptive pathways and their effect on the autonomic nervous system is better described as "intraoperative antinociception" in the anesthetized state, as pain is a subjective experience that requires consciousness.

Antinociception is required intraoperatively, as activation of nociceptive pathways is the primary driver of the stress response and early postoperative pain, as well as probably being implicated in the development of persistent postsurgical pain [1, 2].

The autonomic response to nociception caused by the surgical insult is mediated by the nociceptive-medullary-autonomic circuit [2]. Ascending nociceptive pathways carry signals from peripheral nociceptors via A-delta and C fibers, synapsing in the dorsal horn with secondary neurons that project to several sites in the brainstem. The main driver of the autonomic response is the medullary nucleus tractus solitarius, from which signals travel to the rostrolateral and caudoventrolateral medulla in the brainstem, and thence to the heart and peripheral vasculature via the sympathetic chain, as well as to the adrenal medulla.

Mu opioid receptors are present at multiple sites along these pathways, and their agonism reduces

F. Morell-Ducos (✉)
Pain Management Centre, National Hospital for Neurology and Neurosurgery, London, UK

University College Hospital, London, UK

University College London, London, UK
e-mail: fausto.morell-ducos@ucl.ac.uk

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_8

nociceptive signals and consequently sympathetic output. Opioids are therefore very effective antinociceptive agents. This, along with the fact that they can easily be continued as analgesic agents after emergence from anesthesia, led to their use being widely established in this setting.

This pervasive practice has more recently been questioned due to increasing awareness of the negative perioperative patient outcomes associated with opioid-related adverse drug events (including opioid-induced ventilatory impairment, nausea and vomiting, urinary retention, ileus, constipation, and pruritus), as well as the potential link with persistent postoperative opioid use.

Newer approaches have therefore been developed, centered around the use of alternative agents which, in conjunction with—or instead of—opioids, provide antinociception by disrupting the nociceptive-medullary-autonomic circuit at multiple sites. This approach has been termed multimodal antinociception by some, by analogy to the concepts of multimodal analgesia and balanced anesthesia [3].

Clinical Applications and Techniques

The multimodal antinociceptive approach maximizes the use of multiple antinociceptive agents (including local and regional anesthetic techniques) to block inflammatory, nociceptive, and sympathetic pathways. The use of multiple agents leads to an opioid-sparing effect, which can be maximized to provide opioid-free anesthesia [4].

It is important to note that the hypnotic agents used in general anesthesia also contribute to the suppression of nociceptive transmission by acting synergistically with the antinociceptive agents used, such that lower doses are required to obtain the same reduction in autonomic response to a given insult when used together than if either agent were used alone (i.e., by shifting the dose-response curve to the left) [1].

The reduction or complete avoidance of opioid use, which can be achieved with a multimodal antinociceptive approach, is likely to reduce dose-related early postoperative opioid-related adverse drug events such as nausea and vomiting, reduced intestinal transit, sedation, and opioid-induced ventilatory impairment. This is particularly appealing in those patient groups most at risk of these adverse effects, such as the obese, those with respiratory disease, and patients undergoing abdominal surgery [5].

Avoiding intraoperative and early postoperative opioid use also has the potential of reducing the incidence of opioid-induced hyperalgesia, a phenomenon which is dose-related and which is also known to occur acutely, although its clinical relevance in this setting has not been established [6].

The use of opioid-free and opioid-sparing techniques is also likely to be of particular use in patients who are very opioid tolerant, or who are on buprenorphine-based opioid substitution therapy, in whom very large doses of opioids would otherwise be required.

There is also some preclinical evidence and uncontrolled clinical studies which suggest that opioids may represent a risk factor in cancer recurrence when used in cancer surgery, although there is currently insufficient evidence to support this association [4, 7].

The Table 8.1 below summarizes the *intravenous analgesics and adjuvants* that are frequently used in opioid-free anesthesia and analgesia, namely alpha-2 adrenoreceptor agonists, N-methyl-D-aspartate (NMDA)-receptor antagonists, intravenous local anesthetics, and steroidal and non-steroidal anti-inflammatory drugs. Several combinations and doses can be used, and specific protocols vary.

Table 8.1 Intravenous drugs used in opioid-free anesthesia and analgesia, including mechanisms of action, potential benefits, and adverse effects

Drug	Mechanism of action	Potential benefits	Risks
Opioids	Interruption of afferent nociceptive input and enhancement of descending inhibition through activation of opioid receptors at multiple sites, mainly the periaqueductal gray, dorsal horn, amygdala, rostroventral medulla and cortex	Reduction of sympathetic response to nociception Synergistic decrease in arousal reduces hypnotic agent requirement	Associated with multiple adverse drug effects including postoperative respiratory depression, nausea and vomiting, ileus, pruritus
Ketamine	Interruption of afferent nociceptive input through NMDA receptor antagonism causing increased inhibitory pyramidal interneuron activity and decreased activity of glutamatergic neurones in the parabrachial nucleus and the medial pontine reticular formation to the thalamus and basal forebrain	Reduced postoperative pain intensity and opioid requirements Reduced postoperative nausea and vomiting	At higher doses psychotropic side-effects including hallucinations may occur

(continued)

Table 8.1 (continued)

Drug	Mechanism of action	Potential benefits	Risks
NSAIDs	Decreased prostaglandin synthesis through inhibition of COX 1 and 2 enzymes at sites of surgical tissue damage	Reduced opioid requirement, reduced postoperative pain intensity	Increased risk of kidney injury, GI ulceration, bronchospasm, platelet dysfunction. Concerns regarding adverse effects on bone and anastomotic healing and cardiovascular risk appear to not be clinically significant during short-term use
Paracetamol	Cyclo-oxygenase inhibition Potentiation of cannabinoid receptors	Reduced opioid requirements and reduced postoperative pain intensity	Liver toxicity in overdose
Dexmedetomidine Clonidine	Alpha-2 adrenergic agonists, enhancing descending inhibition and increasing inhibitory interneuron activity at the level of the dorsal horn. Decreased noradrenergic excitatory activity in hypothalamus, thalamus, basal forebrain and cortex	Reduced opioid requirements and postoperative nausea and vomiting. Decreased hypnotic requirements due to decreased nociceptive-induced arousal.	Risk of significant bradycardia and hypotension
Magnesium	Inhibitory effect at central excitatory glutamatergic synapses due to NMDA receptor blockade	Small reduction in postoperative opioid requirements. Decreased nociceptive-induced arousal	Potentiation of neuromuscular blockade, hypotension, arrhythmias

(continued)

Table 8.1 (continued)

Drug	Mechanism of action	Potential benefits	Risks
Locoregional and neuraxial local anaesthetics	Blockade of nociceptive afferent input through blockade of conduction of action potentials secondary to reversible sodium channel blockade	Reduced postoperative opioid requirements	Hypotension (neuraxial administration), motor block, neural injury
Intravenous lidocaine.	Postulated mechanisms include blockade of neutrophil priming and degranulation decreasing inflammatory response	Possible reductions in postoperative pain intensity, opioid requirements, postoperative ileus and postoperative nausea and vomiting	Reports of patient harm secondary to local anaesthetic toxicity
Dexamethasone	'Switching off' of inflammatory gene expression	Small reductions in pain intensity and opioid requirement postoperatively	Small elevations in blood glucose

Adapted from Macintyre et al. [5]

Evidence-Based Practices

The efficacy and importance of different pain management approaches and techniques will vary in different surgical procedures due to several factors:

- different mechanisms of generation of pain, including the anatomical site, type of pain (somatic vs visceral), intensity, and duration of pain,
- different potential consequences of inadequate pain relief (e.g., risk of pulmonary complications in abdominal surgery vs. lower limb arthroplasty) and the resulting effect on recovery, morbidity, and mortality,
- different pain management goals depending on the type of surgery and stage of recovery—e.g., on day 1 after a bowel resection via a midline laparotomy, the main goal is the ability to cough and deep-breathe, whereas in the following days, mobilization and re-establishing oral intake become equally important.

The use of individualized techniques should therefore be based on shared decision-making with the patient, considering the type of surgery, patient co-morbidities and pre-existing medications.

There are several evidence-based procedure-specific recommendations which can be used when planning an antinociceptive intraoperative and postoperative analgesic plan, such as those from the PROSPECT group [8]. This is a collaboration of anesthesiologists and surgeons, supported by the European Society of Regional Anaesthesia and Pain Therapy, which provides

evidence-based recommendations in the management of intraoperative antinociception and postoperative pain after specific surgical procedures, with a particular focus on multimodal strategies and consideration of the risks and benefits of interventions in specific surgical settings.

There is evidence that the use of multimodal antinociception, and its resulting opioid-sparing effects, reduces the incidence of postoperative nausea, vomiting, and sedation, as well as providing improved pain experience (especially with regional analgesia) and reduced opioid use in the early postoperative period [4].

There is so far no evidence that opioid-free anesthesia prevents persistent postoperative opioid use, alters prescribing at discharge, or reduces the risk of diversion and misuse, even with the concurrent use of regional anesthesia [4].

There is also little evidence that a multimodal intraoperative antinociceptive approach resulting in opioid-free anesthesia provides benefits above and beyond those of opioid-sparing anesthesia [2, 5, 9, 10].

Challenges and Considerations

The analgesics and adjuncts used in multimodal antinociception have their own adverse event profiles and contraindications.

Alpha-2 agonists can cause hypotension and sedation, potentially prolonging length of stay in the day-case setting; ketamine can cause psychotropic side effects, even after a single intraoperative dose; beta-blockers can cause hypotension and increase the risk of stroke and death; lidocaine infusions can be associated with local anesthetic toxicity, potentially resulting in death, and magnesium can cause arrhythmias and potentiation of neuromuscular blockade [4, 5, 10].

Many of the agents used cannot be titrated to individual requirements or have a maximum daily dose, such as NSAIDs and paracetamol. Additionally, agents such as ketamine or lidocaine, when used in the postoperative phase, require close monitoring and entail intravenous infusions, which can hinder ambulation and therefore delay recovery.

Of note, gabapentinoids, which were previously commonly recommended in many enhanced recovery pathways as opioid-sparing agents, are no longer routinely recommended in this setting. Their use is associated with a statistically but not clinically significant reduction in postoperative pain and opioid consumption, but it is associated with an increased risk of serious adverse events, including opioid-induced ventilatory impairment when co-administered with opioids [5].

From a practical point of view, the multimodal antinociceptive approach also requires a number of infusions to run simultaneously, increasing the technical complexity of anesthesia provision, as well as increasing cost and the risk for drug errors. Additionally, polypharmacy makes it more difficult to identify the agent causing an adverse drug reaction if one were to occur.

Some authorities advocate the use of antinociception monitoring in addition to processed EEG monitoring in order to guide the dosing of multimodal antinociception agents, instead of relying solely on heart rate and blood pressure fluctuations as a surrogate measure, although such monitors are currently not widely available due to technological limitations and concerns regarding their accuracy [3].

Future Directions and Research

Further research, including randomized trials, is needed to elucidate the impact of a multimodal antinociceptive approach on intraoperative and postoperative outcomes, as much of the current evidence focuses on postoperative analgesic practice.

In particular, further research is needed to explore the interactions between antinociceptive adjuncts and anesthetic agents, which may identify particularly advantageous drug combinations or improved outcomes in specific clinical settings.

Key Takeaways

1. The pharmacologic synergy afforded by intraoperative multimodal antinociception is associated with many advantages, including reduced drug-related side effects, hemodynamic stability, and earlier emergence.
2. The increasing use of antinociceptive adjuncts is associated with reduced intraoperative opioid use, although there is little evidence of a sustained reduction in opioid-related adverse events beyond the immediate perioperative period.
3. The disadvantages associated with many adjuncts (such as ceiling effects, multiple infusions, and extra monitoring) may restrict their use in certain settings.
4. Opioid-free intraoperative antinociception is associated with reduced postoperative nausea and vomiting and sedation, but evidence that it is associated with clinically significant improvements in postoperative pain relief, opioid-prescribing practices, or opioid use after discharge is lacking.
5. Further research is required to identify the most favorable drug combinations or ratios in specific clinical settings.

References

1. Brown EN, Pavone KJ, Naranjo M. Multimodal general anesthesia: theory and practice. Anesth Analg. 2018;127(5):1246–58.
2. Egan TD. Are opioids indispensable for general anaesthesia? Br J Anaesth. 2019;122(6):e127–35.
3. Egan TD, Svensen CH. Multimodal general anesthesia: a principled approach to producing the drug-induced, reversible coma of anesthesia. Anesth Analg. 2018;127(5):1104–6.
4. Kumar K, Kirksey MA, Duong S, Wu CL. A review of opioid-sparing modalities in perioperative pain management: methods to decrease opioid use postoperatively. Anesth Analg. 2017;125:1749–60.
5. Macintyre PE, Quinlan J, Levy N, Lobo DN. Current issues in the use of opioids for the management of postoperative pain. JAMA Surg. 2022;157(2):158–66.
6. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth. 2014;112:991–1004.
7. Sessler DI, Pei L, Huang Y, et al. Recurrence of breast cancer after regional or general anaesthesia: a randomised controlled trial. Lancet. 2019;394:1807–15.
8. Better Postoperative Pain Management – ESRA. (2019, February 20). ESRA. https://esraeurope.org/prospect/.
9. Alexander JC, Patel B, Joshi GP. Perioperative use of opioids: current controversies and concerns. Best Pract Res Clin Anaesthesiol. 2019;33:341–51.
10. Shanthanna H, Ladha K, Kehlet H, Joshi G. Perioperative opioid administration. Anesthesiology. 2021;134:645–59.

Part IV

Immediate Postoperative Care

9 Postoperative Pain Assessment and Management

Sarah Miller, Rohan Krishnan, and Rajnish K. Gupta

Introduction

Postoperative pain management is a critical component of perioperative care, influencing patient recovery, satisfaction, and long-term outcomes. Effective pain control reduces complications, facilitates early mobilization, and minimizes opioid-related adverse effects. This chapter explores the assessment and management of postoperative pain, providing evidence-based strategies for optimizing patient care.

Background and Current Understanding

Pain assessment and management have evolved significantly over the years, with a shift from opioid-dominant approaches to multimodal analgesia. Advances in regional anesthesia, improved understanding of pain pathways, and enhanced recovery protocols have shaped modern pain management strategies. Risk stratification of patients is crucial in determining appropriate techniques to prevent and treat post-surgical pain [1–4].

S. Miller · R. K. Gupta (✉)
Vanderbilt University Medical Center, Nashville, TN, USA
e-mail: raj.gupta@vumc.org

R. Krishnan
Metrohealth Medical Center, Cleveland, OH, USA

Clinical Applications and Techniques

Identifying At-Risk Patients

Preoperative risk factors associated with increased postoperative pain include anxiety, fear of pain, presence of a pre-existing inflammatory condition, and presence of pain prior to surgery. Certain types of surgeries, such as mastectomies, thoracotomies, and amputations, carry a higher risk of postoperative pain and the development of chronic pain. Postoperatively, uncontrolled pain can also lead to the development of chronic pain, further highlighting the importance of early assessment and treatment of postoperative pain.

Pain Assessment Methods

Patient interview, as well as evaluation of vital signs and overall patient appearance, can help delineate the severity of postoperative pain, but it is also important to utilize standardized techniques of pain assessment. Multiple pain measurement scales exist to assist the clinician in further evaluating a patient's experience.

- *Numeric Rating Scale (NRS):* This scale can be given graphically or verbally and consists of a scale, usually with 11 numerical values, with 0 representing no pain and 10 represent-

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_9

ing the worst possible pain. An advantage of this scale is its relative ease of use and the ability to administer it verbally, making it easier to use with patients with visual impairment and some cognitive impairments (Fig. 9.1a).

- *Verbal Rating Scale (VRS):* This scale is given verbally and asks patients to identify their pain in categories such as no pain, mild pain, moderate pain, severe pain, or worst possible pain. This assessment is easily given, however it has more limited answers to categorize pain and implies that the intervals between each descriptor are equal (Fig. 9.1b) [5].
- *Visual Analog Scale (VAS):* Measures pain on a 10 cm continuum from "no pain" to "worst possible pain." This scale has been shown to be sufficiently valid and reliable for measuring pain in the acute setting. The benefits of the VAS include ease of administration and reliability. A downside of this scale is that it requires a paper or electronic medium. In addition, patients with cognitive impairment

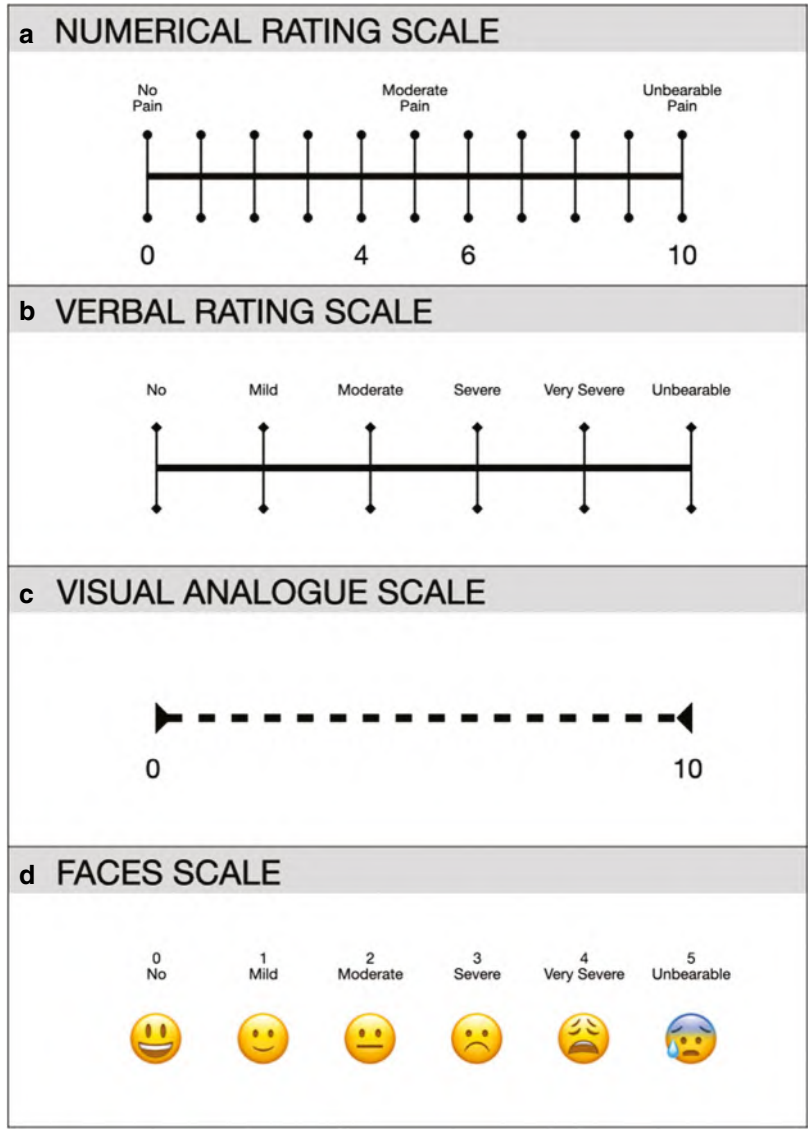


Fig. 9.1 Four types of pain rating scales. 1. **Numerical Rating Scale (a):** A horizontal line marked with numbers from 0 to 10, with labels indicating No Pain at 0, Moderate Pain at 4 and 6, and Unbearable Pain at 10. 2. **Verbal Rating Scale (b):** A horizontal line with verbal descriptors: No, Mild, Moderate, Severe, Very Severe, and Unbearable, each with corresponding markers. 3. **Visual Analogue Scale (c):** A horizontal line with a slider, marked from 0 to 10, without specific labels. 4. **Faces Scale (d):** A series of six faces ranging from a smiling face labeled 0 No to a distressed face labeled 5 Unbearable, with intermediate expressions labeled 1 Mild, 2 Moderate, 3 Severe, and 4 Very Severe.

may have difficulty using the scale accurately and it cannot be used by patients with visual impairment (Fig. 9.1c) [6].

- *Wong-Baker FACES Pain Rating Scale (WBS):* A visual representation of pain levels depicted by faces with progressively worsening facial expressions. Useful for pediatric and nonverbal patients and has been shown to have validity in both chronic and acute pain states (Fig. 9.1d) [7–9].

Pain Management Modalities

Multiple modalities can be used to treat postoperative pain, including regional anesthesia, opioid, and non-opioid medications. Regional anesthesia may reduce the stress response, total opioid consumption intraoperatively and postoperatively, opioid-related side effects, and morbidity in the postoperative period. Peripheral nerve and neuraxial single injections, as well as nerve catheters, are options perioperatively. Ideally, non-opioid medications (NSAIDs, acetaminophen, gabapentinoids, muscle relaxants) should be used first and for pain categorized lower on the pain scales, reserving opioid medication for more intense pain states. Assuming a patient is capable of both PO and IV medications, PO medications should be used for minimal pain states, reserving faster-acting IV medications for more severe pain. Using this method of pain medication escalation helps decrease side effects observed with opioid medications.

Evidence-Based Practices

Given that there are many ways to measure pain, Shafshak et al. aimed to determine whether one scale was more beneficial than others. In a cross-sectional study of 100 patients with chronic low back pain, pain severity was assessed utilizing the VAS scale and NRS scales. Subsequent disability was assessed with the brief pain inventory. The study found that there was no significant difference between the VAS and NRS scales in assessing low back pain severity but did find that a score of 6 on the VAS/NRS scale could aptly predict severe disability [7].

A study conducted by Bielewicz et al. aimed to ascertain the efficacy of the VAS and NRS scales in predicting pain outcomes. In this study, a cohort of patients underwent microdiscectomy, and their pain was assessed on preoperative day 1, 1 month postoperatively, and 3 months postoperatively. The study found that the NRS and VAS scales evaluated different aspects of pain—the AS scale seemed to be a retrospective assessment, whereas the NRS scale seemed to measure pain in current time [8].

A combination of patient evaluation and pain scales such as the VAS and NRS should be used in the postoperative setting to assess pain both subjectively and objectively. Since patients report pain differently, trended values with frequent repeated assessments may be more valuable to assess the efficacy of treatment than any one singular value.

Recent studies have demonstrated the benefits of regional anesthesia and multimodal analgesia in reducing opioid consumption and enhancing recovery [10–14]. For example, enhanced recovery after surgery (ERAS) protocols emphasize opioid-sparing techniques, leading to improved patient outcomes. Comparative studies highlight the reliability of pain assessment scales and their role in guiding treatment strategies.

Challenges and Considerations

- *Opioid Crisis:* Balancing effective pain management with the risks of opioid dependence.
- *Patient Variability:* Individualized pain perception requires tailored interventions.
- *Resource Limitations:* Availability of regional anesthesia techniques and trained personnel can impact implementation.
- *Special Populations:* Managing pain in pediatric, geriatric, and cognitively impaired patients requires adapted strategies.

Case Studies or Clinical Scenarios

Case 1: Regional Anesthesia for Postoperative Pain

A 56-year-old man with a history of chronic knee and low back pain is scheduled to undergo total knee arthroplasty. The patient takes oxycodone once or twice a day as needed for his chronic pain. Preoperative pain on the NRS is 5/10. In order to reduce perioperative and postoperative pain requirements, the patient receives multimodal non-opioid medications preoperatively and a spinal anesthetic for his operation. In the recovery room, the patient reports 8/10 pain in his knee on the NRS. He receives a rescue adductor canal block with a long-acting local anesthetic and is prescribed a regimen of scheduled non-opioid multimodal analgesia along with a short course of PRN opioids. His pain scores remain low, and he requires minimal opioids postoperatively.

Case 2: Managing Pediatric Patients

An 8-year-old patient with scoliosis undergoes 10-level spinal scoliosis correction surgery. A combination of ketamine infusion and non-opioid multimodal analgesia is used preoperatively and intraoperatively to optimize pain control while minimizing opioid exposure. In the recovery room, the Wong-Baker FACES scale is used to assess the level of pain the child is experiencing. Continued scheduled use of NSAIDs, muscle relaxants, and low-dose opioids is used to manage the patient's pain.

Future Directions and Research

- Advancements in artificial intelligence for real-time pain assessment.
- The role of pharmacogenomics in personalized pain management.
- Novel non-opioid analgesics and their clinical applications.
- Integration of virtual reality and augmented reality for pain modulation.

Key Takeaways

1. Effective postoperative pain management improves recovery and reduces complications.
2. Multimodal analgesia is the gold standard for optimizing pain control while minimizing opioid use.
3. Standardized pain assessment tools help tailor pain management strategies.
4. Individualized patient care is essential, considering preoperative risk factors and surgical procedures.
5. Emerging research in AI, pharmacogenomics, and non-opioid therapies is shaping the future of pain management.

References

1. Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. PAIN Rep. 2017;2:e627.
2. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367:1618–25.
3. Kalkman JC, Visser K, Moen J, Bonsel JG, Grobbee ED, Moons MKG. Preoperative prediction of severe postoperative pain. Pain. 2003;105:415–23.
4. Gupta A, Kaur K, Sharma S, Goyal S, Arora S, Murthy RSR. Clinical aspects of acute post-operative pain management & its assessment. J Adv Pharm Technol Res. 2010;1:97–108.
5. Williamson A, Hoggart B. Pain: a review of three commonly used pain rating scales. J Clin Nurs. 2005;14:798–804.
6. Bijur PE, Silver W, Gallagher EJ. Reliability of the visual analog scale for measurement of acute pain. Acad Emerg Med. 2001;8:1153–7.
7. Shafshak TS, Elnemr R. The visual analogue scale versus numerical rating scale in measuring pain severity and predicting disability in low Back pain. JCR J Clin Rheumatol. 2021;27:282–5.
8. Bielewicz J, Daniluk B, Kamieniak P. VAS and NRS, same or different? Are visual analog scale values and

numerical rating scale equally viable tools for assessing patients after microdiscectomy? Pain Res Manag. 2022;2022:5337483.
9. Garra G, Singer AJ, Taira BR, et al. Validation of the Wong-Baker FACES pain rating scale in pediatric emergency department patients. Acad Emerg Med. 2010;17:50–4.
10. Pushpanathan E, Setty T, Carvalho B, Sultan P. A systematic review of postoperative pain outcome measurements utilised in regional anesthesia randomized controlled trials. Anesthesiol Res Pr. 2018;2018:9050239.
11. Karthikeyan VS, Sistla SC, Badhe AS, et al. Randomized controlled trial on the efficacy of bilateral superficial cervical plexus block in thyroidectomy. Pain Pract. 2013;13:539–46.
12. Richman JM, Liu SS, Courpas G, et al. Does continuous peripheral nerve block provide superior pain control to opioids? A meta-analysis. Anesth Analg. 2006;102:248–57.
13. Cheung CW, Wong SSC, Qiu Q, Wang X. Oral oxycodone for acute postoperative pain: a review of clinical trials. Pain Physician. 2017;20:SE33–52.
14. Tedesco D, Gori D, Desai KR, et al. Drug-free interventions to reduce pain or opioid consumption after total knee arthroplasty: a systematic review and meta-analysis. JAMA Surg. 2017;152:e172882–72.

10 Pharmacologic Management: Opioids and Non-opioids—Discussion of Use of Various Medications for Postsurgical Pain Relief

Marcos Izquierdo and Ying Ye

Introduction

The implications of adequate postoperative pain control are vast, ranging from optimized patient comfort and experience to the reduction of sympathetic stress and the risk of chronic postoperative pain [1]. The experience of pain after surgery is a common patient concern and can even exacerbate depression symptoms and lead to increased morbidity [2]. Opioid medications have been the mainstay of pain control since the use of morphine and opium in the post-Civil War era. They became the standard of care for perioperative analgesia when morphine was popularized in the 1900s [3]. However, the opioid pandemic in the early 2000s highlighted the need to balance non-opioid medications in an effort to reduce overall opioid consumption while continuing to optimize pain control.

M. Izquierdo (✉)
Department of Anesthesiology and Pain Management, MetroHealth Medical Center, Cleveland, OH, USA

Case Western Reserve University School of Medicine, Cleveland, OH, USA
e-mail: mizquierdo@metrohealth.org

Y. Ye
Anesthesiology, Perioperative and Pain Medicine Service, Veterans Affairs Palo Alto Health Care System, Palo Alto, CA, USA

Background

Management of postoperative pain starts with a proactive multimodal approach tailored specifically to the patient based on the type of surgery and anticipated pain severity [4]. Opioids are the focal point of pain management given their ability to prevent and treat severe pain along with their rapid onset and ease of administration. Opioid receptors can be found primarily in the central nervous system in the brain, brainstem, or spinal cord. The primary receptors are mu, kappa, and delta. Activation of these opioid receptors leads to nociception via one of three mechanisms: (1) inhibition of Ca^{2+} influx and reduction in substance P release, (2) hyperpolarizing the neurons of nociceptive pathways or (3) modulating the limbic system to alter the perception of painful stimuli [5].

The pharmacokinetic profile of each agent determines the effect observed in clinical practice. All opioids are highly soluble weak bases at physiologic pH that depend on reaching their target neuronal site to exert their desired effect. The clinical use of opioids is determined largely by potency, pKa, lipid solubility and protein binding. PKa correlates with the ratio of ionized to unionized molecules in the solution and thus with how quickly the substance will cross the blood-brain barrier (BBB). Similarly, a highly lipid-soluble opioid such as fentanyl can cross the BBB quickly despite its high pKa, allowing for a

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_10

quick onset of action. Additionally, there are unique adverse effects and metabolites that must be considered by clinicians. For example, morphine can cause significant histamine release, and its active metabolite, morphine-6-glutamate, can cause life-threatening respiratory depression in patients with renal disease. The choice of agent needs to consider the desired onset and duration of action, with special attention given to patient comorbidities and tolerance to opioids preoperatively [5].

Non-opioids can be used in conjunction with opioids in the postoperative phase. Such medications include acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), gabapentinoids, lidocaine, ketamine, skeletal muscle relaxants, and antidepressants. These drugs vary in terms of mechanism of action. Acetaminophen, also known as paracetamol, is one of the most used medications in the perioperative phase. Despite this, its mechanism of action is still not completely elucidated. In part, acetaminophen acts through inhibition of prostaglandin synthesis, thereby altering nociceptive processes in the descending serotoninergic pathways centrally [6, 7]. It is also postulated that acetaminophen produces analgesia peripherally through increasing activity of the endocannabinoid pathway [8]. NSAIDs work similarly to acetaminophen through inhibition of cyclooxygenase (COX) enzymes, specifically COX-1 and COX-2, leading to the inhibition of prostaglandin synthesis. NSAIDs can be categorized based on their selectivity of COX inhibition, with medications such as ibuprofen, aspirin, diclofenac, and naproxen being equally selective for COX-1 and COX-2 inhibition, and drugs such as meloxicam and celecoxib having higher selectivity for COX-2 inhibition [9]. Inhibition of COX-2 is primarily responsible for the analgesic effects of NSAIDs [9, 10]. Gabapentinoids, such as pregabalin and gabapentin, have also been used for postsurgical pain relief. The full mechanism of gabapentinoids is not fully elucidated. Gabapentin was designed to be a GABA (gamma-aminobutyric acid) analogue but has not been shown to bind to GABA receptors [11]. Instead, it is thought that gabapentin produces analgesia through binding to the auxiliary alpha-2-delta subunit of voltage-dependent calcium channels, thereby modulating excitability of neurons and inhibiting release of neurotransmitters involved in neuropathic pain [12, 13]. Gabapentin is also thought to play a role in inhibiting serotonergic facilitation and stimulating descending inhibition [14]. Pregabalin is structurally similar to gabapentin, with a similar mechanism of action in producing analgesia through binding of the alpha-2-delta subunit of voltage-dependent calcium channels [15, 16]. Intravenous lidocaine can be used for postoperative analgesia; studies suggest that lidocaine acts by blocking sodium, potassium and calcium channels in the dorsal root ganglion, reducing the excitability of neurons, thereby producing analgesia [17, 18]. Ketamine is a non-competitive N-methyl-D-aspartate (NMDA) and glutamate receptor antagonist [19]. Analgesic properties of ketamine also arises from ketamine's role as a partial mu-receptor agonist [20] and through inhibiting dopamine and serotonin uptake, thereby leading to an increase in the descending inhibitory serotoninergic pathway [19]. In conjunction with opioids, spasmolytic drugs such as cyclobenzaprine, baclofen, tizanidine, and methocarbamol can be used postoperatively to help with pain relief. Cyclobenzaprine, a skeletal muscle relaxant, acts as a serotonin-receptor antagonist that targets central descending serotonergic pathways in the spinal cord [21]. Baclofen is a presynaptic and postsynaptic GABA agonist and allows for decreased glutamic acid release and increased GABA inhibition. Tizanidine is an alpha-2-adrenergic agonist in the spinal cord and causes decreased spasticity through increased presynaptic inhibition. The mechanism of action of methocarbamol, another skeletal muscle relaxant, is not fully elucidated; it is thought that methocarbamol acts centrally on spinal interneurons and decreases polysynaptic reflexes and muscle contractility [22]. Other medications that can be used as adjuncts to opioids include antidepressants. Such medications include tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin-noradrenaline reuptake inhibitors (SNRIs) [23]. The mechanism by which these medications pro-

duce analgesia is not completely understood, though it is postulated that these medications can alter central levels of serotonin and noradrenaline and inhibit neuropathic pain [24].

Clinical Applications/Techniques

Ideally, the plan for pain control has been formulated and implemented by the time the patient is admitted to the recovery unit. However, it is very common for patients to experience breakthrough pain, with one report acknowledging that up to 30% of patients experience severe postoperative pain within the first 24 h [25]. Ultimately, the safe use of opioids as analgesics in the postoperative period depends on matching the needs and comorbidities of the patient with the pharmacokinetic profile of the medication. Considerations from the patient perspective include comorbidities (respiratory comorbidities, obstructive sleep apnea, coronary disease, opioid use history), concurrent medications (benzodiazepines and neuroleptics can potentiate the respiratory-depressant effects of opioids), and discharge planning [26].

All parenteral opioids should be titrated to the desired analgesic effect with continuous respiratory and cardiac monitoring. The availability of emergency equipment and personnel to intervene immediately in cases of respiratory depression is crucial for the safe administration of opioids [27]. Intravenous opioids are administered as either IV boluses or patient-controlled analgesics (PCAs). PCA has the benefits of providing patient autonomy, adapting to specific patient needs, fast onset of action, and improved patient satisfaction [28]. However, patients in the early phases of recovery often have yet to regain awareness to manage the PCA. Dosing recommendations are specific for opioid-naïve patients, and careful adjustments should be made for opioid-tolerant individuals. Morphine is the standard opioid to which all others are compared. Onset is slower due to its hydrophilic nature, with a peak effect at 20 min. Dosing is 1–3 mg every 5–10 min. Hydromorphone has a faster onset and shorter duration of action and is dosed in 0.2–0.5 mg increments every 5–10 min. Fentanyl is a highly potent synthetic opioid with a quick onset of <1 min. The duration of action of the initial bolus of 25–100 mcg can be as short as 30 min, so redosing with a longer-acting opioid may be needed. Meperidine is less commonly used due to concerns about its active metabolite, normeperidine, which exhibits excitatory effects that can cause tremors and seizures. Dosing starts at 25–50 mg and is typically given as a one-time dose for breakthrough pain [29].

Oral administration of analgesics provides a safe and effective mechanism for analgesia in patients who can tolerate po. Common oral formulations can also be combined with acetaminophen or ibuprofen to enhance the analgesic effects [29]. Compared with parental opioids, oxycodone and hydrocodone are frequently used oral opioids that have a much longer duration of action and can facilitate discharge from the recovery unit. Dosing is 5–10 mg every 4 h, with the dose adjusted based on patient age and kidney and renal function. Codeine is a weaker opioid that depends on hepatic conversion to morphine for its analgesic effect. The FDA issued a black box warning in 2012 to avoid its use in children following tonsillectomy due to its highly variable effect and risk of respiratory depression [30]. Tramadol is a weak opioid agonist that also exhibits serotonergic properties. It can be used at doses of 50–100 mg for mild to moderate pain or in patients at greater risk of respiratory complications.

Non-opioid medications for postoperative pain can be given either orally or intravenously. Standard dosing for acetaminophen, if not given pre-operatively or intraoperatively, ranges from 325 to 1000 mg for a one-time dose. A meta-analysis of randomized controlled trials performed in 2015 found no benefit in providing doses above 1 g of acetaminophen [31]. Some studies have found no benefit of intravenous acetaminophen to oral acetaminophen in controlling pain in the immediate postoperative period [32, 33]. Common NSAIDs given postoperatively include ketorolac, ibuprofen, and celecoxib. Generally, these medications are relatively contraindicated in patients with renal or cardiac disease, or those with gastrointestinal bleeding or

high risk for bleeding risk in the postoperating phase [34, 35]. Ketorolac can be given either orally or intravenously; oral dosing is generally 20 mg, and intravenous dosing ranges from 15 to 30 mg. Ibuprofen can be given either orally or intravenously as well, with dosing ranging from 200 to 800 mg. Oral celecoxib dosing ranges from 200 to 400 mg. While other medications such as gabapentinoids, lidocaine, ketamine, muscle relaxants, and antidepressants can also be used as non-opioid adjuncts, these are less commonly used in the immediate postoperative phase. While many studies support the use of non-opioid adjuncts, which combination of medications, optimal dose, and timing of administration have yet to be determined.

Evidence-Based Practices

The safe administration of perioperative opioids requires clinicians to balance patient comfort and a plethora of potential adverse effects. Acutely, one must monitor for hypoxic events while considering the fact that up to 3% of opioid-naïve patients may develop chronic opioid use >90 days [36]. The updated 2022 CDC guidelines on opioid therapy include the management of acute pain and reinforce the recommendation to minimize the dose and duration of opioid therapy to optimize analgesic effects while preventing unwanted side effects [37]. Nevertheless, untreated postoperative pain remains a pervasive problem, and opioids are the backbone of a multimodal approach to pain control [38].

Enhanced recovery after surgery (ERAS) protocols can differ across healthcare institutions and across different types of surgeries. However, the underlying principle of ERAS protocols share the same goal of reducing postoperative pain. These pathways can be split into pre-operative, intra-operative, and postoperative phases. In all phases, both opioid and non-opioid medications are recommended. Non-opioid adjuncts are used to reduce opioid requirements and, thereby, also reduce the risk of opioid-related side effects such as ileus, respiratory depression, pruritus and opioid-induced nausea and vomiting; however, opioids may still be required for controlling moderate to severe pain. In an ERAS protocol developed at the Stony Brook University Hospital, patients undergoing lumbar fusion surgeries received both PCA and 1500 mg methocarbamol in the PACU [39]. An ERAS protocol designed at the Massachusetts General Hospital for patients undergoing colorectal surgery includes the use of 15 mg of IV ketorolac, 100 mg of gabapentin and 1000 mg of oral acetaminophen in the PACU; in this pathway, narcotic use is to be minimized, and PCAs were not ordered in the immediate postoperative period [40]. Another example of an ERAS protocol involves the use of opioids, systemic acetaminophen and diclofenac after thoracic surgery [41]. Overall, ERAS protocols in the postoperative phase utilizes both opioids and non-opioid medications.

Case Studies/Clinical Scenarios

Case 1 A 38-year-old female with a past medical history significant for obesity (BMI of 35), obstructive sleep apnea (OSA) and history of postoperative nausea and vomiting (PONV) presents for a scheduled laparoscopic appendectomy. She has no history of opioid use and denies any drug use or smoking history; she drinks a glass of wine socially, every 3 months. How can her pain be managed in PACU?

Recommendations: For this opioid-naïve patient, special considerations to be given to her history of obesity, OSA and PONV when considering her postoperative pain medication regimen. In addition to pre-operative and intraoperative multimodal pain management including the use of regional nerve blocks, PACU medications should also involve both opioids and non-opioid medication adjuncts. Care should be taken to limit the amount of opioid medication to decrease risk of respiratory depression associated with opioids, as well as opioid-induced nausea. If she has not been given preoperative or intraoperative acetaminophen, she should be given 1000 mg of oral acetaminophen. She can also be given 30 mg of IV ketorolac as well. If her pain is still not well

tolerated, we would recommend trialing oral oxycodone 5 mg. Small amounts of IV fentanyl (25 mcg) can be given as needed to help with initial break-through pain; opioid use should be used judiciously due to the risk of opioid-related respiratory depression and nausea, especially in obese patients who are opioid-naïve and have history of OSA and PONV. If the patient does not tolerate oral medication, IV formulations can be used.

Case 2 A 65-year-old male with failed back syndrome who underwent total knee arthroplasty. His pain has been managed with a spinal cord stimulator, gabapentin, and oxycodone for breakthrough pain. The patient opted for a general anesthetic and now has severe pain in the PACU. How can his pain be addressed?

Recommendations: The patient has experienced chronic pain and is opioid tolerant. Tolerance to the analgesic effects can develop at a faster rate than tolerance to the respiratory depressant effect, leaving the patient vulnerable to pulmonary complications [42]. Titration of hydromorphone IV in 0.5 mg increments should occur with careful monitoring of the patient's respiratory status. Assuming that nonopioid options are exhausted, intravenous opioids should be used as a bridge to a regional block, such as an adductor canal or pericapsular nerve group (PENG) block. As the patient recovers, the patient can transition to oral oxycodone 5–10 mg or a PCA with hydromorphone.

Future Directions/Research

There remains much to explore and understand about acute postoperative pain management. Mechanisms of non-opioid adjuncts such as acetaminophen and gabapentinoids are still not completely understood. New medications such as oliceridine [43] and new formularies of existing medications such as sublingual sufentanil [44] and intravenous oxycodone [45] are also being developed, which can impact postoperative pain management. There is growing interest in how genetics can affect predisposition and sensitivity to acute postoperative pain and how genetic differences can affect the pharmacokinetics and pharmacodynamics of opioid and non-opioid medications [46]. Advances in pharmacogenetic testing may lead to customized postoperative pain management regimens [47]. In addition to using pharmacogenetics to develop more tailored pain management recommendations, future studies can also be done to optimize ERAS protocols through investigation of optimal regimen, timing, and doses for opioid and non-opioid medications in the acute postoperative phase.

Key Takeaways

- Opioids remain the mainstay for perioperative pain management.
- Patient comorbidities and medication profiles are critical considerations in medication selection.
- Non-opioid analgesics are important adjuncts to reduce perioperative opioid requirements.
- Non-opioid analgesics can have unique side effects which may preclude its use in certain patient populations.
- Enhanced Recovery After Surgery programs can be implemented for efficient and effective use of perioperative analgesics at a systems-level.

References

1. Ishida Y, Okada T, Kobayashi T, Funatsu K, Uchino H. Pain Management of Acute and Chronic Postoperative Pain. Cureus. 2022;14(4):e23999. https://doi.org/10.7759/cureus.23999. PMID: 35547410; PMCID: PMC9086530 Ghoneim, M.M., O'Hara, M.W.
2. Ghoneim MM, O'Hara MW. Depression and postoperative complications: an overview. BMC Surg. 2016;(16):5. https://doi.org/10.1186/s12893-016-0120-y. PMID: 26830195; PMCID: PMC4736276
3. Schmitt K. A brief history of opioids in the U.S. Hopkins Bloomberg. Public Health. 2023;
4. Freye E, Levy JV. Mechanism of action of opioids and clinical effects. In: Opioids in Medicine; 2008.

p. 85–187. https://doi.org/10.1007/978-1-4020-5947-6_2. PMCID: PMC7122075.
5. Schumacher M, Fukuda K. Opioids. In: Miller's Anesthesia. 9th ed. Elsevier; 2020.
6. Oscier CD, Milner QJW. Peri-operative use of paracetamol. Anaesthesia. 2009;64:65–72. https://doi.org/10.1111/j.1365-2044.2008.05674.x.
7. Jóźwiak-Bebenista M, Nowak JZ. Paracetamol: mechanism of action, applications and safety concern. Acta Pol Pharm. 2014;71:11–23.
8. Mallet C, Barrière DA, Ermund A, Jönsson BAG, Eschalier A, Zygmunt PM, et al. TRPV1 in brain is involved in acetaminophen-induced Antinociception. PLoS One. 2010;5:e12748. https://doi.org/10.1371/journal.pone.0012748.
9. Bindu S, Mazumder S, Bandyopadhyay U. Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: a current perspective. Biochem Pharmacol. 2020;180:114147. https://doi.org/10.1016/j.bcp.2020.114147.
10. Cashman JN. The mechanisms of action of NSAIDs in analgesia. Drugs. 1996;52(Suppl 5):13–23. https://doi.org/10.2165/00003495-199600525-00004.
11. Suman-Chauhan N, Webdale L, Hill DR, Woodruff GN. Characterisation of [3H]gabapentin binding to a novel site in rat brain: homogenate binding studies. Eur J Pharmacol Mol Pharmacol. 1993;244:293–301. https://doi.org/10.1016/0922-4106(93)90155-3.
12. Zhou C, Luo ZD. Electrophysiological characterization of spinal neuron sensitization by elevated calcium channel alpha-2-delta-1 subunit protein. Eur J Pain Lond Engl. 2014;18:649–58. https://doi.org/10.1002/j.1532-2149.2013.00416.x.
13. Maneuf YP, Luo ZD, Lee K. α2δ and the mechanism of action of gabapentin in the treatment of pain. Semin Cell Dev Biol. 2006;17:565–70. https://doi.org/10.1016/j.semcdb.2006.09.003.
14. Chincholkar M. Analgesic mechanisms of gabapentinoids and effects in experimental pain models: a narrative review. Br J Anaesth. 2018;120:1315–34. https://doi.org/10.1016/j.bja.2018.02.066.
15. Sills GJ. The mechanisms of action of gabapentin and pregabalin. Curr Opin Pharmacol. 2006;6:108–13. https://doi.org/10.1016/j.coph.2005.11.003.
16. Chincholkar M. Gabapentinoids: pharmacokinetics, pharmacodynamics and considerations for clinical practice. Br J Pain. 2020;14:104–14. https://doi.org/10.1177/2049463720912496.
17. Scholz A. Mechanisms of (local) anaesthetics on voltage-gated sodium and other ion channels. Br J Anaesth. 2002;89:52–61. https://doi.org/10.1093/bja/aef163.
18. van der Wal SEI, van den Heuvel SAS, Radema SA, van Berkum BFM, Vaneker M, Steegers MAH, et al. The in vitro mechanisms and in vivo efficacy of intravenous lidocaine on the neuroinflammatory response in acute and chronic pain. Eur J Pain. 2016;20:655–74. https://doi.org/10.1002/ejp.794.
19. Mion G, Villevieille T. Ketamine pharmacology: an update (pharmacodynamics and molecular aspects, recent findings). CNS Neurosci Ther. 2013;19:370–80. https://doi.org/10.1111/cns.12099.
20. Peltoniemi MA, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: a review of clinical pharmacokinetics and pharmacodynamics in anesthesia and pain therapy. Clin Pharmacokinet. 2016;55:1059–77. https://doi.org/10.1007/s40262-016-0383-6.
21. Kobayashi H, Hasegawa Y, Ono H. Cyclobenzaprine, a centrally acting muscle relaxant, acts on descending serotonergic systems. Eur J Pharmacol. 1996;311:29–35. https://doi.org/10.1016/0014-2999(96)00402-5.
22. Zhang Y, Otto P, Qin L, Eiber N, Hashemolhosseini S, Kröger S, et al. Methocarbamol blocks muscular Nav1.4 channels and decreases isometric force of mouse muscles. Muscle Nerve. 2021;63:141–50. https://doi.org/10.1002/mus.27087.
23. Bonilla-Jaime H, Sánchez-Salcedo JA, Estevez-Cabrera MM, Molina-Jiménez T, Cortes-Altamirano JL, Alfaro-Rodríguez A. Depression and pain: use of antidepressants. Curr Neuropharmacol. 2022;20:384–402. https://doi.org/10.2174/1570159X19666210609161447.
24. Obata H. Analgesic mechanisms of antidepressants for neuropathic pain. Int J Mol Sci. 2017;18:2483. https://doi.org/10.3390/ijms18112483.
25. Small C, Laycock H. Acute postoperative pain management. Br J Surg. 2020;107(2):e70–80. https://doi.org/10.1002/bjs.11477.
26. Shafi S, Collinsworth AW, Copeland LA, Ogola GO, Qiu T, Kouznetsova M, et al. Association of opioid-related adverse drug events with clinical and cost outcomes among surgical patients in a large integrated health care delivery system. JAMA Surg. 2018;153:757–63.
27. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on acute pain management. Anesthesiology. 2012;116(2):248–73. https://doi.org/10.1097/ALN.0b013e31823c1030.
28. Motamed C, Spencer A, Farhat F, Bourgain JL, Lasser P, Jayr C. Postoperative hypoxaemia: continuous extradural infusion of bupivacaine and morphine vs patient-controlled analgesia with intravenous morphine. Br J Anaesth. 1998;80:742–7. https://doi.org/10.1093/bja/80.6.742.
29. Sinatra RS, McQuay H. Oral and parenteral opioid analgesics for acute pain management. In: Acute pain management. Cambridge: Cambridge University Press; 2009. p. 188–203.
30. Food and Drug Administration. Safety review update of codeine use in children; new boxed warning and contraindication on use after tonsillectomy and/or adenoidectomy. 2013. Available at: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM339116.pdf. Accessed 1 Apr 2017.
31. De Oliveira GSJ, Castro-Alves LJ, McCarthy RJ. Single-dose systemic acetaminophen to prevent

postoperative pain: a meta-analysis of randomized controlled trials. Clin J Pain. 2015;31:86. https://doi.org/10.1097/AJP.0000000000000081.
32. Hickman SR, Mathieson KM, Bradford LM, Garman CD, Gregg RW, Lukens DW. Randomized trial of oral versus intravenous acetaminophen for postoperative pain control. Am J Health-Syst Pharm AJHP Off J Am Soc Health-Syst Pharm. 2018;75:367–75. https://doi.org/10.2146/ajhp170064.
33. Kor TM, Naranjo J, Deljou A, Evans KD, Schroeder D, Sprung J, et al. Intravenous versus oral acetaminophen in outpatient cystoscopy procedures: retrospective comparison of postoperative opioid requirements and analgesia scores. Am Surg. 2020;86:1691–6. https://doi.org/10.1177/0003134820945204.
34. Weisman S. Naproxen for postoperative pain. J Pharm Pharm Sci. 2021;24:62–70. https://doi.org/10.18433/jpps31629.
35. Abraham NS, Hlatky MA, Antman EM, Bhatt DL, Bjorkman DJ, Clark CB, et al. ACCF/ACG/AHA 2010 expert consensus document on the concomitant use of proton pump inhibitors and thienopyridines: a focused update of the ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use: a report of the American College of Cardiology Foundation task force on expert consensus documents. Circulation. 2010;122:2619–33. https://doi.org/10.1161/CIR.0b013e318202f701.
36. Vetter TR, Kain ZN. Role of the perioperative surgical home in optimizing the perioperative use of opioids. Anesth Analg. 2017;125(5):1653–7. https://doi.org/10.1213/ANE.0000000000002280.
37. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain—United States, 2022. MMWR Recomm Rep. 2022;71:1–95.
38. Cheung CK, Adeola JO, Beutler SS, Urman RD. Postoperative pain Management in Enhanced Recovery Pathways. J Pain Res. 2022;15:123–35. https://doi.org/10.2147/JPR.S231774. PMID: 35058714; PMCID: PMC8765537.
39. Smith J, Probst S, Calandra C, Davis R, Sugimoto K, Nie L, et al. Enhanced recovery after surgery (ERAS) program for lumbar spine fusion. Perioper Med. 2019;8:4. https://doi.org/10.1186/s13741-019-0114-2.
40. Cavallaro P, Bordeianou L. Implementation of an ERAS pathway in colorectal surgery. Clin Colon Rectal Surg. 2019;32:102–8. https://doi.org/10.1055/s-0038-1676474.
41. Ashok A, Niyogi D, Ranganathan P, Tandon S, Bhaskar M, Karimundackal G, et al. The enhanced recovery after surgery (ERAS) protocol to promote recovery following esophageal cancer resection. Surg Today. 2020;50:323–34. https://doi.org/10.1007/s00595-020-01956-1.
42. Algera MH, Olofsen E, Moss L, Dobbins RL, Niesters M, van Velzen M, Groeneveld GJ, Heuberger J, Laffont CM, Dahan A. Tolerance to opioid-induced respiratory depression in chronic high-dose opioid users: a model-based comparison with opioid-naïve individuals. Clin Pharmacol Ther. 2021;109(3):637–45. https://doi.org/10.1002/cpt.2027. Epub 2020 Oct 5. PMID: 32865832; PMCID: PMC7983936.
43. Goudra B. Oliceridine- opioid of the 21st century. Saudi J Anaesth. 2022;16:69–75. https://doi.org/10.4103/sja.sja_510_21.
44. Reardon CE, Kane-Gill SL, Smithburger PL, Dasta JF. Sufentanil sublingual tablet: a new option for acute pain management. Ann Pharmacother. 2019;53:1220–6. https://doi.org/10.1177/1060028019863144.
45. Pergolizzi JV, Seow-Choen F, Wexner SD, Zampogna G, Raffa RB, Taylor R. Perspectives on intravenous oxycodone for control of postoperative pain. Pain Pract Off J World Inst Pain. 2016;16:924–34. https://doi.org/10.1111/papr.12345.
46. Slepukhina MA, Ivashchenko DV, Sheina MA, Muradian AA, Blagovestnov DA, Sychev DA. Pain pharmacogenetics. Drug Metab Pers Ther. 2020;35 https://doi.org/10.1515/dmpt-2020-2939.
47. Palada V, Kaunisto MA, Kalso E. Genetics and genomics in postoperative pain and analgesia. Curr Opin Anaesthesiol. 2018;31:569–74. https://doi.org/10.1097/ACO.0000000000000633.

11 Regional Analgesia Techniques: Details the Application of Regional Analgesia in Postoperative Pain Management

Justin Jones, Taleb Husein, Nicolas Mario Mas D. Alessandro, and Hesham Elsharkawy

Introduction

Postoperatively, patients experience acute pain as a consequence of surgical procedures. This pain results from a combination of physiological responses and subjective perceptions. Acute, uncontrolled pain can progress to chronic pain, impacting patients physiologically, socially, and economically. It often results in prolonged hospital stays, increased long-term use of pain medications, and the necessity for future medical interventions. Chronic postoperative pain refers to localized surgical site pain that persists for at least 3 months after surgery [1].

Effective pain management is essential for enhanced recovery after surgery (ERAS). Multimodal analgesia, a widely accepted approach, provides balanced perioperative pain management, with regional anesthesia playing a crucial role within this framework [2, 3].

In this chapter, we will review regional analgesia techniques. We will discuss recent advancements, future directions, and exploring both traditional and novel nerve blocks. Additionally, we will highlight the challenges and considerations that pain specialists must take into account.

Background and Current Understanding

Regional anesthesia techniques are vital for effective perioperative pain management, as they block nerve transmission with local anesthetics to prevent pain. This targeted approach enhances recovery and minimizes systemic side effects of surgery [4–6].

Advancements in ultrasound technology have improved regional anesthesia by allowing direct visualization of nerves, enhancing needle placement accuracy, and reducing complications. Techniques like ultrasound-guided fascial plane blocks offer effective alternatives to traditional methods such as thoracic epidurals, especially in breast and thoracic surgeries [5, 6].

These blocks primarily achieve pain relief by blocking sensory nerve transmission within fascial planes and peripheral nociceptors. While some systemic absorption of local anesthetics may occur, it is not the main contributor to analgesia. The use of adjuncts like dexamethasone

J. Jones (✉) · Nicolas Mario Mas D. Alessandro · H. Elsharkawy
Department of Anesthesiology, Case Western Reserve Metrohealth Medical Center, Cleveland, OH, USA

T. Husein
Department of Multi-Specialty Anaesthesiology, Cleveland Clinic Foundation, Cleveland, OH, USA

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_11

and liposomal bupivacaine can further enhance block efficacy and duration [7, 8].

Implementing acute pain services that integrate these advanced regional techniques is essential for improving multimodal pain management, fostering collaboration among specialists, and optimizing patient outcomes.

Regional Techniques

Interscalene

The interscalene block is a regional anesthesia technique for shoulder and upper arm surgeries. It targets the C5–C7 roots of the brachial plexus in the interscalene groove.

On ultrasound, the C5–C7 roots appear as round, hypoechoic structures, distinguishable from distal honeycomb patterns. Key landmarks include the "stoplight sign" (aligned C5, upper C6, and lower C6 fascicles) and the C7 transverse process with its small anterior tubercle. The long thoracic and dorsal scapular nerves can also be visualized within the middle scalene muscle. The procedure involves identifying the interscalene groove at the C6 level using a high-frequency transducer and tracing the plexus cephalad from the supraclavicular region. Injection of local anesthetic under ultrasound guidance ensures optimal spread while minimizing risks to adjacent structures like vessels and the pleura [9, 10].

While effective for analgesia, potential complications include phrenic nerve paralysis, pneumothorax, intrathecal injection, and Horner's syndrome, making patient selection critical [11].

Supraclavicular

The brachial plexus consists of five roots originating from the ventral divisions of C5 to T1, situated between the anterior and middle scalene muscles. The anterior scalene originates from the anterior tubercles of the transverse processes of C3–C6 and inserts on the first rib's scalene tubercle, while the middle scalene arises from the posterior tubercles of the transverse processes of C2–C7 and inserts on the first rib. These roots converge to form three trunks, upper, middle, and lower, within the triangular interscalene groove, which widens as the muscles approach their insertion on the first rib. The subclavian artery runs anterior to the lower trunk of the plexus.

During a supraclavicular block, there is a risk of pleural injury at the pleural dome and the first intercostal space. The pleural dome, located medial to the anterior scalene muscle, is the apex of the parietal pleura defined by the first rib. In contrast, the first intercostal space is primarily infraclavicular and should not be accessed during proper block administration.

The supraclavicular block targets the brachial plexus at the nerve trunks and divisions, providing analgesia from the mid-humerus to the hand. Ultrasound is used to visualize the plexus above the clavicle. Potential complications include pneumothorax, phrenic nerve paralysis, Horner's syndrome, and laryngeal nerve paralysis [12].

Infraclavicular

The procedure starts with finding the arterial pulse on the ultrasound, which acts as a key reference point. Although the deep location of the brachial plexus makes visualizing the needle and nearby anatomy more difficult. However, carefully injecting local anesthetic in a U-shape around the axillary artery can still achieve effective pain relief.

Anatomically, the axillary artery is positioned beneath the pectoralis major and minor muscles, making it essential to obtain clear images of both muscles and their respective fascia. The three cords of the brachial plexus—the lateral, posterior, and medial cords—are typically located around the axillary artery, though their visualization may vary due to anatomical differences among patients. The ultrasound transducer is adjusted to view the axillary artery in cross-section, which usually occurs at depths of 3–5 cm in average-sized individuals. Successful identification of these structures allows for precise targeting of the brachial plexus during the block procedure.

Clinically, the infraclavicular brachial plexus block is effective for providing anesthesia to the upper limb below the shoulder. For patients requiring analgesia on the medial aspect of the upper arm, a supplemental subcutaneous injection

can be administered. This approach is advantageous as it reduces the risk of complications such as phrenic nerve paralysis and pneumothorax, which are more common with nerve blocks performed above the clavicle. Overall, the infraclavicular nerve block is an essential technique for delivering analgesia from the elbow to the hand, making it a valuable option in both surgical and postoperative settings [13].

Axillary

The axillary brachial plexus block is a straightforward procedure with a lower risk of complications compared to interscalene and supraclavicular blocks, making it ideal in cases where access to the upper brachial plexus is limited due to infection or venous catheters. Local anesthetic around the axillary artery usually provides effective anesthesia, even without individual nerve identification.

Ultrasound imaging is crucial for accurately locating the axillary artery and surrounding nerves. The median nerve is positioned lateral and superficial to the artery, the ulnar nerve is medial and superficial, and the radial nerve is posterior to the artery. The musculocutaneous nerve is typically found between the biceps and coracobrachialis muscles. During the procedure, the arm is positioned at a 90-degree angle to facilitate transducer placement. After identifying the axillary artery and nerves, local anesthetic is injected around the artery, often requiring multiple injections for comprehensive coverage. Continuous ultrasound-guided blocks can enhance analgesia through catheter placement near the brachial plexus branches. Proper technique and monitoring are essential to minimize complications such as intravascular injection [14].

Femoral Nerve Block

The femoral nerve block is an effective anesthetic technique for surgeries involving the anterior thigh and superficial procedures on the medial leg, such as quadriceps tendon repairs and postoperative pain management following femur and knee surgeries. This technique not only provides immediate pain relief but also enhances overall pain management when performed continuously, significantly reducing opioid consumption and improving analgesia compared to traditional parenteral methods.

Anatomically, the femoral nerve originates from the lumbar plexus (L2–L4) and travels beneath the fascia iliaca, entering the thigh just below the inguinal ligament, positioned laterally to the femoral artery. It then divides into anterior and posterior branches, which innervate key muscles and provide sensory input to the anterior and medial thigh. Understanding the precise location of the femoral nerve is essential for effective block placement, as improper technique can lead to quadriceps weakness, increasing the risk of falls.

Utilizing ultrasound guidance for the femoral nerve block significantly enhances precision, allowing clinicians to visualize the spread of local anesthetic and adjust needle placement as necessary. This approach reduces the risk of complications, such as puncturing the femoral artery. While nerve stimulation can offer additional safety insights regarding the needle-nerve relationship, it is not strictly necessary for a successful block. The procedure begins by locating the femoral artery at the femoral crease, with adjustments made to isolate the artery and visualize the femoral nerve, which appears as a hyperechoic, triangular or oval structure at a depth of 2–4 cm. Proper transducer management, including slight tilting and optimal pressure application, is crucial to avoid collapsing adjacent veins while ensuring effective local anesthetic distribution. A successful block will anesthetize the anterior and medial thigh down to the knee, extending to a variable strip of skin on the medial leg and foot, affecting the hip, knee, and ankle joints [15].

Adductor Canal Nerve Block

The sartorius muscle runs diagonally across the anterior thigh, forming a "roof" over the adductor canal, which is bordered laterally by the vastus medialis and medially by the adductor longus or magnus. The saphenous nerve appears as a small, hyperechoic structure anterior to the femoral artery and is accompanied by the femoral vein, typically visualized at a depth of 2–3 cm.

The adductor canal block targets the saphenous nerve to provide analgesia for knee and medial lower leg surgeries, performed at the mid-thigh level. This technique offers effective pain relief while minimizing motor block, allowing for improved ambulation postoperatively.

Anatomically, the saphenous nerve pierces the fascia lata between the sartorius and gracilis tendons above the knee, running closely alongside the femoral artery and other vessels. Below the knee, it travels adjacent to the great saphenous vein. While primarily a sensory block, injecting a large volume of local anesthetic into the subsartorial space can also affect motor function in the vastus medialis, necessitating caution regarding patient ambulation following the procedure [16].

Sciatic Nerve Block at the Popliteal Fossa

The sciatic nerve block is an effective anesthetic method for managing pain in the posterior thigh and lower leg. The procedure begins with the ultrasound transducer positioned transversely at the popliteal crease to locate the popliteal artery, typically at a depth of 3–4 cm. The accompanying popliteal vein is positioned just superficial to the artery, while the biceps femoris muscle is lateral and the semimembranosus and semitendinosus muscles are medial.

The tibial nerve appears as a hyperechoic, oval structure located superficial and lateral to the vein. Visualizing the nerve can be aided by instructing the patient to dorsiflex and plantarflex their ankle, which helps differentiate the sciatic nerve branches. The common peroneal nerve (CPN) is found slightly more superficial and lateral to the tibial nerve. As the transducer is moved proximally, adjustments in depth and angle are essential to keep the sciatic nerve visible, typically located at a depth of 2–4 cm.

The block provides anesthesia to the posterior thigh and lower leg, excluding a small medial strip innervated by the saphenous nerve. It specifically targets the tibial and peroneal branches of the sciatic nerve, with various approaches available, including transgluteal, subgluteal, anterior thigh, and popliteal fossa methods. Clinicians must be cautious of potential motor block effects, such as foot drop, which increase fall risk [17].

Obturator Nerve Block

The obturator nerve block is used to provide analgesia for surgeries involving the hip and knee, as well as during transurethral resections of bladder tumors to prevent contraction of the adductor muscles that places the patient at risk of bladder rupture [18]. The proximal approach identifies the obturator nerve between the pectineus muscle and the obturator externus muscle. The proximal approach requires only one injection. In the distal approach, the transducer is placed in the inguinal crease and identifying the anterior branch between the pectineus and adductor brevis muscle. Then the posterior branch is identified in the plane of adductor brevis and adductor magnus muscles.

Fascial Plane Blocks

Pectoral Nerve Block

Pectoral nerve blocks, commonly referred to as PECS 1 and 2, target the medial pectoral nerve, lateral pectoral nerve, and long thoracic nerve. The local anesthesia is deposited between the pectoralis major and pectoralis minor above the third or fourth rib. The PEC 2 block consists of depositing local anesthetic between the pectoralis minor and serratus anterior muscle. The PEC 2 block is used for breast surgeries, placement of cardiac pacemakers, defibrillators, or other anterior chest wall surgeries [19].

Erector Spinae Plane Block

Erector spinae plane (ESP) blocks are gaining prominence for providing regional analgesia across various surgical procedures in the thoracic and abdominal regions. This paraspinal fascial plane block involves depositing local anesthesia between the erector spinae muscles and the transverse processes of the vertebrae, allowing the anesthetic to spread to spinal nerve roots. The evidence supporting ESP blocks is mixed, with indications inconsistent and many based on clini-

cal experience. While some studies reported reduced pain scores and lower opioid consumption after colorectal surgeries and lumbar spine surgery [20, 21] there are other case reports that describe its use in various other surgical procedures [22]. There is also literature suggesting that this block does not improve pain management [23]. Future research should focus on refining techniques, dosages, and comparisons with other analgesic approaches and truncal blocks [24].

Serratus Anterior Plane Block

The serratus anterior block uses ultrasound guidance to deposit local anesthesia between the serratus anterior muscle and the latissimus dorsi, or instead between the serratus anterior muscle and external intercostal muscle. This block targets lateral cutaneous thoracic intercostal nerves to numb the thorax and is used for patients who have anterolateral rib fractures, breast surgeries, and thoracotomies. Pneumothorax is a risk of the serratus anterior block [25].

Transversus Abdominus Plane Block

The transversus abdominal plane block is an ultrasound-guided block where local anesthesic is deposited between the transversus abdominis and internal oblique muscles of the abdomen that target the anterior rami of spinal nerves T6–L1. The block can be done unilaterally or bilaterally. Perforation of abdominal contents may occur when completing this block. The block is used to provide pain relief after abdominal surgeries [25].

External Oblique Intercostal Plane

The external oblique intercostal plane block is a novel block that targets the anterior and lateral cutaneous branches of the T7–T9 intercostal nerves. The block is performed under ultrasound guidance at the sixth rib at the anterior axillary line, and local anesthesia is deposited between the external oblique and intercostal muscles. The block is indicated to cover upper lateral abdominal incisions [26].

Quadratus Lumborum Nerve Block

The quadratus lumborum (QL) is an ultrasound-guided block used for analgesia after abdominal and pelvic surgeries. There are several variations of the QL block with different nomenclature based on where the needle is located during local anesthesia injection, such as lateral/QL1, posterior/QL2, and anterior/QL3 [21]. The local anesthetic spreads along the thoracolumbar fascia, which contains mechanoreceptors, nociceptors, and sympathetic nerve fibers [27].

Rhomboid Intercostal Plane Block

The rhomboid intercostal plane block provides analgesia for thoracic surgeries. The injection occurs between the rhomboid muscle and intercostal muscles medial to the scapula at the T6 and T7 ribs [8].

Clavipectoral Fascial Plane Block

The clavipectoral fascial plan block is an ultrasound-guided nerve block to provide analgesia to the clavicle. Indications are for clavicle fractures and surgery. The needle tip is placed between the clavipectoral fascia and the ostium of the clavicle, and local anesthesia is deposited [28, 29]. While the indications of this block are somewhat unclear, randomized controlled trials (RCTs) and case reports support that this intervention can reduce pain, decrease opioid consumption, and promote early mobilization in surgeries such as breast procedures, thoracotomies, and rib fractures.

Epidural

Epidural anesthesia is primarily used as an adjunct to general anesthesia (GA) in thoracic surgeries, especially for postoperative pain management. It may enhance analgesia and reduce the need for opioids, but its use carries risks such as intraoperative hypotension and bradycardia. The effectiveness of timing for initiating epidural analgesia—whether intraoperatively or postoperatively—remains debated. A sensory level from

T1–T10 is generally adequate for thoracotomy procedures.

For breast surgeries, a mid- to upper thoracic epidural can improve postoperative outcomes, including pain relief and reduced nausea. Sensory levels vary based on the procedure: T1–T7 for breast augmentation and C5–L1 for mastectomy with TRAM flap reconstruction.

Epidural anesthesia can also be beneficial in upper abdominal surgeries, such as esophagectomy and gastrectomy, improving pain control and reducing pulmonary complications. For supragingival vascular procedures, a mid-thoracic epidural enhances pain management while allowing for better hemodynamic stability. In urology, neuraxial anesthesia can be used for prostatectomy and nephrectomy, offering advantages like reduced blood loss and improved recovery.

Overall, epidural anesthesia is a versatile tool that can significantly enhance postoperative recovery across various surgical disciplines when used appropriately.

Adjuncts to Nerve Blocks

Dexamethasone

Dexamethasone is a corticosteroid used to treat inflammation. When added to local anesthesia, multiple studies have shown that dexamethasone prolongs the sensory block for an average of 6 h [8]. Additionally, dexamethasone may prolong the duration of analgesia when administered systemically. Although dexamethasone increases serum glucose [30].

Dexmedetomidine

Dexmedetomidine is an alpha 2 adrenergic agonist thought to have an effect centrally and on peripheral nerves. Studies report single-shot blocks can be extended by 4–5 h by the addition of it. The side effects are bradycardia and hypotension [30].

Clonidine

Clonidine is an alpha-adrenergic agonist that can prolong blocks for 2 h. Side effects are bradycardia and hypotension [30].

Buprenorphine

Buprenorphine is a partial opioid agonist reported to have local anesthesia activity. Studies report that when added to local anesthesia, it can prolong a single-shot nerve block for 8 h. Side effects are nausea and vomiting [30].

Epinephrine

Epinephrine is one of the oldest and most widely used adjuncts for peripheral nerve blocks. It is thought that the vasoconstriction helps the local anesthesia stay around the nerve and prevents absorption by systemic circulation. It also can indicate if the injection of the local mixture is intravascular. There are reports that the vasoconstriction caused by epinephrine may be neurotoxic [31].

Sodium Bicarbonate

Sodium bicarbonate has been added to nerve blocks to decrease the time of onset and pain on injection. Bicarbonate may reduce the time to neuraxial onset, however, not when added to peripheral nerve block solutions [31].

Liposomal Bupivacaine

Bupivacaine is a long-acting amide local anesthetic used in peripheral nerve blocks. In 2011, a formulation of liposomal encapsulated bupivacaine was approved by the FDA for injection into surgical incisions then expanded to peripheral nerve blocks [32]. The lipid encapsulation is thought to delay the release of bupivacaine and increase the duration of the block. This long-acting formulation is a possible alternative to nerve catheters [33]. Recent studies are showing that liposomal bupivacaine does not provide the long-lasting analgesic effect compared to non-liposomal encapsulated bupivacaine [32].

Evidence-Based Practices

There has long been a debate about the benefits of regional anesthesia versus general anesthesia. However, the argument often rests on the patient and what procedure they are undergoing. The use of ultrasound has increased the safety and efficacy of regional anesthesia over the past decades.

Hospital Discharge

The use of regional anesthesia has been shown to reduce hospital discharge time [34]. The same study reported a decreased mortality with regional anesthesia compared to general anesthesia [34].

Hospital Mortality

Two Cochrane reviews indicated that the use of epidural anesthesia after abdominal surgery reduced the risk of postoperative mechanical ventilation, myocardial infarction, and renal complications [35, 36]. However, employing epidurals in cardiac surgery did not reduce stroke, myocardial infarction, or mortality [37]. Additionally, employing spinal anesthesia in elderly patients undergoing hip surgery reduced mortality when compared to general anesthesia [38].

Cost of Regional vs. General Anesthesia Ambulatory Setting

Ambulatory surgery patients are frequently healthier than patients requiring postoperative admissions. A systematic review showed that regional anesthesia cost less than general anesthesia for multiple ambulatory surgeries [39] Patients who received regional anesthesia had a reduced cost partially due to bypassing phase 1 of recovery and shorter post anesthesia care unit stays [39, 40].

Pulmonary Disease

A study comparing epidural, spinal, and peripheral nerve blocks found decreased postoperative pulmonary complications [41]. Interestingly, when epidural was compared to general anesthesia, there were not improved outcomes [41]. Another study found that using regional anesthesia in elderly patients undergoing hip surgery decreased postoperative pulmonary complications such as infection and the need for mechanical ventilation [42].

Prevention of Chronic Postoperative Pain

A Cochrane review looked at multiple surgeries and pain 6–12 months after surgery and found that a paravertebral block compared to general anesthesia may prevent chronic pain in thoracotomies and breast surgeries [43]. There has not been a significant study yet showing that regional anesthesia can prevent the occurrence of phantom limb pain.

Reduced Opioid Use

Regional anesthesia can reduce opioid use when considering the location of the surgery and patient demographics. Metanalysis of multiple diverse surgeries found that pain treated with a continuous peripheral nerve catheter reduced opioid requirements and increased patient satisfaction when compared to treating with opioids alone [41].

Patient Satisfaction

For upper extremity surgery, one study reported greater patient satisfaction with regional anesthesia compared to general anesthesia [44]. Although, another study looking at upper extremity surgery reported patients had more satisfaction with general anesthesia compared to regional anesthesia [43]. A large review of an international registry looking at multiple surgeries reported that they would undergo a repeat nerve block [45]. Patient preoperative education may help relieve some patient anxiety and provide an opportunity to inform them of the benefits of regional anesthesia [37].

Regional Compared to Other Forms of Analgesia

Benefits of regional anesthesia compared to systemic medications are that a nerve block can last hours. Systemic medication needs to be dosed hourly and may require the patient contacting a nurse or doctor. Local anesthesia has fewer systemic side effects.

The benefits for regional anesthesia over general anesthesia likely involve multiple surgical and patient factors. When determining what regional anesthesia technique to use, doctors should consider the current best available evidence regarding surgery and the patient. Patient comorbidities may also limit which regional anesthesia technique we can use. For example, an anticoagulated patient with recent cardiac stents may not be the ideal epidural candidate [7].

Side Effects and Complications to Peripheral Nerve Blocks and Catheters

- *Inadvertent Catheter Removal*: Inadvertent catheter removal occurs in 1% of cases with popliteal catheters secured by tunneling and in 1.4% of femoral catheters secured with adhesive strips or transparent dressings. Suturing catheters has been shown to reduce premature removal rates. The use of 2-octyl cyanoacrylate (Dermabond®) can safely secure catheters but may complicate their removal. Effective techniques for securing peripheral nerve catheters (PNCs) have decreased the risks of inadvertent removal, with a reported 1% incidence for ambulatory interscalene catheters using skin sealant and locking devices.
- *Catheter Kinking, Knotting, and Looping*: Complications related to catheter placement are rare; however, it is recommended to advance catheters 3–10 cm beyond the needle tip to minimize risks. In cases of knotted catheters, fluoroscopy-guided retrieval may be necessary. Case reports have indicated that difficulties with catheter removal can arise, sometimes requiring surgical intervention.
- *Infectious Complications of PNCs*: Local inflammation (0–13.7%) and infections (0–3.2%) are infrequent, while colonization rates range from 7.5% to 57%. The highest colonization rates occur in femoral and axillary catheters, primarily due to skin flora, especially Staphylococcus epidermidis. The risk of infection increases with prolonged catheter indwelling, trauma, and the absence of antibiotics. Adherence to aseptic techniques, including the use of chlorhexidine, is essential to minimize infection rates. Studies indicate that administering antibiotics during PNC placement and postoperative antibiotics can significantly reduce the risk of colonization.
- *Accidental Vascular Puncture and Hematoma Formation*: Vascular puncture occurs in 5.7% of femoral and 6.6% of sciatic catheters. Significant bleeding and complications are rare, though hematoma formation has been reported with certain anticoagulant therapies.
- *PNCs and Anticoagulation*: Adherence to American Society of Regional Anesthesia guidelines is recommended for patients on anticoagulation therapy.
- Case reports indicate complications related to anticoagulation during PNC removal.
- *Local Anesthetic Systemic Toxicity (LAST)*: Local anesthetic systemic toxicity (LAST) presents as mild symptoms like dizziness and tinnitus or severe CNS and cardiovascular events, including seizures and cardiac arrest. While supportive care and lipid emulsion therapy have improved outcomes, LAST remains a significant risk, highlighting the need for proper dosing, careful technique, and vigilance.

Challenges and Considerations

Limitations to effective postoperative pain control can involve patient-specific barriers, providers, and challenges in the healthcare system [21, 22].

The preoperative planning for neuraxial or regional anesthesia use begins with a thorough

discussion between the surgical team, anesthesiologist, and the patient to develop a perioperative plan that fits the patient's needs. For example, the proper preoperative education about the advantages of the use of neuraxial anesthesia instead of general anesthesia may improve a patient's desire to choose neuraxial anesthesia for knee replacement surgery [46].

Elderly patients with underlying cardiac, respiratory, and neurological conditions are increasingly undergoing joint replacement procedures. It is important to evaluate the use of anticoagulation and antiplatelet therapies when considering regional techniques. The risk of bleeding varies based on the site and depth of the nerve block [47].

Regional and neuraxial anesthesia in the pediatric population is increasing as a part of the multimodal pain management approach [9]. The effect of general anesthesia and the use of opioids on developing brains have been studied for decades. The fear of long-term effects might remain questionable, especially with patients undergoing multiple anesthesia exposures. The use of regional and neuraxial anesthesia could be an alternative to general anesthesia in neonates and pediatric age groups.

Case Study: Thoracic Epidural vs. Chest Wall Blocks for Bilateral Lung Transplant

Patient Profile

- 70–year-old male patient undergoing bilateral lung transplant
- Past Medical History: Interstitial lung disease on 5 liters of oxygen, pulmonary hypertension, atrial fibrillation, T2DM
- Past Surgical History: Inguinal hernia repair, total hip arthroplasty

Preoperative Assessment

- ASA class 4
- Pulmonary Status: Baseline oxygen use 5 liters/min, daily albuterol use, tadalafil for pulmonary hypertension
- Cardiovascular Status: A-fib on Elquis

Anesthetic Plan

- General Anesthesia with endotracheal tube
- Hemodynamic monitoring with A-line and central venous line
- Intraoperative use of norepinephrine, vasopressin, and heprain
- Plan for thoracic epidural for pain control post extubation.

Postoperative Pain Management

- Patient extubated on postoperative day 1
- Pain was managed with Fentanyl PCA, Tylenol, Gabapentin but the patient was still complaining of severe incisional pain
- Postoperative deep venous thrombosis in Left leg for which patient was started on low molecular weight heparin
- Thoracic epidural can't be inserted due to the risk of neuraxial hematoma
- Anesthesiologist performed Bilateral Erector Spinae Blocks under ultrasound guidance.
- Anesthetic mixture used include 40 ml of 0.25% Bupivicaine and 20 ml 1.3% Liposomal Bupivicaine

Outcomes

- Pain was adequately controlled after the blocks
- Patient was transferred from ICU to the regular floor on room air

Discussion

Although thoracic epidural analgesia (TEA) may provide optimal analgesia after thoracotomy, paravertebral block (PVB) and emerging fascial plane blocks may offer effective alternatives.

Thoracic epidural has shown many benefits for patients undergoing lung transplantation. The use of thoracic epidural improves the patients' pain and satisfaction. The surgical approach is usually through posterolateral thoracotomy or bilateral thoracosternotomy (clam-shell) incisions, which causes severe postoperative pain. The source of the pain includes intercostal nerves, ribs, pleura, and thoracic muscles [48]. In addition, thoracic epidural usage has shown benefits in reducing the duration of mechanical ventila-

tion, respiratory complications, and overall ICU stay [49].

Alternatives for thoracic epidurals have been evolving, including chest wall blocks and intercostal nerve cryoablations. Cryoanalgesia has been shown to be an effective substitute for thoracic epidurals, especially with patients suffering from hypotension or patients receiving anticoagulation [48].

Future Directions and Research

Postoperative pain is often sub-optimally treated and remains a challenge to manage [50]. However, further studies are needed to evaluate the efficacy and safety of these techniques compared to conventional methods and local anesthetics. Future research should focus on prolonging analgesia using the least invasive regional techniques while comparing new local anesthetics with existing ones [51] .

The future of perioperative pain management may be a personalized plan based on the patient's surgery, medical history, current medications, socioeconomic and demographic factors, baseline testing, pharmacogenetics, and trajectory modeling. Such an approach will allow for advanced preoperative planning and provide patients with a truly patient-centered experience [52].

Postoperative anxiety may be stabilized by multimodal approaches to pain management that include regional anesthetic blocks and biobehavioral interventions [53].

Excellence in regional anesthesia can be achieved by combining adequate sono-anatomical knowledge with skilled needle-transducer experience [54]. The training of neuraxial and peripheral nerve block performance can be augmented by using simulation aids [55]. These simulation models are crucial for patient safety and improve the first pass attempt. The combination of high-sensitivity software and human body manikins can be adopted by training programs. Moreover, the advances in ultrasound software including the use of 3D and 4D imaging will provide the practitioner with better needle visualization [56].

Multimedia online resources for regional anesthesia are part of the e-learning experience in the twenty-first century [57]. Anatomy textbooks, previously the gold standard for regional anesthesiologists, have been replaced by various online platforms providing up-to-date videos, 3-D images, and techniques to master regional anesthesia.

References

1. Werner MU, Kongsgaard UE. I. Defining persistent post-surgical pain: is an update required? Br J Anaesth. 2014;113(1):1–4.
2. Brennan TJ. Pathophysiology of postoperative pain. Pain. 2011;152(3):S33–40.
3. Chitnis SS, Tang R, Mariano ER. The role of regional analgesia in personalized postoperative pain management. Korean J Anesthesiol. 2020;73(5):363–71.
4. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367(9522):1618–25.
5. Barrington MJ, Kluger R. Ultrasound guidance reduces the risk of local anesthetic systemic toxicity following peripheral nerve blockade. Reg Anesth Pain Med. 2013;38(4):289–97.
6. Yamak Altinpulluk E, Turan A. Future in regional anesthesia: new techniques and technological advancements. Minerva Anestesiol. 2021;87(1)
7. Elsharkawy H, Pawa A, Mariano ER. Interfascial plane blocks. Reg Anesth Pain Med. 2018;43(4):341–6.
8. Elsharkawy H, Saifullah T, Kolli S, Drake R. Rhomboid intercostal block. Anaesthesia. 2016;71(7):856–7.
9. van Geffen GJ, Moayeri N, Bruhn J, Scheffer GJ, Chan VW, Groen GJ. Correlation between ultrasound imaging, cross-sectional anatomy, and histology of the brachial plexus. Reg Anesth Pain Med. 2009;34(5):490–7.
10. Franco CD, Williams JM. Ultrasound-guided interscalene block. Reg Anesth Pain Med. 2016;41(4):452–9.
11. Zisquit J, Nedeff N. Interscalene Block. 2024.
12. D'Souza RS, Johnson RL. Supraclavicular Block. 2024.
13. Williams LM, Singh K, Dua A, Singh A, Cummings A. Infraclavicular Nerve Block. 2024.
14. Janjua MS, Pak A. Axillary block. 2024.
15. Sykes Z, Pak A. Femoral nerve block. 2024.
16. Arnold C, Alvarado AC, Brady MF. Saphenous Nerve Block. 2024.
17. Rodziewicz TL, Stevens JB, Ajib FA, Tunnell DJ. Sciatic Nerve Block. 2024.
18. Yoshida T, Nakamoto T, Kamibayashi T. Ultrasound-guided obturator nerve block: a focused review on anatomy and updated techniques. Biomed Res Int. 2017;2017:1–9.

19. Battista C, Krishnan S. Pectoralis nerve block. 2024.
20. Muneeb Akhtar SM, Fareed A, Afzal U, Asghar MS, Mumtaz M, Faraz F, et al. Effectiveness of erector spinae plane block in reducing opioid consumption after colorectal surgery: a comprehensive meta-analysis. Am J Surg. 2024;232:31–44.
21. Wilson AA, Schmid AM, Pestaña P, Tubog TD. Erector Spinae plane block on postoperative pain and opioid consumption after lumbar spine surgery: a systematic review and meta-analysis of randomized controlled trials. J Perianesth Nurs. 2024;39(1):122–31.
22. Kot P, Rodriguez P, Granell M, Cano B, Rovira L, Morales J, et al. The erector spinae plane block: a narrative review. Korean J Anesthesiol. 2019;72(3):209–20.
23. Oostvogels L, Weibel S, Meißner M, Kranke P, Meyer-Frießem CH, Pogatzki-Zahn E, et al. Erector spinae plane block for postoperative pain. Cochrane Database Syst Rev. 2024;2024(2)
24. Krishnan S, Cascella M. Erector Spinae plane block. 2024.
25. Southgate SJ, River GF, Herbst MK. Ultrasound-Guided Serratus Anterior Blocks. 2024.
26. Elsharkawy H, Kolli S, Soliman LM, Seif J, Drake RL, Mariano ER, et al. The external oblique intercostal block: anatomic evaluation and case series. Pain Med. 2021;22(11):2436–42.
27. Elsharkawy H, El-Boghdadly K, Barrington M. Quadratus Lumborum Block. Anesthesiology. 2019;130(2):322–35.
28. Ince I, Kilicaslan A, Roques V, Elsharkawy H, Valdes L. Ultrasound-guided clavipectoral fascial plane block in a patient undergoing clavicular surgery. J Clin Anesth. 2019;58:125–7.
29. Labandeyra H, Heredia C, Váldes-Vilches LF, Prats-Galino A, Sala-Blanch X. Clavipectoral fascia plane block in midshaft clavicle fractures: a cadaveric study. J Clin Anesth. 2024;96:111469.
30. Ranganath Y, Seering M, Marian A. Curb your enthusiasm: local anesthetic adjuvants for peripheral nerve blocks. ASRA News. 2020;45(4)
31. Brummett CM, Williams BA. Additives to local anesthetics for peripheral nerve blockade. Int Anesthesiol Clin. 2011;49(4):104–16.
32. Hussain N, Speer J, Abdallah FW. Analgesic effectiveness of liposomal bupivacaine *versus* plain local anesthetics for abdominal fascial plane blocks: a systematic review and meta-analysis of randomized trials. Anesthesiology. 2024;140(5):906–19.
33. Malik O, Kaye A, Kaye A, Belani K, Urman R. Emerging roles of liposomal bupivacaine in anesthesia practice. J Anaesthesiol Clin Pharmacol. 2017;33(2):151.
34. Bulka CM, Shotwell MS, Gupta RK, Sandberg WS, Ehrenfeld JM. Regional anesthesia, time to hospital discharge, and in-hospital mortality. Reg Anesth Pain Med. 2014;39(5):381–6.
35. Werawatganon T, Charuluxananan S. Patient controlled intravenous opioid analgesia versus continuous epidural analgesia for pain after intra-abdominal surgery. In: Werawatganon T, editor. The cochrane database of systematic reviews. Chichester: Wiley; 2005.
36. Guay J, Kopp S. Epidural pain relief versus systemic opioid-based pain relief for abdominal aortic surgery. Cochrane Database Syst Rev. 2016;2017(3)
37. Svircevic V, van Dijk D, Nierich AP, Passier MP, Kalkman CJ, van der Heijden GJMG, et al. Meta-analysis of thoracic epidural anesthesia *versus* general anesthesia for cardiac surgery. Anesthesiology. 2011;114(2):271–82.
38. Luger TJ, Kammerlander C, Gosch M, Luger MF, Kammerlander-Knauer U, Roth T, et al. Neuroaxial versus general anaesthesia in geriatric patients for hip fracture surgery: does it matter? Osteoporos Int. 2010;21(S4):555–72.
39. Graff V, Gabutti L, Treglia G, Pascale M, Anselmi L, Cafarotti S, et al. Perioperative costs of local or regional anesthesia versus general anesthesia in the outpatient setting: a systematic review of recent literature. Braz J Anesthesiol (English Edition). 2023;73(3):316–39.
40. Kopp SL, Horlocker TT. Regional anaesthesia in day-stay and short-stay surgery. Anaesthesia. 2010;65(s1):84–96.
41. Hausman MS, Jewell ES, Engoren M. Regional versus general anesthesia in surgical patients with chronic obstructive pulmonary disease. Anesth Analg. 2015;120(6):1405–12.
42. Neuman MD, Silber JH, Elkassabany NM, Ludwig JM, Fleisher LA. Comparative effectiveness of regional *versus* general anesthesia for hip fracture surgery in adults. Anesthesiology. 2012;117(1):72–92.
43. Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. Br J Anaesth. 2013;111(5):711–20.
44. Suresh P, Mukherjee A. Patient satisfaction with regional anaesthesia and general anaesthesia in upper limb surgeries: an open label, cross-sectional, prospective, observational clinical comparative study. Indian J Anaesth. 2021;65(3):191.
45. Ironfield CM, Barrington MJ, Kluger R, Sites B. Are patients satisfied after peripheral nerve blockade? Results from an international registry of regional anesthesia. Reg Anesth Pain Med. 2014;39(1):48–55.
46. Elkassabany NM, Abraham D, Huang S, Kase B, Pio F, Hume E, et al. Patient education and anesthesia choice for total knee arthroplasty. Patient Educ Couns. 2017;100(9):1709–13.
47. Shams D, Sachse K, Statzer N, Gupta RK. Regional anesthesia complications and contraindications. Clin Sports Med. 2022;41(2):329–43.
48. Cason M, Naik A, Grimm JC, Hanna D, Faraone L, Brookman JC, et al. The efficacy and safety of epidural-based analgesia in a case series of patients undergoing lung transplantation. J Cardiothorac Vasc Anesth. 2015;29(1):126–32.

49. Pottecher J, Falcoz PE, Massard G, Dupeyron JP. Does thoracic epidural analgesia improve outcome after lung transplantation? Interact Cardiovasc Thorac Surg. 2011;12(1):51–3.
50. McCaughan JS. Development of a laser center. Med Instrum. 1983;17(6):417–8.
51. Hamilton C, Alfille P, Mountjoy J, Bao X. Regional anesthesia and acute perioperative pain management in thoracic surgery: a narrative review. J Thorac Dis. 2022;14(6):2276–96.
52. Sullivan GA, Huang LW, Schäfer WLA, Tian Y, Reiter AJ, Essner B, et al. Association of multimodal pain control with patient-reported outcomes in children undergoing surgery. J Pediatr Surg. 2023;58(6):1206–12.
53. Malinowski MN, Jain S, Jassal N, Deer T. Spinal cord stimulation for the treatment of neuropathic pain: expert opinion and 5-year outlook. Expert Rev Med Devices. 2020;17(12):1293–302.
54. Fox B, Pawa A. Future directions in regional anaesthesia: a reply. Anaesthesia. 2020;75(4):555.
55. Fusco P, Petroni G, Tullj S, Arcangeli V, Balestra G, Marinangeli F. 196 Innovative and hi-fidelity simulator for fascial plane blocks. In: Peripheral nerve blocks. BMJ Publishing Group Ltd; 2021. p. A102.2–A102.
56. Sen S, Ge M, Prabhakar A, Moll V, Kaye RJ, Cornett EM, et al. Recent technological advancements in regional anesthesia. Best Pract Res Clin Anaesthesiol. 2019;33(4):499–505.
57. Prineas S, Cuyx L, Smet J. E-learning in regional anesthesia. Curr Opin Anaesthesiol. 2021;34(5):626–33.

Comprehensive Perioperative Pain Management

12

Mital Lavani, Chase Jennings, and Veena Graff

Introduction

Globally, most perioperative pain treatment strategies rely primarily on pharmacologic management. Despite the prevalence of pharmacologic therapies, multimodal regimens remain the gold standard for perioperative pain management.

A patient's overall experience of pain is more complex than the painful sensation itself. It is not merely the activation of pain receptors; the pain experience is a biopsychosocial phenomenon—emotional components such as anxiety, fear, anticipation of pain, and the memory of pain can all greatly magnify or diminish the intensity of the experience.

This chapter briefly introduces nonpharmacologic modalities available to treat perioperative pain and ease the associated physical and emotional components. The modalities discussed in this chapter include music therapy, acupuncture, physical manipulation/positioning, massage therapy, meditation, aromatherapy, and virtual reality technologies.

M. Lavani · C. Jennings · V. Graff (✉)
Department of Anesthesiology & Critical Care, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA
e-mail: veena.graff@pennmedicine.upenn.edu

Background and Current Understanding

Since ancient times, music has been used as a therapeutic and healing aid. It has long been informally understood to have spiritual, emotional, and physical healing qualities, and today, there is growing scientific interest in its therapeutic effects, particularly its potential to treat pain. By providing a sense of distraction from the source of pain, it can produce favorable changes in heart rate, blood pressure, and respiratory rate and patterns [1]. This calming effect reduces stress and anxiety, lowering the emotional response to pain.

Acupuncture has been an important part of traditional Chinese medicine for thousands of years. The practice entails inserting needles into specific body locations, known as acupuncture points or acupoints, to trigger physiological reactions that restore equilibrium and encourage healing. Acupuncture is widely used to manage pain, especially chronic pain. Many clinical trials and meta-analyses have shown it to be beneficial in lowering pain intensity, boosting quality of life, and improving function in a variety of populations [2].

Perioperative positioning is an essential part of pain management and prevention, as it helps prevent injury to the patient and optimizes surgical access.

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_12

Massage therapy has been used for centuries to help alleviate pain. To ease stress and pain, a therapeutic massage involves kneading or rubbing areas of the body, such as muscles and joints, usually with the hands. In the perioperative setting, implementing massage can aid pain management by reducing pain and anxiety [3].

The goal of meditation is to focus the mind to attain stability and clarity. Meditation and the practice of mindfulness and mental focus can be effective in addressing the psychological components of pain, which are a major part of the overall distress experienced by the patient, particularly with chronic pain.

For centuries, essential oils have been used in traditional and folk medicine to improve a variety of therapeutic goals, including overall well-being, relaxation, relief of stress and anxiety, and reduction of sleep disturbances and some may also have direct physiological benefits through analgesia or by fighting inflammatory processes. Essential oils can be inhaled, applied to or massaged into the skin [4].

Virtual reality immerses users in a computer-generated environment that mimics a realistic experience through the combination of vision, sound, and haptics (mechanically generated sensations). Users can look around and interact with the virtual environment as if they were physically there. Virtual experience provides many different effects, ranging from distraction of the patient's attention from pain to training responses to real or phantom pain [5].

Clinical Applications and Techniques

The diversity of available nonpharmacologic techniques provides many opportunities to increase patient well-being. Nevertheless, a lack of familiarity with the methods and the difficulty of standardization have presented barriers to entry for many doctors. However, the following techniques can be applied effectively.

Acupuncture is effective against many kinds of pain and other factors, including depression, nausea, and even migraine prevention [6]. Children's hospitals across America provide acupuncture services to prevent and treat illnesses. For example, the Medical Acupuncture Service through Boston Children's Anesthesiology Department uses the LI-4 acupuncture point, called "He Gu" in Chinese, for chronic tension headache treatment. LI-4 is posteriorly between the first and second metacarpal bones, and firm pressure to this area is thought to help ease headaches [7]. The scientific theory underlying acupuncture is believed to involve the release of endorphins and other neurotransmitters in the central nervous system that modulate pain perception.

It is known and practiced that surgical positioning, prolonged periods spent in one position with limited mobility, can lead to increased pain, patient discomfort, and injury. Frequent repositioning and elevating of the affected area can reduce pressure, improve blood circulation, and decrease muscle stiffness and cramping.

Massage can stimulate blood flow and reduce muscle tension, stress, and anxiety, which play a role in pain. This can decrease the experience of pain and reduce the need for analgesic agents, improving outcomes.

Evidence-Based Practices: Recent Research and Clinical Trials

Nonpharmacologic techniques can be used in multimodal treatment in the perioperative setting, but what evidence is available that these techniques are effective and safe?

Music affects the pain experience by distracting a patient from the source. It can also have an indirect but significant effect by producing favorable changes in heart rate, blood pressure, and respiratory rate and patterns. A systematic review and meta-analysis conducted by the Department of Anesthesiology at the Hospital of Guangzhou University of Chinese Medicine by Guanzhu Li examined 19 randomized controlled trials, and the results showed statistically significant reductions in postoperative pain and anxiety and decreased fluctuations in blood pressure and heart rate [1].

Acupuncture has been studied many times, and based on a paper by Nielsen including 17 meta-analyses and 22 systematic reviews, there seems to be validity in acupuncture as an adjunct treatment to treat acute pain and reduce opioid reliance [2].

Systematic reviews and meta-analyses of randomized controlled trials involving individuals in the general population with pain indicated that massage therapy should be strongly recommended as a pain management alternative and additionally shows benefit for anxiety treatment [3].

An integrated review conducted in 2019 on guided imagery relaxation therapy for postoperative pain management revealed that medication was an effective adjuvant to meditation-assisted analgesia. In a 2018 prospective, randomized, controlled study, patients exposed to intraoperative music had significantly lower postoperative pain and anxiety and better psychological well-being than did patients in the control group. This study examined the use of intraoperative music as an adjunct to subarachnoid block for improving postoperative outcomes following cesarean section [8].

The effect of the inhalation of geranium oils on pain and physiological indices after an appendectomy, compared to those who did not receive this form of treatment, showed significant and favorable differences in terms of the mean heart rate, systolic and diastolic blood pressure, blood oxygen percentage, and pain [9]. Due to its effects on the mind and body, aromatherapy can be viewed as one component of a multimodal approach to pain management.

Virtual reality has not been an established methodology in the perioperative setting. In one RCT published by the Journal of the American Medical Association, virtual reality in the form of playing Angry Birds for 15 min 4 days after head and neck surgery reduced the need for opioids for up to 8 h after intervention. This intervention was compared to the use of Angry Birds without virtual reality on a handheld smartphone [7]. Many randomized clinical trials have demonstrated that patients receiving VR interventions have lower postoperative pain scores than those receiving standard care.

Challenges and Considerations

Many of these techniques have not been extensively used, particularly in Western medicine, and therefore have not been adequately studied. Further engagement from providers and patients would help the medical community and patient care facilities improve our understanding of how best to apply these techniques.

In addition to the further need for research, the implementation of adjunct perioperative pain therapies remains a challenge, as there are no official guidelines on their use. A lack of a standard of implementation limits the understanding of the efficacy and the subjective responses to therapies, as providers may be discouraged from new techniques requiring training, resources, and time. In addition, cost remains a forefront barrier to implementation. These modalities require further training and specialists to provide services, increasing costs. With more experience and use, adjunctive therapies can become the standard of care and potentially justify the cost of patient satisfaction.

Case Studies or Clinical Scenarios

There are numerous ways to implement nonpharmacologic pain management therapies in perioperative and clinical settings.

An example of how this can be implemented can be shown in a fictional example: a 67-year-old female arrives for a cholecystectomy. She arrives in the preoperative area visibly anxious. She is offered a combination of music therapy, aromatherapy, and virtual reality as adjuncts to her pain plan.

She is given noise-canceling headphones with a selection of soothing music playlists. She chooses classical music. She is offered a lavender stick, which appears to help her relax; she takes a few deep breaths, helping her feel calm. Before entering the operating room, she is offered a VR experience that takes her through a peaceful walk on the beach.

In the postoperative setting, these therapies may also be continued. The same soothing

classical playlist is played in the recovery area as she regains full consciousness. A lavender spray is used.

The calming qualities of lavender and chamomile help create a relaxing preoperative and postoperative atmosphere. Surgical incisions or tired muscles may help cool the surgical site and reduce discomfort. It has also been used to help alleviate postoperative nausea. One study in the journal of Asian Nursing Research showed that aromatherapy utilized in patients undergoing cholecystectomy was effective in reducing stress and pain [4].

This example demonstrates how nonpharmacologic therapies including music therapy, aromatherapy, and virtual reality can be used to effectively manage pain and reduce anxiety. By combining these strategies, the anesthesia team may provide a comprehensive approach to perioperative care by reducing the need for pharmaceutical interventions and improving the patient experience overall.

Future Directions and Research: This Section Discusses Potential Future Developments and Areas for Further Research

There are many areas in which high-quality research on nonpharmacologic pain treatments is needed. Individual studies support the use of aromatherapy, music, acupuncture, etc., as components of a program to reduce pain and anxiety in the perioperative period, but concrete and standardized guidelines are needed.

For instance, what types of music are most effective in perioperative, postoperative, and chronic pain settings? Which acupuncture techniques are effective, for which surgical procedures they are used, and under what circumstances? Which positions or massages provide the most relief for patients? How can adequate meditation or mindfulness be ensured in the perioperative setting? What are the most effective essential oil mixes and application techniques for aromatherapy? What should practitioners show or emphasize about VR both preoperatively and postoperatively?

Most adjunctive therapies need general guidelines to help with standardized implementation. Although this approach would be difficult to implement due to the differences in resources in hospitals across the country, basic guidelines can streamline and ease the process of implementing music, aroma, acupuncture, meditation, and mechanical compression therapies. Furthermore, standard guidelines make it easier to conduct meaningful research on the efficacy of treatment.

Key Takeaways

There are holistic practices that can address pain in the perioperative setting.

As we use multimodal pharmacologic regimens to treat pain, we should also use cost-effective and noninvasive strategies.

Current research illuminates the possible advantages of music therapy, acupuncture, positioning, massage, meditation, aromatherapy, and virtual reality, although further research and practical implementation have yet to become standardized.

It is important to address both the physiological causes and psychological perceptions that can exacerbate pain.

Pain is a subjective and individualized experience. One happy implication of this fact is that the individual differences that make us experience pain differently provide the scope for diverse treatment modalities.

References

1. Li G, et al. Effects of perioperative music therapy on patients with postoperative pain and anxiety: a systematic review and meta-analysis. J Integr Complement Med. 2023;30(1):37–46. https://doi.org/10.1089/jicm.2022.0803.
2. Nielsen A, Dusek JA, Taylor-Swanson L, Tick H. Acupuncture therapy as an evidence-based nonpharmacologic strategy for comprehensive acute pain care: the academic consortium pain task force white paper update. Pain Med. 2022;23:1582–612.
3. Kaye AD, et al. Non-opioid perioperative pain strategies for the clinician: a narrative review. Pain

Ther. 2020;9(1):25–39. https://doi.org/10.1007/s40122-019-00146-3.
4. Lee J, Hur M-H. The effects of aroma essential oil inhalation on stress, pain, and sleep quality in laparoscopic cholecystectomy patients: a randomized controlled trial. Asian Nurs Res. 2022;16(1):1–8. https://doi.org/10.1016/j.anr.2021.11.002.
5. Slomski A. Virtual reality lessens postoperative pain. JAMA. 2022;328(7):610. https://doi.org/10.1001/jama.2022.13772.
6. Zheng H, et al. Acupuncture for patients with chronic tension-type headache. Neurology. 2022;99(14) https://doi.org/10.1212/wnl.0000000000200670.
7. Lin YC, Tassone RF, Jahng S, Rahbar R, Holzman RS, Zurakowski D, et al. Acupuncture management of pain and emergence agitation in children after bilateral myringotomy and tympanostomy tube insertion. Pediatr Anesth. 2009;19(11):1096–101. https://doi.org/10.1111/j.1460-9592.2009.03129.x.
8. Gasti V, Kurdi M. Intraoperative meditation music as an adjunct to subarachnoid block for the improvement of postoperative outcomes following cesarean section: a randomized placebo-controlled comparative study. Anesth Essays Res. 2018;12(3):618. https://doi.org/10.4103/aer.aer_114_18.
9. Gazerani A, et al. The effect of inhalation aromatherapy of geranium on pain and physiological indices after appendectomy: a double-blind randomized clinical trial. Int J Surg Open. 2021;28:44–9. https://doi.org/10.1016/j.ijso.2020.12.004.

13 Inpatient Pain Management (Subacute and Chronic Inpatient Pain): Explores Design and Operation of an Inpatient Pain Service

Brenda Beck, Emma Fu, and Faria Nisar

Introduction

There are a growing number of surgical procedures performed each year, and managing acute postoperative pain can be challenging. The undertreatment of acute postsurgical pain can lead to various complications, including delayed recovery, increased length of hospital stays, increased economic costs, as well as chronic or persistent postsurgical pain (PPP) [1, 2]. PPP can have a prevalence of 10–50% [3]; thus, postsurgical patients are at risk of chronic opioid use, which can lead to opioid dependence and increased health care costs related to chronic pain [4]. In addition, chronic pain patients having surgery are at an increased risk of developing PPP [1].

B. Beck (✉)
Department of Anesthesiology and Pain Management, Pain and Healing Center, The MetroHealth System, Cleveland, OH, USA

Case Western Reserve University, Cleveland, OH, USA
e-mail: bbeck@metrohealth.org

E. Fu
Department of Anesthesiology and Pain Medicine, The University of Washington, Seattle, WA, USA

F. Nisar
Case Western Reserve University, Cleveland, OH, USA

Department of Anesthesiology and Pain Management, The MetroHealth System, Cleveland, OH, USA

An inpatient pain service or inpatient pain team (IPT) aims to provide a comprehensive and multimodal pain control (MMPC) approach to the management of hospitalized patients with acute, subacute, or chronic pain. The IPT is often built around a collaborative multidisciplinary team. It can also be a subset of a Transitional Pain Service (TPS) or function within different service models: an acute pain service (with focus on surgical and trauma patients), chronic pain management, or a consultative model.

The IPT can help facilitate the perioperative management of inpatient analgesic care in the pharmacologic, interventional, and psychological realms [3, 5]. As part of the patient's inpatient or postsurgical hospital stay, an IPT can help institute an MMPC analgesic regimen (that is, utilizing two or more agents in different classes) for optimizing postoperative pain control [6]. Chronic pain interventions such as radiofrequency ablation (RFA), cryoneurolysis, Botox injections, and neuromodulation can also be considered as treatment modalities in the perioperative setting [7]. These approaches would aim to reduce acute postoperative pain, (especially for those patients at risk of PPP) but can also offer longer-standing relief of pain for patients awaiting surgery.

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_13

Background and Current Understanding

Pain can be inherently difficult to manage due to its' subjective nature. The pain experience can be both physiological and emotional, with patients having a varying threshold for the perception of and the response to different components of pain [1]. This can be true in the outpatient and inpatient settings. With the rising number of elective surgical procedures performed, there is a probability of encountering a patient with chronic pain on chronic opioid therapy. This can pose a risk to poorly managed postoperative pain due to opioid tolerance and hyperalgesia. Complex patients can consist of those with underlying chronic pain, but also with a history of underlying substance use disorder. Management of these patients in the outpatient and inpatient setting can be difficult. It can be challenging to manage acute-on-chronic or acute pain in the perioperative setting in these patient subgroups, as both conditions are associated with worse postoperative outcomes including refractory pain, decreased functional status, increased readmission rates, and increased economic costs [1].

Complete pain relief (especially after a surgery) may not be achievable. Rather, the focus should be on restoring or increasing functional status [1].

Clinical Applications and Techniques

An IPT can be comprised of physicians (attendings, fellows, and residents), nurses, physician assistants, psychologists, physiotherapists, occupational therapists, or pharmacists [5, 8]. An IPT can be made up of a standalone team (led by an anesthesiologist physician or pain management-trained physician) or a hybrid model in which the anesthesiologist covers operating room obligations and the hospital floor [9]. It can also be blended with the acute pain service (APS) or regional anesthesia (RA) team, as studies have implicated that an inpatient APS/RA service can help lower overall hospital length of stay and decrease opioid consumption postoperatively [9]. The goal of the IPT is (based on each individual patient's needs) to effectively manage acute, acute-on-chronic pain, or chronic pain while maintaining patient function for daily activities and helping aid their participation in the recovery process. Patients on long-term opioid therapy for chronic pain can develop tolerance and may require higher doses of opioids or more potent opioids after an operation or traumatic injury. This can generate fear and uncertainty among general providers which in turn can lead to the overtreatment with opioids that may necessitate naloxone use [10]. Thus, as inadequately controlled acute pain can increase the risk of developing chronic pain, the institution of an IPT can help manage complex inpatient patients with the overall goals of lowering opioid consumption, increasing functional status, and monitoring the efficacy of the given interventions.

Patients with multiple repeat admissions due to pain, high outpatient opiate usage (greater than 180 mg oral morphine equivalence), or a history of substance abuse would benefit from an evaluation by the IPT [5]. Other patients who could be referred to the IPT service include those followed by the APS for more than 3 days postoperatively due to poorly controlled postoperative pain [8], patients consuming more than 90 mg/day of oral morphine equivalents on postoperative day one, patients with a plan to be discharged with long-acting opioids, patients with psychological risk factors for persistent opioid use (e.g., anxiety, depression, high pain catastrophizing scores), and patients with multiple emergency department visits for pain-related issues. Patients with a history of chronic pain, drug abuse, current or previous opioid usage, or on methadone or buprenorphine maintenance therapy are at a higher risk of developing PPP [8, 11]. The IPT can work in conjunction with, or collaborate with the Addiction Medicine team as well as the Palliative Care team. The IPT can also facilitate communication with regard to the analgesic plan to the patient's additional care providers in the hospital or in the outpatient setting.

Evidence-Based Practices

Postoperative pain can contribute to a patient's anxiety and fears around their surgical procedure; postoperative pain has been reported as the most feared surgical complication by patients [9]. A multimodal approach, rather than the use of opioids alone, is a practice guideline [6]; thus, the IPT should be knowledgeable in regional techniques, MMPC regimens, be able to manage and/or make recommendations for patient-controlled analgesia (PCA), and be familiar with analgesic infusion therapies (ketamine and/or lidocaine).

Multimodal pharmacological strategies may include the use of gabapentinoids, N-methyl-D-aspartate (NMDA) receptor antagonists (ketamine, memantine), tricyclic antidepressants (amitriptyline, nortriptyline), serotonin-norepinephrine reuptake inhibitors (duloxetine, venlafaxine), and alpha-2 receptor agonists (clonidine, dexmedetomidine) [6, 7]. Meta-analyses of randomized controlled trials report lower pain and decreased opioid consumption when intravenous opioids are combined with calcium channel blocking agents (gabapentin, pregabalin) versus the use of intravenous opioids alone [6]. Strong recommendations exist (unless contraindicated) for the scheduled use of acetaminophen, a cyclooxygenase-2 (COX-2) selective non-steroidal anti-inflammatory (NSAID), or a non-selective NSAID [6]. Non-pharmacological management can include cognitive behavioral therapy and acupuncture.

Chronic pain interventional techniques that may have a role perioperatively to decrease pain signal transmission include radiofrequency ablation (RFA), cryoneurolysis, and neuromodulation. RFA uses radiofrequency waves to heat the surrounding tissue and nerve, leading to thermal destruction by creating a localized lesion, thus decreasing pain transmission. Cryoneurolysis utilizes cold temperatures to achieve the blockage of nerve conduction [7]. These techniques may be particularly useful for joint pain (shoulder, hip, knee). Neuromodulation utilizes electrical activity to activate large nerve fibers that, in turn, dampen pain signal transmission of the smaller pain nerve fibers [7].

Challenges and Considerations

Many centers are implementing a TPS and IPT as there has been a realization of the need to "bridge the gap" between acute perioperative pain and to hasten the development of PPP [9]. However, difficulties may be faced in developing an IPT. This can include staffing availability for 24/7 coverage for inpatient pain services. With large institutions or trauma hospitals, 24/7 coverage would be paramount; however, it may not be feasible, as is the case at The MetroHealth System inpatient pain team. Without around-the-clock coverage, this could impact the consulting services' satisfaction regarding the ability to evaluate patients in a timely manner, which in turn could negatively impact the patients' pain management [9].

The cost to implement and maintain an IPT may also be a barrier for hospitals to offer this service [12]. Interdisciplinary team rounds could reduce the need for separate consultations, but starting with a consultative model by assigning current staff (anesthesiologists) to see consults could allow for the service to gradually expand to limit upfront costs. A physician-led team with trainees could allow for lower operating costs and more autonomy for the trainees but, due to high turnover, would compromise consistency in implementing protocols for inpatient care [9]. Utilizing physician assistants and nurse practitioners can allow for consistency and established protocols but would increase operating expenses [9].

In addition, interventional fluoroscopic guided procedures may not be available to offer patients in the inpatient setting. Thus, implementing chronic pain interventions could be difficult due to the lack of equipment, staffing, or space available to perform the procedure.

Case Studies or Clinical Scenarios

A middle-aged woman with a past medical history significant for anxiety, depression, bipolar disorder, post-traumatic stress disorder (PTSD), complex regional pain syndrome (CRPS) I of the

lower extremity (with a spinal cord stimulator in place), and fibromyalgia presents as a referral to the TPS from her gynecologist. The patient is experiencing irregular menses with menorrhagia and is scheduled for a laparoscopic hysterectomy. The surgical team is seeking guidance on postoperative pain control.

As an outpatient, she is maintained on ketamine/lidocaine infusions (30 mg/300 mg, respectively) monthly, which help her pain from CRPS I and fibromyalgia. She is maintained on Topamax 75 mg at bedtime and doxepin 50 mg at bedtime, and has oral oxycodone/acetaminophen (5 mg/325 mg) once daily if needed for breakthrough pain. A multidisciplinary approach is recommended for perioperative pain control: continuation of her home medications, oral oxycodone as needed for moderate and severe pain, intravenous (IV) Dilaudid as needed for breakthrough pain, regional anesthesia, and an intraoperative ketamine infusion.

On the day of surgery, the APS/RA team performs a preoperative transversus abdominis plane block bilaterally. Intraoperatively, the patient intravenously receives 32 micrograms of dexmedetomidine, 50 mg of Ketamine, and 30 mg of Toradol. Postoperatively, the IPT makes their recommendations. She is continued on her Topamax 75 mg at bedtime and doxepin 50 mg at bedtime. She is given scheduled Tylenol 1000 mg every 6 h and, per her surgical team, Celebrex 200 mg twice daily. She is allowed oral oxycodone 5 mg and 10 mg every 4 h as needed for moderate/severe pain, respectively, along with IV Dilaudid 0.2 mg every 4 h as needed for breakthrough pain. The patient reports greater than expected postoperative pain, but it is otherwise tolerable. She consumed five doses of the 10 mg oral oxycodone and utilized two doses of the IV Dilaudid for breakthrough pain throughout her hospital stay. She is routinely discharged (on her home medications, with a short course of oral oxycodone 5 mg every 6 h as needed) on post operative day 1 with a tolerable amount of pain. She is instructed to continue with her ketamine and lidocaine infusions outpatient and will follow up with her surgical team along with the TPS.

Future Directions and Research

While MMPC strategies (e.g., regional anesthesia, intravenous lidocaine infusions, ketamine) can be helpful in lowering opioid consumption immediately postoperatively, studies in terms of the long-term efficacy of these interventions in reducing chronic opioid use after surgery are lacking, and more research can be done when looking at overall long-term consumption of opioids [4]. Thus, utilizing additional analgesic strategies including chronic pain interventions can be considered. However, this may be difficult to implement in the perioperative period due to insurance coverage or the availability of proper equipment in the hospital. More data is needed on which patients would benefit the most from these chronic pain interventions, as to date no reliable model is available to predict greater-than-expected acute pain and PPP [7]. In addition, research is needed to compare the effectiveness of chronic pain interventions or the combination of these interventions in preventing PPP [7]. There is an emphasis on enhanced multimodal analgesia. Novel sodium channel-inhibiting medications are emerging to improve acute pain management without the risks associated with opioids. In addition, incorporating more nonpharmacologic strategies like cognitive behavioral therapy, acupuncture, and virtual reality can be considered in acute and chronic pain management.

Key Takeaways

- There are a growing number of surgical procedures performed each year.
- PPP can have a prevalence of 10–50% in surgical patients, which leads to concern for opioid dependence and increased health care costs related to the management of chronic pain.
- As part of a TPS, an inpatient pain team can help facilitate the management of patients with complex pain.

- Studies are still needed to examine whether an MMPC strategy lowers the overall chronic, long-term use of opioids after a surgery.
- Chronic pain interventions can be considered as part of the MMPC strategy. More data is needed on which patients would benefit the most, but can be considered in patients at the highest risk for PPP.

References

1. Charipova K, Gress KL, Urits I, Viswanath O, Kaye AD. Management of patients with chronic pain in ambulatory surgery centers. Cureus. 2020. https://doi.org/10.7759/cureus.10408
2. Tawfic QA m, Faris AS. Acute pain service: past, present and future. Pain Manag. 2015;5(1):47–58. https://doi.org/10.2217/pmt.14.48.
3. Bolívar M, Toro M, Seijas ME, Bolívar A, Bolívar M. Transitional pain clinic. Rev Soc Esp Dolor. 2020;27 https://doi.org/10.20986/RESED.2020.3840/2020.
4. Hah JM, Bateman BT, Ratliff J, Curtin C, Sun E. Chronic opioid use after surgery: implications for perioperative management in the face of the opioid epidemic. Anesth Analg. 2017;125(5):1733–40. Lippincott Williams and Wilkins. https://doi.org/10.1213/ANE.0000000000002458.
5. Mordecai L, Vindrola-Padros C, Wood VJ, Swart N, Morris S, Williams A, Curran N, Moonesinghe R. A novel inpatient complex pain team: protocol for a mixed-methods evaluation of a single-centre pilot study. BMJ Open. 2018;8(3) https://doi.org/10.1136/bmjopen-2017-019058.
6. Practice Guidelines for Acute Pain Management in the Perioperative Setting. (2012). http://journals.lww.com/anesthesiology
7. Ye Y, Gabriel RA, Mariano ER. The expanding role of chronic pain interventions in multimodal perioperative pain management: a narrative review. Postgrad Med. 2022;134(5):449–57). Taylor and Francis Ltd. https://doi.org/10.1080/00325481.2021.1935281.
8. Clarke H, Azargive S, Montbriand J, Nicholls J, Sutherland A, Valeeva L, et al. Opioid weaning and pain management in postsurgical patients at the Toronto General Hospital Transitional Pain Service. Can J Pain. 2018;2(1):236–47.
9. Al-Saidi I, Russell A, Dizdarevic A. The acute perioperative pain service: impact, organization, and future directions. Curr Pain Headache Rep. 2023;27(9) https://doi.org/10.1007/s11916-023-01133-2.
10. Lin RJ, Reid MC, Chused AE, Evans AT. Quality assessment of acute inpatient pain management in an Academic Health Center. Am J Hosp Palliat Med. 2016;33(1):16–9. https://doi.org/10.1177/1049909114546545.
11. Sutherland AM, Clarke HA. The role of anesthesiologists in reducing opioid harm. Can J Anesth. 2022;69(8):917–22). Springer. https://doi.org/10.1007/s12630-022-02274-5.
12. Sun EC, Mariano ER, Narouze S, et al. Making a business plan for starting a transitional pain service within the US healthcare system. Reg Anesth Pain Med. 2021;46:727–31.

Part V

Extended Postoperative Care (Days 1–30)

14 Transitioning from Acute to Chronic Pain Management: Addresses Strategies to Prevent the Progression from Acute to Chronic Pain

Anna McCarter, QiLiang Chen, and J. David Clark

Introduction

Chronic post-surgical pain (CPSP) is one of the most common complications after surgery. It negatively impacts patient satisfaction and quality of life, contributes to the opioid epidemic, decreases societal productivity, and increases healthcare spending. Identifying the risk factors for CPSP and improving pain control in the acute postoperative period could reduce the incidence and severity of CPSP [1–3].

Background and Current Understanding

Mechanisms implicated in the development of CPSP include dysregulated inflammatory responses to tissue damage and changes to central and peripheral nervous system pain-modulating pathways [4]. Central sensitization, in which dysfunctional neural signaling in the central nervous system alters the processing of pain and sensory stimuli, is thought to be another key driver for CPSP, and delineating this dysfunctional process could offer important clues for treatment discovery [5–8].

Some patient and surgical factors associated with the risk of developing CPSP have been identified. Gender, genetics, psychiatric conditions, and chronic pain predispose patients to persistent postoperative pain [5–7, 9–12]. Surgical factors linked to the development of CPSP include the type and duration of surgery, postoperative infection, neoadjuvant chemotherapy, and radiation [3]. Perhaps unsurprisingly, the intensity and duration of postoperative pain are also associated with a greater incidence of CPSP [13–16]. These topics are further discussed in other chapters.

Clinical Applications, Techniques, and Evidence-Based Practices

Many approaches to reducing the risk of developing CPSP have been tried with variable success. Studies examining the modification of surgical techniques, such as minimally invasive surgery, have shown mixed results [17, 18]. Instead, the current chapter will focus on regional anesthesia techniques and pharmacologic approaches for treating complex perioperative pain. Although these perioperative techniques have shown promise in reducing CPSP, many conclusions drawn from studies are limited by small sample sizes, disparate treatment parameters, and lack of stratification of patients.

A. McCarter · Q. Chen · J. D. Clark (✉)
Department of Anesthesiology, Perioperative and Pain Medicine, Stanford Medical School, Stanford University, Palo Alto, CA, USA
e-mail: djclark@stanford.edu

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_14

Neuraxial and Regional Analgesia

Neuraxial analgesia, such as epidural catheters, has long been utilized to attenuate the patient's physiologic response to surgery and provide postoperative pain control. Thoracic epidural analgesia improves postoperative pain and functional outcomes after open abdominal and thoracic procedures, although their efficacy in preventing CPSP is less clear [19, 20]. A 2013 Cochrane meta-analysis of seven studies encompassing 499 patients showed a reduction in CPSP rates 6 months after thoracotomy with epidural analgesia [21].

Regional analgesia techniques targeting the neural plexus, particularly erector spinae plane blocks and paravertebral blocks, may help prevent CPSP. A meta-analysis of 40 RCTs showed that regional anesthesia used perioperatively for thoracotomy, breast surgery, and cesarean section significantly reduced the incidence of CPSP [21]. Data regarding the use of regional anesthesia for iliac crest bone graft, prostatectomy, and hysterectomy was inconclusive in that same meta-analysis. Based on the current literature, neuraxial and regional analgesia may reduce the incidence of CPSP in a subset of patients undergoing painful thoracic or abdominal surgery.

Other perineural anesthesia techniques targeting specific peripheral nerves to disrupt nociceptive afferents have also risen in popularity for both intraoperative and postoperative pain control. Examples include femoral nerve blocks for hip procedures, adductor canal and popliteal blocks for knee and ankle procedures, interscalene blocks for shoulder procedures, and brachial plexus nerve blocks for upper extremity procedures. As these techniques have become more prevalent, so too have studies regarding the impact of perineural analgesia on the development of CPSP. The best evidence exists for fascial plane blocks in thoracic and abdominal procedures; deep serratus anterior blocks reduce CPSP at 3 months in one prospective cohort study of patients undergoing breast-conserving surgery and at three and 6 months in another RCT of patients undergoing modified radical mastectomy [22, 23]. The data on transverse abdominus plane blocks is less clear: one study showed no reduction of CPSP in colorectal surgery patients who got transverse abdominus blocks, while another study in inguinal hernia repair patients failed to reach statistical significance [24, 25]. There is also less evidence for non-truncal peripheral nerve blocks. A single study of 166 total knee replacement patients showed adductor canal block and infiltration in the space between the popliteal artery and the capsule of the posterior knee significantly reduced CPSP incidence 2 years following the procedure [26]. There are also few studies on peripheral nerve catheters for the prevention of CPSP. One observational study in patients undergoing below-the-knee amputations found that sciatic nerve perineural catheters administering high-dose ropivacaine for a median of 30 days resulted in lower rates of phantom limb pain [27]. However, a recent multicenter RCT comparing 6-day catheter perineural ropivacaine infusion to placebo for upper and lower limb amputations saw no benefit at 12 months [28]. More trials examining the efficacy of perineural catheters for the prevention of CPSP in other contexts are needed.

Local anesthesia infiltrated at the surgical incision site has been shown to reduce early postoperative pain. However, the literature on its role in preventing CPSP remains elusive. For example, one study of intraoperative bupivacaine infiltration at the incision in total knee arthroplasty patients did not demonstrate a reduced incidence of CPSP at 12 months, while another study of open nephrectomy patients showed reduced CPSP incidence with 72-h continuous infiltration to the incision site [18, 21]. One reason for the variable results from these studies might lie in the duration of treatment, and their efficacy could also be procedure- and site-dependent.

NMDA Antagonists

Activation of NMDA receptors is thought to potentiate nociceptive inputs and is implicated in CPSP through central sensitization following surgery. Intravenous ketamine, an NMDA receptor antagonist, has been shown to reduce opioid

consumption and acute postoperative pain [29, 30]. A meta-analysis of 14 studies on perioperative ketamine saw a modest but statistically significant reduction in the incidence of CPSP [31]. However, the most recent Cochrane meta-analysis of 27 studies encompassing more than 2700 patients showed no significant treatment effect of ketamine on the prevalence of pain at 3-, 6-, or 12-month time points [32]. A specific NMDA blocker, memantine, showed a statistically significant pain reduction in post-mastectomy patients 3 months after surgery in a small-scale clinical study, although RCTs examining this drug are still lacking [33].

Gabapentinoids

Gabapentinoids (e.g., gabapentin and its sister drug, pregabalin) are anticonvulsant agents commonly used to treat neuropathic pain and have increasingly been used to prevent CPSP. A meta-analysis of 26 studies, including ~3700 patients, showed pregabalin reduces the prevalence of moderate to severe pain at three and 6 months when it was administered for >24 h. Subgroup analyses of this study demonstrated pregabalin usage leads to significant pain reduction at 3 months following cardiac surgery or total knee arthroplasty. However, post-hoc analyses failed to show treatment effects when the medication was administered for <24 h or for other types of surgical procedures [32]. Although these medications are generally well-tolerated, one must note the side-effect profile of gabapentinoids, including sedation, respiratory depression, dizziness, and visual disturbances. This could increase the risk of pulmonary complications and ICU admissions, tempering enthusiasm about their use in high-risk patients during the perioperative period [34–36].

Intravenous Lidocaine Infusion

Intravenous (IV) lidocaine, an amide local anesthetic with analgesic and anti-inflammatory properties, has shown benefit for a subset of post-surgical patients. Meta-analysis of ten studies, including 800 patients, demonstrated significantly reduced pain at 6 months in breast surgery patients who received less than 24 h of IV lidocaine perioperatively. Similar results were seen in patients undergoing robot-assisted thyroidectomy and nephrectomy. A recent network meta-analysis of 12 RCTs showed perioperative IV lidocaine therapy significantly reduces CPSP incidence at 6 months post-procedure [37]. However, there was limited evidence for pain reduction beyond 6 months or opiate use in the same network analysis. Interestingly, two RCTs suggest that continuous intravenous local anesthetic infusion after breast cancer surgery may be at least equally effective to regional analgesia [38, 39]. There is a need for more studies comparing intravenous lidocaine with epidural analgesia, particularly in terms of dosing and timing of the infusion [32, 40]. Lastly, one must also consider the practicality of prolonged lidocaine infusions, as it necessitates frequent lidocaine-level monitoring, which increases cost and labor, making this intervention impractical for outpatient surgery centers.

Antidepressants

The neurotransmitters serotonin and noradrenaline are critical in nociceptive signaling and processing in the central nervous system. Duloxetine, a serotonin and norepinephrine reuptake inhibitor (SNRI), has been used to ameliorate central sensitization in fibromyalgia and peripheral neuropathy. A study examining a 6-week course of duloxetine in patients undergoing total knee arthroplasty who screened positive for central sensitization preoperatively has reduced pain at 2–12 weeks postoperatively [41]. Similar efficacy at the 4- and 12-week timepoint was seen when duloxetine was used in conjunction with opiate therapy in a single-center RCT of 68 spine patients [42]. However, another study in total knee arthroplasty patients did not show any improvement in pain in the duloxetine arm, suggesting that only a particular subset of patients may benefit most from duloxetine therapy [43].

While tricyclic antidepressants and selective serotonin reuptake inhibitors have also been used in the management of chronic pain, studies regarding their efficacy in preventing CPSP are considered too heterogeneous to draw meaningful conclusions [18, 44].

Alpha-2 Agonists

Alpha2-adrenoreceptor agonists, which have sedative, analgesic, and sympatholytic properties, have also been studied for post-operative pain control. A recent network meta-analysis of dexmedetomidine (a highly selective alpha2 agonist) showed data trends that it could reduce pain and opiate when used short-term (less than 6 months) after surgery [37]. Clonidine, a less selective alpha2-agonist than dexmedetomidine, has also been used for the treatment of chronic pain conditions. Intrathecal injection of clonidine was shown to reduce cancer pain and chronic pain from complex regional pain syndrome [45]. A study of intrathecal or epidural administration of clonidine and bupivacaine significantly reduced the incidence of CPSP after gastrointestinal surgery at 6 and 12 months, compared with bupivacaine alone [46]. However, the optimal dosing and route of administration of these alpha-2 agonists for preventing CPSP are not yet known.

Reduction of Opioid Use Perioperatively

It is believed that chronic preoperative opioid use is associated with persistent postoperative pain. Reduction of preoperative opioid use by greater than 50% in patients undergoing knee surgery has been shown to improve outcomes, including pain scores, at 6 and 12 months postoperatively [18]. On the other hand, the data on intraoperative opioid use and CPSP is less clear. A high intraoperative dose of remifentanil has been associated with a higher incidence of CPSP following cardiac surgery, but low-dose remifentanil used in conjunction with propofol proved superior to sevoflurane-based anesthesia in terms of CPSP incidence [47–49]. A meta-analysis comparing opioid-free general anesthesia to opioid-based general anesthesia showed strict opioid-free anesthesia could significantly reduce both postoperative adverse events and opioid consumption, while also lowering pain scores immediately after surgery [50]. However, none of the studies in this meta-analysis examined pain beyond 48 h postoperatively. There is also limited clinical evidence regarding postoperative opioid use and the development of CPSP.

Other Pharmacologic Agents of Multimodal Analgesia

Most studies on glucocorticoids and NSAIDs do not support their use for the prevention of CPSP [31, 32, 51–53]. No randomized controlled trial has been conducted to examine the effect of acetaminophen on preventing CPSP. Other systemic drugs without evidence that they reduce the incidence of CPSP include magnesium and antispasmodics [32].

Case Studies or Clinical Scenarios

Consider the case of a 40-year-old female patient with a history of depression and anxiety, new breast cancer, and a BRCA2+ diagnosis, undergoing bilateral mastectomy. A plan for intraoperative analgesia backed by current evidence would include erector spinae plane blocks with a catheter infusion of local anesthetic and multimodal pharmacologic management with dexmedetomidine, NSAIDs, ketamine, and opiates as needed. Postoperatively, the regional anesthesia catheters should be continued, as well as scheduled acetaminophen and NSAIDs. A gabapentinoid could be used if the patient tolerates the side effect profile. Duloxetine could also be utilized postoperatively, though the duration of treatment remains unclear. In the event of severe postoperative pain refractory to these medications, intravenous infusions of ketamine or lidocaine could be considered.

Challenges and Considerations

While recent studies and meta-analyses suggest that neuraxial and regional analgesia, NMDA antagonists, intravenous lidocaine, antidepressants, and alpha2 agonists might prevent the development of CPSP, there remain numerous challenges in the clinical implementation of this evidence. Developing accurate, personalized predictive models for identifying patients at risk of developing CPSP remains challenging [54–57]. When assessing the current literature regarding interventions for the prevention of CPSP, the need for larger randomized controlled trials becomes evident. Meta-analyses of the numerous smaller trials are hampered by variance in dosing, duration, and timing of pain assessment, making it difficult to draw meaningful conclusions about treatment strategies and efficacy of the interventions. Finally, strategies for preventing the transition from acute post-surgical pain to CPSP remain inadequate.

Future Directions and Research

There are few studies examining interventions at greater than 6 months postoperatively; given the chronic nature of CPSP, longer-term follow-up is needed to assess the efficacy of interventions. There is also a need for studies regarding multimodal pain regimens, as opposed to single-agent interventions, for better understanding the synergistic effects of these strategies. Another avenue for future research is in multidisciplinary approaches, combining physical therapy and psychological support with therapeutics. Finally, intraoperative and postoperative electroanalgesia devices are in development, but they are not yet widely used due to cost and limited data demonstrating effectiveness [58]. Finally, a better understanding of pathophysiologic mechanisms that give rise to CPSP is needed to aid therapeutic development.

Key Takeaways

- Chronic post-surgical pain is pervasive, and the mechanisms leading to its development are complex.
- Patient factors and surgical approaches can increase the likelihood of a patient experiencing chronic post-surgical pain.
- Acute intervention in the perioperative and postoperative period may reduce the incidence of chronic post-surgical pain.
- Evidence-based methods to reduce the incidence of chronic post-surgical pain include the use of neuraxial and regional techniques, ketamine, gabapentinoids, intravenous lidocaine, SNRIs, and alpha-2 agonists.
- Future directions include better algorithms for identifying patients at risk for the development of chronic post-surgical pain, improved treatments for the prevention of its development, and more studies into multidisciplinary management.

References

1. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede RD. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. Pain. 2019;160(1):45–52.
2. Rosenberger DC, Pogatzki-Zahn EM. Chronic post-surgical pain – update on incidence, risk factors and preventive treatment options. BJA Educ. 2022;22(5):190–6.
3. Fletcher D, Stamer UM, Pogatzki-Zhan E, Zaslansky R, Tanase NV, Perruchoud C, et al. Chronic postsurgical pain in Europe. Eur J Anaesthesiol. 2015;32(10):725–34.
4. Chapman CR, Vierck CJ. The transition of acute postoperative pain to chronic pain: an integrative overview of research on mechanisms. J Pain. 2017;18(4):359.E1–359.E38.
5. Glare P, Aubrey KR, Myles PS. Transition from acute to chronic pain after surgery. Lancet. 2019;393(10180):1537–46.
6. Richebé P, Capdevila X, Rivat C. Persistent postsurgical pain. Anesthesiology. 2018;129(3):590–607.

7. Lavand'homme PM. Transition from acute to chronic pain after surgery. Pain. 2017;158(1):S50–4.
8. Pogatzki-Zahn E, Segelcke D, Zahn P. Mechanisms of acute and chronic pain after surgery. Curr Opin Anaesthesiol. 2018;31(5):575–85.
9. Schnabel A, Yahiaoui-Doktor M, Meissner W, Zahn PK, Pogatzki-Zahn EM. Predicting poor postoperative acute pain outcome in adults: an international, multicentre database analysis of risk factors in 50,005 patients. PAIN Rep. 2020;5(4):e831.
10. Montes A, Roca G, Sabate S, Lao JI, Navarro A, Cantillo J, et al. Genetic and clinical factors associated with chronic postsurgical pain after hernia repair, hysterectomy, and thoracotomy. Anesthesiology. 2015;122(5):1123–41.
11. Pagé GM, Kudrina I, Zomahoun HT, Croteau J, Ziegler D, Ngangue P, et al. A systematic review of the relative frequency and risk factors for prolonged opioid prescription following surgery and trauma among adults. Ann Surg. 2020;271(5):845–54.
12. Giuisti EM, Lacerenza M, Manzoni GM, Castelnuovo G. Psychological and psychosocial predictors of chronic postsurgical pain: a systematic review and meta-analysis. Pain. 2020;162(1):10–30.
13. Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. PAIN Rep. 2017;2(6):e627.
14. Blitchfeldt-Eckhardt MR, ϕrding H, Andersen C, Licht PB, Toft P. Early visceral pain predicts chronic pain after laparoscopic cholecystectomy. Pain. 2014;155(11):2400–7.
15. Lavand'homme PM, Grosu I, France MN, Thienpont E. Pain trajectories identify patients at risk of persistent pain after knee arthroplasty: an observational study. Clin Orthop Relat Res. 2014;472(5):1409–15.
16. Martinez V, Ben Ammar S, Judet T, Bouhassira D, Chauvin M, Fletcher D. Risk factors predictive of chronic postsurgical neuropathic pain: the value of the iliac crest bone harvest model. Pain. 2012;153(7):1478–83.
17. McCormack K, Scott NW, Go PM, Ross S, Grant AM, EU Hernia Trialists Collaboration. Laparoscopic techniques versus open techniques for inguinal hernia repair. Cochrane Database Syst Rev. 2003;2003:CD001785.
18. Steyaert A, Lavand'homme P. Prevention and treatment of chronic postsurgical pain: a narrative review. Drugs. 2018;78(3):339–54.
19. Guay J, Nishimori M, Kopp SL. Epidural local anesthetics versus opioid-based analgesic regimens for postoperative gastrointestinal paralysis, vomiting, and pain after abdominal surgery: a Cochrane review. Anesth Analg. 2016;123(6):1591–602.
20. Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. Br J Anaesth. 2013;111(54):711–20.
21. Levene JL, Weinstein EJ, Cohen MS, Andreae DA, Chao JY, Johnson M, et al. Local anesthetics and regional anesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children: a Cochrane systematic review and meta-analysis update. J Clin Anesth. 2019;55:116–27.
22. Fuzier R, Salvignol G, Gilbert O, Bremaud M, Bataille B, Izard P. Influence of deep serratus anterior plane block on chronic pain at 3 months after breast-conserving surgery: prospective, Cohort Study. Clin J Pain. 2022;38(6):418–23.
23. Qian B, Huang S, Liao X, Junbei W, Lin Q, Lin Y. Serratus anterior plane block reduces the prevalence of chronic postsurgical pain after modified radical mastectomy: a randomized controlled trial. J Clin Anesth. 2021;74:110410.
24. Pan ZY, Hu ZH, Zhang F, Xie WX, Tang YZ, Liao Q. The effect of transversus abdominis plane block on the chronic pain after colorectal surgery: a retrospective cohort study. BMC Anesthesiol. 2020;20(1):116.
25. Paasch C, Fiebelkorn J, De Santo G, Azarhoush S, Boettge K, Anders S, et al. The transversus abdominis plane block may reduce chronic postoperative pain one year after TAPP ingunial hernia repair. Ann Med Surg. 2020;55:190–4.
26. Sreckovic S, Ladjevic N, Milicic B, Tulic G, Milovanovic D, Djukanovic M, Kadija M. Chronic post-surgical pain after knee arthroplasty: a role of peripheral nerve blocks. Front Med (Lausanne). 2024;10:1335405. https://doi.org/10.3389/fmed.2023.1335405. eCollection 2023. PMID: 3827444
27. Borghi B, D'Addabbo M, White PF, Gallerani P, Toccaceli L, Raffaeli W, et al. The use of prolonged peripheral neural blockade after lower extremity amputation. Anesth Analg. 2010;111(5):1308–15.
28. Ilfeld BN, Khatibi B, Maheshwari K, Madison SJ, Ali Sakr Esa W, Mariano ER, et al. Ambulatory continuous peripheral nerve blocks to treat postamputation phantom limb pain: a multicenter, randomized, quadruple-masked, placebo-controlled clinical trial. Pain. 2021;162(3):938–55.
29. Loftus RW, Yeager MP, Clark JA, Brown JR, Abdu WA, Sengupta DK, et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology. 2010;113(3):639–46.
30. Schwenk E, Viscusi ER, Buvanendran A, Hurley RW, Wasan AD, Narouze S, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43(5):456–66.
31. Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database Syst Rev. 2013;2013:CD001785.
32. Carley ME, Chaparro LE, Choinière M, Kehlet H, Moore RA, Van Den Kerkhof E, et al. Pharmacotherapy for the prevention of chronic pain after surgery in

adults: an updated systematic review and meta-analysis. Anesthesiology. 2021;135(2):304–25.
33. Morel V, Joly D, Villatte C, Dubray C, Durando X, Daulhac L, et al. Memantine before mastectomy prevents post-surgery pain: a randomized, blinded clinical trial in surgical patients. PLoS One. 2016;11(4):e0152741.
34. Kharasch ED, Clark JD, Kheterpal S. Perioperative gabapentinoids: deflating the bubble. Anesthesiology. 2020;133(2):251–4.
35. Verret M, Lauzier F, Zarychanski R, Perron C, Savard X, Pinard AM, et al. Perioperative use of gabapentinoids for the management of postoperative acute pain: a systematic review and meta-analysis. Anesthesiology. 2020;133(2):265–79.
36. Fabritius ML, Strom C, Koyuncu S, Jaeger P, Petersen PL, Geisler A, et al. Benefit and harm of pregabalin in acute pain treatment: a systematic review with meta-analyses and trial sequential analyses. Br J Anaesth. 2017;119:775–91.
37. Doleman B, Mathiesen O, Sutton AJ, Cooper NJ, Lund JN, Williams JP. Non-opioid analgesics for the prevention of chronic postsurgical pain: a systematic review and network meta-analysis. Br J Anaesth. 2023;130(6):719–28.
38. Grigoras A, Lee P, Sattar F, Shorten G. Perioperative intravenous lidocaine decreases the incidence of persistent pain after breast surgery. Clin J Pain. 2012;28(7):567–72.
39. Terkawi AS, Sharma S, Durieux ME, Thammishetti S, Brenin D, Tiouririne M. Perioperative lidocaine infusion reduces the incidence of post-mastectomy chronic pain: a double-blind, placebo-controlled randomized trial. Pain Physician. 2015;18(3):E139–46.
40. Weibel S, Jelting Y, Pace NL, Helf A, Eberhart LH, Hahnenkamp K, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. Cochrane Database Syst Rev. 2018;6(6):CD009642.
41. Koh IJ, Kim MS, Sohn S, Song KY, Choi NY, In Y. Duloxetine reduces pain and improves quality of recovery following total knee arthroplasty in centrally sensitized patients. J Bone Joint Surg. 2019;101(1):64–73.
42. Hyer L, Scott C, Mullen CM, McKenzie LC, Robinson JS. Randomized double-blind placebo trial of duloxetine in perioperative spine patients. J Opioid Manag. 2015;11(2):147–55.
43. YaDeau JT, Brummett CM, Mayman DJ, Lin Y, Goytizolo EA, Padgett DE, et al. Duloxetine and subacute pain after knee arthroplasty when added to a multimodal analgesic regimen: a randomized, placebo-controlled, triple-blinded trial. Anesthesiology. 2016;125(3):562–72.
44. Wong K, Phelan R, Kalso E, Galvin I, Goldstein D, Raja S, et al. Antidepressant drugs for prevention of acute and chronic postsurgical pain: early evidence and recommended future directions. Anesthesiology. 2014;121(3):591–608.
45. Ackerman LL, Follett KA, Rosenquit RW. Long-term outcomes during treatment of chronic pain with intrathecal clonidine or clonidine/opioid combinations. J Pain Symptom Manag. 2003;26(1):668–77.
46. Lavand'homme P, Kock M. The use of intraoperative epidural or spinal analgesia modulates postoperative hyperalgesia and reduces residual pain after major abdominal surgery. Acta Anaesthesiol Belg. 2006;57:373–9.
47. Brown CR, Chen Z, Khurshan F, Groeneveld PW, Desai ND. Development of persistent opioid use after cardiac surgery. JAMA Cardiol. 2020;5(8):889.
48. van Gulik L, Ahlers SJGM, van de Garde EMW, Bruins P, van Boven WJ, Tibboel D, et al. Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. Br J Anaesth. 2012;109(4):616–22.
49. Subramaniam K, Ibarra A, Ruppert K, Mallikarjun K, Orebaugh S. Intraoperative remifentanil infusion and postoperative pain outcomes after cardiac surgery—results from secondary analysis of a randomized, open-label clinical trial. J Cardiothorac Vasc Anesth. 2021;35(2):458–66.
50. Olausson A, Svensson CJ, Andrell P, Jildenstal P, Thorn S, Wolfe A. Total opioid-free general anaesthesia can improve postoperative outcomes after surgery, without evidence of adverse effects on patient safety and pain management: a systematic review and meta-analysis. Acta Anaesthesiol Scand. 2021;66(2):170–85.
51. De Oliveira GS, Agarwal D, Benzon HT. Perioperative single dose ketorolac to prevent postoperative pain: a meta-analysis of randomized trials. Anesth Analg. 2012;114(2):424–33.
52. Nielsen RV, Fomsgaard J, Mathiesen O, Dahl JB. The effect of preoperative dexamethasone on pain 1 year after lumbar disc surgery: a follow-up study. BMC Anesthesiol. 2016;16(1):112.
53. Nielsen RV, Siegel H, Fomsgaard JS, Andersen JD, Martusevicius R, Mathiesen O, et al. Preoperative dexamethasone reduces acute but not sustained pain after lumbar disk surgery. Pain. 2015;156(12):2538–44.
54. van Driel MEC, van Dijk JFM, Baart SJ, Meissner W, Huygen FJPM, Rijsdijk M. Development and validation of a multivariable prediction model for early prediction of chronic postsurgical pain in adults: a prospective cohort study. Br J Anaesth. 2022;129(3):407–15.
55. Tanguay-Sabourin C, Fillingim M, Guglietti GV, Zare A, Parisien M, Norman J, et al. A prognostic risk score for development and spread of chronic pain. Nat Med. 2023;29(7):1821–31.
56. Beloeil H, Sion B, Rousseau C, Albaladejo P, Raux M, Aubrun F, et al. Early postoperative neuropathic pain assessed by the DN4 score predicts an increased risk of persistent postsurgical neuropathic pain. Eur J Anaesthesiol. 2017;34(10):652–7.

57. Montes A, Roca G, Cantillo J, Sabate S. Presurgical risk model for chronic postsurgical pain based on 6 clinical predictors: a prospective external validation. Pain. 2020;161(11):2611–8.

58. White PF, Elvir Lazo OL, Galeas L, Cao X. Use of electroanalgesia and laser therapies as alternatives to opioids for acute and chronic pain management. F1000Res. 2017;6:2161.

15 Rehabilitation and Physical Therapy

Behnum A. Habibi, Terence Hillery, and Chong H. Kim

Introduction

Postoperative rehabilitative care is critical to patients' recovery after surgery and plays an essential role in effective pain management. Pharmacologic interventions for postoperative pain control are increasingly complemented by physical rehabilitation strategies, which not only alleviate pain but also enhance overall functional recovery. This chapter explores the scientific principles, clinical applications, and evidence supporting physical rehabilitation in postoperative pain management. By reviewing fundamental concepts and modern clinical practices, we aim to provide a comprehensive framework for all clinicians involved in postoperative care.

Consider one of the world's leading causes of disability and pain, lumbar disc herniation: in one study of patients requiring lumbar discectomy, those who participated in an early, aggressive postoperative medical exercise program had substantially lower pain and disability postoperatively [1]. Furthermore, given the long-term safety record of rehabilitative approaches, there are compelling reasons to emphasize physical rehabilitation in the postoperative period.

Background and Current Understanding

Physical rehabilitation in postoperative pain management is grounded in principles that prioritize restoring function, reducing pain, and preventing complications. Specific goals vary by body region, pain physiology, and rehabilitation-specific diagnoses (e.g., amputations, brain injury, spinal cord injury, and arthritis) [2]. In general, however, primary goals include enhancing joint and muscle mobility, promoting tissue healing through increased blood flow and reduced inflammation, and improving overall quality of life. These objectives are primarily achieved through therapeutic exercises targeting muscle strength and flexibility, in addition to manual therapies to improve range of motion. Patient education to ensure proper technique and adherence is, of course, vital to long-term efficacy. Thus, physical rehabilitation requires an interdisciplinary team, including therapists, nurses, and physicians, working collaboratively to optimize outcomes by addressing the patient's specific rehabilitative needs.

B. A. Habibi (✉)
Portland Pain Medicine, Portland, OR, USA
e-mail: bah@portlandpainmedicine.com

T. Hillery · C. H. Kim
MetroHealth, Cleveland, OH, USA

Case Western Reserve University, Cleveland, OH, USA

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_15

Clinical Applications and Techniques

Preoperative Rehabilitation "Prehabilitation" or "pre-hab" involves a regimen of exercises and therapies designed to prepare a patient for upcoming surgery. This proactive approach aims to enhance strength, flexibility, and overall physical condition, potentially leading to a quicker recovery post-surgery. For instance, in the case of a total knee replacement, pre-hab might include targeted leg exercises to strengthen the quadriceps and hamstrings. For shoulder replacement, it could involve exercises to improve shoulder mobility and strengthen the surrounding muscles.

Early Mobilization Initiating movement shortly after surgery, known as early mobilization, is critical in preventing complications such as deep vein thrombosis and muscle atrophy. Studies consistently show that early mobilization reduces hospital stay duration and recovery time [3].

Therapeutic Exercise and Manipulation A decrease in mobility, particularly of the spine, hip, shoulder, and knee joints, has substantial implications for lifelong pain and function. Tailored exercise programs, including strength training, flexibility exercises, and manual therapy, are essential for postoperative care. These interventions help restore joint mobility, strengthen muscles, and reduce pain [4, 5].

Modalities for Pain Control Techniques such as topical heat and cold application, therapeutic ultrasound (US), and Transcutaneous Electrical Nerve Stimulation (TENS) are frequently employed postoperatively as part of multimodal rehabilitative care. Topical cold therapy reduces inflammation and numbs pain, while heat therapy improves circulation and relaxes muscles. US promotes warmth and blood flow, and TENS interferes with the transmission of pain signals to the brain [6].

Biofeedback This technique involves using electronic monitoring (typically surface electromyography) to convey information about physiological processes (e.g., muscle tension, contractile effort). By providing real-time feedback about the degree of muscle activity, biofeedback encourages conscious changes in motor output and improves postoperative muscle strength, pain control, and functionality [7]. Proposed mechanisms of action are multifactorial and may include leveraging Hebbian plasticity or similar processes, which facilitate synaptic changes through repeated practice [8]. Additionally, biofeedback may aid in reducing stress and anxiety related to muscle tension, promoting better overall recovery and rehabilitation outcomes.

Assistive Devices and Adaptive Techniques Tools such as prosthetics, orthotics, and mobility aids (e.g., crutches, walkers) facilitate mobility and independence, allowing patients to perform daily activities with less pain (Table 15.1). In one study, postoperative device users, when compared with controls, reported higher levels of energy, less pain interference, lower perceived pain, and less reliance on pain medication, and returned to activities of daily living faster [9].

Summary of mobility options and their potential benefits for postoperative device users.

Table 15.1 Mobility options and outcomes

Assistive Device	Description	Benefits
Prosthetics	Artificial devices that replace missing body parts	Facilitate mobility, enhance independence
Orthotics	Supportive device for joints and muscles	Provide stability, reduce pain, and aid in functional movement
Mobility aids	Devices like crutches and walkers	Assist in movement, reduce pain, and improve balance

Multidisciplinary Approach Integrating multiple healthcare professionals and perspectives is essential to postoperative pain control, particularly in complex or refractory cases. Given that complex postoperative pain is multifactorial, it follows that multimodal, multidisciplinary care is preferred over a single pharmacologic or regional intervention. This care model, at a minimum, includes a pain specialist, physical therapist, and nursing professional [10].

Patient Education and Engagement Educating patients about their condition and involving them in their rehabilitation plan improves adherence and outcomes. For example, a study of a 1-month tailored educational program for patients after breast cancer surgery showed that rehabilitation education improved health literacy as well as nearly all components of the International Classification of Functioning, Disability, and Health status [11].

Evidence-Based Practices

A robust body of evidence supports the efficacy of physical rehabilitation in managing postoperative pain. For instance, a systematic review of clinical trials highlights that early mobilization (often within 24 h of surgery) significantly reduces length of stay, improves range of motion, muscle strength, and health-related quality of life as reported by patients, and does not increase the risk of complications [12].

A recent meta-analysis of one physical modality in the postoperative period, TENS, demonstrated a statistically significant decrease in morphine requirements and the incidence of postoperative nausea and vomiting, dizziness, and pruritus [13].

Furthermore, a systematic review and meta-analysis of randomized controlled trials published in 2023 revealed moderate-certainty evidence that prehabilitation (strength training before surgery) improves function following total knee replacement at 6 weeks postoperatively and following lumbar surgery at 6 months [14].

Challenges and Considerations

Implementing physical rehabilitation postoperatively presents several challenges. Patient-specific factors such as age, comorbidities, and the type of surgery can influence the rehabilitation process. Additionally, barriers to access, including socioeconomic factors and geographical limitations, may hinder participation in rehabilitation programs.

Adherence to rehabilitation protocols is another critical issue. Strategies to enhance adherence should emphasize personalized care plans, multimodal treatments, and multidisciplinary approaches. Ensuring cultural competence and tailoring interventions to meet the needs of diverse patient populations are also essential.

Future Directions and Research

Emerging technologies like virtual reality (VR) and robotics offer exciting possibilities for postoperative rehabilitation. VR can create immersive rehabilitation environments that enhance patient engagement and pain distraction. At the same time, robotic-assisted therapy can provide precise and repetitive movements crucial for recovery with less physical reliance on care providers.

Home-based tele-rehabilitation has emerged as an alternative to traditional rehabilitation settings. For example, a recent meta-analysis of home versus hospital-based rehabilitation, including data from nine studies with a total of 1,944 patients, showed comparable long-term outcomes in pain, mobility, physical function, and patient-reported health status after primary total knee arthroplasty [15].

Large-scale studies are needed on the long-term benefits of different rehabilitation techniques and their cost-efficacy. Additionally, exploration of precision medicine approaches, such as personalized rehabilitation protocols based on genetic and phenotypic characteristics, could lead to more effective interventions.

Interdisciplinary approaches will likely evolve, integrating novel therapies such as regenerative medicine and neuromodulation. Finally, prehabilitation has shown promising results, suggesting additional settings and protocols for the use of physical medicine and rehabilitation in perioperative care.

Key Takeaways

1. Understand the foundational principles of physical rehabilitation and its role in postoperative pain management.
2. Recognize the state of the evidence of postoperative rehabilitation protocols.
3. Acknowledge the benefits of exercise and early mobilization in reducing pain and improving recovery.
4. Appreciate the value of a multidisciplinary approach in providing comprehensive care and optimizing rehabilitation outcomes.
5. Recognize the necessity of large-scale and long-term studies to evaluate postoperative rehabilitation's efficacy and tailor rehabilitation strategies to specific conditions.

References

1. Danielsen JM, Johnsen R, Kibsgaard SK, Hellevik E. Early aggressive exercise for postoperative rehabilitation after discectomy. Spine. 2000;25(8):1015–20.
2. Frontera WR, Silver JK. Essentials of physical medicine and rehabilitation E-book: musculoskeletal disorders, pain, and rehabilitation. Philadelphia: Elsevier Health Sciences; 2018.
3. Yakkanti RR, Miller AJ, Smith LS, Feher AW, Mont MA, Malkani AL. Impact of early mobilization on length of stay after primary total knee arthroplasty. Ann Transl Med. 2019;7(4):69. https://doi.org/10.21037/atm.2019.02.02. PMID: 30963064; PMCID: PMC6409239.
4. Keating EM, Ritter MA, Harty LD, Haas G, Meding JB, Faris PM, Berend ME. Manipulation after total knee arthroplasty. J Bone Joint Surg Am. 2007;89(2):282–6. https://doi.org/10.2106/JBJS.E.00205.
5. Evgeniadis G, Beneka A, Malliou P, Mavromoustakos S, Godolias G. Effects of pre-or postoperative therapeutic exercise on the quality of life, before and after total knee arthroplasty for osteoarthritis. J Back Musculoskelet Rehabil. 2008;21(3):161–9.
6. Elvir-Lazo OL, White PF. Postoperative pain management after ambulatory surgery: role of multimodal analgesia. Anesthesiol Clin. 2010;28(2):217–24.
7. Karaborklu Argut S, Celik D, Yasacı Z. Effectiveness of therapeutic electromyographic biofeedback after orthopedic knee surgeries: a systematic review. Disabil Rehabil. 2022;44(14):3364–72.
8. Loriette C, Ziane C, Hamed SB. Neurofeedback for cognitive enhancement and intervention and brain plasticity. Rev Neurol. 2021;177(9):1133–44.
9. Babski-Reeves KL, Tran GM. Efficacy of an assistive intervention for abdominal surgery patients in postoperative care. Disabil Rehabil Assist Technol. 2006;1(3):191–7.
10. Admiraal M, Hermanides J, Meinsma SL, Wartenberg HC, Rutten MV, Ward-van der Stam VM, Hollmann MW, Hermanns H. Current multidisciplinary approaches to preventing chronic postoperative pain. Br J Anaesth. 2021;127(3):331–5.
11. Huang SC, Kuo SF, Tsai PS, Tsai CY, Chen SS, Lin CY, Lin PC, Hou WH. Effectiveness of tailored rehabilitation education in improving the health literacy and health status of postoperative patients with breast cancer: a randomized controlled trial. Cancer Nurs. 2020;43(1):E38–46.
12. Guerra ML, Singh PJ, Taylor NF. Early mobilization of patients who have had a hip or knee joint replacement reduces length of stay in hospital: a systematic review. Clin Rehabil. 2015;29(9):844–54.
13. Viderman D, Nabidollayeva F, Aubakirova M, Sadir N, Tapinova K, Tankacheyev R, Abdildin YG. The impact of transcutaneous electrical nerve stimulation (TENS) on acute pain and other postoperative outcomes: a systematic review with meta-analysis. J Clin Med. 2024;13(2):427.
14. Punnoose A, Claydon-Mueller LS, Weiss O, Zhang J, Rushton A, Khanduja V. Prehabilitation for patients undergoing orthopedic surgery: a systematic review and meta-analysis. JAMA Netw Open. 2023;6(4):e238050.
15. Zhang H, Wang J, Jiang Z, Deng T, Li K, Nie Y. Home-based tele-rehabilitation versus hospital-based outpatient rehabilitation for pain and function after initial total knee arthroplasty: a systematic review and meta-analysis. Medicine (Baltimore). 2023;102(51):e36764. https://doi.org/10.1097/MD.0000000000036764.

16

Outpatient Transitional Pain Clinics and Referrals: The Role of Specialized Outpatient Clinics in Ongoing Postoperative Pain Management

Elizabeth Woodford, Ala Mahamid, Joel Katz, and Hance Clarke

The development of chronic postsurgical pain (CPSP) is a significant contributor to patient morbidity. Evidence has shown that the incidence of acute neuropathic pain after surgery is estimated between 1% and 3% [1, 2]. Of these, more than half are expected to transition to chronic pain [1], as will others whose pain is missed at this early stage or who develop pain at a later time. Given the prevalence of chronic pain in postsurgical patients, the need for acute, transitional, and chronic pain management services is essential. Transitional Pain Services (TPS) provides value to perioperative patients by enabling preoperative assessments to gauge risk, educate, set expectations regarding pain management, optimize medications, and intervene prior to surgery. In the postoperative period, once an acute pain service has signed off, the service can be contacted to continue pain services in the subacute/transitional pain period longitudinally on an outpatient basis. This outpatient clinic model uses a multidisciplinary approach, including pain specialist physicians, physiotherapists, nurse practitioners, psychologists, and psychiatry, to support to address postoperative pain, attempt to change patient trajectories, and reduce the incidence of chronic postsurgical pain as well as the development of persistent opioid use.

E. Woodford
Eastern-Urban Zone, NL Health Services, Memorial University, St. John's, NF, Canada

A. Mahamid
Nova Scotia Health Authority, Eastern Zone, Cape Breton Regional Hospital, Sydney, NS, Canada

J. Katz
Department of Psychology, York University, Toronto, ON, Canada

Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, ON, Canada

Department of Anesthesiology & Pain Medicine, University of Toronto, Toronto, ON, Canada

H. Clarke (✉)
Department of Anesthesiology & Pain Medicine, University of Toronto, Toronto, ON, Canada

Toronto General Hospital, University Health Network, Toronto, ON, Canada
e-mail: hance.clarke@uhn.ca

Background and Current Understanding

Chronic postsurgical pain is often defined as pain related to a surgical procedure which persists for at least 3 months [3, 4]. It is estimated that 8% of all surgical patients (over 300 million surgeries occur globally each year) report pain disability as a consequence of their surgery at 12 months. An acute pain which becomes chronic can have multiple deleterious physical, mental, and financial effects which negatively impact patients' quality

P. Gulur et al. (eds.), *Perioperative Pain Management*,
https://doi.org/10.1007/978-3-032-11484-6_16

of life. Additionally, evidence shows that chronic pain can be associated with persistent postoperative opioid use (PPOU) [3]. While definitions of PPOU vary, many accept a timeframe of greater than 3 months of opioid use after an operation [5]. Some evidence has shown that the incidence of PPOU is as high as 25% in opioid-naïve and 75% of non-opioid-naïve patients [6]. Access to opioid medications in at-risk patients can potentially lead to misuse and the development of an opioid use disorder [5]. Furthermore, preoperative opioid use is thought to be associated with increased rates of postoperative complications, CPSP, opioid misuse, and medical complications including immunosuppression [7]. In the context of the ongoing opioid epidemic within North America and beyond, consensus statements/guidelines have been created to reduce excessive opioid prescribing in the postoperative setting [8–10]. Outside of concerns of misuse, patients with persistent postoperative opioid use are more likely to rate their own global health lower and rate their pain-related interference with mood, work and physical functioning higher as compared to non-opioid-using patients [11].

A Transitional Pain Service aims to identify those patients at risk for developing CPSP and provide multidisciplinary care to prevent the transition from acute to chronic pain. The Transitional Pain Service at the Toronto General Hospital is the first of its kind to provide comprehensive preoperative and postoperative pain management to address the rising incidence of CPSP and inappropriate PPOU, and to improve overall patient functioning and quality of life [12].

Clinical Applications and Techniques Utilized by a Transitional Pain Service

A Transitional Pain Service aims to serve patients in the postoperative outpatient by reducing the development of chronic postsurgical pain and persistent opioid use. By assessing at-risk patients and intervening early in the process, the data show that patients who are struggling in the immediate postoperative period have improved outcomes at 6 months and beyond [6, 13, 14]. Transitional pain teams can be comprised of anesthesiologists, other physicians, and psychologists with specialized training and experience in acute and chronic pain management, psychiatrists, nurses and nurse practitioners, physical therapists, as well as administrative staff. Transitional pain patients are ideally identified either preoperatively by surgeons, in preadmission assessments completed by anesthesiologists, or immediately postoperatively by the acute pain team. At-risk patients are identified by one or more of the following factors: a history of chronic pain, preoperative opioid use, significant preoperative emotional distress, postoperative pain and/or distress not in keeping with the norm while managed by the acute pain service in-hospital, high postoperative opioid requirements [12]. Other potential preoperative referral criteria may include a history of depression, anxiety, pain catastrophizing, and substance use disorder [15].

Transitional Pain Services provide multidisciplinary care to complex patients. Pain physicians assess patients preoperatively to ensure their pain medications are optimized and provide management postoperatively with pharmacotherapies and interventional treatments. Nurse practitioners within the pain team/clinic are critical in managing patients in the acute postoperative setting through the Acute Pain Services as well as identifying those patients who would be best served by a TPS team post discharge on an expedient outpatient basis. Nurse practitioners also serve as important team members in assessing and managing patients in the TPS clinic. Psychologists are essential in providing support to patients with a history of anxiety, depression, PTSD, and a history of chronic pain with high opioid requirements [12]. The psychologists at the TPS at the Toronto General Hospital provide patients with a variety of psychotherapeutic interventions (e.g., Acceptance and Commitment Therapy, Cognitive Behavioral Therapy, clinical hypnosis, etc.) which include pain education and coping skills which are aimed at targeting pain interference, anxiety and depression as well as opioid weaning [16]. A psychiatrist is pivotal in

managing mental health problems which merit pharmacologic therapies and ongoing management. It is well accepted that physiotherapy is an important facet of recovery after surgery. Physical therapists work with inpatients and outpatients to improve mobility and function and to reduce pain using various modalities (TENS, acupuncture, etc.).

Evidence-Based Practices

An important objective of any Transitional Pain Service is to ensure patients are weaned appropriately from their opioids in the postoperative period. Opioid weaning in the postoperative period can be achieved only with the mutual agreement and commitment of patient and provider. Transitional pain clinics offer non-pharmacologic multidisciplinary interventions, pharmacologic multimodal non-opioid agents, and interventions (peripheral nerve blocks) to meet this common goal. In a 2023 retrospective cohort study by Yu et al. including 140 solid organ transplant patients, opioid consumption was measured preoperatively, postoperatively, and at discharge from the TPS. The median length of treatment by the Transitional Pain Service in this study was 210 days. Preoperatively, more than half (67%) were receiving opioids with a median of 15 morphine equivalents per day. By the last TPS visit, mean daily opioid use was reduced significantly from 22.56 to 9.61 mg in morphine equivalents (MME) per day ($p < 0.001$). There was also a significant reduction in pain severity as measured by the Brief Pain Inventory and Short-Form McGill Pain Questionnaire-2 [7]. A 2023 retrospective cohort study [13] that matched 209 TPS patients as closely as possible with 209 controls who received surgery at other centers and did not receive TPS care showed that the mean daily dose of opioids (in mg morphine equivalents) over the 12-month period after surgery decreased by a significantly greater extent in TPS patients (3.53 MME) than controls (1.05 MME), indicating that TPS care resulted in a faster opioid dose reduction [13].

As mentioned, opioid weaning in the postoperative period can be achieved through a variety of non-pharmacologic techniques. A recent randomized controlled trial by Rosenbloom et al. (2024) assessed the impact of clinical hypnosis pre- and postoperatively on opioid consumption, pain intensity, and pain interference. Ninety-two adult patients undergoing surgical oncology procedures were randomized to a control group (no hypnosis) or a clinical hypnosis group in which patients received one session preoperatively and one in the postoperative period. Patients randomized to the hypnosis group consumed a significantly lower dose of opioids on the first day ($p = 0.01$) and the fourth day ($p = 0.04$) after surgery compared to controls patients [17].

Challenges and Considerations

There are multiple inherent challenges that a Transitional Pain Service will encounter. A TPS clinic approaches pain assessment and management using a multidisciplinary approach, and therefore access to psychology, physiotherapy, nursing and psychiatry are pivotal to a clinic's success. With the startup of a new TPS clinic at any centre, several resource barriers must be addressed, both professional and systemic. The availability of essential professions involved in TPS care may be limited. Another potential challenge for a TPS service is gaining buy-in from surgical and nursing colleagues. Patient referrals should come from surgeons and acute pain service nurses and nurse practitioners who correctly identify and refer only patients who would benefit from the service.

Beyond reducing pain disability long term, one of the objectives of a TPS is to wean patients from postoperative opioids in a timely manner (within 6 months) and have a plan in place to discharge patients back to their family physicians. In the current era of the family physician shortage [18], this can add barriers to TPS patient discharge and contribute to limited capacity for new referrals.

Given that society has been pointing to the peri-operative setting as an area in which patients

are exposed to opioid medications and potentially persist on their opioids long term and develop an opioid use disorder, appropriate prescribing of opioids in the postoperative setting is paramount. A 2020 consensus statement set out expert recommendations for prescribing opioids in opioid-naïve patients undergoing elective surgical procedures [8]. The recommendations include comprehensive patient and family education and managing expectations regarding pain and recovery in the postoperative period. Patients and families should be given information on how to appropriately manage their pain with multimodal agents, including non-opioid and opioid agents where necessary. Education and guidance must be provided for appropriate use and disposal of unused opioid medications, as well as suitable weaning approaches. Patients should be screened preoperatively for risk factors for PPOU, including a history of anxiety, depression, PTSD, chronic pain syndromes, age 18–30 years, history of alcohol or substance use disorders. For patients identified as high risk, special care is warranted to provide opioid-sparing multi-modal analgesia in the perioperative period and a careful weaning protocol should be instituted. Postsurgical pain is ideally managed with a combination of non-opioid medications (including acetaminophen and non-steroidal anti-inflammatories) and non-pharmacological approaches as a first-line treatment. When these approaches do not adequately control pain, opioids can be added. Opioids should be given on an outpatient basis to patients who received opioids as inpatients in quantities based on the length of recovery expected for a given surgical procedure. Procedures range from rapid recovery (resuming regular activities within 2 weeks) requiring up to 3 days of opioids, to long-term recovery (resuming regular activities greater than 4 weeks after discharge) requiring up to 14 days of opioid medications. Patients who have not needed opioids in the 24 hours prior to discharge should not be prescribed opioids at hospital discharge [19]. The consensus statement includes a recommendation that all opioid prescriptions should expire within 30 days of discharge from hospital. Patients who have persistent pain beyond 30 days should be referred to a transitional pain service clinic if not identified within their in-hospital postsurgical admission [8].

A Case Study

A typical Transitional Pain Service patient is one who is seen as an outpatient in the early postoperative period within the first 2–3 weeks of being discharged. However, patients can be consulted and identified early as postoperative patients by the acute pain service to provide guidance on the management of acute pain in the postoperative setting for patients with complex pain problems.

The case of Mr. P, a patient presenting for laparotomy for a bleeding duodenal ulcer, was described in a 2017 case report by Weinrib et al. [14]. This patient had a history significant for chronic pains related to osteoarthritis, kyphoscoliosis, degenerative disc disease, fibromyalgia, and multiple sclerosis. He also had a past medical history significant for bipolar disorder. Preoperatively, this patient was receiving transdermal fentanyl 37.5 mcg/hour as well as 65 mg oral hydromorphone daily, equating to a morphine equivalent dose of 460 mg daily. He was also taking high dose Ibuprofen for several years leading up to his presentation for bleeding ulcers. Additionally, Mr. P had a history of a substance and alcohol use disorder. He was an ex-smoker with a 70 pack-year history. In his postoperative course, a consult was made to the TPS to address his high pain intensity and opioid requirements. The TPS enlisted a multidisciplinary approach to address this patient's issues. The TPS pain physician first initiated multimodal therapies including gabapentin as an opioid sparing strategy. Other modalities that may have been considered include antidepressants such as duloxetine, or amitriptyline, nonsteroidal anti-inflammatories (NSAIDS), acetaminophen, or cannabinoids. For Mr. P, he was unable to receive antidepressants due to his history of bipolar disorder. He was also unable to receive ongoing NSAID therapy due to his presentation for bleeding ulcers. Furthermore, he had previously tried nabilone for his chronic pains with

no perceived benefits. Physiotherapy is an integral part of recovery from surgery and the management of chronic pains. Mr. P participated in community physiotherapy on a regular basis. He also participated in individual and group behavioural interventions by the TPS psychologists. Mr. P attended 5 individual sessions and 22 group sessions, both rooted in ACT (acceptance and commitment therapy). These sessions incorporate mindfulness of pain sensations and acceptance strategies. Within 8 months of his operation, the patient weaned down on his opioids from 460 MEQs to 345 MEQs. However, he admitted to behaviours consistent with opioid dependence including using his opioids to avoid withdrawal symptoms he experienced when he inadvertently missed a dose. The patient had expressed severe emotional distress around being dependent on his opioid medications. The TPS pain physicians were able to rotate his opioid therapy to buprenorphine/naloxone. While it is unexpected that buprenorphine/naloxone would provide more pain relief than a full mu-agonist opioid, the conversion to buprenorphine/naloxone likely demonstrated that Mr. P was likely also experiencing opioid induced hyperalgesia. With the help of the Toronto General Hospital TPS multidisciplinary team, Mr. P, was able to address his concomitant pain and opioid use disorder, and improve his functioning and overall quality of life [14].

Future Directions and Research

The primary goal of Transitional Pain Services is to improve the trajectories of patients who are struggling with pain and opioid use and to avoid the development of the dual problems of chronic postsurgical pain and persistent opioid use. Cannabinoids are considered a third-line agent for the treatment of neuropathic pain [20]. There is increasing interest in the potential use of medical cannabis as an opioid-sparing agent [21]. This is a developing area of current and potential future research in both Canada and the United States of America.

Furthermore, there is a dearth of evidence to support the use of early outpatient interventional pain procedures (e.g., erector spinae plane blocks) in the postoperative period. What is often used as a surrogate for an acceptable timeframe to perform such an intervention is surgeon approval. There are multiple reasons why clinicians may be reluctant to perform interventional pain procedures in this setting, including increased risk for bleeding, infection, or disruption of tissue planes in the healing patient. Evidence supporting the utility of these procedures in outpatient clinics to prevent CPSP is an area that requires future attention. A recent publication demonstrated that patients receiving care from the Toronto General Hospital Transitional Pain Service were able to achieve opioid dose reduction faster than control cohorts using data obtained from a public administrative database [13]. Finally, an ongoing study entitled Reducing Opioid Use for Chronic Pain Patients Following Surgery (i.e., the RECOUP trial) is a multicenter randomized controlled trial in Ontario, Canada, which aims to determine whether a TPS program is more effective than a control intervention for reducing 12-month pain disability, with a secondary outcome of opioid reduction over a similar time frame.

Key Takeaways

- The development of chronic postsurgical pain negatively impacts multiple domains of everyday life, including physical, psychological, and emotional functioning, as well as having financial implications for patients, who, as a result, may lose income and/or their jobs.
- Transitional Pain Services use a multidisciplinary approach to address acute postoperative pain, reduce conversion to chronic postsurgical pain, and decrease persistent opioid use in the perioperative setting.
- Persistent opioid use after surgery has been implicated as one driver of the opioid crisis; Transitional Pain Services can serve as an effective method for opioid stewardship.

- Medical cannabis for chronic postsurgical pain, the utility of early interventional pain procedures in the postoperative setting, and hypnosis are areas of interest for future research.

References

1. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother. 2009;9(5):723–44.
2. Hayes C, Browne S, Lantry G, Burstal R. Neuropathic pain in the acute pain service: a prospective survey. Acute Pain. 2002;4(2):45–8.
3. Bansal N, Ang S, Chen LC. Prevalence and determinants of chronic pain and persistent opioid use after surgery: a review of systematic reviews. Br J Pain. 2024;18(1):95–103.
4. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede RD, Pain ITftCoC. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. Pain. 2019;160(1):45–52.
5. Kent ML, Hurley RW, Oderda GM, Gordon DB, Sun E, Mythen M, et al. American Society for enhanced recovery and perioperative quality initiative-4 joint consensus statement on persistent postoperative opioid use: definition, incidence, risk factors, and health care system initiatives. Anesth Analg. 2019;129(2):543–52.
6. Clarke H, Azargive S, Montbriand J, Nicholls J, Sutherland A, Valeeva L, et al. Opioid weaning and pain management in postsurgical patients at the Toronto General Hospital transitional pain service. Can J Pain. 2018;2(1):236–47.
7. Yu HC, Kleiman V, Kojic K, Slepian PM, Cortes H, McRae K, et al. Prevention and management of chronic postsurgical pain and persistent opioid use following solid organ transplantation: experiences from the Toronto General Hospital transitional pain service. Transplantation. 2023;107(6):1398–405.
8. Clarke HA, Manoo V, Pearsall EA, Goel A, Feinberg A, Weinrib A, et al. Consensus statement for the prescription of pain medication at discharge after elective adult surgery. Can J Pain. 2020;4(1):67–85.
9. Thiels CA, Ubl DS, Yost KJ, Dowdy SC, Mabry TM, Gazelka HM, et al. Results of a prospective, multicenter initiative aimed at developing opioid-prescribing guidelines after surgery. Ann Surg. 2018;268(3):457–68.
10. Hill MV, Stucke RS, Billmeier SE, Kelly JL, Barth RJ Jr. Guideline for discharge opioid prescriptions after inpatient general surgical procedures. J Am Coll Surg. 2018;226(6):996–1003.
11. Huang A, Azam A, Segal S, Pivovarov K, Katznelson G, Ladak SS, et al. Chronic postsurgical pain and persistent opioid use following surgery: the need for a transitional pain service. Pain Manag. 2016;6(5):435–43.
12. Katz J, Weinrib A, Fashler SR, Katznelzon R, Shah BR, Ladak SS, et al. The Toronto General Hospital transitional pain service: development and implementation of a multidisciplinary program to prevent chronic postsurgical pain. J Pain Res. 2015;8:695–702.
13. Ladha KS, Vachhani K, Gabriel G, Darville R, Everett K, Gatley JM, et al. Impact of a transitional pain service on postoperative opioid trajectories: a retrospective cohort study. Reg Anesth Pain Med. 2023;49:650.
14. Weinrib AZ, Burns LC, Mu A, Azam MA, Ladak SS, McRae K, et al. A case report on the treatment of complex chronic pain and opioid dependence by a multidisciplinary transitional pain service using the ACT matrix and buprenorphine/naloxone. J Pain Res. 2017;10:747–55.
15. Transitional Pain Service TGH. For health professionals: referring guidelines for pre- and post-surgical patients 2024. Available from: https://www.transitionalpainservice.ca/for-health-professionals.
16. Abid Azam M, Weinrib AZ, Montbriand J, Burns LC, McMillan K, Clarke H, Katz J. Acceptance and commitment therapy to manage pain and opioid use after major surgery: preliminary outcomes from the Toronto General Hospital Transitional Pain Service. Can J Pain. 2017;1(1):37–49.
17. Rosenbloom BN, Slepian PM, Azam MA, Aternali A, Birnie KA, Curtis K, et al. A randomized controlled trial of clinical hypnosis as an opioid-sparing adjunct treatment for pain relief in adults undergoing major oncologic surgery. J Pain Res. 2024;17:45–59.
18. Smart K. Critical family physician shortage must be addressed: CMA: Canadian Medical Association; 2022. Available from: https://www.cma.ca/about-us/what-we-do/press-room/critical-family-physician-shortage-must-be-addressed-cma.
19. Clarke H, Katz J. Patterns of opioid use after surgical discharge: pain management beyond the first postoperative week. Anaesthesia. 2024;79:909.
20. Moulin D, Boulanger A, Clark AJ, Clarke H, Dao T, Finley GA, et al. Pharmacological management of chronic neuropathic pain: revised consensus statement from the Canadian Pain Society. Pain Res Manag. 2014;19(6):328–35.
21. Meng H, Hanlon JG, Katznelson R, Ghanekar A, McGilvray I, Clarke H. The prescription of medical cannabis by a transitional pain service to wean a patient with complex pain from opioid use following liver transplantation: a case report. Can J Anaesth. 2016;63(3):307–10.

17

Advanced Interventional Techniques for Perioperative Pain Management: Continuous Peripheral Nerve Blocks and Ultrasound-Guided Percutaneous Cryoneurolysis

John J. Finneran IV and Brian M. Ilfeld

Introduction

Pain following surgery is often severe and may transition from acute pain, experienced in the hours and days following surgery, to chronic postsurgical pain (CPSP), which persists for months or years and may be associated with significant disability [1]. The incidence of CPSP varies widely—from less than 10% to greater than 50%—and is dependent on a multitude of patient and surgical factors, including the type of surgery (breast surgery, joint replacement, and amputations having particularly high incidence of CPSP), perioperative nerve injury resulting in neuropathic pain, patient genetic predisposition, and a continuing inflammatory response postoperatively [2]. Inadequate perioperative pain control has recently been identified as an independent risk factor for the development of CPSP, and time spent in severe pain during the acute postoperative period directly correlates with the incidence of CPSP at 12 months following surgery [3]. At the physiologic level, this may be the related to the central sensitization that occurs when noxious stimuli are encountered (i.e., painful stimuli increase the brain's excitability to further painful stimuli) [4]. Thus, optimizing acute postoperative pain management is critical for both improving the perioperative patient experience and potentially decreasing the long term suffering and disability caused by CPSP as well.

Peripheral nerve blocks (PNBs) with local anesthetics are commonly utilized to alleviate postoperative pain. Unfortunately, the pain following surgery often exceeds the duration of the analgesia provided by a single injection of local anesthetic. A continuous peripheral nerve block (CPNB), or perineural local anesthetic infusion, and percutaneous peripheral nerve cryoneurolysis are perioperative analgesic modalities with the potential to provide much longer-lasting perioperative pain control compared to single-injection PNBs [5, 6]. Recent evidence suggests the use of these techniques perioperatively not only decreases pain scores and opioid requirements in the acute postoperative timeframe, but may also decrease the transition from acute to chronic postoperative pain [7–12].

Continuous Peripheral Nerve Blocks

Background and Current Understanding The first described use of a continuous infusion of local anesthetic via an indwelling catheter occurred in 1951 as a treatment for intractable

J. J. Finneran IV (✉) · B. M. Ilfeld
Department of Anesthesiology, University of California, San Diego, San Diego, CA, USA
e-mail: jfinneran@health.ucsd.edu

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_17

singultus (hiccups) [13]. Today, CPNBs, or "perineural local anesthetic infusions," may be utilized as inpatient or ambulatory therapy to provide several days of potent analgesia following surgery. Although perineural catheters have been inserted using nerve stimulation and simple tactile-based techniques, real-time ultrasound imaging has become the predominant modality for catheter insertion [5]. Continuous techniques have been described for most of the commonly utilized single-injection nerve block locations in the torso as well as the upper and lower extremities [14]. There is substantial evidence that CPNBs improve pain scores and decrease opioid consumption following painful orthopedic and thoracic surgery; however, most investigations have focused on pain scores and opioid consumption during the *acute* postoperative period [5, 14].

Clinical Applications, Techniques, and Evidence-Based Practices Given the relationship between perioperative pain management and the development of CPSP, improved pain control during the acute postoperative period provided by CPNBs would be expected to reduce the incidence of CPSP. To test this hypothesis, Ilfeld et al. randomized patients undergoing mastectomy with a single-injection ropivacaine paravertebral nerve block to receive a 3-day infusion of ropivacaine vs. placebo. Not only did participants who received the continuous ropivacaine infusion have lower pain scores during the acute postoperative period, but they also had a lower incidence of pain and less pain-related physical and emotional dysfunction 1 year following mastectomy [7]. This trial provided evidence that—at least for breast surgery—improved pain control during the early postoperative period with the use of a CPNB may decrease the occurrence of CPSP one year following surgery. Additional supporting evidence has been provided by studies involving breast surgery [8], knee arthroplasty [9, 10], and procedures of the ankle [11].

Challenges and Considerations The duration of analgesia provided by CPNBs is primarily limited by infection risk, which increases with the duration of therapy, catheter migration from the target nerve, and the size of the local anesthetic reservoir patients can comfortably carry when using ambulatory pumps [5]. Factors increasing the risk of infection include intensive care unit stay, implantation duration greater than 24 h, absence of prophylactic antibiotics during surgery, axillary and femoral catheter locations, and frequent changes of catheter site dressings. However, the overall infection rate of perineural catheters is relatively low (0–3%) and infections are generally resolve with antibiotic therapy when they do occur [15].

Perineural catheters generally are not secured internally, thus migration of the catheter tip from the target nerve is probable as postsurgical patients ambulate and participate in physical therapy. This may be especially true for catheters inserted at anatomic sites with a high degree of mobility (e.g., femoral) [16]. Thus, as perineural catheters remain in situ for prolonged periods, the amount of local anesthetic delivered to the target nerve may decrease over time. In hospitalized patients, there is no absolute upper limit on the duration of a perineural infusion. However, for ambulatory patients, carrying a pump and local anesthetic reservoir becomes increasingly cumbersome as the volume–and weight–of the local anesthetic increases. Thus, ambulatory CPNBs are generally limited to approximately 500 mL [14].

Future Directions and Research Because the volume of the local anesthetic reservoir limits the duration of ambulatory CPNBs, recent investigations have focused on decreasing the rate of consumption of local anesthetic while continuing to provide comparable analgesia. Finneran et al. demonstrated that the use of start-delay timers and replacing continuous infusions with automated boluses of local anesthetic prolonged the overall duration of ambulatory continuous popliteal sciatic blocks following painful foot and ankle surgery. Analgesia was improved *both* while each infusion was running and after the continuous infusion group had exhausted their local anesthetic reservoir [17]. As perioperative pain control is related to the risk of CPSP,

extending the duration of CPNBs following painful surgeries may decrease the incidence of CPSP. However, this has yet to be investigated.

Whether the improvement in the occurrence of CPSP when CPNBs are utilized for postoperative analgesia is isolated to breast surgery patients or applies more broadly to other painful, high-CPSP-risk is a question that remains to be answered. An ongoing randomized trial utilizing extended-duration femoral and sciatic continuous bupivacaine infusions following lower extremity amputation may provide insight into the generalizability of CPNBs for prevention of CPSP (NCT03461120).

Cryoneurolysis

Background and Current Understanding The use of cold as a treatment for pain—termed cryoanalgesia—has ancient origins. Cryoneurolysis specifically refers to the application of extreme cold temperatures to reversibly ablate peripheral nerves. When exposed to temperatures in the −20 to −100 °C range (approximately), peripheral nerves undergo Wallerian degeneration, the process of axonal degradation distal to the site of treatment. As the surrounding connective tissues remain intact, the nerves regenerate at a rate of 1–2 mm per day. Thus, cryoneurolysis produces a reversible block with a duration potentially measured in weeks or months. Early applications of cryoneurolysis required surgical exposure of peripheral nerves for direct application of a cryoprobe; however, the development of percutaneously inserted cryoprobes now allows this procedure to be performed by healthcare providers with ultrasound guidance [6].

Clinical Applications, Techniques, and Evidence-Based Practices Modern cryoneurolysis devices utilize a tube within a tube design in which room-temperature gas at high pressure flows down the length of the cryoprobe and through a narrow annulus at the distal end. The decrease in pressure distal to the annulus produces a drop in temperature at the tip and freezing of the surrounding tissue due to the Joule-Thomson effect. The gas exits out through the central compartment of the probe so that nothing is injected into the patient (Fig. 17.1) [6].

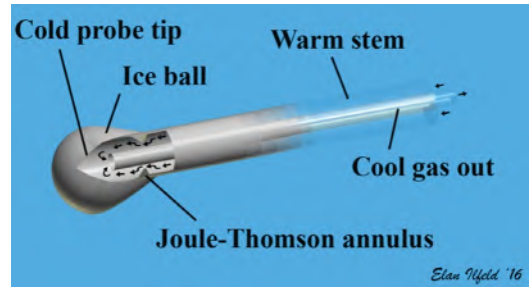


Fig. 17.1 Schematic of a cryoprobe with warm gas flowing at high pressure through an annulus at the tip leading to a decrease in pressure and temperature. (Used with permission from Brian M. Ilfeld, MD, MS, who retains the rights to the image)

As the technique for ultrasound-guided cryoneurolysis of peripheral nerves is very similar to conventional ultrasound-guided nerve blocks, this skill is usually easy to incorporate into a regional anesthesiologist's practice. The cryoprobe is positioned under ultrasound guidance adjacent to the target nerve and activated. Ultrasound visualization of the frozen tissue, or "ice ball," is maintained throughout the procedure to ensure the ice ball (1) encompasses the entire nerve and (2) does not move substantially, as this could theoretically lead to tearing of the surrounding tissues (Fig. 17.2).

With a potential duration measured in months, cryoneurolysis may afford extremely long-duration analgesia. However, the target sites are limited when compared to CPNBs due to the effects of the prolonged sensory, proprioceptive, and motor block. Thus, target nerves for cryoneurolysis are generally limited to those with no or minimal motor function (e.g., lateral femoral cutaneous, infrapatellar branch of the saphenous, intercostal, and suprascapular nerves) and clinical scenarios in which a prolonged block is acceptable (e.g., sciatic nerve cryoneurolysis for below-knee amputation). As with CPNBs, the extremely long duration of analgesia that may be provided by cryoneurolysis and the resultant

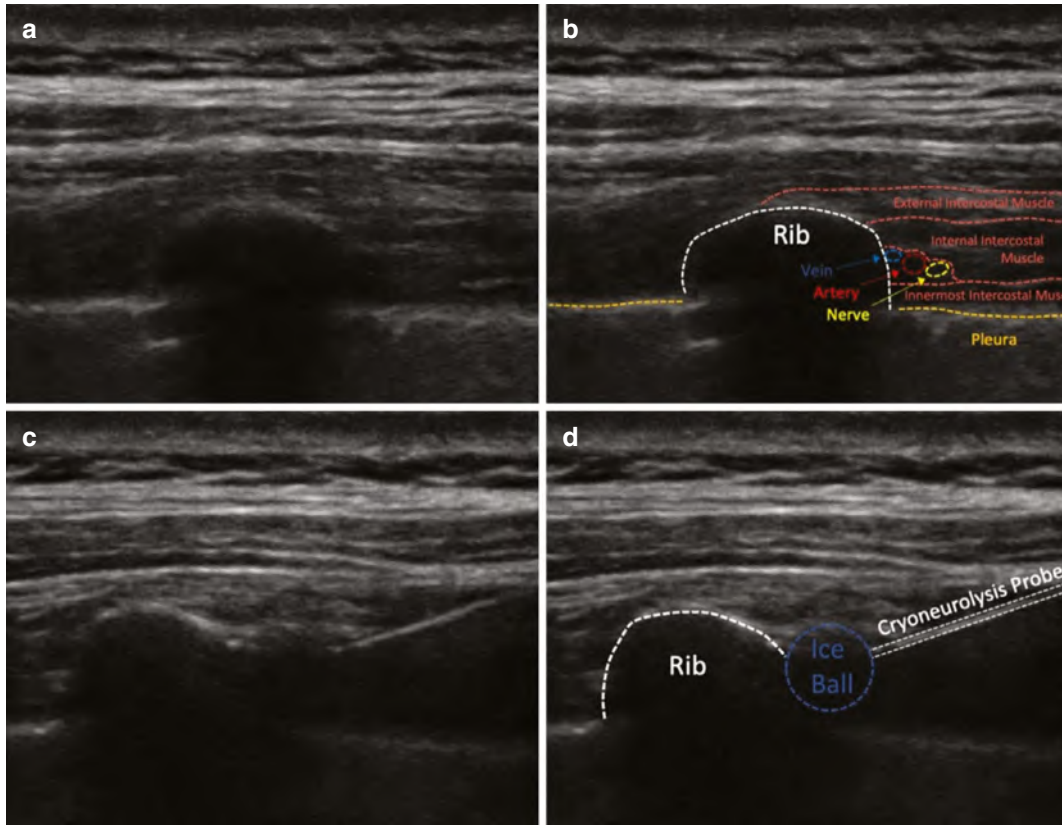


Fig. 17.2 Ultrasound images of percutaneous cryoneurolysis of an intercostal nerve. (Used with permission from John J. Finneran IV, MD, who retains the rights to the image)

decrease in acute postoperative pain would be expected to decrease the incidence of CPSP. However, most investigations have focused on pain during the acute period.

In a randomized comparison, preoperative intercostal cryoneurolysis of the second through fifth intercostal nerves was found by Ilfeld et al. to decrease pain scores and pain-related physical and emotional dysfunction up to one-year following mastectomy, in addition to decreasing opioid consumption for the first 3 weeks after surgery [8]. In this study, the investigators compared active cryoneurolysis to a sham procedure, with all participants receiving a continuous ropivacaine nerve block for 2 days following surgery. Thus, the observed benefits of cryoneurolysis in this study were in addition to the benefit expected from the CPNB. At 1 year following mastectomy, no participant in the active cryoneurolysis group was experiencing phantom breast pain, compared to 19% of those in the sham group. Critically important, as the time spent in *severe* pain correlates with the development of CPSP, 45% of participants in the sham cryoneurolysis group experienced severe pain—defined as a pain score of 7 or greater on an 11-point numeric rating scale—at some point during the year following surgery, while no participant in the active cryoneurolysis group experienced severe pain at any point during this year [8].

Challenges and Considerations As mentioned above, the primary limitation of cryoneurolysis is also its main benefit: an extremely long-duration block. Thus, cryoneurolysis is contraindicated in any clinical scenario in which prolonged motor block would be unacceptable. When utilizing cryoneurolysis for lower extremity amputations,

it is imperative to ensure that (1) there is no chance of an intraoperative decision to cancel the amputation and (2) the location (proximal vs. distal) chosen for cryoneurolysis will not interfere with rehabilitation following amputation [18].

There is tremendous variability in cryoneurolysis administration protocols in the published literature regarding (1) the time devoted to freezing and thawing in each cycle, (2) the total number of cycles applied to each nerve, and (3) whether a local anesthetic block is performed in addition to the cryoneurolysis procedure [6]. When cryoneurolysis is utilized on a single nerve, the time requirement is generally not substantially greater than single-injection nerve blocks. However, with several minutes spent freezing in each freeze/thaw cycle—and potentially multiple cycles per nerve—the time commitment can be substantial when utilized for multiple nerves (e.g., cryoneurolysis of 10 intercostal nerves for bilateral mastectomies).

Contraindications to cryoneurolysis are similar to those for any percutaneous regional anesthesia procedures (i.e., local infection, patient refusal, coagulopathy) but also include cold-activated conditions such as cryoglobulinemia, cold urticaria, paroxysmal cold hemoglobinuria, cryofibrinogenemia, and Raynaud's disease [6]. Potential risks of cryoneurolysis are similar to those for local anesthetic-based nerve blocks, although the infection risk appears to be extremely low. In contrast to CPNBs, with an infection rate as high as 3%, there has only been a single suspected infection caused by cryoneurolysis in the more than 50-year history of its use [15, 19].

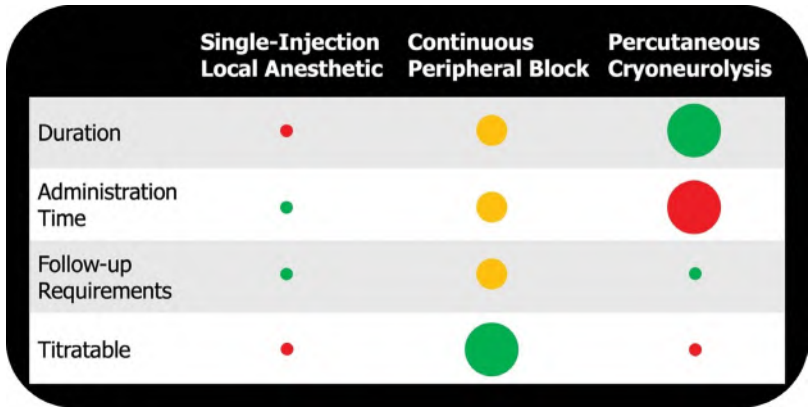
Future Directions and Research Recent evidence suggests the use of intercostal cryoneurolysis may decrease the incidence of CPSP following mastectomy when used in conjunction with a continuous ropivacaine paravertebral block [12]. An ongoing multicenter randomized trial will help confirm the generalizability of these results and determine whether this benefit is still observed when intercostal cryoneurolysis is combined with single-injection nerve blocks for postoperative analgesia following mastectomy (NCT05444361). Cryoneurolysis of other nerves has been utilized for analgesia following other painful surgical procedures (e.g., lateral femoral cutaneous nerve for skin graft donor sites, infrapatellar branch of the saphenous nerve for knee arthroplasty, suprascapular nerve for shoulder surgery) in case series and small pilot studies that have primarily focused on pain during the acute period [6, 18, 20]. Additional research appears warranted to determine whether the analgesia provided by cryoneurolysis in these circumstances results in a reduction in CPSP.

The time requirement for cryoneurolysis, especially when multiple nerves are treated, is substantial. Recent animal models have suggested that injection of a biocompatible ice slurry can be utilized to accomplish peripheral nerve cryoneurolysis [21]. This method could potentially decrease the time requirement for peripheral nerve cryoneurolysis and make both the time requirement and the technique more similar to that of single-injection PNBs.

Key Takeaways

CPNBs and percutaneous cryoneurolysis offer regional anesthesiologists the ability to provide days to months of analgesia following both inpatient and ambulatory surgery, far exceeding that of single-injection PNBs (Table 17.1). Because pain management during the acute perioperative phase is linked to the development of CPSP, these analgesic modalities may help reduce the transition from acute to chronic postsurgical pain.

Table 17.1 Comparison of duration, administration time, follow-up requirements, and titratability of single-injection local anesthetic nerve blocks, CPNBs, and percutaneous cryoneurolysis. Circle color represents whether a technique is favorable or unfavorable for a given feature (e.g., green for single-injection block administration time, red for percutaneous cryoneurolysis administration time), and size represents degree of favorability (e.g., largest circle represents longest duration for cryoneurolysis)



References

1. Crombie IK, Davies HT, Macrae WA. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. Pain. 1998;76(1–2):167–71.
2. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367(9522):1618–25.
3. Fletcher D, Stamer UM, Pogatzki-Zahn E, Zaslansky R, Tanase NV, Perruchoud C, Kranke P, Komann M, Lehman T, Meissner W, euCPSP group for the Clinical Trial Network group of the European Society of Anaesthesiology. Chronic postsurgical pain in Europe: an observational study. Eur J Anaesthesiol. 2015;32(10):725–34.
4. Woolf CJ. Evidence for a central component of postinjury pain hypersensitivity. Nature. 1983;306:686–8.
5. Ilfeld BM. Continuous peripheral nerve blocks: an update of the published evidence and comparison with novel, alternative analgesic modalities. Anesth Analg. 2017;124(1):308–35.
6. Ilfeld BM, Finneran JJ. Cryoneurolysis and percutaneous peripheral nerve stimulation to treat acute pain in the time of the opioid crisis: a review. Anesthesiology. 2020;133:1127–49.
7. Ilfeld BM, Madison SJ, Suresh PJ, Sandhu NS, Kormylo NJ, Malhotra N, Loland VJ, Wallace MS, Mascha EJ, Xu Z, Wen CH, Morgan AC, Wallace AM. Persistent postmastectomy pain and pain-related physical and emotional functioning with and without a continuous paravertebral nerve block: a prospective 1-year follow-up assessment of a randomized, triple-masked, placebo-controlled study. Ann Surg Oncol. 2015;22(6):2017–25.
8. Karmakar MK, Samy W, Li JW, Lee A, Chan WC, Chen PP, Ho AM. Thoracic paravertebral block and its effects on chronic pain and health-related quality of life after modified radical mastectomy. Reg Anesth Pain Med. 2014;39(4):289–98.
9. Peng L, Ren L, Qin P, Chen J, Feng P, Lin H, Su M. Continuous femoral nerve block versus intravenous patient controlled analgesia for knee mobility and long-term pain in patients receiving total knee replacement: a randomized controlled trial. Evid Based Complement Alternat Med. 2014;2014:569107.
10. Wegener JT, van Ooij B, van Dijk CN, Karayeva SA, Hollmann MW, Preckel B, Stevens MF. Long-term pain and functional disability after total knee arthroplasty with and without single-injection or continuous sciatic nerve block in addition to continuous femoral nerve block: a prospective, 1-year follow-up of a randomized controlled trial. Reg Anesth Pain Med. 2013;38(1):58–63.
11. Blumenthal S, Borgeat A, Neudörfer C, Bertolini R, Espinosa N, Aguirre J. Additional femoral catheter in combination with popliteal catheter for analgesia after major ankle surgery. Br J Anaesth. 2011;106(3):387–93.
12. Ilfeld BM, Finneran JJ, Swisher MW, Said ET, Gabriel RA, Sztain JF, Khatibi B, Armani A, Trescot A, Donohue MC, Schaar A, Wallace AM. Preoperative ultrasound-guided percutaneous cryoneurolysis for the treatment of pain following mastectomy: a randomized, participant- and observer-masked, sham-controlled study. Anesthesiology. 2022;137(5):529–42.
13. Sarnoff SJ, Sarnoff LC. Prolonged peripheral nerve block by means of indwelling plastic catheter. Treatment of Hiccup. Anesthesiology. 1951;12:270–5.

14. Finneran JJ IV, Ilfeld BM. Continuous peripheral nerve blocks for analgesia following painful ambulatory surgery: a review with focus on recent developments in infusion technology. Curr Opin Anesthesiol. 2023;36(5):525–32.
15. Capdevila X, Bringuier S, Borgeat A. Infectious risk of continuous peripheral nerve blocks. Anesthesiology. 2009;110(1):182–8.
16. Marhofer D, Marhofer P, Triffterer L, Leonhardt M, Weber M, Zeitlinger M. Dislocation rates of perineural catheters: a volunteer study. Br J Anaesth. 2013;111(5):800–6.
17. Finneran JJ IV, Said ET, Curran BP, Swisher MW, Black JR, Gabriel RA, Sztain JF, Abramson WB, Alexander B, Donohue MC, Schaar A, Ilfeld BM. Basal infusion versus automated boluses and a delayed start timer for "continuous" sciatic nerve blocks following ambulatory foot and ankle surgery: a randomized, clinical trial. Anesthesiology. 2022;136(6):970–82.
18. Finneran JJ, Schwartz AK, Girard PJ, Kent WT, Al-Nouri O, Trescot A, Ilfeld BM. Ultrasound-guided percutaneous cryoneurolysis for perioperative analgesia following major lower extremity amputation: a randomized, participant- and observer-masked, sham-controlled pilot study. Cureus. 2024;16(2):e53563.
19. Cahani D, Chacko J, Hahn B. Myonecrosis: a rare complication of cryoneurolysis. J Emerg Med. 2019;57:e73–6.
20. Swisher MW, Ball ST, Gonzales FB, Cidambi KR, Trescot AM, Ilfeld BM. A randomized controlled pilot study using ultrasound-guided percutaneous cryoneurolysis of the infrapatellar branch of the saphenous nerve for analgesia following total knee arthroplasty. Pain Ther. 2022;11(4):1299–307.
21. Garibyan L, Moradi Tuchayi S, Wang Y, Khodorova A, Stemmer-Rachamimov A, Purschke M, Osseiran S, Evans CL, Mao J, Strichartz G, Anderson RR. Neural selective cryoneurolysis with ice slurry injection in a rat model. Anesthesiology. 2020;133(1):185–94.

18 Peripheral Nerve Stimulation (PNS)

Scott Pritzlaff, Amitabh Gulati, and Hesham Elsharkawy

Introduction

Historical Evolution of Peripheral Nerve Stimulation

The ancient Egyptians were among the first to have discovered and used peripheral nerve stimulation (PNS) for pain management. Historical records suggest they used electric fish, specifically the Nile catfish and electric rays, to relieve pain. This method involved placing these electric fish on painful body areas to produce electric shocks that would alleviate the pain [1].

The Ebers Papyrus, an ancient Egyptian medical text dating back to around 1550 BCE, documents this practice. This illustrates an early understanding of using electrical stimulation for therapeutic purposes, predating the experiments of Luigi Galvani by millennia. In modern medicine, PNS was first described by Shelden and colleagues in 1966, who reported using implanted peripheral nerve stimulation to treat trigeminal neuralgia. Throughout the next decade, various types of equipment, surgical implantation techniques, and peripheral nerve stimulation applications were developed.

The initial approach for PNS involved surgically dissecting to visualize the nerve and placing the PNS lead. Percutaneous PNS lead placement was introduced in 1999 for patients with occipital neuralgia [2]. Renewed interest in peripheral nerve stimulation arose due to advancements in commercially available spinal cord stimulator systems, an increasing number of patients, and advanced imaging techniques such as fluoroscopy and ultrasound. Despite the progress, multiple challenges persisted, including tunneling to the implantable pulse generator, migration, and multiple incisions.

Over the past decade, significant technological advancements in PNS devices have revolutionized pain medicine. The application of electrical stimulation of peripheral nerves has also impacted other fields.

Background and Current Understanding

Therapy Principles and Mechanism of Action: Peripheral nerve stimulation (PNS) utilizes electrical impulses delivered through elec-

S. Pritzlaff (✉)
Division of Pain Medicine, Department of Anesthesiology and Pain Medicine, University of California, Davis, Sacramento, CA, USA
e-mail: spritzlaff@health.ucdavis.edu

A. Gulati
Department of Anesthesiology and Critical Care, Memorial Sloan Kettering Cancer Center, New York, NY, USA

H. Elsharkawy
Department of Pain Medicine, MetroHealth, Cleveland, OH, USA

P. Gulur et al. (eds.), *Perioperative Pain Management*,
https://doi.org/10.1007/978-3-032-11484-6_18

trodes placed near peripheral nerves to modulate pain signals, manage pain, or treat certain neurological conditions. This technique can be employed for pain management, muscle stimulation, and other therapeutic purposes.

Mechanism of Action: Studies have shown that PNS modulates pain transmission peripherally and centrally, indicating that the gate control theory alone cannot fully explain the mechanism.

Gate Control Theory: Gate control theory was first described in 1965 and suggests that non-nociceptive signals close the gate to nociceptive signals at the dorsal horn of the spinal cord, preventing the transfer of pain signals [3]. When nociceptive input is sensed by afferent nerves, carried by thinly myelinated Aδ (delta) fibers and unmyelinated C fibers, the inhibitory interneurons at the dorsal horn are inhibited, opening the gate for pain transmission. Nonpainful stimuli, such as pressure or vibration, are transmitted through large myelinated Aβ fibers, which activate the inhibitory interneurons at the dorsal horn, close the gate, and block the nociceptive input.

Other Mechanisms: Chronic pain has been shown to increase local levels of endorphins and prostaglandins, as well as blood flow to certain areas. PNS may decrease levels of inflammation markers and reduce pain transmission. It can also decrease ectopic discharges and Wallerian degeneration of nerves.

Central Mechanisms and Modulation of Nerve Activity: PNS inhibits the spinothalamic tract and affects regional cerebral blood flow, as demonstrated in studies using positron emission tomography (PET). Electrical impulses alter nerve activity, which can help reduce pain signals sent to the brain or enhance nerve function [4]. PNS decreases central sensitization and hyperalgesia by reducing peripheral nociceptive activity in the spinal cord, inhibiting wide dynamic range neurons in the dorsal horn, and decreasing Aβ fiber-induced activity in the medial lemniscal pathway in the brain. This leads to peripheral reconditioning of the central nervous system through long-term changes in central plasticity [5, 6].

In 2004, Chae et al. showed that intramuscular electrostimulation decreased pain perception in a subset of patients. Muscular stimulation reduces endplate noise, normalizes muscle blood flow, and elicits antinociceptive effects by engaging the dorsal periaqueductal gray and descending pain inhibitory systems. This may restore the balance of peripheral inputs to the central nervous system and reverse maladaptive changes in central pain processing [7].

Clinical Applications and Techniques

There is growing interest in PNS for its potential to modulate pain signaling, decrease neuronal sensitization, and reduce the need for opioids. This could lower the incidence of hyperalgesia, allodynia, and the severity of chronic postoperative pain.

Neurostimulation has long been used to treat chronic pain from various causes, but its application in treating postsurgical pain is limited. Traditionally, peripheral stimulation lead implantation required invasive surgery. Efforts to overcome these limitations with transcutaneous electrical nerve stimulation failed because the stimulation intensities needed for deep nerve activation caused discomfort and pain by activating cutaneous nerve endings [8, 9].

The advent of temporary percutaneous leads, which can be implanted for up to 60 days, has facilitated using PNS in the acute to subacute postoperative period without requiring permanent implants or increasing the risk of infection [10, 11]. PNS in perioperative settings offers several advantages:

- Adjustability: Electrical impulse intensity, frequency, and duration can be tailored to the patient's response and therapeutic needs.
- Minimally Invasive: Compared to other surgical interventions for pain management, PNS is less invasive.

Experts have proposed two approaches for incorporating PNS into acute pain management.

One approach involves using a single injection or continuous infusion of local anesthetic peripheral nerve block, followed by PNS after the nerve block wears off. The second approach is to place a PNS lead alongside a local anesthetic peripheral nerve block, enabling its use as the nerve block resolves.

Currently, evidence supporting PNS for acute pain is limited, but the data are promising. In a randomized controlled trial (RCT), Ilfeld et al. demonstrated that patients who received brachial plexus or sciatic nerve stimulation after surgery experienced significantly lower pain levels and reduced opioid use compared to those given a sham treatment. The active treatment group reported better pain relief and less impact on daily activities throughout the first 2 weeks of recovery [12, 13]. More data are needed to better understand the role of PNS in the perioperative period.

PNS has also emerged as a versatile and evolving therapy for managing chronic pain and, more recently, neurological and psychiatric disorders. Over the past five decades, research has expanded its applications beyond traditional pain management, with studies demonstrating its efficacy in treating conditions such as plexus injuries, migraines, pelvic pain, mononeuropathies, postamputation pain, complex regional pain syndrome (CRPS), and various forms of joint and limb pain [14–19]. Additionally, reports highlight its successful use in treating trigeminal neuralgia, postherpetic neuralgia, and joint pain, further solidifying its role in neuromodulation [19–21].

Clinical trials continue to reinforce the long-term benefits of PNS, with pivotal studies such as Schoenen et al.'s 2013 randomized controlled trial demonstrating a ≥50% reduction in pain intensity or attack frequency in 68% of patients treated for cluster headaches. Moreover, the ReActiv8-B trial, a 5-year randomized, sham-controlled, double-blinded study, confirmed the durability and safety of ReActiv8 Restorative Neurostimulation for nonsurgical, mechanical chronic low back pain (CLBP) linked to multifidus dysfunction [22]. As evidence accumulates, PNS is increasingly recognized not only as a symptomatic treatment but also as a potential restorative therapy, continually expanding its applications in pain medicine and beyond.

The cost of PNS limits its widespread use, underscoring the need to develop more affordable therapeutic options. Stratifying the risk of developing persistent postoperative pain is a crucial strategy that could make PNS a cost-effective preventative measure and timely intervention for high-risk surgeries or patients. Nevertheless, significant hurdles remain before PNS can be available for routine practice.

The Diversity of Percutaneous PNS Systems

PNS devices have significant design differences, allowing various systems to be uniquely used for patient care. Differentiating factors include lead/contact design, power source placement, and connectivity between the lead/receiver and the power source. PNS devices may be divided into monopolar or multicontact devices. Monopolar devices tend to have the cathode contacts/leads placed near the target nerve, while the anode tends to be at the power source (battery). For example, temporary PNS systems (SPR Therapeutics, Cleveland, OH) have a monopolar cathode at the nerve site. The lead extends out of the skin and is directly attached to an external battery (placed on the patient's skin surface). This device will have the anode at the battery site. Since the lead is directly connected to the battery, the transmission of the waveform occurs directly from the battery through the lead into the contact.

Conversely, a permanent monopolar or multicontact system for general PNS targets requires an external battery placement, and the lead/contact, with the corresponding receiver, is implanted within the patient. Therefore, the receiver must conduct the energy from the battery, which is usually transmitted by radiofrequency or inductive current. Many devices in the United States use this technology. Monopolar systems (Bioventus SimRouter, Durham, NC), for example, have three small contacts, which act as a cathode, and the anode is the external battery.

Multicontact systems (Curonix Freedom, Pompano Beach, FL, and Nalu Medical, Carlsbad, CA) have anodes and cathodes at the end of the lead near the neural target (Fig. 18.1). Thus, the nerve may be exposed to multiple waveforms and stimulation patterns. All devices have external power sources that must be placed near the respective device receiver to operate correctly.

To reduce the reliance on external power sources, internalized devices have the energy source (battery) and lead implanted as one unit within a patient. These devices tend to be designed for specific neural targets. For example, a multicontact system with an internal battery (Mainstay Medical Reactiv8, San Diego, CA) is designed to stimulate the multifidus muscles via the medial branch nerves in the lumbar spine. Similarly, bladder stimulators are used to target the sacral nerve roots. These devices will need replacement if not rechargeable or regular external charging if a rechargeable system. Understanding the PNS system device specifications will allow for optimal stimulation of a peripheral nerve.

PNS Waveform Delivery and Electrical Programming Variables

Frequency, Pulse Width, Intensity, Specialized Waveforms for PNS, and Certain Pain Target Nerves: Novel waveforms allow for unique variations in stimulation tailored to the patient's specific pain condition. Designed for different PNS applications, these waveforms enable providers to adjust settings for patient comfort. The efficacy of PNS can also be influenced by factors such as the distance of leads from the target nerve, tissue impedance, consistency, and duration of PNS delivery, lead shape, and the electrical field. These bioelectronic effects of PNS continue to be explored in ongoing studies.

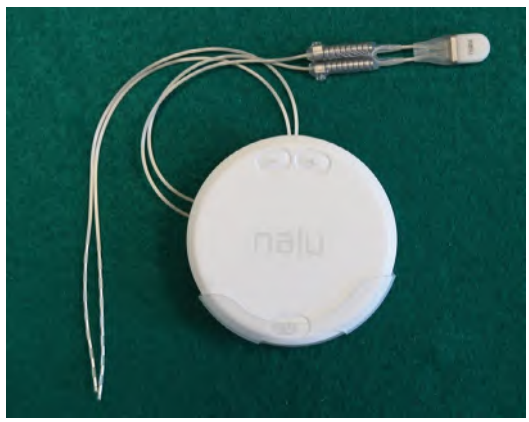


Fig. 18.1 Permanent PNS system with dual lead configuration

Closed-Loop Systems: Closed-loop neuromodulation systems, already available for SCS, hold potential for PNS. These systems, which can monitor physiological responses and adjust stimulation parameters in real time, are currently under development.

Enhanced Programming and Monitoring: Device advances now allow for more precise programming of stimulation parameters, with the potential for remote programming and monitoring capabilities.

Miniaturization of Implantable and Wireless Peripheral Nerve Stimulator Devices

Many systems no longer require implanted batteries; instead utilize external power sources. Multiple options exist for the percutaneous placement of leads, which can be directly stimulated with an external power source/impulse generator (IPG) or hybrid systems with an internal IPG powered via an external source—new systems in development feature small IPGs.

Evidence-Based Practice

Significant clinical evidence in the literature supports the exponential growth in the use of PNS devices. This next saction highlights seminal studies supporting the use of PNS in the chronic pain population.

In 2016, Deer et al. described an implanted PNS system with an external pulse generator for treating chronic pain [23]. The study was randomized, double-blinded, prospective, and had a

partial crossover to study treatment efficacy for 3 months and safety for 12 months. Of the 94 patients, 45 were implanted with the PNS system, showing a higher response rate (38% versus 10%) than the control group. Pain reduction was 27.2% in the treatment group versus 2.3% in the control group. There were no serious side effects within the treatment group. Overall, this study supported further investigations in the field of peripheral nerve stimulation.

The use of PNS systems for the treatment of migraines has been established in the literature. Silberstein et al. (and Dodick et al. with the extension of the Silberstein trial data) target the occipital nerve using an implanted PNS system [18, 24]. Silberstein's study showed a 30% improvement in pain and a 6-day (versus 3-day in control) reduction in migraine headache days per month. The Dodick study extended data to 12 months, showing that 60% of patients had 30% durable pain relief. However, in these studies, 70% had a device-related side effect, a significant consequence for fully implanted systems targeting the occipital nerves.

The prominence of specialized 60-day PNS treatments is indicated for extracranial peripheral nerves in the United States. Pritzlaff et al. present compelling prospective data in the literature supporting long-term effects using 2-month stimulation devices [25]. Specific data includes evidence of low back pain, acute postsurgical pain, phantom limb pain, and shoulder pain. These temporary devices show efficacy for 12 and, in some cases, 24 months of relief after removal of the device.

Recently, the largest postmarket randomized controlled trial demonstrated the efficacy of a PNS system using an implanted lead with a micro-implanted pulse generator with an external power source [19]. Targeting ankle, shoulder, knee, and lower back in a 2:1 implanted device to conservative medical management, the research group reported 3- and 6-month data. The treatment group had an 88% responder rate with a 70% reduction in pain, with the control group only having a 3% responder rate with a 6% improvement in pain. Furthermore, there were no reported significant side effects, and this trial is ongoing for 3 years.

Finally, 5-year data is presented for a fully implanted PNS system targeting the lumbar medial branch nerves for low back pain [22]. In a pivotal trial for this device, Gilligan et al. studied 204 patients suffering from refractory mechanical low back pain, with a 5-year follow-up of 126 patients. At 5 years, 71.8% of patients have 50% improvement, and functional improvements of 20 points or more on the Oswestry Disability Index occurred for 61% of patients. Notably, 46% of patients discontinued opioid medications. This study supports the long-term use of PNS in the chronic pain patient population.

Challenges and Considerations

PNS represents a significant advancement in pain management, offering potential solutions for complex peripheral neuropathic pain and central pain conditions such as postamputation pain (PLP/RLP) and hemiplegic shoulder pain (HSP) [14, 16, 26]. Despite this promise and a growing body of high-quality evidence, PNS faces several critical challenges and considerations that need to be addressed to maximize its potential in clinical practice.

Patient-Related Factors and Technical Challenges: Patient-specific factors such as comorbidities, psychological state, and individual pain perception can significantly influence the success of PNS. Personalized treatment plans that consider these factors are essential for optimizing outcomes. Strategies to overcome these challenges include thorough patient screening, multidisciplinary approaches involving pain specialists, psychologists, and physical therapists, and ongoing patient education and support.

In addition to patient-related factors, technical challenges also pose significant hurdles. Current PNS systems, both temporary and permanent, typically rely on external power sources, which

can be cumbersome and require active patient engagement. This dependency can affect the convenience and overall treatment compliance. Furthermore, the limitations of MRI conditionality with most systems represent a notable concern. Many PNS devices have significant MRI limitations, restricting the ability to perform necessary imaging studies and complicating comprehensive patient care.

Insurance Coverage: Insurance coverage remains a substantial barrier to the widespread adoption of PNS. Many private payers continue to have noncoverage policies for PNS, even considering significant evidence supporting its use in various pain conditions. This financial barrier can prevent patients from accessing this potentially beneficial therapy. To overcome this challenge, it is crucial to continue advocacy for PNS, along with comprehensive cost-benefit analyses demonstrating its long-term benefits and potential cost savings [27, 28], Additionally, collaborating with insurance companies to develop clear guidelines and coverage policies can help facilitate broader adoption.

No Current Framework for Acute Pain: While PNS has shown promise in managing chronic pain, there is currently no established framework for its use in acute pain settings. Most of the research on acute pain has been conducted within the VA or military populations or experimental settings, limiting its generalizability. Pioneering work by Ilfeld et al. in prospective randomized controlled trials (RCTs) has shown immense promise for PNS in managing acute pain and preemptive analgesia for surgical procedures [12, 13, 29]. However, there is currently no CPT code for these specific applications, complicating reimbursement and broader clinical implementation. Developing protocols and conducting further research focused on the application of PNS for acute pain are necessary steps. Establishing evidence-based guidelines and integrating PNS into multimodal pain management strategies could enhance postoperative pain control and reduce reliance on opioids.

Case Example

A 73-year-old woman presented with chronic left knee pain, persisting for over 7 years following a left total knee arthroplasty (TKA), despite multiple surgical interventions, including two TKA revisions. After temporary relief from genicular and saphenous nerve blocks, but ineffective genicular nerve ablations, she underwent a peripheral nerve stimulation (PNS) trial targeting the superomedial and superolateral genicular nerves with 8-contact leads placed via fluoroscopic guidance. The trial resulted in over 70% pain relief, prompting her to proceed with permanent PNS placement using tined, 4-contact leads and an implantable pulse generator positioned in the left medial thigh. Postimplantation, she reported >80% pain relief with improved walking distance and overall function (Fig. 18.2).

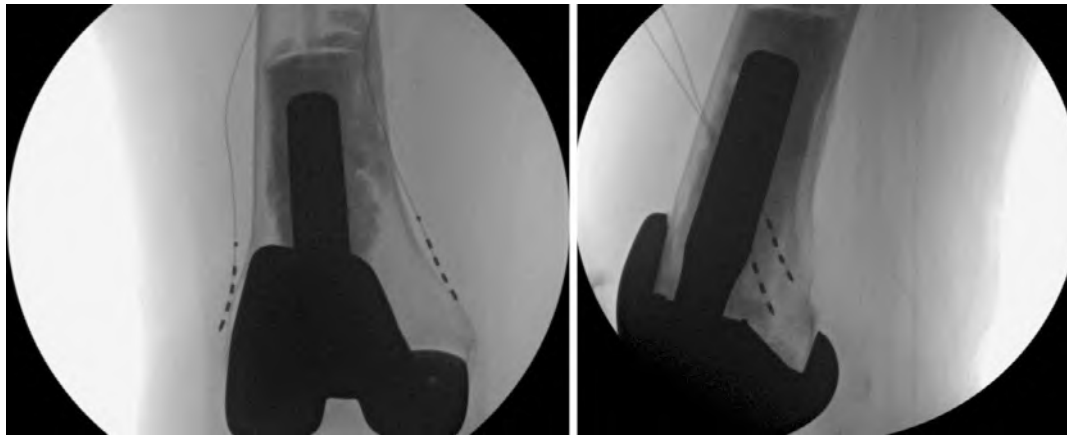


Fig. 18.2 Fluoroscopic AP (left) and lateral (right) views of PNS targeting the superomedial and superolateral genicular nerves. The leads were advanced to the posterior border of the femur to allow for robust programming and coverage

Future Directions and Research

Upcoming Technologies: Innovations in PNS technology are on the horizon, promising to enhance the precision, efficacy, and patient experience. Developments such as user-friendly interfaces, increasing waveform diversity and stimulation parameters, and miniaturized implants continue to revolutionize the field. These technologies aim to provide targeted therapy, reduce procedural invasiveness, and improve patient compliance.

Research Gaps and Future Exploration: There is a need for large-scale, randomized controlled trials to establish the long-term efficacy (12-month data and beyond) and safety of PNS across various pain conditions. Further research into the mechanisms of action of PNS will provide deeper insights into optimizing stimulation parameters and improving patient selection. Additionally, exploring the role of PNS in acute pain management represents an important area for future investigation.

Key Takeaways

1. Comprehensive Pain Management: PNS offers significant potential for addressing complex peripheral neuropathic pain as well as central pain problems like postamputation pain (PLP/RLP) and hemiplegic shoulder pain. Incorporating PNS into multimodal analgesia can improve patient outcomes.
2. Technical and Patient Challenges: Successful PNS implementation requires overcoming technical challenges like reliance on external power sources, MRI conditionality issues, and patient-specific factors such as comorbidities and psychological diagnosesl.
3. Insurance Coverage Advocacy: Improving insurance coverage through evidence-based advocacy and cost-benefit analyses is essential to making PNS more accessible to patients.
4. Acute Pain Framework Development: Despite promising RCT studies [13, 30], protocols and CPT codes for the use of PNS in acute pain and preemptive analgesia for surgical procedures need to be developed and established.

5. Focus on Innovation and Research: Embrace upcoming technologies like fully implantable stimulators and closed-loop systems and support ongoing research to fill gaps and expand the evidence base for PNS across diverse pain conditions.

References

1. Ottestad E, Orlovich DS. History of peripheral nerve stimulation-update for the 21st century. Pain Med Malden Mass. 2020;21(Suppl 1):S3–5. https://doi.org/10.1093/pm/pnaa165.
2. Weiner RL, Reed KL. Peripheral neurostimulation for control of intractable occipital neuralgia. Neuromodulation Technol Neural Interface. 1999;2(3):217–21. https://doi.org/10.1046/j.1525-1403.1999.00217.x.
3. Melzack R, Wall PD. Pain mechanisms: a new theory. Science. 1965;150(3699):971–9. https://doi.org/10.1126/science.150.3699.971.
4. Papuć E, Rejdak K. The role of neurostimulation in the treatment of neuropathic pain. Ann Agric Environ Med. 2013;Spec no. 1:14–7.
5. Ellrich J, Lamp S. Peripheral nerve stimulation inhibits nociceptive processing: an electrophysiological study in healthy volunteers. Neuromodulation J Int Neuromodulation Soc. 2005;8(4):225–32. https://doi.org/10.1111/j.1525-1403.2005.00029.x.
6. Deer TR, Eldabe S, Falowski SM, et al. Peripherally induced reconditioning of the central nervous system: a proposed mechanistic theory for sustained relief of chronic pain with percutaneous peripheral nerve stimulation. J Pain Res. 2021;14:721–36. https://doi.org/10.2147/JPR.S297091.
7. Chae J, Yu DT, Walker ME, et al. Intramuscular electrical stimulation for hemiplegic shoulder pain: a 12-month follow-up of a multiple-center, randomized clinical trial. Am J Phys Med Rehabil. 2005;84(11):832–42. https://doi.org/10.1097/01.phm.0000184154.01880.72.
8. Hymes AC, Raab DE, Yonehiro EG, Nelson GD, Printy AL. Electrical surface stimulation for control of acute postoperative pain and prevention of ileus. Surg Forum. 1973;24:447–9.
9. Rakel BA, Zimmerman BM, Geasland K, et al. Transcutaneous electrical nerve stimulation for the control of pain during rehabilitation after total knee arthroplasty: a randomized, blinded, placebo-controlled trial. Pain. 2014;155(12):2599–611. https://doi.org/10.1016/j.pain.2014.09.025.
10. Finneran Iv JJ, Ilfeld BM. Percutaneous cryoneurolysis for acute pain management: current status and future prospects. Expert Rev Med Devices. 2021;18(6):533–43. https://doi.org/10.1080/17434440.2021.1927705.
11. Tsui BCH, Gupta RK. Role of neuromodulation in acute pain settings. Reg Anesth Pain Med. 2023;48(6):338–42. https://doi.org/10.1136/rapm-2022-103837.
12. Ilfeld BM, Plunkett A, Vijjeswarapu AM, et al. Percutaneous peripheral nerve stimulation (neuromodulation) for postoperative pain: a randomized, Sham-controlled Pilot Study. Anesthesiology. 2021;135(1):95–110. https://doi.org/10.1097/ALN.0000000000003776.
13. Ilfeld BM, Plunkett A, Vijjeswarapu AM, et al. Percutaneous neuromodulation of the brachial plexus and sciatic nerve for the treatment of acute pain following surgery: secondary outcomes from a multicenter, randomized, controlled pilot study. Neuromodulation J Int Neuromodulation Soc. 2021; https://doi.org/10.1111/ner.13492.
14. Gilmore CA, Ilfeld BM, Rosenow JM, et al. Percutaneous 60-day peripheral nerve stimulation implant provides sustained relief of chronic pain following amputation: 12-month follow-up of a randomized, double-blind, placebo-controlled trial. Reg Anesth Pain Med. 2020;45(1):44–51. https://doi.org/10.1136/rapm-2019-100937.
15. Deer TR, Grider JS, Lamer TJ, et al. A systematic literature review of spine neurostimulation therapies for the treatment of pain. Pain Med Malden Mass. 2020;21(7):1421–32. https://doi.org/10.1093/pm/pnz353.
16. Wilson RD, Gunzler DD, Bennett ME, Chae J. Peripheral nerve stimulation compared with usual care for pain relief of hemiplegic shoulder pain: a randomized controlled trial. Am J Phys Med Rehabil. 2014;93(1):17–28. https://doi.org/10.1097/PHM.0000000000000011.
17. Chmiela MA, Hendrickson M, Hale J, et al. Direct peripheral nerve stimulation for the treatment of complex regional pain syndrome: a 30-year review. Neuromodulation J Int Neuromodulation Soc. 2021;24(6):971–82. https://doi.org/10.1111/ner.13295.
18. Silberstein SD, Dodick DW, Saper J, et al. Safety and efficacy of peripheral nerve stimulation of the occipital nerves for the management of chronic migraine: results from a randomized, multicenter, double-blinded, controlled study. Cephalalgia Int J Headache. 2012;32(16):1165–79. https://doi.org/10.1177/0333102412462642.
19. Hatheway J, Hersel A, Song J, et al. Clinical study of a micro-implantable pulse generator for the treatment of peripheral neuropathic pain: 3-month and 6-month results from the COMFORT-randomised controlled trial. Reg Anesth Pain Med. 2024; https://doi.org/10.1136/rapm-2023-105264.
20. Kurklinsky S, Palmer SC, Arroliga MJ, Ghazi SM. Neuromodulation in postherpetic neuralgia: case reports and review of the literature. Pain Med Malden Mass. 2018;19(6):1237–44. https://doi.org/10.1093/pm/pnx175.

21. Stidd DA, Wuollet AL, Bowden K, et al. Peripheral nerve stimulation for trigeminal neuropathic pain. Pain Physician. 2012;15(1):27–33.
22. Gilligan C, Volschenk W, Russo M, et al. Five-year longitudinal follow-up of restorative neurostimulation shows durability of effectiveness in patients with refractory chronic low back pain associated with multifidus muscle dysfunction. Neuromodulation J Int Neuromodulation Soc. 2024;27(5):930–43. https://doi.org/10.1016/j.neurom.2024.01.006.
23. Deer T, Pope J, Benyamin R, et al. Prospective, multicenter, randomized, double-blinded, partial crossover study to assess the safety and efficacy of the novel neuromodulation system in the treatment of patients with chronic pain of peripheral nerve origin: a PNS system for the treatment of chronic pain. Neuromodulation Technol Neural Interface. 2016;19(1):91–100. https://doi.org/10.1111/ner.12381.
24. Reddy SG, Prabhakar S, Kumar A, Banerji J, Singh RP. Higher order optical vortices and formation of speckles. Opt Lett. 2014;39(15):4364–7. https://doi.org/10.1364/OL.39.004364.
25. Pritzlaff SG, Latif U, Rosenow JM, et al. A review of prospective studies regarding percutaneous peripheral nerve stimulation treatment in the management of chronic pain. Pain Manag. 2024;14(4):209–22. https://doi.org/10.1080/17581869.2024.2352398.
26. Wilson RD, Bennett ME, Nguyen VQC, et al. Fully implantable peripheral nerve stimulation for hemiplegic shoulder pain: a multi-site case series with two-year follow-up: fully implantable PNS for HSP. Neuromodulation Technol Neural Interface. 2018;21(3):290–5. https://doi.org/10.1111/ner.12726.
27. Addressing Patient Access to PNS Treatments. Accessed June 8, 2024. https://www.neuromodulation.org/uploads/1/4/5/5/145560650/letter_to_humana_hum_1140_000.pdf.
28. News - North American Neuromodulation Society. Accessed 8 June 2024. https://www.neuromodulation.org/news/nans-leads-response-to-humanas-new-policy-excluding-pns-coverage.
29. Ilfeld BM, Ball ST, Gabriel RA, et al. A feasibility study of percutaneous peripheral nerve stimulation for the treatment of postoperative pain following total knee arthroplasty: percutaneous PNS for postoperative pain. Neuromodulation Technol Neural Interface. 2018; https://doi.org/10.1111/ner.12790.
30. Macres S, Aldwinckle RJ, Saldahna U, et al. Reconceptualizing acute pain management in the 21st century. Adv Anesth. 2023;41(1):87–110. https://doi.org/10.1016/j.aan.2023.06.006.

19 The Business of Acute and Transitional Pain Management: Focuses on the Economic and Administrative Aspects of Perioperative Pain Management, Including Cost-Effectiveness, Revenue Streams, and Business Models in Pain Management Services

Rodney A. Gabriel

Introduction

Adequate postoperative pain management is essential for improving patient outcomes and potentially healthcare costs [1]. Inadequate pain control may result in delayed recovery, extended hospital stays, and increased healthcare expenses. Pain after surgery may be divided into three phases, including the acute (e.g., generally the first week after surgery), subacute/transitional (e.g., up to 3 months after surgery), and chronic pain period (e.g., pain occurring generally more than 3 months after surgery). To optimize postsurgical pain management, in addition to pain management by the primary service, effective multimodal opioid-sparing analgesia may be provided by acute pain services (APS) [2] during a patient's inpatient stay and/or a transitional pain service (TPS) [3, 4], during the outpatient postoperative period in order to potentially prevent conversion of pain to chronic pain and persistent opioid use or dependence. As perioperative providers, it is important to understand the financial implications behind APS and TPS [5, 6]. Thus, in this book chapter, we review the current literature related to this topic.

Background and Current Understanding

Postoperative pain management may be challenging especially for surgeries associated with moderate-to-severe pain, including joint arthroplasty, complex spine surgery, thoracic surgery, and major abdominal surgery. Inadequate pain control during the acute and subacute period may lead to chronic postsurgical pain, which imposes significant burden in the United States. Over 50 million adults are affected by chronic pain, which may incur significant cost burden related to direct (e.g., costs of treatment) and indirect costs (e.g.,

R. A. Gabriel (✉)
Division of Regional Anesthesia, Department of Anesthesiology, University of California, San Diego, La Jolla, CA, USA

Division of Perioperative Informatics, Department of Anesthesiology, University of California, San Diego, La Jolla, CA, USA
e-mail: Ragabriel@health.ucsd.edu

P. Gulur et al. (eds.), *Perioperative Pain Management*,
https://doi.org/10.1007/978-3-032-11484-6_19

personal loss of labor productivity due to inability to work). For example, a person with moderate chronic pain may generate an excess of $4516 in healthcare expenditures compared with an individual without pain [6]. Thus, from both a patient outcomes and healthcare costs perspective, it is essential that adequate resources are placed to manage acute and subacute pain and reduce incidence of chronic pain.

APS and TPS may both be multidisciplinary teams consisting of anesthesiologists and other specialists. An APS team may consist of a combination of mid-level providers and anesthesiologists, particularly those specialized in regional anesthesia and/or chronic pain medicine. The purpose of APS is to manage acute postoperative pain, generally in the hospital setting, as it relates to multimodal opioid-sparing analgesia protocols that may consist of performing and managing various regional anesthesia interventions, including peripheral nerve blockade and neuraxial analgesia (e.g., epidural or intrathecal opioid injections) [7–9]. Pioneered at the Toronto General Hospital, a TPS bridges the gap between pain management following acute pain but before the occurrence of chronic pain [3]. Such services are generally outpatient and consist of expert care related to pharmacologic (e.g., opioid weaning and multimodal nonopioid prescriptions), procedural (e.g., outpatient regional techniques including cryoneurolysis and acupuncture), and nonpharmacological interventions (e.g., electronic health applications for pain coping skills, cognitive-behavioral therapy, biofeedback, and counseling) [6].

As one could imagine, successful execution of both APS and TPS requires institutional investment and valuable resources. While the potential benefits toward patient outcomes may be clearer, the cost-effectiveness and financial gains may be less clear. One approach is to frame the business model for both APS and TPS by comparing its costs against financial savings to an institution. These savings may be related to the prevention of complications and reduction of hospital expenditures reported in the literature [2]. For example, for APS, there has been some evidence related to the reduction of hospital length of stay as well as decreased opioid consumption, which may lead to reduced risk of opioid-related complications, such as ileus, oversedation, respiratory events, and other related adverse events [10, 11]. In regard to TPS, the institutional investment may focus on how such a service may reduce rates of unexpected healthcare utilization, including hospital readmissions, emergency room visits, or immobility issues related to uncontrolled pain [12].

While such services may not always be profitable from a business standpoint, it is essential to highlight their cost-savings potential. For example, one article suggests that new persistent opioid use after surgery is associated with $11,000 to $17,000 cost per patient in medical spending during the first year after surgery [10]. Furthermore, there are essential steps in the billing process for care provided by APS/TPS teams that should be practiced to further optimize the cost-savings potential [13, 14]. In the next section, we delve into more details regarding billing considerations.

Clinical Applications and Techniques

With regional anesthesia and APS consultations for perioperative care, accurate billing documentation is necessary to maintain financial stability for such services. Compliance is important for appropriate reimbursement to maintain viability. Here we review the key components of documentation related to procedures performed by APS [13, 14]. First, medical necessity needs to be established. Per the Centers for Medicare and Medicaid Services (CMS), the surgeon is already paid to provided postoperative pain control as part of the global fee-for-service [15]; however, they may request expert consultation from anesthesiologists to provide pain services outside of a surgeon's scope. This necessity needs to be adequately documented, preferably as a formal documented consultation. Next, billing of a regional anesthetic will be based on if it is required for intraoperative anesthesia versus postoperative pain control. The former determined if the primary

anesthesia is dependent on regional anesthesia (e.g., "surgical block") and thus would be billed with the American Society of Anesthesiologists coding system with no additional billing for the nerve block. The latter would thus would be billed separately using the Current Procedural Terminology (CPT) coding system. Additional components of adequate documentation for regional anesthesia billing include a preoperative evaluation designating the appropriateness of the nerve block and procedure note [13]. For APS, there are more in-hospital services that may be billed for pain management, generally billed via the CPT coding system. These include an initial visit (e.g., inpatient acute pain consult), peripheral nerve catheter follow-up, intrathecal opioid follow-up, epidural follow-up, lidocaine or ketamine infusion follow-up, and phone follow-up for at-home nerve catheters. Of note, CMS does not allow anesthesiologists to bill for APS activities while concurrently supervising operating room anesthesia [16]. In conclusion, to optimize cost savings associated with APS, it is important to follow guidelines set forth by CMS and provide sufficient documentation as described.

In regard to costs associated with a TPS, this will depend on the staffing model, which may differ from one institution to another [12]. TPS may be a multidisciplinary practice consisting of anesthesiologists who specialize in acute and/or chronic pain, nonanesthesiology providers specialized in chronic pain (e.g., physical medicine and rehabilitation, neurology), mid-level providers (e.g., nurse practitioners, physician assistants), psychologists, physical therapists, palliative medicine specialists, physiologist, and/or medical acupuncturists [3, 4]. Thus, depending on the size of practice, the cost of a TPS could range between $2 million and $7 million annually to cover staff salaries [6]. In order to maintain financial stability of a TPS, providers must consider several points, including the staffing size and services provided, reimbursement related to clinic visits and procedures performed, surgical volume, clinical need, and reduction in incidence of persistent postoperative pain. A pay-for-performance (rather than fee-for-service) model may be an appropriate model for TPS to make financial sense at an institutional level. In this payment model, healthcare providers are paid based on quality measures determined by long-term outcomes. Examples of these payment models include the Merit-Based Incentive Payment System and the Alternative Payment Model Program [17, 18]. Interestingly, one study demonstrated that implementation of a TPS for orthopedic surgical patients although led to an increase in outpatient visits, there was no increase in outpatient costs and no added costs for managing chronic opioid use patients [19].

Evidence-Based Practice and Challenges and Considerations

The challenges regarding the business models related to APS and TPS have been described above. Despite these financial challenges, there have been several evidence-based reports of the benefits of such services for surgical patients. These positive outcomes need to be highlighted and part of high-level discussions with hospital administration when pitching the necessity of APS and TPS. Examples of positive postoperative outcomes afforded by APS and regional anesthesia include surgical populations in microsurgical breast reconstruction [20], robot-assisted laparoscopic nephrectomy [21], ventral hernia repair with abdominal wall reconstruction [22], cytoreductive surgery with hyperthermic intraperitoneal chemotherapy [23], pancreaticoduodenectomy [24], and cardiac surgery [25]. Furthermore, several studies have demonstrated the potential benefit of TPS in improving postoperative opioid trajectories [26] and preventing persistent postsurgical pain after cancer surgery [27], obstetric surgery [28], major shoulder surgery [29], orthopedic surgery [19, 30], and in patients with preexisting opioid use disorder [31].

Future Directions and Research

Precision medicine is the concept describing the personalized tailored care for individual patients based on their own clinical and social background [Jameson 26014593]. Rather than design a TPS that targets all surgical patients, another approach to allocating resources could be based on a precision medicine design, in which only high-risk patients (for chronic postsurgical pain) would be managed by TPS. Determining high-risk patients can be challenging, but the use of predictive modeling using preoperative electronic medical record data may be a solution [32–37]. For example, various machine learning models have been reported that predict the odds of persistent postoperative opioid use (e.g., > 3 months after surgery) following spine surgery [32, 33], hip and knee arthroplasty [34], sports medicine procedures [35, 36], and among other surgeries [37]. Thus, future studies should integrate such models in clinical workflow to determine if indeed high-risk patients may be accurately identified and, thus, appropriately allocated to the resources provided by APS and TPS.

Key Takeaways

Conclude with a highlighted box listing five important learnings covered in your chapter.

1. Cost implications of APS/TPS implementation.
2. Cost savings through opioid-sparing techniques.
3. Long-term cost-benefits through improved patient outcomes, reduced lengths of stay, and decreased complication-related costs.
4. Long-term return on investment—positive impact on patient quality of life.
5. Effective billing practices are crucial for the financial sustainability of acute and transitional pain services.
6. Role of AI and predictive modeling in APS/TPS.

References

1. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, Carter T, Cassidy CL, Chittenden EH, Degenhardt E, Griffith S, Manworren R, McCarberg B, Montgomery R, Murphy J, Perkal MF, Suresh S, Sluka K, Strassels S, Thirlby R, Viscusi E, Walco GA, Warner L, Weisman SJ, Wu CL. 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. J Pain. 2016;17:131–57.
2. Wu CL, Raja SN. Treatment of acute postoperative pain. Lancet. 2011;377:2215–25.
3. Katz J, Weinrib A, Fashler SR, Katznelzon R, Shah BR, Ladak SS, Jiang J, Li Q, McMillan K, Santa Mina D, Wentlandt K, McRae K, Tamir D, Lyn S, de Perrot M, Rao V, Grant D, Roche-Nagle G, Cleary SP, Hofer SO, Gilbert R, Wijeysundera D, Ritvo P, Janmohamed T, O'Leary G, Clarke H. The Toronto General Hospital Transitional Pain Service: development and implementation of a multidisciplinary program to prevent chronic postsurgical pain. J Pain Res. 2015;8:695–702.
4. Katz J, Weinrib AZ, Clarke H. Chronic postsurgical pain: from risk factor identification to multidisciplinary management at the Toronto General Hospital Transitional Pain Service. Can J Pain. 2019;3:49–58.
5. Macario A, Weinger M, Carney S, Kim A. Which clinical anesthesia outcomes are important to avoid? The perspective of patients. Anesth Analg. 1999;89:652–8.
6. Sun EC, Mariano ER, Narouze S, Gabriel RA, Elsharkawy H, Gulur P, Merrick SK, Harrison TK, Clark JD. Making a business plan for starting a transitional pain service within the US healthcare system. Reg Anesth Pain Med. 2021;46:727–31.
7. Gabriel RA, Swisher MW, Sztain JF, Furnish TJ, Ilfeld BM, Said ET. State of the art opioid-sparing strategies for post-operative pain in adult surgical patients. Expert Opin Pharmacother. 2019;20:949–61.
8. Al-Saidi I, Russell A, Dizdarevic A. The acute perioperative pain service: impact, organization, and future directions. Curr Pain Headache Rep. 2023;27:399–405.
9. Swenson JD, Davis JJ, Johnson KB. Postoperative care of the chronic opioid-consuming patient. Anesthesiol Clin North Am. 2005;23:37–48.
10. Brummett CM, Evans-Shields J, England C, Kong AM, Lew CR, Henriques C, Zimmerman NM, Sun EC. Increased health care costs associated with new persistent opioid use after major surgery in opioid-naive patients. J Manag Care Spec Pharm. 2021;27:760–71.

11. Oderda GM, Said Q, Evans RS, Stoddard GJ, Lloyd J, Jackson K, Rublee D, Samore MH. Opioid-related adverse drug events in surgical hospitalizations: impact on costs and length of stay. Ann Pharmacother. 2007;41:400–6.
12. Zubieta CS, Shabet C, Lin J, Muzaurieta A, Arora A, Maghsoodi N, Brummett CM, Edelman A. Financial model for a transitional pain service at a large tertiary academic center in the USA. Reg Anesth Pain Med. 2023;
13. Webb CAJ, Kim TE. Establishing an acute pain service in private practice and updates on regional anesthesia billing. Anesthesiol Clin. 2018;36:333–44.
14. May KA, Craven JM, Wright C, Tran B. Regional anesthesia and the acute pain service: compliance and controversies. Curr Opin Anaesthesiol. 2022;35:224–9.
15. National correct coding initiative policy manual for medicare services. https://www.cms.gov/Medicare/Coding/NationalCorrectCodinitED/index.html.
16. CMS Manual System. https://www.cms.gov/Regulations-and-Guidance/Guidance/Transmittals/2017Downloads/R3747CP.pdf.
17. Shrestha M, Sharma H, Mueller KJ. Differences in utilization of preventive services for primary care clinicians participating in MIPS and ACOs. Qual Manag Health Care. 2024;
18. Sawar K, Sawar L, Chen K. Call for specialty-specific benchmarks for cross-specialty quality measures in the quality payment program. Cureus. 2024;16:e61618.
19. Yoo M, Buys MJ, Nelson RE, Patel S, Bayless KM, Anderson Z, Hales JB, Brooke BS. Effect of multidisciplinary transitional pain service on health care use and costs following orthopedic surgery. Fed Pract. 2023;40:418–25.
20. Clark RC, Segal R, Kordahi A, Sendek G, Alving-Trinh A, Abramson W, Sztain J, Swisher M, Gabriel RA, Gosman A, Said ET, Reid CM. An interdisciplinary, comprehensive recovery pathway improves microsurgical breast reconstruction delivery. Ann Plast Surg. 2024;92:549–56.
21. Meineke MN, Losli MV, Sztain JF, Swisher MW, Abramson WB, Martin EI, Furnish TJ, Salmasi A, Derweesh IH, Gabriel RA, Said ET. Robot-assisted laparoscopic nephrectomy: early outcome measures with the implementation of multimodal analgesia and intrathecal morphine via the acute pain service. World J Urol. 2024;42:117.
22. Said ET, Drueding RE, Martin EI, Furnish TJ, Meineke MN, Sztain JF, Abramson WB, Swisher MW, Jacobsen GR, Gosman AA, Gabriel RA. The implementation of an acute pain service for patients undergoing open ventral hernia repair with mesh and abdominal wall reconstruction. World J Surg. 2021;45:1102–8.
23. Said ET, Sztain JF, Abramson WB, Meineke MN, Furnish TJ, Schmidt UH, Manecke GR, Gabriel RA. A dedicated acute pain service is associated with reduced postoperative opioid requirements in patients undergoing cytoreductive surgery with hyperthermic intraperitoneal chemotherapy. Anesth Analg. 2018;127:1044–50.
24. Said ET, Sztain JF, Swisher MW, Martin EI, Sood D, Lowy AM, Gabriel RA. Association of an acute pain service with postoperative outcomes following pancreaticoduodenectomy. J Perioper Pract. 2019;30:309–14.
25. Cogan J, Eipe N, Vargas-Schaffer G, Ouimette MF, Belisle S. "CAPS" cardiac acute pain services-a nationwide survey from Canada. J Cardiothorac Vasc Anesth. 2017;31:1235–40.
26. Ladha KS, Vachhani K, Gabriel G, Darville R, Everett K, Gatley JM, Saskin R, Wong D, Ganty P, Katznelson R, Huang A, Fiorellino J, Tamir D, Slepian M, Katz J, Clarke H. Impact of a transitional pain service on postoperative opioid trajectories: a retrospective cohort study. Reg Anesth Pain Med. 2024;49:650–5.
27. Thota RS, Ramkiran S, Jayant A, Kumar KS, Wajekar A, Iyer S, Ashwini M. Bridging the pain gap after cancer surgery - evaluating the feasibility of transitional pain service to prevent persistent postsurgical pain - a systematic review and meta-analysis. Indian J Anaesth. 2024;68:861–74.
28. Blanco R, Ansari T. Transitional pain services updates and a novel service for the obstetric population. Curr Opin Anaesthesiol. 2024;37:513–9.
29. Sroka O, Featherall J, Bayless K, Anderson Z, Da Silva A, Brooke BS, Buys MJ, Chalmers PN, Tashjian RZ. A transitional pain management program is associated with reduced opioid dependence after major shoulder surgery. J Shoulder Elbow Surg. 2024;
30. Buys MJ, Anderson Z, Bayless K, Zhang C, Presson AP, Hales J, Brooke BS. Postsurgical opioid prescribing among veterans using community care for orthopedic surgery at non-VA hospitals compared to a VA hospital with a transitional pain service: a retrospective cohort study. Reg Anesth Pain Med. 2024;50:531.
31. Liu O, Leon D, Gough E, Speed T, Hanna M, Jaremko K. A retrospective analysis of perioperative medications for opioid-use disorder and tapering additional postsurgical opioids via a transitional pain service. Br J Clin Pharmacol. 2024;90:3010.
32. Simpson S, Zhong W, Mehdipour S, Armaneous M, Sathish V, Walker N, Said ET, Gabriel RA. Classifying high-risk patients for persistent opioid use after major spine surgery: a machine-learning approach. Anesth Analg. 2024;139:690–9.
33. Karhade AV, Cha TD, Fogel HA, Hershman SH, Tobert DG, Schoenfeld AJ, Bono CM, Schwab JH. Predicting prolonged opioid prescriptions in opioid-naive lumbar spine surgery patients. Spine J. 2020;20:888–95.

34. Gabriel RA, Harjai B, Prasad RS, Simpson S, Chu I, Fisch KM, Said ET. Machine learning approach to predicting persistent opioid use following lower extremity joint arthroplasty. Reg Anesth Pain Med. 2022;47:313–9.
35. Gabriel RA, Simpson S, Zhong W, Burton BN, Mehdipour S, Said ET. A neural network model using pain score patterns to predict the need for outpatient opioid refills following ambulatory surgery: algorithm development and validation. JMIR Perioper Med. 2023;6:e40455.
36. Kunze KN, Polce EM, Alter TD, Nho SJ. Machine learning algorithms predict prolonged opioid use in opioid-naive primary hip arthroscopy patients. J Am Acad Orthop Surg Glob Res Rev. 2021;5(e21):00093–8.
37. Hur J, Tang S, Gunaseelan V, Vu J, Brummett CM, Englesbe M, Waljee J, Wiens J. Predicting postoperative opioid use with machine learning and insurance claims in opioid-naive patients. Am J Surg. 2021;222:659–65.

Part VI

Long-Term Postoperative Care (Days 31–90)

Chronic Postsurgical Pain: Identification and Management

20

Timothy V. Feldheim and Patrick Tighe

Case Report

A 34-year-old female presents to a local pain physician with ongoing pain 5 months after having a partial mastectomy due to ductal carcinoma in situ. Pain is described as burning, constant, and made worse by palpation. She has a prior medical history of obesity, type 2 diabetes, scoliosis, peptic ulcer disease, anxiety, and breast cancer status post mastectomy as described. Prior to surgery, she was taking hydrocodone 5–325 mg every 6–8 hours for her chronic back pain secondary to scoliosis. Prior to surgery, an epidural was attempted to be placed for intraoperative and postoperative pain control. However, the catheter could not be passed. The anesthesiologist utilized a TIVA with propofol and remifentanil. The surgery was deemed successful and overall was uneventful. Her postoperative course was uncomplicated with the exception of significant acute postoperative pain, which was poorly controlled with opioid analgesics. Pain has only slightly improved over the subsequent months. Her workup has been negative for recurrence of malignancy or infection. She has been maintained on an opioid regimen of 10 mg oxycodone every 6 hours for the past 6 months.

T. V. Feldheim (✉) · P. Tighe
Department of Anesthesia, University of Florida College of Medicine, Gainesville, FL, USA
e-mail: tfeldheim@anest.ufl.edu

Introduction

Chronic postsurgical pain (CPSP) is one of the most undesirable and unfavorable outcomes after any surgical procedure. While acute postsurgical pain is to be expected with many surgeries, chronic postsurgical pain is usually unanticipated though there are possible indications and risk factors to help predict when it is more likely to occur [1]. Acute postsurgical pain can vary in length, with pain sometimes lasting days to weeks if experienced and majority of patients making an eventual recovery [2, 3]. However, persistent or chronic postsurgical pain is a debilitating condition that can have deleterious effects on those who develop the condition [2].

Background and Current Understanding

The first definition of chronic postsurgical pain (CPSP) was in 1999 by Macrae and Davies, and was later updated by Macrae in 2001 [4, 5]. He described CPSP as pain that lasted a minimum of 2 months after surgical intervention without other potential cause, including presurgical pain. Over the years, the definition has expanded. In 2014, Werner and Kongsgaard proposed several updates, many of which became part of the current definition of CPSP [6].

P. Gulur et al. (eds.), *Perioperative Pain Management*,
https://doi.org/10.1007/978-3-032-11484-6_20

As of 2019, the International Association for the Study of Pain has combined the previous descriptions with that of chronic posttraumatic pain. It is now defined as "chronic pain that develops or increases in intensity after a surgical procedure or a tissue injury and persists beyond the healing process, i.e., at least 3 months after the surgery or tissue trauma" [2]. Other criteria that must be met include:

1. That the pain must be localized to either:
   (a) The surgical field or field of injury
   (b) Projected to the innervated territory of a nerve situated in the surgical area
2. All other causes of pain be excluded such as:
   (a) Preexisting pain conditions
   (b) Infection
   (c) Malignancy
3. May or may not show characteristics of neuropathic pain

Furthermore, CPSP is discernable from posttraumatic pain in that it originates after a controlled surgical procedure as a part of a therapy, whereas posttraumatic pain develops after an accidental and uncontrolled event. Patients who develop CPSP will often show several features of neuropathic pain as well [2].

The mechanism behind the development of CPSP is not well understood, though animal models have helped to get us a better appreciation [7–11]. It is understood that there is commonly a neuropathic component to the pain development, even if no direct insult to neural structures, which is in of itself a potential cause of CPSP [8, 12]. Peripheral sensitization is likely a key component to the development of CPSP [8]. Incisional and surgical stimulation, as well as the inflammatory response from healing, lead to the activation of nociceptive fibers, which results in a release of several cytokines and other molecules in the primary sensory nerve fibers at the level of the dorsal root ganglion [8]. The sustained stimulus can then lead to peripheral sensitization. This in turn can lead to central sensitization at the level of the spinal cord in the dorsal horn, which is also thought to be a key component in the development of CPSP [8, 11]. The brain also undergoes neuroplastic changes in response to the sustained noxious stimuli, primarily in thalamic pathways [13]. A genetic component is also thought to play a part in the development of CPSP and may influence as much as 50% of its development [14].

The incidence of CPSP is variable and related to the surgical procedure performed [1]. Over 230 million major surgical procedures are estimated to be performed annually across the globe [15]. Acute pain is expected to range from 5% to 85%, depending on the procedure performed, with about 10–50% converting to CPSP [16]. Moderate to severe CPSP, which may affect quality of life, ranges from 2% to 15% of CPSP patients [13].

Besides a higher incidence after certain procedures, several other risk factors can be predictive of the development of CPSP [1, 17]. One of the most consistent risk factors found across studies is that the younger age of adults has been shown to correlate with increased incidence of CPSP but not in the pediatric population [9, 17]. Females also seem to be at higher risk of CPSP development, as well as patients with a higher BMI [1, 17]. Smoking has also been implicated as a potential risk factor for CPSP [18]. Anxiety, depression, and pain catastrophizing have all been studied as potential risk factors of CPSP development [19, 20].

As stated earlier, genetic predisposition is likely a major factor [21, 22]. The impairment of diffuse noxious inhibitory control has been associated with CPSP in postthoracotomy patients [23]. Genetic variability of genes involving neurotransmission, especially COMT, potassium and calcium ion channel activity, NF-κ-B, and immune response have all been implicated as well in potentially predisposing patients to the development of CPSP [24, 25].

There are nondemographic preoperative risk factors as well. Patients with higher preoperative pain scores also seem to be more at risk of devel-

opment of CPSP [20, 26]. These can be related to injury or the cause for surgery but can also be due to other pain pathologies such as fibromyalgia [8, 27]. Preoperative opioid use, whether it be for the surgical pathology itself or for other pain pathologies, is also seen as a risk factor for CPSP development [8, 28].

The type of surgical procedure performed carries an individualized risk of developing CPSP. Certain procedures carry with them an increased likelihood of nerve injury, another independent intraoperative risk for CPSP development. Surgical technique can be another factor in the development of CPSP, with minimally invasive approaches often correlating to lower incidence of CPSP development than those approaches requiring larger incisional exposure [17]. However, this is not always the case, and the type of tissue insulted during the procedure, such as viscera compared to fascia, seems to matter more than the technique used [1]. Longer length of surgery has also been associated with increased incidence of CPSP [20]. An interesting but controversial link is the use of high-dose remifentanil during surgery, as this can cause opioid-induced hyperalgesia, which has been linked to the potential development of CPSP [8, 29, 30–32].

In the immediate postoperative period, one can also find risk factors that predict CPSP development. Possibly the most consistent predictor of CPSP is severe acute postoperative pain, especially in the first week [9, 33]. While pain is to be expected, patients displaying out-of-control postoperative pain, signs of hyperalgesia, or neuropathic pain are at higher risk of developing CPSP [8, 17]. Other postoperative risk factors for CPSP involve the potential for tissue manipulation and irritation. Radiation therapy and repeat surgery have both been found to be potential risk factors for CPSP [8, 34]. Table 20.1 reviews the risk factors associated with CPSP development.

Table 20.1 Risk factors for CPSP development

Patient centered	Procedure related
Younger age	Procedures with large incision
Female sex	Procedures with high risk of nerve injury
High BMI	Procedures requiring visceral manipulation
Smokers	Long length of surgery
Anxiety	Use of remifentanil
Depression	Repeat surgery
Catastrophizing	Radiation therapy
Genetic predisposition	
High preoperative pain score	
Preopeative opioid use	

Clinical Applications and Techniques/Evidence-Based Practices

Preventative Therapy

The treatment of CPSP after it develops, like most types of chronic pain, is inherently difficult. Therefore, preventative analgesia should be the goal of the perioperative team [35]. Preventative analgesia relies on the utilization of multimodal analgesic techniques and medications to provide adequate pain control in the perioperative period in order to reduce peripheral and central sensitization [36]. Multimodal analgesia has been shown to be effective in providing superior analgesia from acute pain [37].

Surgical techniques can also potentially affect the development of CPSP. Minimally invasive techniques can help reduce tissue manipulation and damage, as well as potentially avoid nerve damage [38]. However, the purposeful avoidance of nerve damage in several studies has shown varying results in limiting CPSP development [39, 40]. In addition, while minimally invasive techniques have been shown to limit CPSP in cer-

tain procedures, such as in laparoscopic hernia repairs, many laparoscopic procedures involving removal or manipulation of viscera, such as kidney and colorectal tissue, show no difference in CPSP development compared to open procedures [41, 42].

The use of regional anesthesia has been well documented as a useful technique as part of a multimodal pain regimen, as it helps reduce the response from nociceptive pain fibers in the central nervous system [1, 43]. Several studies have shown the benefit of epidural and peripheral nerve blockades at helping to reduce both acute surgical pain and CPSP [44–46]. Evidence for epidural anesthesia is better than several other regional techniques, but evidence is moderate at best [47]. Intravenous lidocaine infusions perioperatively also have potential for reducing CPSP, though only a few studies exist at this time and conclusions cannot yet be made [1, 48, 49].

As the name suggests, multimodal analgesia can be attained using multiple classes of pharmacologic analgesic medications [37]. Ketamine, an NMDA antagonist, has been widely used as an adjunct analgesic perioperatively for decades. Several studies have already shown ketamine to potentially reduce acute postoperative pain and postoperative opioid consumption [50, 51], but its potential for reducing CPSP has thus far been inconclusive [8, 48]. Despite being a mainstay of treatment for chronic neuropathic pain, gabapentinoids such as pregabalin and gabapentin have not been shown to reduce the risk of development of CPSP when used in the perioperative period [48]. Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as duloxetine and venlafaxine have shown some promise, but data is sparse and more studies are needed [52, 53].

Nonsteroidal antiinflammatory drugs (NSAIDs) and cyclooxygenase inhibitors have been sparsely studied in the prevention of CPSP with some positive results, but overall their utilization has been inconclusive [48, 54]. While acetaminophen has been utilized in several multimodal regimens and there is some data regarding its use for acute pain control, it has never been studied as a potential preventative therapy for CPSP [55, 56]. To date, two studies have shown mixed results on the efficacy of steroids for preventing CPSP [48, 56].

Opioids are still a mainstay of acute pain management in the perioperative period. Studies have shown their efficacy in the treatment of moderate to severe acute pain and for prevention of CPSP [54, 57]. However, judicious use of opioids and earlier reduction is advised for several reasons, including reducing tolerance to opioids, limiting the expedition of central sensitization, and altering descending inhibition, among others [1, 8]. Therefore, utilizing other techniques such as regional and multimodal analgesia to reduce opioid use is recommended [11].

The management of subacute pain, or pain in the first 3 months following surgery, has also been linked to limiting CPSP, as patients with pain that is left untreated or fail to improve in the first couple of months after surgery are more likely to develop CPSP [58, 59]. Subacute pain after discharge can be expected, but if severe it can lead to delays in recovery and potential readmission [59]. During this timeframe, multimodal analgesia tailored to the patient's needs in the setting of a rehab hospital has been shown to help prevent CPSP, usually in the first 1 to 3 months [57]. Further follow-up and development of pain services dedicated to treating subacute pain have shown good initial results at preventing CPSP [60, 61].

Management of CPSP

Prompt identification of CPSP by a thorough history and physical is crucial to begin providing care for the patient. Of equal importance is confirming that no other etiology is present, such as infection, hardware malfunction, or recurrence of malignancy, depending on the initial surgery [62]. Furthermore, distinguishing between the type of pain or pain state, such as neuropathic vs. nociceptive pain, is also critical as this will direct the treatment [56]. Despite the characteristics of the pain, an approach using multimodal therapies offers the greatest benefit to pain reduction and quality of life improvement [62]. These therapeutic regimens can include pharmacologic, inter-

ventional, lifestyle, and psychosocial approaches to achieve pain management [63, 64].

Several pharmacotherapies can be utilized for the management of CPSP. Should the pain be more neuropathic in nature, gabapentinoids, tricyclic antidepressants, and SNRIs can be utilized to help with pain control [56, 65]. Tylenol, NSAIDs, and opioids have been utilized to control pain as well. However, opioid therapy must be done judiciously to avoid adverse effects such as tolerance, dependence, addiction, and opioid-induced hyperalgesia. That said, the data for all medication management are suboptimal at best [56, 54, 65].

Interventional therapies have also shown some benefit. Several case reports and case series have reported successful peripheral nerve blocks providing pain relief in patients with various types and locations of CPSP [62]. Furthermore, nerve ablation via phenol, alcohol, or radiofrequency has also shown good evidence for CPSP management [54, 62]. The injection of botulinum toxin has been shown to be a successful therapy in the treatment of certain types of CPSP [65]. There is also evidence for epidural steroid injections to provide some relief in patients with prior spine surgeries [66–68]. Neuromodulation via spinal cord stimulation has emerged as a viable therapy for CPSP, especially in cases of prior back surgery [65, 69]. Likewise, targeted drug delivery via intrathecal pain pumps is another potential therapy, albeit with limited evidence [70].

Challenges and Considerations

Currently, the biggest challenge and consideration is the lack of consensus among experts in the field. This is driven by the lack of, and sometimes disputed, evidence that exists for both the prevention and treatment of CPSP. Most of the evidence for prevention, and even more so for treatment, are based on small studies with significant flaws in study design [65]. Furthermore, no study has ever looked at multimodal and multidisciplinary studies specifically for the CPSP population [65]. More research with better-designed studies with multimodal therapeutic regimens is needed to come up with better recommendations for care of the CPSP population.

Future Directions and Research

More high-powered, quality studies are needed to ascertain optimal therapies for the prevention and treatment of CPSP [65]. These must include multimodal pharmacological, psychosocial, and interventional regimens targeting specific procedural CPSP. As stated in this chapter, genetic testing has great potential for early identification and potential prevention of developing CPSP. The Human Pain Genetics Database is an ongoing study into genetic variations and single nucleotide polymorphisms that looks at variants associated with phenotypic pain profiles; it currently contains 434 genetic variants based on 294 studies [71]. This may show promise for identifying patients at high risk of developing CPSP.

Machine learning and artificial intelligence also show promise as predictive tools for both risk assessment and response to different therapies in the future [72, 73]. Several studies have already examined the use of machine learning for the prediction of persistent opioid use across different surgical populations [74–78]. Further work is necessary to better understand how artificial intelligence can contribute to improved mechanistic understanding, diagnosis, and treatment of CPSP.

Key Takeaways

1. CPSP can be a debilitating condition that leads to ongoing pain and suffering for a patient.
2. Prevention of CPSP should be a primary focus for providers, identifying which risk factors may make a patient more susceptible to developing CPSP.
3. Several modalities, including pharmacologic, interventional, physical therapy and exercise, and neuromodulation, among others, can be utilized to treat CPSP.

4. Further research is needed in the form of high-powered clinical trials, genetic sampling, and advancements in machine learning to obtain a better understanding of who is at risk of developing CPSP, as well as which treatments would be most beneficial to CPSP patients.

References

1. Rosenberger DC, Pogatzki-Zahn EM. Chronic post-surgical pain - update on incidence, risk factors and preventive treatment options. BJA Educ. 2022;22(5):190–6.
2. Schug SA, Lavand'homme P, Barke A, Korwisi B, Rief W, Treede RD, et al. The IASP classification of chronic pain for ICD-11: chronic postsurgical or posttraumatic pain. Pain. 2019;160(1):45–52.
3. Crombie IK, Davies HT, Macrae WA. Cut and thrust: antecedent surgery and trauma among patients attending a chronic pain clinic. Pain. 1998;76(1–2):167–71.
4. Macrae WADH. Chronic post surgical pain. In: Combie IK, editor. Epidemiology of pain. Seattle: IASP Press; 1999. p. 125–42.
5. Macrae WA. Chronic pain after surgery. Br J Anaesth. 2001;87(1):88–98.
6. Werner MU, Kongsgaard UE. I. Defining persistent post-surgical pain: is an update required? Br J Anaesth. 2014;113(1):1–4.
7. Brennan TJ. Pathophysiology of postoperative pain. Pain. 2011;152(3 Suppl):S33–40.
8. Richebe P, Capdevila X, Rivat C. Persistent postsurgical pain: pathophysiology and preventative pharmacologic considerations. Anesthesiology. 2018;129(3):590–607.
9. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother. 2009;9(5):723–44.
10. Brennan TJ, Vandermeulen EP, Gebhart GF. Characterization of a rat model of incisional pain. Pain. 1996;64(3):493–502.
11. Pogatzki-Zahn EM, Segelcke D, Schug SA. Postoperative pain-from mechanisms to treatment. Pain Rep. 2017;2(2):e588.
12. Haroutiunian S, Nikolajsen L, Finnerup NB, Jensen TS. The neuropathic component in persistent postsurgical pain: a systematic literature review. Pain. 2013;154(1):95–102.
13. Fletcher D, Stamer UM, Pogatzki-Zahn E, Zaslansky R, Tanase NV, Perruchoud C, et al. Chronic postsurgical pain in Europe: an observational study. Eur J Anaesthesiol. 2015;32(10):725–34.
14. Clarke H, Katz J, Flor H, Rietschel M, Diehl SR, Seltzer Z. Genetics of chronic post-surgical pain: a crucial step toward personal pain medicine. Can J Anaesth. 2015;62(3):294–303.
15. Weiser TG, Regenbogen SE, Thompson KD, Haynes AB, Lipsitz SR, Berry WR, et al. An estimation of the global volume of surgery: a modelling strategy based on available data. Lancet. 2008;372(9633):139–44.
16. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet. 2006;367(9522):1618–25.
17. Schug SA, Bruce J. Risk stratification for the development of chronic postsurgical pain. Pain Rep. 2017;2(6):e627.
18. Peul WC, Brand R, Thomeer R, Koes BW. Influence of gender and other prognostic factors on outcome of sciatica. Pain. 2008;138(1):180–91.
19. Hinrichs-Rocker A, Schulz K, Jarvinen I, Lefering R, Simanski C, Neugebauer EA. Psychosocial predictors and correlates for chronic post-surgical pain (CPSP) - a systematic review. Eur J Pain. 2009;13(7):719–30.
20. Chapman CR, Vierck CJ. The transition of acute postoperative pain to chronic pain: an integrative overview of research on mechanisms. J Pain. 2017;18(4):359 e1–e38.
21. Montes A, Roca G, Sabate S, Lao JI, Navarro A, Cantillo J, et al. Genetic and clinical factors associated with chronic postsurgical pain after hernia repair, hysterectomy, and thoracotomy: a two-year multicenter cohort study. Anesthesiology. 2015;122(5):1123–41.
22. Mogil JS. Pain genetics: past, present and future. Trends Genet. 2012;28(6):258–66.
23. Yarnitsky D, Crispel Y, Eisenberg E, Granovsky Y, Ben-Nun A, Sprecher E, et al. Prediction of chronic post-operative pain: pre-operative DNIC testing identifies patients at risk. Pain. 2008;138(1):22–8.
24. Hoofwijk DM, van Reij RR, Rutten BP, Kenis G, Buhre WF, Joosten EA. Genetic polymorphisms and their association with the prevalence and severity of chronic postsurgical pain: a systematic review. Br J Anaesth. 2016;117(6):708–19.
25. Chidambaran V, Gang Y, Pilipenko V, Ashton M, Ding L. Systematic review and meta-analysis of genetic risk of developing chronic postsurgical pain. J Pain. 2020;21(1–2):2–24.
26. VanDenKerkhof EG, Peters ML, Bruce J. Chronic pain after surgery: time for standardization? A framework to establish core risk factor and outcome domains for epidemiological studies. Clin J Pain. 2013;29(1):2–8.
27. Brummett CM, Urquhart AG, Hassett AL, Tsodikov A, Hallstrom BR, Wood NI, et al. Characteristics of fibromyalgia independently predict poorer long-term analgesic outcomes following total knee and hip arthroplasty. Arthritis Rheumatol. 2015;67(5):1386–94.
28. Waljee JF, Cron DC, Steiger RM, Zhong L, Englesbe MJ, Brummett CM. Effect of preoperative opioid exposure on healthcare utilization and expenditures

following elective abdominal surgery. Ann Surg. 2017;265(4):715–21.
29. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth. 2014;112(6):991–1004.
30. de Hoogd S, Ahlers SJ, van Dongen EP, van de Garde EM, Hamilton-Ter Brake TA, Dahan A, et al. Is intraoperative remifentanil associated with acute or chronic postoperative pain after prolonged surgery? an update of the literature. Clin J Pain. 2016;32(8):726–35.
31. van Gulik L, Ahlers SJ, van de Garde EM, Bruins P, van Boven WJ, Tibboel D, et al. Remifentanil during cardiac surgery is associated with chronic thoracic pain 1 yr after sternotomy. Br J Anaesth. 2012;109(4):616–22.
32. Salengros JC, Huybrechts I, Ducart A, Faraoni D, Marsala C, Barvais L, et al. Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. J Cardiothorac Vasc Anesth. 2010;24(4):608–16.
33. Perkins FM, Kehlet H. Chronic pain as an outcome of surgery. A review of predictive factors. Anesthesiology. 2000;93(4):1123–33.
34. Hamood R, Hamood H, Merhasin I, Keinan-Boker L. Chronic pain and other symptoms among breast cancer survivors: prevalence, predictors, and effects on quality of life. Breast Cancer Res Treat. 2018;167(1):157–69.
35. Dworkin RH, McDermott MP, Raja SN. Preventing chronic postsurgical pain: how much of a difference makes a difference? Anesthesiology. 2010;112(3):516–8.
36. Vadivelu N, Mitra S, Schermer E, Kodumudi V, Kaye AD, Urman RD. Preventive analgesia for postoperative pain control: a broader concept. Local Reg Anesth. 2014;7:17–22.
37. Buvanendran A, Kroin JS. Multimodal analgesia for controlling acute postoperative pain. Curr Opin Anaesthesiol. 2009;22(5):588–93.
38. Borsook D, Kussman BD, George E, Becerra LR, Burke DW. Surgically induced neuropathic pain: understanding the perioperative process. Ann Surg. 2013;257(3):403–12.
39. Bischoff JM, Aasvang EK, Kehlet H, Werner MU. Does nerve identification during open inguinal herniorrhaphy reduce the risk of nerve damage and persistent pain? Hernia. 2012;16(5):573–7.
40. Freeman SR, Washington SJ, Pritchard T, Barr L, Baildam AD, Bundred NJ. Long term results of a randomised prospective study of preservation of the intercostobrachial nerve. Eur J Surg Oncol. 2003;29(3):213–5.
41. Alper I, Yuksel E. Comparison of acute and chronic pain after open nephrectomy versus laparoscopic nephrectomy: a prospective clinical trial. Medicine (Baltimore). 2016;95(16):e3433.
42. Joris JL, Georges MJ, Medjahed K, Ledoux D, Damilot G, Ramquet CC, et al. Prevalence, characteristics and risk factors of chronic postsurgical pain after laparoscopic colorectal surgery: retrospective analysis. Eur J Anaesthesiol. 2015;32(10):712–7.
43. Rivat C, Bollag L, Richebe P. Mechanisms of regional anaesthesia protection against hyperalgesia and pain chronicization. Curr Opin Anaesthesiol. 2013;26(5):621–5.
44. Weinstein EJ, Levene JL, Cohen MS, Andreae DA, Chao JY, Johnson M, et al. Local anaesthetics and regional anaesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children. Cochrane Database Syst Rev. 2018;4(4):CD007105.
45. Andreae MH, Andreae DA. Regional anaesthesia to prevent chronic pain after surgery: a Cochrane systematic review and meta-analysis. Br J Anaesth. 2013;111(5):711–20.
46. Levene JL, Weinstein EJ, Cohen MS, Andreae DA, Chao JY, Johnson M, et al. Local anesthetics and regional anesthesia versus conventional analgesia for preventing persistent postoperative pain in adults and children: a Cochrane systematic review and meta-analysis update. J Clin Anesth. 2019;55:116–27.
47. Elsharkawy H, Clark JD, El-Boghdadly K. Evidence for regional anesthesia in preventing chronic postsurgical pain. Reg Anesth Pain Med. 2025;50(2):153–9.
48. Carley ME, Chaparro LE, Choiniere M, Kehlet H, Moore RA, Van Den Kerkhof E, et al. Pharmacotherapy for the prevention of chronic pain after surgery in adults: an updated systematic review and meta-analysis. Anesthesiology. 2021;135(2):304–25.
49. Weibel S, Jelting Y, Pace NL, Helf A, Eberhart LH, Hahnenkamp K, et al. Continuous intravenous perioperative lidocaine infusion for postoperative pain and recovery in adults. Cochrane Database Syst Rev. 2018;6(6):CD009642.
50. Richebe P, Rivat C, Laulin JP, Maurette P, Simonnet G. Ketamine improves the management of exaggerated postoperative pain observed in perioperative fentanyl-treated rats. Anesthesiology. 2005;102(2):421–8.
51. Schwenk ES, Viscusi ER, Buvanendran A, Hurley RW, Wasan AD, Narouze S, et al. Consensus guidelines on the use of intravenous ketamine infusions for acute pain management from the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain Medicine, and the American Society of Anesthesiologists. Reg Anesth Pain Med. 2018;43(5):456–66.
52. Koh IJ, Kim MS, Sohn S, Song KY, Choi NY, In Y. Duloxetine reduces pain and improves quality of recovery following total knee arthroplasty in centrally sensitized patients: a prospective, ran-

domized controlled study. J Bone Joint Surg Am. 2019;101(1):64–73.
53. Wong K, Phelan R, Kalso E, Galvin I, Goldstein D, Raja S, et al. Antidepressant drugs for prevention of acute and chronic postsurgical pain: early evidence and recommended future directions. Anesthesiology. 2014;121(3):591–608.
54. Fuller AM, Bharde S, Sikandar S. The mechanisms and management of persistent postsurgical pain. Front Pain Res (Lausanne). 2023;4:1154597.
55. Reuben SS, Ekman EF. The effect of initiating a preventive multimodal analgesic regimen on long-term patient outcomes for outpatient anterior cruciate ligament reconstruction surgery. Anesth Analg. 2007;105(1):228–32.
56. Thapa P, Euasobhon P. Chronic postsurgical pain: current evidence for prevention and management. Korean J Pain. 2018;31(3):155–73.
57. Morrison RS, Flanagan S, Fischberg D, Cintron A, Siu AL. A novel interdisciplinary analgesic program reduces pain and improves function in older adults after orthopedic surgery. J Am Geriatr Soc. 2009;57(1):1–10.
58. Morze CJ, Johnson NR, Williams G, Moroney M, Lamberton T, McAuliffe M. Knee pain during the first three months after unilateral total knee arthroplasty: a multi-centre prospective cohort study. J Arthroplasty. 2013;28(9):1565–70.
59. Joshi GP, Ogunnaike BO. Consequences of inadequate postoperative pain relief and chronic persistent postoperative pain. Anesthesiol Clin North Am. 2005;23(1):21–36.
60. Katz J, Weinrib A, Fashler SR, Katznelzon R, Shah BR, Ladak SS, et al. The Toronto General Hospital Transitional Pain Service: development and implementation of a multidisciplinary program to prevent chronic postsurgical pain. J Pain Res. 2015;8:695–702.
61. De Kock M. Expanding our horizons: transition of acute postoperative pain to persistent pain and establishment of chronic postsurgical pain services. Anesthesiology. 2009;111(3):461–3.
62. Steyaert A, Lavand'homme P. Prevention and treatment of chronic postsurgical pain: a narrative review. Drugs. 2018;78(3):339–54.
63. Scascighini L, Toma V, Dober-Spielmann S, Sprott H. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. Rheumatology (Oxford). 2008;47(5):670–8.
64. Gatchel RJ, Peng YB, Peters ML, Fuchs PN, Turk DC. The biopsychosocial approach to chronic pain: scientific advances and future directions. Psychol Bull. 2007;133(4):581–624.
65. Wylde V, Dennis J, Beswick AD, Bruce J, Eccleston C, Howells N, et al. Systematic review of management of chronic pain after surgery. Br J Surg. 2017;104(10):1293–306.
66. Abdi S, Datta S, Trescot AM, Schultz DM, Adlaka R, Atluri SL, et al. Epidural steroids in the management of chronic spinal pain: a systematic review. Pain Physician. 2007;10(1):185–212.
67. Manchikanti L, Malla Y, Cash KA, McManus CD, Pampati V. Fluoroscopic cervical interlaminar epidural injections in managing chronic pain of cervical postsurgery syndrome: preliminary results of a randomized, double-blind, active control trial. Pain Physician. 2012;15(1):13–25.
68. Manchikanti L, Singh V, Cash KA, Pampati V, Datta S. Management of pain of post lumbar surgery syndrome: one-year results of a randomized, double-blind, active controlled trial of fluoroscopic caudal epidural injections. Pain Physician. 2010;13(6):509–21.
69. Grider JS, Manchikanti L, Carayannopoulos A, Sharma ML, Balog CC, Harned ME, et al. Effectiveness of spinal cord stimulation in chronic spinal pain: a systematic review. Pain Physician. 2016;19(1):E33–54.
70. Hayek SM, Veizi E, Hanes M. Intrathecal hydromorphone and bupivacaine combination therapy for post-laminectomy syndrome optimized with patient-activated bolus device. Pain Med. 2016;17(3):561–71.
71. Meloto CB, Benavides R, Lichtenwalter RN, Wen X, Tugarinov N, Zorina-Lichtenwalter K, et al. Human pain genetics database: a resource dedicated to human pain genetics research. Pain. 2018;159(4):749–63.
72. Ahsan MM, Luna SA, Siddique Z. Machine-learning-based disease diagnosis: a comprehensive review. Healthcare (Basel). 2022;10(3)
73. Huang K, Xiao C, Glass LM, Critchlow CW, Gibson G, Sun J. Machine learning applications for therapeutic tasks with genomics data. Patterns (N Y). 2021;2(10):100328.
74. Karhade AV, Ogink PT, Thio Q, Cha TD, Gormley WB, Hershman SH, et al. Development of machine learning algorithms for prediction of prolonged opioid prescription after surgery for lumbar disc herniation. Spine J. 2019;19(11):1764–71.
75. Simpson S, Zhong W, Mehdipour S, Armaneous M, Sathish V, Walker N, et al. Classifying high-risk patients for persistent opioid use after major spine surgery: a machine-learning approach. Anesth Analg. 2024;139(4):690–9.
76. Karhade AV, Cha TD, Fogel HA, Hershman SH, Tobert DG, Schoenfeld AJ, et al. Predicting prolonged opioid prescriptions in opioid-naive lumbar spine surgery patients. Spine J. 2020;20(6):888–95.
77. Zhang Y, Fatemi P, Medress Z, Azad TD, Veeravagu A, Desai A, et al. A predictive-modeling based screening tool for prolonged opioid use after surgical management of low back and lower extremity pain. Spine J. 2020;20(8):1184–95.
78. Yen HK, Ogink PT, Huang CC, Groot OQ, Su CC, Chen SF, et al. A machine learning algorithm for predicting prolonged postoperative opioid prescription after lumbar disc herniation surgery. An external validation study using 1316 patients from a Taiwanese cohort. Spine J. 2022;22(7):1119–30.

21 Medication Management and Tapering Strategies: Approaches to Effectively Manage and Taper Pain Medications

Terence Hillery, Behnum Habibi, and Chong Kim

Introduction

Well documented is the story of Dr. William T.G. Morton, who first publicly employed ether as a surgical anesthetic in 1846. Less is known about the patient, Edward Abbott's, postoperative course. The short-term goal of perioperative pain management is to reduce severe postoperative pain. To this end, derivatives and analogues of the opium poppy have played a prominent role for millennia. Over time, clinicians have increasingly focused on the long-term goal of reducing risk for chronic postoperative pain. There is a natural conflict in these goals, as prolonged postoperative opioid analgesia has been linked with short-term adverse effects and inferior long-term pain outcomes [1]. Today, physicians have an expanding set of data with which to plan the introduction and weaning of medications for perioperative pain [2]. This chapter will cover the background for the current landscape of perioperative medication management, as well as recent guidelines and other evidence addressing clinical applications, special populations, clinical challenges, and future directions.

Background and Current Understanding

Over the preceding half-century, medical leadership sought to improve postoperative pain management and change societal perception of postoperative pain [3]. Previously, fear of postoperative pain was a more prominent barrier to many patients in need of surgical care. This coincided with a shift toward a more permissive approach to the prescription of opioids. More recently, the link between perioperative opioid use and chronic postoperative pain has strengthened. Two main strategies have been introduced to reduce perioperative opioid consumption. Acute multimodal pain care, as exemplified by enhanced recovery pathways (ERP), stresses multimodal pharmacology, such as the use of acetaminophen, nonsteroidal antiinflammatory drugs (NSAIDs), muscle relaxers, benzodiazepines, and gabapentinoids. Additionally, new policies and guidance have sought to reduce postoperative opioid intake. While these efforts continue, the United States still far outstrips other nations in postoperative opioid intake [4].

T. Hillery (✉) · C. Kim
Metrohealth/Case Western Reserve University,
Cleveland, OH, USA
e-mail: thillery@metrohealth.org

B. Habibi
Portland Pain Medicine, Portland, OR, USA

P. Gulur et al. (eds.), *Perioperative Pain Management*,
https://doi.org/10.1007/978-3-032-11484-6_21

Perioperative Guidelines and Policies: Applications and Techniques

Guidelines and Policies

Several clinical practice guidelines are available to guide clinicians in various aspects of perioperative medication management [5, 6]. These guidelines recommend utilization of a dedicated, continuously available Acute Pain Service. Surgical societies have also published ERP guidelines with specific recommendations for particular operations. For example, the American Society for Enhanced Recovery (ASER) has published specific treatment algorithms for colorectal surgery, including recommended medication doses at specified time points. These ERP guidelines focus mostly on initiation and weaning of nonopioid medications and modalities [7, 8].

Preoperative Period

It is widely agreed that a comprehensive assessment of both medical and psychosocial factors linked to patient outcomes should be undertaken in the preoperative period. This includes assessment of medication history, opioid use, other medication use, alcohol, and illicit drug use. Directed perioperative pain management plans have been shown to reduce opioid use and speed time to discharge [9]. Medication abstinence syndromes, such as may be encountered with discontinuation of benzodiazepines, opioids, antipsychotics, and antidepressants, should be anticipated and managed.

Postoperative

The guidelines recommend clinicians consider techniques including regional anesthesia, epidural catheters, and PCA-delivered medication in a patient-centered approach. Multimodal techniques are preferred, with the drug, route, dose, and duration of therapy to be documented, individualized, and responsive to patient assessment tools.

Opioid Tapering

Introduction

While ERP programs emphasize nonopioid care, the majority of US surgical patients are still treated with opioid medication [10]. To meet the twin goals of opioid harm reduction and prevention of chronic postoperative pain, opioid tapering after surgery is a growing area of focus. It is now understood that the risks and benefits of continued opioid therapy vary significantly by clinical situation. For example, the risks and benefits of postoperative opioid therapy after a dental procedure in a 19-year-old differ significantly from that of a 72-year-old recovering from spinal fusion.

Perioperative Opioid Tapering

The surgical literature strongly suggests that timely tapering of opioids is linked with improved functional outcomes and lower risk of adverse outcomes. Opioid liberalization and altered societal expectations for postoperative pain have contributed to longer and sometimes chronic postoperative opioid therapy [3]. It is also known that inadequate postoperative pain control is linked with chronic postsurgical pain. Thus, both insufficient pain control and prolonged opioid therapy put patients at higher risk of adverse chronic pain outcomes. This highlights both the importance and challenge of providing evidence-based care throughout the postoperative period.

From the surgical literature, several methods have been proposed for opioid tapering. For example, one approach utilizes standardized dosage recommendations [11]. An expert panel published specific recommendations for the number of 5 mg oxycodone tablets to be prescribed after common dental procedures. After tooth extractions, zero tablets were recommended; after bone grafting procedures, 0–12 tablets were recommended. Similarly, in the hand surgery literature, authors collaborated to characterize usual practice for opioid prescription after common procedures. They then studied patient out-

comes after opioid reduction education was provided to clinicians, which were favorable. Citing this evidence, the authors gave specific dosage guidelines, recommending no more than ten 5 mg oxycodone tablets be prescribed after carpal tunnel release [12]. Another approach calculates individualized tapers based on total opioid consumption on the day prior to discharge using a decay function [13].

Acute to Subacute Transition

It is clear from the literature that guideline-driven tapers of opioid pain medication in the acute postsurgical period have been successfully implemented. Further work remains in refining and implementing guidance for specific procedures and patient populations. At present, many patients are continued on opioid therapy in the weeks and months after surgery for a broad range of procedures. Evidence and guidance [14] suggest prolonged therapy changes the risks and benefits of tapering opioid medication.

Subacute and Chronic Opioid Therapy Risk Analysis

During subacute or chronic opioid management of pain, a clinician may determine that the risks of continued opioid therapy outweigh the benefits [15]. This may be particularly true for younger patients, for whom the long-term risks are most pronounced [16]. Failure of therapeutic benefit of opioid therapy may present as inadequate pain relief or insufficient functional improvement on opioid therapy. Risks include physical dependence, addiction, and death, but may also include unacceptable side effects, decreased physical ability, and social isolation. This may present as falls, accidents, and worsening symptoms of comorbid cognitive or psychiatric conditions. Guidelines consider the benefit threshold to be a 30% improvement in pain level or function. Tools including the three-question PEG tool are validated for this use [17].

Another manifestation of risk may be failure to adhere to the opioid treatment agreement. A chronic or subacute opioid treatment agreement typically specifies that the patient must abstain from alcohol, illicit drugs, and possibly other neurotrophic prescription medications; the patient also agrees they may only receive opioids from the named physician. This agreement is maintained through regular office visits, drug screening, pill counts, and substance abuse screening tools.

A common and prominent risk with chronic opioid therapy is the concomitant administration of benzodiazepines and gabapentinoids, which has been shown to increase mortality [18]. Separate evidence and guidance suggest that high-dose opioid therapy is linked to death and other adverse outcomes [15]. Recent guidance suggests this threshold for increased risk begins at 50 milligram morphine equivalents [14]. These factors should be considered when weighing the risks and benefits of continued opioid therapy.

Subacute and Chronic Opioid Taper Techniques

Whether initiated by the patient or the clinician, the patient should be engaged in a clear, open discussion of the timeline and expected experiences.

At least nine distinct categories of tapering protocols have been reported in the literature, including tapering using the patient's current opioid medication, substituting a long-acting opioid such as methadone, and the addition of alpha 2 adrenergic agonists (clonidine and lofexidine). A partial opioid such as buprenorphine may be substituted, and naltrexone may be used at the conclusion phase of a taper. For example, in a patient with opioid use disorder (OUD), a buprenorphine-only taper strategy may be employed. Clinicians have also studied drug-induced withdrawal, though this is not common in clinical practice [19]. High-risk patients may benefit from referral to a pain medicine specialist.

Most opioid taper techniques rely on calculation and conversion of the morphine milligram equivalent (MME) of a regimen. Commonly, a taper is initiated by recording the total opioid intake (oral and intravenous) over a 24-hour period, then converted to MME. This daily dose is reduced by a 25–50% safety factor, then divided into as-needed doses of immediate-release opioid medication. From there, reductions of between 10% and 25% of total MME every 1–4 weeks have been recommended [10]. In chronic opioid tapers, there is some evidence to suggest that rapid tapering [20] is associated with negative outcomes, and slower tapering may be associated with greater adherence [21]. Patient input is important when considering how to enact a dose reduction, such as the decision to divide tablets or take less frequently.

Case Study

A 50-year-old patient who underwent lumbar spinal fusion 16 weeks ago is currently taking 30 mg extended-release oxycodone twice daily and a total of 40 mg instant-release oxycodone per day. The 24-hour MME is 150. The first step in the taper could be to decrease the MME by 25–50%, maintained for 1–4 weeks. This may be accomplished by converting entirely to instant-release oxycodone, such as by prescribing instant-release oxycodone 15 mg (MME 135) to be taken every 4 hours. Subsequent steps in the taper could include lengthening dosing intervals or decreasing individual doses to reduce daily MME by 10–25% every 1–4 weeks.

Special Populations

Opioid Use Disorder

Opioid use disorder presents particular challenges for perioperative management. Multiple guidelines discourage routine discontinuation of suboxone in the perioperative period [22, 23]. Guidelines recommend dividing buprenorphine doses (2–3 doses per day). Within this strategy, a buprenorphine only (with increase to 24–32 mg per day) and a buprenorphine plus full, high-affinity mu opioid receptor agonism (fentanyl, hydromorphone) paradigms have been employed [6, 15]. Postoperative and postdischarge opioid taper planning must be considered carefully in light of both the expected recovery timeline and the possibility (and implications) of opioid withdrawal. Opioid sparing strategies have been implemented to treat chronic postoperative pain in this population, including the use of periodic intravenous ketamine infusions.

Challenges and Considerations

The challenges to implementing these recommendations are numerous. Factors that influence the development of chronic postoperative pain and opioid use may begin years before the operation. Recommendations to date presuppose a high level of care coordination and collaboration (such as commonly agreed pathways and care plan templates) between specialties. The consequences of decades of opioid liberalization pose further challenges, both in OUD and in the societal expectations for perioperative pain control. Chronic opioid tapering is currently an area of intense debate, with some guidance emphasizing the risks of continued opioid therapy, while other guidance stresses the risks of abrupt opioid tapering [24].

Future Directions

Chronic postoperative pain and opioid use disorder continue to impose an enormous burden on population health and healthcare resources. Significant work remains in clarifying perioperative risk and protective factors for these conditions. While expense and care-coordination remain significant hurdles, progress may be expected by expansion and implementation of guidance, including ERP programs and guideline-directed acute postoperative opioid tapering.

Neuromodulation, complementary and alternative medicine, and perioperative psychological care may hold promise.

An area ripe for opportunity is the expansion of guidance and the implementation of guideline-directed opioid tapering in the acute postoperative period. Successful implementation using a variety of techniques has been demonstrated [11–13]. For most clinicians, opioid management is not the focus of their training or practice. Specific evidence-based guidance may be helpful in motivating and instilling confidence in clinicians to implement timely opioid tapers in their postsurgical patients.

Key Takeaways

- Opioid consumption in the perioperative period is a key factor linked to both opioid use disorder and chronic postoperative pain.
- A multidisciplinary approach to perioperative medication management, though challenging and expensive, has been shown to be effective in reducing opioid use.
- Patient education is critical in adhering to the directed perioperative medication management plan.
- Special populations, such as patients with opioid use disorder, require individualized plans and close monitoring.
- Progress may be expected as the gap between the guideline-recommended multidisciplinary approach and clinical care delivered is bridged.

References

1. Singla P, Renwick C, Kohan L, Yalamuru B. Working with acute pain colleagues on opioid reduction in the postsurgical population. ASRA Pain Med News. 2022;47
2. Banik GL, Kraimer KL, Shindo ML. Opioid prescribing in patients undergoing neck dissections with short hospitalizations. Otolaryngol Head Neck Surg. 2021;164(4):792–8. https://doi.org/10.1177/0194599820957980. Epub 2020 Sep 22.
3. Hyland SJ, Brockhaus KK, Vincent WR, Spence NZ, Lucki MM, Howkins MJ, Cleary RK. Perioperative pain management and opioid stewardship: a practical guide. Healthcare (Basel). 2021;9(3):333. https://doi.org/10.3390/healthcare9030333. PMID: 33809571; PMCID: PMC8001960.
4. El Moheb M, Mokhtari A, Han K, van Erp I, Kongkaewpaisan N, Jia Z, Rodriguez G, Kongwibulwut M, Kaafarani HM, International Patterns of Opioid Prescribing Workgroup. Pain or no pain, we will give you opioids: relationship between number of opioid pills prescribed and severity of pain after operation in US vs non-US patients. J Am Coll Surg. 2020;231(6):639–48. https://doi.org/10.1016/j.jamcollsurg.2020.08.771. Epub 2020 Sep 22.
5. American Society of Anesthesiologists Task Force on Acute Pain Management. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012;116(2):248–73. https://doi.org/10.1097/ALN.0b013e31823c1030.
6. Mariano ER, Dickerson DM, Szokol JW, Harned M, Mueller JT, Philip BK, Baratta JL, Gulur P, Robles J, Schroeder KM, Wyatt KEK, Schwalb JM, Schwenk ES, Wardhan R, Kim TS, Higdon KK, Krishnan DG, Shilling AM, Schwartz G, Wiechmann L, Doan LV, Elkassabany NM, Yang SC, Muse IO, Eloy JD, Mehta V, Shah S, Johnson RL, Englesbe MJ, Kallen A, Mukkamala SB, Walton A, Buvanendran A. A multisociety organizational consensus process to define guiding principles for acute perioperative pain management. Reg Anesth Pain Med. 2022;47(2):118–27. https://doi.org/10.1136/rapm-2021-103083. Epub 2021 Sep 22.
7. Scott MJ, McEvoy MD, Gordon DB, Grant SA, Thacker JKM, Wu CL, Gan TJ, Mythen MG, Shaw AD, Miller TE, Perioperative Quality Initiative (POQI) I Workgroup. American Society for Enhanced Recovery (ASER) and Perioperative Quality Initiative (POQI) joint consensus statement on optimal analgesia within an enhanced recovery pathway for colorectal surgery: part 2-from PACU to the transition home. Perioper Med (Lond). 2017;6:7. https://doi.org/10.1186/s13741-017-0063-6. Erratum in: Perioper Med (Lond). 2018 Apr 10;7:4. PMID: 28413628; PMCID: PMC5390469.
8. List of Guidelines. Enhanced Recovery After Surgery (ERAS) (R) Society. Available online: https://erassociety.org/guidelines/list-of-guidelines/. Accessed on 14 Sept 2020.
9. Furdon SA, Eastman M, Benjamin K, Horgan MJ. Outcome measures after standardized pain management strategies in postoperative patients in the neonatal intensive care unit. J Perinat Neonatal Nurs. 1998;12(1):58–69.
10. Young JC, Dasgupta N, Chidgey BA, Jonsson Funk M. Postsurgical opioid prescriptions and risk of long-term use: an observational cohort study across the United States. Ann Surg. 2021;273(4):743–50. https://doi.org/10.1097/SLA.0000000000003549. PMID: 31404007; PMCID: PMC7440649.

11. Farooqi OA, Bruhn WE, Lecholop MK, Velasquez-Plata D, Maloney JG, Rizwi S, Templeton RB, Goerig A, Hezkial C, Novince CM, Zieman MT, Lotesto AMN, Makary MA. Opioid guidelines for common dental surgical procedures: a multidisciplinary panel consensus. Int J Oral Maxillofac Surg. 2020;49(3):397–402. https://doi.org/10.1016/j.ijom.2019.09.001. Epub 2019 Oct 12. PMID: 31611048; PMCID: PMC8771805.
12. Dwyer CL, Soong M, Hunter A, Dashe J, Tolo E, Kasparyan NG. Prospective evaluation of an opioid reduction protocol in hand surgery. J Hand Surg Am. 2018;43(6):516–522.e1. https://doi.org/10.1016/j.jhsa.2018.01.021. Epub 2018 Mar 12.
13. Chen EY, Betancourt L, Li L, Trucks E, Marcantonio A, Tornetta P 3rd. Standardized, patient-specific, postoperative opioid prescribing after inpatient orthopaedic surgery. J Am Acad Orthop Surg. 2020;28(7):e304–18. https://doi.org/10.5435/JAAOS-D-19-00030.
14. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain - United States, 2022. MMWR Recomm Rep. 2022;71(3):1–95. https://doi.org/10.15585/mmwr.rr7103a1. PMID: 36327391; PMCID: PMC9639433.
15. Rich RC, Chou R, Mariano ER, Dopp AL, Sullenger R, Burstin H, Pain Management Guidelines and Evidence Standards Working Group. Best practices, research gaps, and future priorities to support tapering patients on long-term opioid therapy for chronic non-cancer pain in outpatient settings. NAM Perspect. 2020;2020 https://doi.org/10.31478/202008c. PMID: 35291734; PMCID: PMC8916797.
16. United States Department of Veterans Affairs and Department of Defense. VA/DoD clinical practice guideline for opioid therapy for chronic pain; 2017. Available at: https://www.healthquality.va.gov/guidelines/Pain/cot/VADoDOTCPG022717.pdf. Accessed on 31 Oct 2019.
17. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain--United States, 2016. JAMA. 2016;315(15):1624–45. https://doi.org/10.1001/jama.2016.1464. PMID: 26977696; PMCID: PMC6390846.
18. Gomes T, Juurlink DN, Antoniou T, Mamdani MM, Paterson JM, van den Brink W. Gabapentin, opioids, and the risk of opioid-related death: a population-based nested case-control study. PLoS Med. 2017;14(10):e1002396. https://doi.org/10.1371/journal.pmed.1002396. PMID: 28972983; PMCID: PMC5626029.
19. Fishbain DA. Opioid tapering/detoxification protocols, a compendium: narrative review. Pain Med. 2021;22(7):1676–97. https://doi.org/10.1093/pm/pnab019.
20. Mark TL, Parish W. Opioid medication discontinuation and risk of adverse opioid-related health care events. J Subst Abus Treat. 2019;103:58–63. https://doi.org/10.1016/j.jsat.2019.05.001. Epub 2019 May 5.
21. Berna C, Kulich RJ, Rathmell JP. Tapering long-term opioid therapy in chronic noncancer pain: evidence and recommendations for everyday practice. Mayo Clin Proc. 2015;90(6):828–42. https://doi.org/10.1016/j.mayocp.2015.04.003.
22. VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives. Perioperative pian management guidance for patients on chronic buprenorphine therapy undergoing elective or emergent procedures; 2022.
23. Kohan L, Potru S, Barreveld AM, Sprintz M, Lane O, Aryal A, Emerick T, Dopp A, Chhay S, Viscusi E. Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel. Reg Anesth Pain Med. 2021;46(10):840–59. https://doi.org/10.1136/rapm-2021-103007. Epub 2021 Aug 12.
24. Fenton JJ, Magnan E, Tseregounis IE, Xing G, Agnoli AL, Tancredi DJ. Long-term risk of overdose or mental health crisis after opioid dose tapering. JAMA Netw Open. 2022;5(6):e2216726. https://doi.org/10.1001/jamanetworkopen.2022.16726. Erratum in: JAMA Netw Open 2022 Jul 01;5(7):e2224285. doi: 10.1001/jamanetworkopen.2022.24285. PMID: 35696163; PMCID: PMC9194670.

22 Psychosocial Aspects of Long-Term Pain: Examines the Psychological Impact of Chronic Postoperative Pain

Frank Kenner, Lauren Abshire, and Sara Davin

Introduction

Approximately one in three Americans live with chronic pain [1], with ~8% having high impact chronic pain (HICP) [2]. HICP is characterized by disabling persistent pain [2] and associated with higher psychosocial challenges and opioid use [3]. HICP is one of the most up to date terms in the literature to describe the debilitating nature of severe chronic pain conditions. With 313 million surgeries performed worldwide each year [3] it is reasonable to expect that many individuals seek surgery to address long-term pain. Rate of preoperative HICP range from as high as 71.6% to as low as 15.2% in the spine surgery population [4]. Psychosocial factors are repeatedly implicated in the discussions of HICP and in postsurgical outcomes, including the transition to persistent postsurgical pain [5] (PPSP). Given that PPSP and postoperative HICP are associated with exceedingly more healthcare costs, disability, and opioid use [4], it is reasonable and empirically supported to optimize patients from a comprehensive psychosocial perspective to enhance outcomes and reduce risk for continued pain. This chapter will highlight the relevant literature on the psychosocial impact of chronic pain in the perioperative setting, provide real-world applications of psychologically based perioperative treatments and discuss challenges and future directions to enhance understanding and utilization of psychologically informed perioperative care.

Background and Current Understanding

A growing body of research supports the biopsychosocial model of disease proposed by Engel [5] including its application to chronic pain conditions [6]. The identification and possible remediation of associated psychosocial factors that can affect outcomes following medical procedures is of paramount importance. Taylor and colleagues [7] examined nonpsychosocial patient and technology factors as predictors of pain relief following spinal cord stimulator (SCS) implantation for failed back surgery patients with chronic leg and back pain. These factors included location, duration, and initial level of pain, litigation/worker's compensation status, age, gender, duration of follow-up, type of SCS lead used, and method of lead placement. Their meta-regression analysis revealed no associations among these

F. Kenner
Division of Physical Medicine & Rehabilitation, MetroHealth Parma Medical Center, Parma, OH, USA

L. Abshire (✉) · S. Davin
Comprehensive Pain Recovery, Center for Spine Health, Neurological Institute, Cleveland Clinic, Cleveland, OH, USA
e-mail: abshirL2@ccf.org

P. Gulur et al. (eds.), *Perioperative Pain Management*,
https://doi.org/10.1007/978-3-032-11484-6_22

factors and postoperative pain reduction. They concluded all patients benefited from SCS placement, with substantial variability in the level of pain relief obtained. In contrast, psychosocial factors have been shown to be robust predictors of outcomes following surgical or other interventions for chronic pain and related conditions [8, 9]. These factors, according to systematic reviews [10–12] on PPSP, include depression, anxiety, stress, catastrophizing, and psychological vulnerability [13]. Furthermore, state anxiety and pain magnification, one of the dimensions of pain catastrophizing, predicted postsurgical pain intensity at 3 months postsurgery irrespective of the surgical model (total knee arthroplasty versus breast surgery for cancer), even in the absence of presurgical pain [14]. This finding suggests these factors are not mere remnants of preexisting chronic pain, but potential risk factors for new onset PPSP. Similarly, Giusti and colleagues [15] showed pain catastrophizing was associated with pain intensity in the acute postsurgery phase and emotional distress was associated with pain intensity and pain interference at 1 month and pain interference at 3 months postsurgery. A meta-analysis [12] of 15 relatively high-quality studies revealed a pooled odds ratio of between 1.55 and 2.10 for the association between fear/catastrophizing and PPSP.

Certain protective factors have been identified which are associated with improved outcomes postsurgery. Higher levels of self-efficacy is associated with less impairment, affective distress, and pain severity in chronic pain patients [16] and greater improvement in functional ability following knee replacement surgery in the 1–5-year postoperative period [17, 18].

Perhaps less studied than the *intra*personal factors related to postop pain outcomes are the *inter*personal factors—the social aspect—but these are no less influential. Hanley and colleagues [19] showed that increased social support and decreased spousal solicitousness at 1-month postamputation explained 22% of the variance in pain interference in patients following lower limb amputations at 2 years postsurgery. An oversolicitous spouse (or other influential person) who offers to take on responsibilities once handled by the recovering patient provides an incentive to increase pain behaviors and reduce overall physical functioning as physical activities are increasingly avoided [20]. It can also interfere with developing pain-related self-efficacy that can only come from efforts to function adaptively despite pain.

Research into intervention efforts to mitigate risk factors for PPSP is at an early stage. Wang and colleagues [21] completed a meta-analysis on the effectiveness of perioperative psychotherapy on PPSP. They found psychoeducation alone was not effective in mitigating PPSP; however, psychoeducation plus cognitive behavioral therapy (CBT) or relaxation training was effective in reducing PPSP and physical impairments in the postoperative period. They suggested further research focus on exploring targeting more psychologically vulnerable surgical patients to provide psychotherapy in the perioperative period.

Evidence-Based Practices

Preliminary evidence exists for the efficacy of cognitive behavioral therapy (CBT) on postsurgical outcomes. In CBT, a psychologist or therapist focuses on modifying a person's maladaptive cognitive, behavioral, and emotional propensities to elicit change in these response patterns by implementing more adaptive coping strategies to improve quality of life. A systematic review of randomized-controlled trials (RCTs) [22] investigating perioperative CBT-based interventions showed that four of six studies reported reduced pain intensity and five of five studies reported reduced pain disability. The authors noted substantial heterogeneity with respect to timing and delivery of the interventions and length of follow-up; however, this makes recommendations for specific treatment approaches uncertain. An earlier meta-analysis [23] of CBT-based RCTs using chronic pain patients revealed a median effect size of 0.5 versus waitlist control for all outcomes including pain experience, pain behaviors, mood, cognitive coping, social role functioning, and use of the health care system. Smaller

effect sizes were seen versus active controls and were limited to the domains of pain experience, cognitive coping, and pain behaviors.

Empowered relief is a single session 2-hour CBT-based intervention to treat chronic pain created by Dr. Beth Darnall at Stanford University that has been adapted for acute pain and surgical populations. The pilot study of this adapted version of empowered relief, called "My Surgical Success" showed participants who engaged in the course stopped opioids 6.5 days sooner after surgery when compared to the control group [24]. Another study on orthopedic trauma surgery patients demonstrated significant reductions in pain after surgery and sustained analgesia 3 months later [25]. Overall, findings suggest this single session evidence-based intervention may be an effective way to proactively intervene to reduce the risk of PPSP. Additionally, this class is often administered in a group format which increases accessibility of psychological interventions.

There has also been a growing interest in acceptance- and mindfulness-based interventions for chronic pain. Acceptance and Commitment Therapy (ACT) emphasizes the need to accept pain as an inevitable consequence of certain conditions and to focus one's efforts toward achieving valued life goals in spite of pain, rather than pain relief [26]. Mindfulness-based stress reduction (MBSR) [27] and mindfulness-based cognitive therapy (MBCT) [28] utilize meditative and other awareness focused interventions to promote acceptance of pain and other difficult sensations. The focus is on observation and awareness (versus avoidance) of these sensations with a nonjudgmental and nonreactive mindset. Meta-analyses of these approaches revealed moderate effects sizes on pain, depression [29], anxiety, and pain interference [30].

Hypnosis is another behavioral intervention utilized independently or in conjunction with other psychological modalities. Hypnosis has been used for pain relief for centuries and involves inducing a hypnotic state through specific suggestions promoting changes in sensations, emotions, behaviors, and cognitions prior to reorienting them to their surroundings [31]. One study of the perioperative use of hypnosis demonstrated short-term analgesic benefits 1 week after surgery [32].

Challenges and Considerations

Patients may experience unexpected vulnerabilities in the postoperative period, such as acute postoperative pain, changes in medications, restrictions on physical abilities resulting in muscle atrophy, boredom, fear of movement, negative changes in mood, and maladaptive cognitions. As a result, it can be difficult to determine which interventions to administer and when to optimize surgical success due to inconsistencies in the research [33]. While there are certain risk factors that may increase the risk of developing PPSP, accurately identifying and providing an intervention to patients can pose a challenge. Additionally, there is limited access to pain psychologists despite a national call in 2016 to increase pain education for psychologists at all levels of training [34]. Increasing accessibility of interventions is of paramount importance. Implementing group interventions, digital, and/or self-paced options for psychological interventions may help improve access.

Heightened levels of negative emotional or cognitive stress in the postoperative period may contribute to an increase in stress hormones and inflammatory responses [33]. This prolonged stress response can result in changes to the nociceptive transmission and pain awareness in the corticolimbic circuit [35]. Therefore, it is crucial to target and treat the stress response and associated negative emotional and cognitive stress promptly to mitigate the risk of developing PPSP. A meta-analysis of the research to date suggests psychological interventions in the postoperative period or in both the pre- and postoperative period tend to be more effective than preoperative interventions alone [31]. This may be an important consideration in deciding when to implement an intervention to be the most effective. Interventions in the preoperative period should be reinforced throughout the perioperative pathway or introduced postoperatively.

Application of Evidence-Based Therapies to the Clinical Treatment Pathway

While available evidence supports a psychologically informed perioperative pathway for pain management, practical models to guide organizations are missing. It is notable that well-established protocols exist to support surgery recovery in certain disease states (such as bariatric surgery for obesity); however, there are virtually no protocols that routinely incorporate behavioral skills training for reducing pain postsurgery.

The typical clinical scenario involves a patient with multiple complex and overlapping pain syndromes that is recommended for surgery to address one of the pain syndromes. For example, a patient may be experiencing lumbar radiculopathy in the setting of chronic back pain, while also having a history of fibromyalgia. Especially in the case of HICP, the patient may present as highly motivated for pain relief from surgery, while also understandably apprehensive about the outcome due to the impact that persistent pain has had on their quality of life. Pain-related fear and avoidance are very common, alongside elevations in clinical scales of depression, anxiety, and sleep disturbance. Despite the array of psychosocial variables that are also apparent, the preoperative pathway is mostly dedicated to medical clearance appointments and education around surgery in and of itself. It is often quarterbacked by a nursing team who are bombarded with clinical tasks for each patient. Psychologically informed strategies to prepare for surgery are missing.

Psychological evaluations to determine *readiness* for spine procedures such as neuromodulation and surgery have been part of regular practice and required by payors for many years. In fact, in some states, the Bureau for Workman's Compensation require all spine surgery candidates to undergo a health and behavior assessment prior to surgery. While such efforts underscore the opportunities to target key psychological variables that may enhance or inhibit surgical outcome, *they fail to provide targeted strategies to support patients' vulnerabilities such as opioid use, fear of pain, and pain control in the surgical period and beyond.*

One major healthcare system operationalized a clinical pathway integrating targeted behavioral pain skill training as standard of care for spine surgery patients. The development of this pathway, which includes applying evidence-based behavioral pain interventions in a group, virtual format, is discussed in detail in a separate report [36]. Of note, this example shows patients readily engage in behavioral treatment in the perioperative pathway and indicate they intend to use the skills they learn to support their surgery. The focus of such intervention includes: pain education, instruction in concrete skills to self-regulate pain such as relaxation, and enhancing patients' ability to counter a negative pain mindset. These clinical applications offer promise for feasibility and acceptability, but certainly much more work needs to be done. Strategies for identifying high-risk patients, tracking progress, medication use, and pain postsurgery are the necessary next steps to extend behavioral skills into the postsurgery/recovery period.

Future Directions and Research

Most research on psychological interventions in the perioperative period has been done preoperatively. Research suggests postoperative interventions may be more beneficial; therefore, future research should focus on examining the efficacy of behavioral interventions in the postoperative period or in both preop and postop periods. Additionally, many of the studies on behavioral interventions in the perioperative period have relatively small sample sizes, making it difficult to determine how effective the intervention may be in mitigating PPSP. However, research supporting behavioral interventions for analgesia benefits is promising. Future research should also focus on how to best identify high-risk patients and explore ways to provide a low-burden and low-risk behavioral intervention in the perioperative period, which is often busy for patients and clinicians.

Key Takeaways

- Being able to identify and intervene for patients with high-risk factors can positively impact outcomes.
- Psychological interventions in the perioperative period can help with surgical optimization.
- Certain psychosocial factors can contribute to poor surgical outcomes.
- The timing of a psychological intervention, as well as selecting appropriate patients, is important. Research suggests that postoperative interventions may be more effective.
- CBT, ACT, mindfulness-based therapies, and empowered relief are some of the most clinically supported psychological interventions to optimize surgical success at this time.

References

1. Cohen SP, Vase L, Hooten WM. Chronic pain: an update on burden, best practices, and new advances. Lancet. 2021;397(10289):2082–97. https://doi.org/10.1016/S0140-6736(21)00393-7. PMID: 34062143.
2. Dahlhamer J, Lucas J, Zelaya C, Nahin R, Mackey S, DeBar L, Kerns R, Von Korff M, Porter L, Helmick C. Prevalence of chronic pain and high-impact chronic pain among adults - United States, 2016. MMWR Morb Mortal Wkly Rep. 2018;67(36):1001–6. https://doi.org/10.15585/mmwr.mm6736a2. PMID: 30212442; PMCID: PMC6146950.
3. Meara JG, Leather AJ, Hagander L, Alkire BC, Alonso N, Ameh EA, et al. Global surgery 2030: evidence and solutions for achieving health, welfare, and economic development. Lancet. 2015;386:569–624. https://doi.org/10.1016/S0140-6736(15)60160-X.
4. Cook CE, George SZ, Lentz T, Park C, Shaffrey CI, Goodwin CR, Than KD, Gottfried ON. High-impact chronic pain transition in lumbar surgery recipients. Pain Med. 2023;24(3):258–68. https://doi.org/10.1093/pm/pnac150. PMID: 36200873.
5. Engel GL. The need for a new medical model: a challenge for biomedicine. Science. 1977;196(4286):129–36.
6. Gatchel RJ. Comorbidity of chronic pain and mental health disorders: the biopsychosocial perspective. Am Psychol. 2004;59(8):795–805.
7. Taylor RS, Desai MJ, Rigoard P, Taylor RJ. Predictors of pain relief following spinal cord stimulation in chronic back and leg pain and failed back surgery syndrome: a systematic review and meta-regression analysis. Pain Pract. 2013;14(6):489–505.
8. Block AR, Ohnmeiss DD, Guyer R, Rashbaum RF, Hochschuler SH. The use of presurgical psychological screening to predict the outcome of spine surgery. Spine J. 2001;1:274–82.
9. Celestin J, Edwards RR, Jamison RN. Pretreatment psychosocial variables as predictors of outcomes following lumbar surgery and spinal cord stimulation: a systematic review and literature synthesis. Pain Med. 2009;10(4):639–53.
10. Weinrib AZ, Azam MA, Birney KA, Burns LC, Clark H, Katz J. The psychology of chronic post-surgical pain: new frontiers in risk factor identification, prevention and management. Br J Pain. 2017;11(4):169–77.
11. Hinrichs-Rocker A, Schulz K, Järvinen I, Lefering R, Simanski C, Neugebauer EAM. Psychosocial predictors and correlates for chronic post-surgical pain (CPSP)—a systematic review. Eur J Pain. 2009;13:719–30.
12. Theunissen M, Peters ML, Bruce J, Gramke H-F, Marcus MA. Preoperative anxiety and catastrophizing: a systematic review and meta-analysis of the association with chronic postsurgical pain. Clin J Pain. 2012;28(9):819–41.
13. Jess P, Jess T, Beck H, Bech P. Neuroticism in relation to recovery and persisting pain after laparoscopic cholecystectomy. Scand J Gastroenterol. 1998;33:550–3.
14. Masselin-Dubois A, Attal N, Fletcher D, Jayr C, Albi A, Fermanian J, Bouhassira D, Baudic S. Are psychological predictors of chronic postsurgical pain dependent on the surgical model? A comparison of total knee arthroplasty and breast surgery for cancer. J Pain. 2013;14(8):854–64.
15. Giusti EM, Lacerenza M, Gabrielli S, Manzoni GM, Manna C, D'Amario F, et al. Psychological factors and trajectories of post-surgical pain: a longitudinal prospective study. Pain Pract. 2022;22:159–70.
16. Jackson T, Wang Y, Wang Y, Fan H. Self-efficacy and chronic pain outcomes: a meta-analytic review. J Pain. 2014;15(8):800–14.
17. Wylde V, Dixon S, Blom AW. The role of preoperative self-efficacy in predicting outcome after total knee replacement. Musculoskelet Care. 2012;10:110–8.
18. Wylde V, Trela-Larsen L, Whitehouse MR, Blom AW. Preoperative psychosocial risk factors for poor outcomes at 1 and 5 years after total knee replacement. Acta Orthop. 2017;88(5):530–6.
19. Hanley MA, Jensen MP, Ehde DM, Hoffman AJ, Patterson DR, Robinson LR. Psychosocial predictors of long-term adjustment of lower limb amputation and phantom limb pain. Disabil Rehabil. 2004;26(14–15):882–93.
20. Katz J, Seltzer Z. Transition from acute to chronic postsurgical pain: risk factors and protective factors. Expert Rev Neurother 2009;9950 723-744.

21. Wang L, Chang Y, Kennedy SA, Hong PJ, Chow N, Couban RJ, McCabe RE, Bieling PJ, Busse JW. Perioperative psychotherapy for persistent post-surgical pain and physical impairment: a meta-analysis of randomized trials. Br J Anesthes. 2018;120(6):1304–14.
22. Nicholls JL, Azam MA, Burns LC, Englesakis M, Sutherland AM, Weinrib AZ, Katz J, Clarke H. Psychological treatments for the management of postsurgical pain: a systematic review of randomized controlled trials. Patient Relat Outcome Meas. 2018;9:49–64.
23. Morley S, Eccleston C, Williams A. Systematic review and meta-analysis of randomized controlled trials of cognitive behavior therapy and behavior therapy for chronic pain in adults excluding headache. Pain. 1999;80:1–13.
24. Darnall BD, Ziadni MS, Krishnamurthy P, Mackey IG, Heathcote L, Taub CJ, Flood P, Wheeler A. "My surgical success": impact of a digital behavioral pain medicine intervention on time to opioid cessation after breast cancer surgery. Pain Med. 2019. pii: pnz094; https://doi.org/10.1093/pm/pnz094.
25. Ziadni MS, Anderson SR, Gonzalez-Castro L, Darnall BD. "My surgical success": feasibility and impact of a single-session digital behavioral pain medicine intervention on pain intensity, pain catastrophizing, and time to opioid cessation after orthopedic trauma surgery- a randomized rial. Anesth Analg. 2022;
26. Hayes SC, Strosahl KD, Wilson KG. Acceptance and commitment therapy: the process and practice of mindful change. 2nd ed. New York: Guilford; 2012.
27. Kabat-Zinn J. Full catastrophe living. Using the wisdom of your body and mind to face stress, pain and illness. New York: Delta; 1990.
28. Segal ZV, Williams JMG, Teasdale JD. Mindfulness-based cognitive therapy for depression: a new approach to preventing relapse. New York: Guilford; 2002.
29. Veehof MM, Oskam M-J, Shreurs KMG, Bohlmeijer ET. Acceptance-based interventions for the treatment of chronic pain: a systematic review and meta-analysis. Pain. 2011;152:533–42.
30. Veehof MM, Trompeter HR, Bohlmeijer ET, Shreurs KMG. Acceptance- and mindfulness-based interventions for the treatment of chronic pain: a meta-analytic review. Cogn Behav Ther. 2016;45(1):5–31.
31. Geagea D, Ogez D, Kimble R, Tyack Z. Redefining hypnosis: a narrative review of theories to move towards an integrative model. Complement Ther Clin Pract. 2024;54:101826.
32. Moreno Hernandez D, Tellez A, Sanchez-Jauregui T, Garcia CH, Garcia-Solis M, Valdez A. Clinical hypnosis for pain reduction in breast cancer mastectomy: a randomized clinical trial. Int J Clin Exp Hypn. 2022;70(1):4–15.
33. Peters M. Can perioperative psychological interventions reduce chronic pain after surgery? Br J Hosp Med (Lond). 2023;84(5):1–8.
34. Darnall BD, Scheman J, Davin S, Burns JW, Murphy JL, Wilson AC, Kerns RD, Mackey SC. Pain psychology: a global needs assessment and national call to action. Pain Med. 2016;17(2):250–63. https://doi.org/10.1093/pm/pnv095. Epub 2016 Jan 23. PMID: 26803844; PMCID: PMC4758272.
35. Munk A, Reme SE, Jacobsen HB. What does CATS have to do with cancer? The cognitive activation theory of stress (CATS) forms the SURGE model of chronic post-surgical pain in women with breast cancer. Front Psychol. 2021;12:630422.
36. Davin SA, Savage J, Thompson NR, Schuster A, Darnall BD. Transforming standard of care for spine surgery: integration of an online single-session behavioral pain management class for perioperative optimization. Front Pain Res (Lausanne). 2022;3:856252. https://doi.org/10.3389/fpain.2022.856252. PMID: 35599968; PMCID: PMC9118343.

23

Interdisciplinary Pain Management Approaches: Highlights a Multidisciplinary Strategy for Managing Chronic Pain

Jessica Anyaso, Brittany Melvin, and Daila H. Elmofty

Introduction

Chronic pain is a national public health crisis impacting millions of Americans and is associated with physical, emotional, and societal costs. An estimated 100 million US adults suffer from chronic pain with annual costs estimated at over $500 billion [1]. Chronic pain continues to be challenging to treat with poor patient outcomes resulting from the fragmented nature of care along with the disjointed treatment from multiple providers [2]. The use of a multi/interdisciplinary approach to manage chronic pain can overcome some of these challenges. This type of healthcare model incorporates and emphasizes the use of the biopsychosocial framework and the importance of diverse clinical skill sets from physician and nonphysician disciplines involved in addressing chronic pain.

J. Anyaso · D. H. Elmofty (✉)
University of Chicago, Chicago, IL, USA
e-mail: delmofty@bsd.uchicago.edu

B. Melvin
Department of Physical Medicine & Rehabilitation, Sinai Health System, Chicago, IL, USA

Background and Current Understanding

The concept of a multi/interdisciplinary pain management was first established in 1960 by John J. Bianca, M.D. at the University of Washington. The multidisciplinary pain clinic was described as a diagnostic clinic that brought multiple medical subspecialties together to focus on the treatment of chronic pain patients [3]. In 1982, a multidisciplinary inpatient evaluation program for patients who suffer from chronic, intractable pain was introduced but was later terminated in 1997 due to financial factors of the health care system in the United States [4]. The correlation between a patient's psychosocial comorbidities and the negative impact it had on outcomes from invasive procedures was acknowledged. This resulted in the introduction of educational courses on treatment of chronic pain and the physical component with various cognitive and behavioral therapy components [3].

The fundamental principles of multi/interdisciplinary pain management are based on a biopsychosocial model of care in the treatment algorithm. It is an individual-centered model that suggests pain is a complex experience influenced by biological, psychological, and social environments (Fig. 23.1) [5]. Multi/interdisciplinary programs are primarily based on the concept that

P. Gulur et al. (eds.), *Perioperative Pain Management*,
https://doi.org/10.1007/978-3-032-11484-6_23

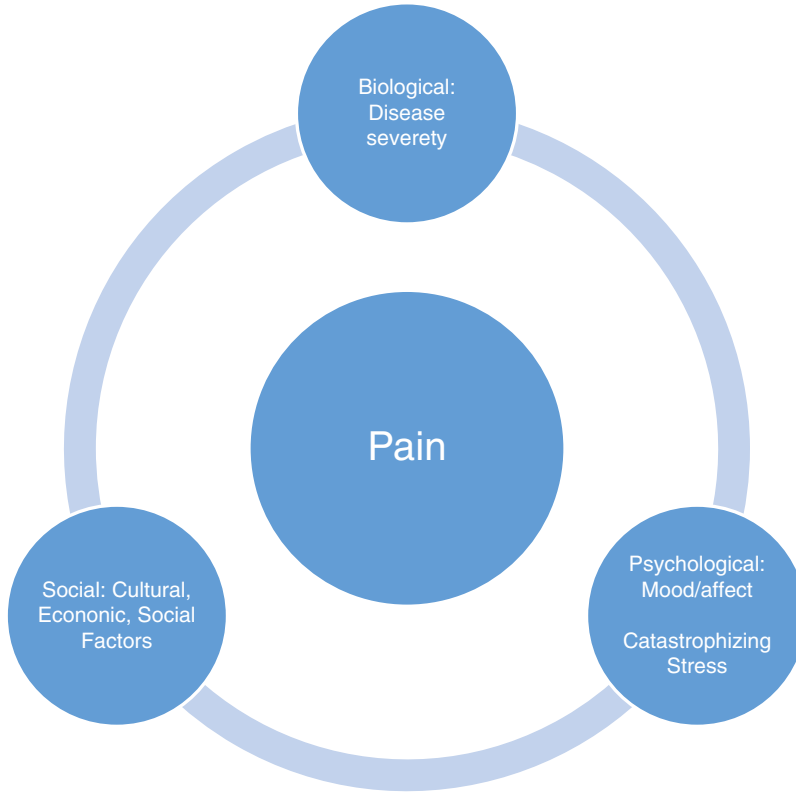


Fig. 23.1 Biopsychosocial model of pain: biological, psychological, and the social environment
The biopsychosocial model of pain is a framework that explains pain is a complex interaction between biological, psychological, and social factors that influence pain perception

there is "no purely nociceptive pain" and that the lack of nociceptive pain should not exclude patients from treatment standards [6]. Nociceptive pain is often correlated with an acute injury; in chronic pain, you do not have to have an acute injury to be eligible for standard of care treatment for pain [7]. Many of the chronic pain patients suffer from nonnociceptive pain along with psychological comorbidities that lead to significant dysfunction that can be successfully managed in a multidisciplinary setting [6]. Multi/interdisciplinary programs focus on obtaining expertise from disciplines such as pain management, medicine, surgery, nursing, physical and occupational therapy, chiropractor, pharmacology, and psychology to provide holistic and comprehensive patient care. Implementing this model is not easy as it requires stellar communication and collaboration among various members of the team. It can be highly effective if executed properly and can ultimately decrease healthcare costs and contribute to optimal patient outcomes.

Clinical Applications and Techniques

Introducing a multi/interdisciplinary pain management program requires education and planning for proper implementation. Interdisciplinary education plays a key role in understanding how to navigate a multi/interdisciplinary framework for the treatment of chronic pain. This is described as interprofessional education (IPE) or interprofessional learning (IPL) and consists of "educators and learners from two or more health professions and their foundational disciplines who jointly create and foster a collaborative

learning environment, aiming to develop knowledge, skills and attitudes that result in interprofessional team behaviors and competence in order to improve the quality of patient care" [8]. This ultimately leads to interdisciplinary healthcare workers providing patients with a broad variety of services and treatment options personalized to their specific needs. Collaborative and communication skills with other members of the healthcare team are aspects that can be nurtured in the classroom setting. Having different subspecialties in one classroom setting to learn how to treat pain in an interdisciplinary manner can have significant impacts on patient outcomes. The World Health Organization (WHO) emphasized the importance of interprofessional education to enhance the skills of healthcare professionals [9]. There has been an increased interest in IPE/IPL, but slight progress has been made in implementation. This form of learning continues to lack in the undergraduate and graduate level [9].

A single medical profession will not have the required medical knowledge or support to address the complex health needs of a chronic pain patient. A multidisciplinary model of practicing doctors, nurses, and nonphysician caregivers can better serve this patient population. To integrate a multi/interdisciplinary approach, the key players that make up the team need to be identified with a clear understanding of roles and responsibilities. The team typically consists of a primary care physician, psychologist, physical therapist, occupational therapist, pain specialist, surgeon, clinical pharmacologist, and nursing staff. The role of the primary care physician is to coordinate patients care with other subspecialties and to evaluate and track treatment outcomes. The psychologist provides behavioral health approaches to address psychological factors impacting a patient's pain and supports effective communication with the medical staff. The physical and occupational therapists help to improve the functional status of the patient. The pain specialist provides multimodal therapy and interventional treatment options. The surgeon addresses anatomical defects contributing to the pain that can be repaired. The pharmacologist helps to assess any drug-drug interactions and synergistic value of drug combinations. The nurse monitors the implementation of treatment options and serves as a steward for the patient. The team members should collaborate on a regular basis and suggest various diagnostic and treatment modalities to best assist the patient. This type of integration of expertise from various disciplines can lead to improved patient outcomes.

Evidence-Based Practices

Multiple systematic reviews and meta-analyses of multi/interdisciplinary chronic pain management programs have shown that these programs provide positive outcomes for chronic pain patients that include relief of their suffering and return to functional lifestyles [10–13]. Murphy et al. analyzed the benefits of an interdisciplinary pain rehabilitation program that was introduced within the Veteran Affairs (VA) pain program. The study reported average reductions of 31% in pain catastrophizing, 22% in pain-related domains of functioning such as mobility, and a 16% decrease in sleep difficulties [14]. A 10-week outpatient interdisciplinary chronic pain rehabilitation program showed significant improvements in pain severity, pain-related life interference, psychological issues, pain catastrophizing, and opioid dose reduction [15]. The improvement in pain catastrophizing is significant because patients with this condition are more vulnerable to chronic pain disability and less likely to respond favorably to conventional treatments [14, 15].

A systematic review of 12 studies that incorporated "interdisciplinary teamwork and teaming" to manage chronic pain found modest evidence for the benefits of interdisciplinary team-based pain care [16]. The authors found that over 50% of interventions had improvement in over half of the measurement tools. This systematic review focused on the specific team structures and processes that are required when bringing multiple disciplines together to manage chronic pain. The review highlights the benefits of having a dedicated manager to direct and

coordinate patient care. The care managers coordinate the care of chronic pain patients and fosters a patient-centered approach through added patient support. The care managers responsibilities included baseline patient assessment, patient follow-up, and team case review. Other clinician roles included in the interventions that demonstrated beneficial clinical effect on pain outcomes included the patient's primary care physician, psychologist or mental health practitioner, physical therapist, a chiropractor, and pain physician [16].

Another study by Ghafouri et al. assessed real-world effects of interdisciplinary pain rehabilitation programs on neuropathic compared to nonneuropathic chronic pain and found equal or in some cases slightly superior outcomes for neuropathic pain conditions compared to nonneuropathic pain conditions [17].

Multi/interdisciplinary programs are superior to the historic multimodal approach to pain management by a single provider. These programs have been shown to be cost-effective [6]. Harmonizing of disciplines is superior to multimodal approach where disciplines stay within their boundaries and do not benefit from the team approach [10]. Interdisciplinary chronic pain clinics have been shown to significantly reduce emergency and primary care visits as well as decrease opioid usage [18, 19].

Challenges and Considerations

Despite the early invention of this approach to pain management, there continues to be lag in its implementation. There is a significant body of literature that supports the clinical and cost-effectiveness of multi−/interdisciplinary chronic pain programs, yet the number of programs in the United States has significantly decreased [7]. The insurance industry has had a negative impact on the expansion of multi/interdisciplinary pain management programs as it deemed these treatment options as expensive with a bias against funding care that was not provided by a medical doctor [7].

Managing chronic pain through a multi/interdisciplinary approach is a complex process that faces several challenges. Coordinating care among various professionals requires effective communication and collaboration [16]. The success of the treatment plan depends on the patient's willingness and ability to participate in different interventions. This can further be hindered by physical or psychological ailments along with the availability and accessibility of equipment and staff, especially in regions with limited healthcare resources. Costs and funding are a limiting factor to implementing multi/interdisciplinary pain programs. Many insurance companies refuse to cover the cost of interdisciplinary programs despite their proven cost-effectiveness, reduction in hospital readmission, and overall improvement in quality of life [20]. Insurance companies fail to realize that in the long run, these pain management programs are more efficient and associated with long-term cost savings compared to outdated treatment protocols [21]. The multi/interdisciplinary approach demands significant changes in the training of medical specialists and joint decision-making, which poses educational challenges and calls for the development of interdisciplinary training courses [9]. Successful implementation for IPE/IPL requires leadership to be informed and provide the required resources. Clinical faculty development and preparing current clinical practitioners is key to effective student learning and improved patient outcomes [22]. There is a need for further research and policy development to improve the effectiveness and accessibility of multi/interdisciplinary care for chronic pain management.

Case Studies or Clinical Scenarios

A 73-year-old male with history of hypertension, pulmonary embolism on Xarelto, prostate and rectal cancer receiving chemotherapy with metastasis to the liver and spine presents with metastasis at the 5th lumbar vertebral body. A recent magnetic resonance imaging (MRI) of the lumbar spine showed progressive enlargement of the

previously noted 5th lumbar vertebral body lesion with associated vertebral body height loss and associated soft tissue thickening and enhancement of the left prevertebral soft tissue. He reports low back pain that radiates down the lateral aspect of his bilateral lower extremities. After discussion of the patient's case at an interdisciplinary spine tumor boards that included subspecialist from neurology, oncology, neurosurgery, radiology, radiation and cellular oncology, and interventional pain, it was decided that patient would benefit from a L5 kyphoplasty with radiofrequency ablation (RFA) by the interventional pain specialist to stabilize the bone upfront and avoid interruption with his chemotherapy then to be followed by potential stereotactic body radiation therapy (SBRT).

Tertiary care centers have successfully demonstrated the implementation of multi/interdisciplinary programs yielding superior outcomes for patients who suffer from chronic noncancer and cancer pain. This involves initiatives such as cancer rounds, spine tumor boards, and the vertebral body compression fracture pathway.

Cancer rounds bring together a team of experts that include healthcare professionals from hematology/oncology, surgical oncology, radiational oncology, palliative/hospice care, psychiatry, physical therapy, social worker, and pain management. This collective unit deliberates and strategizes the management of intricate cancer cases with integrated treatment recommendations from all specialties involved. In parallel, the spine tumor board comprises a care coordinator and diverse specialists from neurology, neurosurgery, orthopedic spine, radiology, and pain management. This board comprehensively discusses complex spine tumors and develops effective treatment plans. The vertebral body compression fracture pathway is another initiative that utilizes an inpatient multi/interdisciplinary approach to vertebral fractures. In this pathways, hospitalized patients that are diagnosed with a symptomatic vertebral body compression fracture via X-ray findings by radiology department are immediately fitted with a brace by the physical therapy specialist. Results from magnetic resonance imaging (MRI) or computed tomography scan (CT scan) and presence of a neurologic deficit trigger either an emergency orthopedic spine or neurosurgical consult or interventional radiology or pain management consult. Open surgical or minimally invasive procedures such as kyphoplasty or epidural steroid injections can be offered. Post hospitalization, patients have a care coordinator that ensures follow-up appointments in an outpatient clinic. These narratives emphasize the profound potential and effectiveness of interdisciplinary care in managing complex cases of chronic noncancer and cancer pain and highlight the importance of adopting a holistic approach to pain management.

Future Directions and Research

Multi/interdisciplinary pain management programs will play a crucial role in providing comprehensive diagnoses and treatment to reduce reliance on drugs, medical therapies, and caregiver dependence [6]. Use of this approach can decrease healthcare costs and disability [6]. Implementing these programs requires collaboration and resource allocation. Revision of professional training approaches and creating more interdisciplinary courses will improve the effectiveness of collaboration [9]. Given the variety of compelling formats, centers have room for creativity and flexibility in their development [14].

Revised reimbursement policies are vital to broadening access to these programs that provide long-lasting benefits to those suffering from chronic pain [14, 20]. Creating the role of care manager was associated with significantly positive outcomes and played a significant role in coordination of care [16]. Overcoming socioeconomic and cultural barriers is essential to ensure patient access to effective multi/interdisciplinary care [6, 19].

Pragmatic clinical trials (PCTs) aim to generate high-quality data within a clinical setting to inform practice guidelines and should be considered when conducting future research on multi/interdisciplinary pain management programs [23]. The limitations of the gold-standard randomized controlled trial in generating findings

that directly impact patients with chronic pain have led to an increased interest in PCTs. There is a lack of clarity within the literature about what type of rehabilitation therapies are indicated for different pain syndromes and emphasizing the need for further exploration [6]. Pain specialists should lead the path in advancing the use of multi/interdisciplinary pain programs in patient who suffer from chronic pain.

Key Takeaways

1. Chronic pain incorporates physical, psychological, and social aspects unique to each individual, thus making it challenging to manage in a "one size fits all model." Patient outcomes can be improved with a multi/interdisciplinary approach.
2. Developing and nurturing collaboration and communication skills within the healthcare team (i.e., primary care physician, nurses, psychologist, physical therapist, occupational therapist, pain specialist, surgeon, and clinical pharmacologist) is crucial for effective multi/interdisciplinary pain management and should be fostered in the professional students' classroom setting.
3. Multi/interdisciplinary pain programs have demonstrated efficacy in managing chronic pain, reducing healthcare costs, lowering opioid usage, and enhancing quality of life for patients.
4. Critical challenges within the multi/interdisciplinary approach include patient participation, intervention accessibility, funding and insurance constraints, and the necessity for changes in medical education. The uniqueness of effective programs offers innumerable diverse solutions to these challenges.
5. Future research endeavors can optimize patient outcomes by investing in pragmatic clinical trials, overcoming socioeconomic and cultural barriers, and involving pain specialists early.

References

1. Von Korff M, Scher AI, Helmick C, et al. United States National Pain Strategy for Population Research: concepts, definitions, and pilot data. Pain. 2016;17(10):1068–80. Institute of Medicine (US) Committee on Advancing Pain Research, Care, and Education. Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington (DC): National Academies Press (US); 2011.
2. Giannitrapani KF, Ahluwalia SC, Day RT, Pisciotta M, Dobscha S, Lorenz K. Challenges to teaming for pain in primary care. Healthcare. 2018;6(1):23–7.
3. Butler SH, Loeser JD. Multidisciplinary pain management: a tale of two outcomes. Anesthesiology. 2023;138(3):312–5.
4. Loeser JD, Egan K. Managing the chronic pain patient: theory and practice at the University of Washington Pain Clinic. New York: Raven Press; 1982.
5. Guzman J, Esmail R, Karjalainen K, Malmivaara A, Irvin E, Bombardier C. Multidisciplinary bio-psychosocial rehabilitation for chronic low back pain. Cochrane Database Syst Rev. 2002;1:CD000963.
6. Manchikanti L, Singh V, Kaye AD, Hirsch JA. Lessons for better pain management in the future: learning from the past. Pain and Therapy. 2020;9(2):373–91.
7. Schatman ME. The demise of multidisciplinary pain management clinics? Pract Pain Manag. https://www.practicalpainmanagement.com/resources/practice-management/demise-multidisciplinary-pain-management-clinics. Accessed 12 Sept 2024.
8. De Oliveira VF, Bittencourt MF, Pinto ÍF, Lucchetti AL, da Silva Ezequiel O, Lucchetti G. Comparison of the readiness for interprofessional learning and the rate of contact among students from nine different healthcare courses. Nurse Educ Today. 2018;63:64–8.
9. Romm M. Interdisciplinary education involving chronic pain management: the way forward. J Rehab Pain Med. 2023;1(1):61–71.
10. Flor H, Fydrich T, Turk DC. Efficacy of multidisciplinary pain treatment centers: a meta-analytic review. Pain. 1992; 49:221–30. Turk DC, Okifuji A. Treatment of chronic pain patients: clinical outcomes, cost-effectiveness, and cost-benefits of multidisciplinary pain centers. Crit Rev Phys Rehab Med. 1998; 10:181–208.
11. Okifuji A, Turk DC, Kalauoklani D. Clinical outcome and economic evaluation of multidisciplinary pain centers. In: Block AR, Kramer EF, Fernandez E, editors. Handbook of pain syndromes: biopsychosocial perspectives. Mahwah: Lawrence Erlbaum Associates; 1999. p. 77–97.
12. Turk DC. Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain. Clin J Pain. 2002;18:355–65.

13. Schonstein E, Kenny DT, Keating J, Kord BW. Work conditioning, work hardening and functional restoration for workers with back and neck pain. Cochrane Database Syst Rev. 2003;
14. Murphy JL, Palyo SA, Schmidt ZS, Hollrah LN, Banou E, Van Keuren CP, Strigo IA. The resurrection of interdisciplinary pain rehabilitation: outcomes across a veterans affairs collaborative. Pain Med. 2021;22(2):430–43.
15. Craner JR, Lake ES, Bancroft KA, George LL. Treatment outcomes and mechanisms for an ACT-based 10-week interdisciplinary chronic pain rehabilitation program. Pain Pract. 2020;20(1):44–54.
16. Connell NB, Prathivadi P, Lorenz KA, Zupanc SN, Singer SJ, Krebs EE, Yano EM, Wong H, Giannitrapani KF. Teaming in interdisciplinary chronic pain management interventions in primary care: a systematic review of randomized controlled trials. J Gen Intern Med. 2022;37(6):1501–12.
17. Ghafouri N, Bäckryd E, Dragioti E, Rivano Fischer M, Ringqvist Å, Gerdle B. Effects of interdisciplinary pain rehabilitation programs on neuropathic and non-neuropathic chronic pain conditions—a registry-based cohort study from Swedish Quality Registry for Pain Rehabilitation (SQRP). BMC Musculoskelet Disord. 2023;24(1):357.
18. Rodríguez MJ, García AJ. A registry of the etiology and costs of neuropathic pain in pain clinics: results of the registry of etiologies and costs (REC) in neuropathic pain disorders study. Clin Drug Investig. 2007;27(11):771–82.
19. Scascighini L, Toma V, Dober-Spielmann S, Sprott H. Multidisciplinary treatment for chronic pain: a systematic review of interventions and outcomes. Rheumatology. 2008;47(5):670–8.
20. Danilov A, Danilov A, Barulin A, Kurushina O, Latysheva N. Interdisciplinary approach to chronic pain management. Postgrad Med. 2020;132(52):5–9.
21. Takahashi N, Takatsuki K, Kasahara S, et al. Multidisciplinary pain management program for patients with chronic musculoskeletal pain in Japan: a cohort study. J Pain Res. 2019;12:2563–76.
22. Schmitt MH, Gilbert JH, Brandt BF, Weinstein RS. The coming of age for interprofessional education and practice. Am J Med. 2013;126(4):284–8.
23. Mackey SC, Pearl RG. Pain management: optimizing patient care through comprehensive, interdisciplinary models and continuous innovations. Anesthesiol Clin. 2023;41(2):xv–xvii.

Part VII

Special Considerations

24 Pain Management in the Elderly and Pediatric Populations

Rachel Garza and Yuri C. Martins

Introduction

The management of pain in the elderly and pediatric populations can be challenging. These populations differ from the general adult population in terms of physiology, pharmacodynamics, pharmacokinetics, perception of pain, and communicability of pain [1–3]. Research has typically focused on otherwise healthy adults with pain conditions, but age disparities in the incidence, assessment, treatment, and outcomes of pain are common [1]. For example, despite an increased incidence of chronic pain and high-impact pain with advancing age [4], adults older than 65 are less likely to receive opioids than younger adults [5]. A similar phenomenon occurs in the pediatric population. Despite evidence that neonates and infants do experience pain, due to misconceptions, concerns about safety, and practice variability, they were seldom given analgesics for surgery well into the twentieth century [1, 6]. In addition, nowadays children with pain from multiple surgical reasons still receive less analgesia on a per weight basis than adults with similar conditions [7–9].

This shows that the elderly and pediatric populations have unique needs and characteristics that should be considered to ensure effective pain relief while minimizing risks. In this chapter, we aim to provide an overview of appropriate considerations regarding elderly and pediatric perioperative pain assessment, dosing and administration guidelines for pharmacologic therapy, and other treatment modalities such as regional anesthesia or nonpharmacological adjuncts.

Pain Management in the Elderly

Life expectancy has been increasing for the past decades which, coupled with a global decrease in human fertility rate, made people aged 65 years and older outnumber children under 5 years globally for the first time in human history in 2018 [10]. The risk for chronic pain development increases with age with the prevalence of chronic pain in individuals over 85 years being as high as 79% [11–13]. The incidence of persistent postsurgical pain appears to decrease with aging [14], but elderly patients undergo surgery four times more often than younger age groups which makes the prevalence of persistent postoperative pain higher in older patients [3, 15]. Geriatric pain compromises quality of life and happiness, being associated with reduced activity, falls, mood disorders, sleep disturbances, isolation, and substantial disability [11]. In addition, chronic pain in the elderly is associated with frailty, a significant

R. Garza · Y. C. Martins (✉)
Department of Anesthesiology, Saint Louis University School of Medicine,
Saint Louis, MO, USA
e-mail: ychavesmartins@slu.edu

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_24

predictor of poor surgical and medical outcomes in this population [13, 16]. It is unclear why persistent pain after surgery and chronic pain are common in the elderly, but it is hypothesized that it may be associated to an increase in prevalence of chronic health conditions that can cause pain, such as musculoskeletal disorders, diabetes, neuropathy, and cancer [3, 17]. While there are practice guidelines for pharmacologic management of persistent pain in older persons [18], specific guidelines regarding perioperative pain assessment and management in the elderly have not been developed, and only general advice regarding pharmacological treatment and clinical assessment have been proposed.

Aging influences pain sensitivity and processing, with evidence supporting a general increase in pain threshold and reduced pain tolerance in the elderly [19, 20]. The reduced sensitivity to pain with advancing age, particularly for thermal pain, was classically attributed to loss in the quantity and function of peripheral Aδ fibers and CNS pathways involved in the detection, transmission, and processing of noxious stimuli [20, 21]. However, these findings have not been confirmed by more recent evidence [22]. Reduced pain tolerance in the elderly appears to be associated with decreased endogenous pain-modulating capacities due to impairment in the opioid and nonopioid endogenous pain inhibitory pathways [23, 24] and enhancement in temporal summation of noxious stimuli in the CNS [25].

The elderly population often faces unique challenges when it comes to pain assessment. Elderly patients tend to be reluctant to report pain-related symptoms due to cultural reasons such as the belief that pain is a necessary part of older life, fear of being negatively judged for having pain, or that pain foreshadows death or serious illness [26, 27]. In addition, evaluation of perioperative pain in the elderly can be complicated by diminished ability to communicate due to cognitive impairment, anxiety, depression, hearing impairment, and social or family isolation associated with aging [2]. For example, postoperative delirium has a higher incidence (up to 32%) in the elderly [28]. Elderly patients with dementia and other communication barriers are more likely to have their pain undertreated, which can result in adverse outcomes such as poor sleep, impaired cognition, increased disability, depression, and reduced quality of life [21, 29]. Older adults with cognitive impairment, such as dementia, may also have difficulty understanding treatment options.

Therefore, healthcare providers should be aware of these challenges and take steps to ensure that pain is adequately assessed in this population. A directed pain history focusing on previous pain conditions, substance use disorder, pain strategies that have worked in the past, and preferences for pain control should be done during the preoperative period [30]. It is imperative for the clinician to ask elderly patients directly about the presence and quantity of preoperative pain [21, 31]. There is strong evidence that preoperative pain assessment and education can decrease postoperative pain and anxiety [32, 33]. Preoperative education consists of explaining the anticipated degree of postoperative pain and the assessment tools that will be used in the perioperative period whenever possible [30]. Cognitively intact elderly patients can reliably report their pain intensity with visual analogue or numeric rating scales [30]. In mild to moderately demented elderly patients, the verbal descriptor scale or the faces pain scale can be used to measure pain [21, 34]. Patients with significant advanced dementia or with significant postoperative delirium may require particular attention to nonverbal pain behaviors, such as changes in gait, changes in function, withdrawal, and agitation [34, 35]. Caregivers may also be able to provide additional information that is relevant to the pain assessment in this population [36]. As in any other population, laboratory testing, diagnostic imaging, and other diagnostic tests for pain conditions preoperatively must only be obtained based on history and clinical examination findings in the elderly. Additionally, the clinician should keep in mind that elderly patients have an increased risk of incidental findings in diagnostic tests [37].

Multimodal nonpharmacological treatments for perioperative pain management, such as physical therapy, self-management programs,

rehabilitation, exercise programs, and cognitive-behavioral therapy, should be tried and encouraged in older adults due to the potential for fewer side effects and interactions with other medications. Evidence-based options that are available for the acute postoperative period include distraction strategies, guided imagery, and mindful breathing [38]. However, for these modalities to be maximally effective, the provider should ensure that the older adult has the physical and mental abilities to learn and utilize the chosen nonpharmacologic pain management strategy preoperatively [30, 38]. In addition, while there are a few studies evaluating nonpharmacological perioperative pain management therapies in the elderly, several factors limit the generalizability of their findings [30, 39]. Data regarding efficacy, safety, treatment adherence, and longitudinal designs are needed to determine optimal strategies for the delivery of nonpharmacological approaches. Research on cost of nonpharmacologic methods for the management of pain is also needed to inform policy decisions and standards of care [38, 39].

Pharmacological perioperative pain management of older adults can be challenging for various reasons: a) specific physiologic changes interfere with pharmacodynamic and pharmacokinetic properties of pain medications; b) polypharmacy is common, making pharmacologic interactions frequent; c) chronic comorbidities can contribute to worse perioperative pain and affect the efficacy and safety of analgesics [2, 11, 21]. Due to these factors, dosing and timing of administration adjustments for some analgesics in the perioperative period are recommended (Table 24.1) [30, 36, 40, 41].

Reduced muscle mass and total body water content with consequent decrease in intravascular volume and greater fat-to-lean body mass ratio change drug distribution in the elderly [36, 42–44]. This can result in an increased volume of distribution of fat-soluble drugs and in an increased plasma level of hydrophilic drugs [43–45]. Furthermore, a state of reduced renal function without underlying kidney disease is present in older adults due to the 6–10% per decade physiological decrease in renal clearance (glomerular filtration, tubular reabsorption, and secretion) beginning at age 30 years [45]. This requires adjustments in the dosage of pain medications that are renally metabolized, excreted, or may affect kidney function, particularly at initiation of treatment [15, 18, 46]. One example is the recommendation to use nonsteroidal antiinflammatory drugs with caution and limit their use to the lowest effective dose and shortest duration by the American Geriatrics Society, American College of Rheumatology, and the European League Against Rheumatism because of the high risk of adverse effects on the gastrointestinal, cardiovascular, and renal systems [18, 35, 36, 47].

Hepatic clearance is also reduced in the elderly due to a 40% decrease in hepatic blood flow, a 30% decrease in liver mass, and a selective impairment of phase I drug metabolism with no significant reduction in phase II metabolism [48]. These changes cause impaired hepatic drug clearance with flow-limited drugs being reduced to a greater extent than capacity-limited drugs in older people [49]. Hence, evidence indicates that initial doses of most drugs with high hepatic extraction ratios and particularly those that undergo phase I metabolism should be reduced by approximately 40–50% in older people to achieve similar pharmacokinetic profiles to young people [49, 50]. First-pass metabolism rate also declines with aging. Therefore, in older people, drugs undergoing extensive first-pass metabolism have increased bioavailability [44, 49]. On the contrary, prodrugs may have slower first-pass activation in the aged liver [44]. It is important to notice that pharmacokinetic alterations can be potentiated by the presence of frailty which was shown to be independently associated with reduced clearance of hydrophilic drugs [51].

In addition, elderly patients also present pharmacodynamic changes related to the number and affinity of target receptors and signal transduction that vary between drug classes and make their effects much more difficult to predict [44]. For example, interindividual variability in opioid sensitivity has been reported in several studies with reports of increased, decreased, or unchanged sensitivity in older patients compared to younger adults [52–54]. Prescribers must also

Table 24.1 Recommended changes to perioperative analgesic medication dosing and potential side effects in older adults

Medication	Recommended changes	Side effects	Special considerations
α2-agonists	Cardiac side effects are more pronounced in the elderly. Intraoperative/postoperative dose: dexmedetomidine loading dose ≤0.7 μg/kg IV followed by 0.2–0.4 μg/kg/h infusion. Clonidine is not recommended. Although there is data suggesting that PO tizanidine can decrease postoperative pain, data in the elderly population is rare	hypertension, bradycardia, hypotension, dry mouth	Caution in patients with LVEF<30% or another cardiac comorbidity
Acetaminophen	No age-related dose reduction in absence of liver disease. Preoperative dose: 1G IV or PO; Postoperative dose: 500–1000 mg PO or IV q6h (max dose 3G/day)	Hepatotoxicity	Reduce maximum dose (2000 mg/day) if malnourished (<50 kg) or hepatic insufficiency
Dexamethasone	Intraoperative dose: 0.11–0.2 mg/kg IV bolus	Hyperglycemia, perineal pruritus when given preoperatively	
Gabapentinoids	Dose reduction or even avoidance (Beers criteria) may be advised. Preoperative dose: gabapentin 600 mg PO, pregabalin 150 mg PO; Postoperative dose: gabapentin 600 mg PO q12h (max dose 2400mg/day), pregabalin 150 mg PO q12h (max dose 300mg/day)	Respiratory depression, sedation, dizziness. Recent evidence suggests perioperative use associated with increased risk of delirium, new antipsychotic use, and pneumonia	Increased rates of respiratory depression when combined with opioids
Ketamine	Unclear if ketamine affects postoperative pain after major surgery in older adults. Unknown if older patients are more sensitive to psychogenic side effects of ketamine, so no dose reductions recommended. Intraoperative dose: 0.25–1 mg/kg IV bolus or 2–5 μg/kg/min IV infusion	Hallucinations, nightmares	May offer protection against postoperative cognitive dysfunction
Systemic Lidocaine	Lidocaine clearance may be decreased by as much as 30–40% in the elderly due to decrease in hepatic blood flow. Intraoperative dose: 1–2 mg/kg/h IV infusion. Optimal dose range or duration of infusion in elderly patients has not been established		
Magnesium ($MgSO_4$)	Intraoperative dose: 30–50 mg/kg IV bolus over 15–30 min followed or not by 8–15 mg/kg/h IV infusion (max dose 30–40g/day)	Hypotension, flushing, burning or heat sensation	May decrease risk of PONV and shivering
NSAIDs	Dose reductions (25–50%) are recommended. Preoperative dose: celecoxib 200 mg PO; Postoperative dose: celecoxib 200 mg BID (max dose 400mg/day), ketorolac 15 mg IV q6h (max dose 60mg/day)	GI bleeding, PUD, renal dysfunction	Nonselective COX inhibitors potentially inappropriate. Avoid selective COX-2 inhibitors in cardiovascular disease. CrCl<50 mL/min is a contraindication

(continued)

Table 24.1 (continued)

Medication	Recommended changes	Side effects	Special considerations
Opioids	Initial dose reductions (25%–50%) are recommended. Titrate in small doses until adequate analgesia is achieved. Consider PCA when prolonged postoperative IV route is required. Meperidine should be avoided, especially in patients with low renal function	Respiratory depression, sedation, tolerance, addiction risks, cognitive dysfunction, delirium, hallucinations	Use equianalgesic table when converting. There is significant interindividual variation in opioid requirements in older patients

AKI acute kidney injury, *GI* gastrointestinal, *IV* intravenous, *NSAIDs* nonsteroidal anti-inflammatory drugs, *PCA* patient-controlled analgesia, *PUD* peptic ulcer disease, *PONV* postoperative nausea and vomiting

account for the narrower therapeutic index of most medications in older adults compared with younger individuals [55].

Polypharmacy can also interfere with perioperative pharmacologic pain management in the elderly. Therefore, a careful review of a patient's medication list should be done in the preoperative period due to an increased potential of drug interactions when utilizing or prescribing pain medications for older adults [30]. Focus should be given to chronic opioid use, presence of opioid use disorder, or other substances or drugs that can affect pain management such as central nervous system depressants (e.g., benzodiazepines, alcohol), opioid antagonists, and psychiatric medications [39]. Polypharmacy also increases the risk and the persistence of delirium [56].

Regional or neuraxial anesthesia can be used in older adults and should be considered if appropriate for the operation [57–59]. Meta-analyses and systematic reviews indicate that regional and neuraxial techniques are associated with decreased pain scores, decreased need for analgesic medication, decreased surgical complications, and improved recovery of functional parameters postoperatively in some surgical procedures [60–64]. However, these effects are not universal, being highly dependent on the surgical procedure and technique used with the same level of evidence indicating no difference between regional or neuraxial anesthesia versus general anesthesia when other types of surgery are considered [65, 66]. In addition, theoretically regional and neuraxial anesthesia could help reduce postoperative complications common in the elderly population such as urinary retention, cognitive dysfunction, sedation, and delirium. Nonetheless, evidence examining the impact of regional and neuraxial techniques in the elderly when compared to younger patients is limited [67].

Neuraxial techniques are more difficult to perform in the elderly due to anatomical changes associated with aging. These changes include a decrease in intervertebral and epidural spaces, calcification of ligamentum flavum, and a more frequent presence of degenerative disk disease and vertebral changes such as compression fractures [37, 68]. Of clinical importance is the increased cephalad spread of epidural solution with increasing age, which may result in adverse events and increase the risk of complications [69]. Therefore, a reduced epidural infusion dose may be required in older patients. Evidence suggests that peripheral nerves become more susceptible to local anesthetics with increasing age [70]. Because of this, regional anesthesia in the elderly has an increased risk for nerve damage, a faster onset, and prolonged duration when compared to younger patients [70–73]. Because elderly patients may be anticoagulated for various conditions, standard guidelines regarding anticoagulation and regional and neuraxial analgesia should be followed [74, 75].

Pain Management in Pediatrics

Pain management in pediatric populations presents its own unique challenges such as reliable pain assessment, communication barriers, and differences in dosing and administration. The perception that young children do not

remember or respond to pain to the same degree as adults is extremely untrue. Although the pediatric population may have different pain thresholds and responses to pain compared to adults, pain transmission and perception are functioning as early as 24 weeks of gestation [76]. In addition, the misunderstanding of safe dosing guidelines for pain medications in pediatrics commonly results in underdosing and poor pain control [7–9].

One important consideration in pain management for pediatric patients is the use of pain assessment tools that are appropriate in terms of age and communication ability. These tools can help healthcare providers assess pain in children who may not be able to communicate their pain verbally. There are multiple validated assessment tools: (1) the Faces Pain Scale-Revised for children aged 4 and older; (2) the Face, Legs, Activity, Cry, and Consolability (FLACC) scale for infants and young children; (3) the Cry, Requires O_2, Increased vital signs, Expression, Sleeplessness (CRIES) Neonatal Pain Assessment Scale; (4) and the Non-Communicating Children's Pain Checklist (NCCPC) which is helpful for pediatric patients with developmental communication disorders (Table 24.2). In addition, healthcare providers must rely on other cues such as vital signs and valuable information from caregivers and nursing providers to assess pain in this population.

Another consideration in pain management for pediatric patients is the use of age-appropriate pain medications and dose adjustments (Table 24.3). Children may require different doses or formulations of pain medications than adults, and healthcare providers should carefully consider the appropriate dose and route of administration for each child. For example, glomerular filtration rate is highly reduced in neonates and newborns, not reaching adult levels until about 8–12 months of age [77]. Hence, acetaminophen has a lower renal clearance rate in neonates, as compared to children and adults [78]. Therefore, it is recommended that a reduced dose of acetaminophen should be used for intravenous administration when compared to oral or rectal [78].

Neonates and infants have a very large volume of distribution due to increased total body water and extracellular fluid, leading to extended bioavailability of water-soluble opioids such as morphine [76, 79, 80]. The blood brain barrier is also more permeable in neonates, leading to less fat-soluble opioids such as morphine and hydromorphone to cause increased respiratory depression [80]. Furthermore, most opioids undergo biotransformation in the liver prior to being excreted

Table 24.2 Pediatric pain assessment tools

Assessment tool and type	Target patient population	Evaluated criteria	Rating system
Numeric pain scale, self report	8 years or older	0–10 pain scale	0–10 (mild 0–3, moderate 4–6, severe 7–10)
Visual analog scale, self report	8 years or older	Straight line with boundaries delineated as the limits	Patient points to location on line which best represents their pain
Wong Baker Faces scale, self report	3 years and older	6 faces to demonstrate pain experience	"No Hurt" to "Hurts Worst," patient chooses which face represents their pain experience
CRIES scale	Neonates	Crying, oxygen requirements, vital signs, expression, sleepless	0–2 points per parameter for a 0–10 total scale
FLACC scale	2 years or older, non verbal, cognitively impaired	Face, legs, activity, cry, consolability	0–2 points per parameter for a 0–10 total scale
NCCPC scale	Cognitively impaired, non verbal	Vocal, social, facial, activity, body and limbs, physiological, eating/sleeping	0–3 points per parameter in each category, varying total scale

CRIES Cry, Requires O2, Increased vital signs, Expression, Sleeplessness, *FLACC* = Face, Legs, Activity, Cry, and Consolability, *NCCPC* Non-communicating Children's Pain Checklist

Table 24.3 Pediatric dosing guidelines for perioperative analgesic medications

Medication	Dosing recommendations	Special considerations
Morphine	0.05–0.1 mg/kg	Reduction in dose for neonates and infants
Fentanyl	0.5–1 mcg/kg bolus, re-dose as needed	Reduction in dose for neonates and infants
Acetaminophen	15 mg/kg every 6–8 h	Reduction in dose for <1 year old
Ibuprofen	10 mg/kg every 6–8 h	Reduction in dose for 6 months—1 year old
Ketorolac	0.5 mg/kg up to 30mg IV	Children ≥1 years old
Ketamine	0.25–0.5 mcg/kg bolus, IV infusion range 2–4 mcg/kg/min	Not recommended in <1 year old, contraindicated in <3 months old
Dexmedetomidine	0.25–0.5 mcg/kg bolus, IV infusion range 0.5–1.5 mcg/kg/hr	Reduced dose in neonates and infants due to bradycardia
Gabapentin	5–20 mg/kg/day in divided doses 3 times daily	Children ≥3 years old, give first dose pre op
Diazepam	0.05 mg/kg IV q8h as needed	Skeletal muscle spasm in large abdominal or orthopedic surgeries, not recommended in neonates or infants

by the kidneys, and utilize the Cytochrome P450 system which is immature at birth and does not achieve equal levels compared to adults until 1–2 months of life [76, 81]. For this reason, there can be prolonged metabolism of some opioids and dosing guidelines should be utilized carefully with appropriate monitoring of the patient whether it be due to young age or pathologic liver and kidney dysfunction. Pharmacokinetic and pharmacodynamic data on fentanyl, sufentanil, and alfentanil show that these drugs are cleared much more rapidly in infants and older children compared to neonates [82–84]. Therefore, the dosage of most synthetic opioids should be reduced in neonates during the first 2–4 weeks of life, and for premature neonates, until they reach at least 44 weeks postconceptual age [80]. However, remifentanil has a similar effective half-life in neonates as it does in older children and adults, so no dosage adjustment is needed for this drug. There is limited data on the use of methadone for perioperative pain control in infants and children. Methadone has been better studied in healthy adolescents undergoing major surgery suggesting that dosing should be similar to adults [80]. When choosing the best opioid medication and dose for pediatric patients, it is also important to consider other possible side effects such as pruritus, emesis, and ileus, and treat them appropriately if encountered.

Analgesic medications other than opioids can be safely used independently or in combination to provide a multimodal approach to pediatric pain control [80]. Appropriate dosing guidelines based on the age and weight of the patient should be carefully considered. Some examples include acetaminophen, ibuprofen, ketorolac, ketamine, dexmedetomidine, gabapentin, and muscle relaxants such as methocarbamol, cyclobenzaprine, baclofen, and diazepam. Therefore, the use of perioperative opioids should be reserved for instances where surgical and postoperative pain cannot be managed by nonopioid analgesics.

The use of regional anesthesia in the pediatric population also has the potential to highly reduce perioperative pain, decrease opioid consumption, and be used as a powerful adjunct for general anesthesia in a variety of pediatric surgical procedures. The anatomy of peripheral nerves in pediatric patients has minimal differences compared to adults, therefore the procedural technique is very similar. However, in smaller patients, a more precise injection of local anesthetic is necessary due to the inability to safely use a large volume of the anesthetic. In addition, to be safely performed, regional anesthesia techniques require cooperation from the patient. For this reason, regional techniques such as peripheral nerve blocks or neuraxial techniques such as epidural or caudal injections are commonly done under general anesthesia or sedation. Furthermore, it is important to understand the differences in how local anesthetics are metabolized in infants and children when deciding on the appropriate dose

of medication. Infants and young children have lower protein binding and decreased internal clearance of local anesthetics, leading to increased free forms of amino-amide local anesthetics and decreased metabolism [85, 86]. This can result in a higher likelihood of neurotoxicity and cardiotoxicity associated with elevated concentrations of local anesthetics in the blood in infants and young children compared to adults.

Nonpharmacological approaches to pain management, such as distraction techniques, relaxation techniques, acupuncture, heat compress, ice packs, behavioral therapy, and physical therapy, are often preferred for pediatric patients due to the potential for fewer side effects and interactions with other medications [87–90]. The goals of these techniques are to minimize fear and stress, making pain more tolerable. These techniques are often utilized postoperatively for acute surgical pain, and as part of physical and occupational therapy throughout recovery. Distraction techniques are commonly used for short perioperative procedures such as peripheral IV placement or regional anesthesia [90]. However, in some cases, pharmacological interventions may be necessary, and healthcare providers should carefully consider the risks and benefits of different pain medications for children.

Most anesthesia providers will encounter a pediatric patient with persistent chronic pain presenting for an unrelated surgery or procedure. It is important to consider the unique management of these patients in efforts to not worsen their existing pain condition in the setting of new acute surgical pain. In addition, proactive perioperative pain management has been shown to reduce the development of common pediatric pain disorders such as complex regional pain syndrome, diffuse musculoskeletal pain, abdominal pain, and headaches [81].

Conclusion

In conclusion, perioperative pain management in the elderly and pediatric populations requires careful consideration of their unique needs. Healthcare providers should carefully assess pain in these populations and consider nonpharmacological approaches to pain management when appropriate. Additionally, healthcare providers should carefully consider the risks and benefits of different pain medications and interventions for these populations and take steps to minimize the risk of adverse drug interactions, overdose, and side effects.

Key Takeaways

- Perioperative pain management in the elderly and pediatric populations should involve a multidisciplinary approach, including multimodal medications, selected interventions, physical therapy, rehabilitation, and psychological treatments.
- There are unique considerations to selecting medications in older adults, neonates, and children, including changes in pharmacokinetics, pharmacodynamics, and likelihood of side effects.
- The high prevalence of polypharmacy in elderly patients increases the risk of drug interactions and adverse effects, necessitating careful review and management of all medications during perioperative pain treatment to minimize complications and optimize outcomes.
- Pediatric pain is often undertreated due to a misunderstanding of safe dosing guidelines. Utilizing appropriate dosing recommendations for opioid and nonopioid medications will assist providers in treating these patients effectively.
- Developmentally appropriate pain assessment tools must be used to properly evaluate pediatric pain for successful pain control.

References

1. Nguyen LH, Dawson JE, Brooks M, Khan JS, Telusca N. Disparities in pain management. Anesthesiol Clin. 2023;41(2):471–88.
2. Schofield P. The assessment and management of peri-operative pain in older adults. Anaesthesia. 2014;69:54–60.

3. Jin J, Zhang T, Xiong X, Chen H, Jiang Y, He S. A prospective study of chronic postsurgical pain in elderly patients: incidence, characteristics and risk factors. BMC Geriatr. 2023;23(1):289.
4. Grol-Prokopczyk H. Sociodemographic disparities in chronic pain, based on 12-year longitudinal data. Pain. 2017;158(2):313–22.
5. Morales ME, Yong RJ. Racial and ethnic disparities in the treatment of chronic pain. Pain Med. 2021;22(1):75–90.
6. Rodkey EN, Pillai RR. The infancy of infant pain research: the experimental origins of infant pain denial. J Pain. 2013;14(4):338–50.
7. Selbst SM, Clark M. Analgesic use in the emergency department. Ann Emerg Med. 1990;19(9):1010–3.
8. Brown JC, Klein EJ, Lewis CW, Johnston BD, Cummings P. Emergency department analgesia for fracture pain. Ann Emerg Med. 2003;42(2):197–205.
9. Furyk J, Sumner M. Pain score documentation and analgesia: a comparison of children and adults with appendicitis. Emerg Med Australas. 2008;20(6):482–7.
10. United Nations DoEaSA, Population Division. World population ageing 2019 (ST/ESA/SER.A/444). New York: United Nations; 2020.
11. Makris UE, Abrams RC, Gurland B, Reid MC. Management of persistent pain in the older patient: a clinical review. JAMA. 2014;312(8):825–36.
12. Miaskowski C, Blyth F, Nicosia F, Haan M, Keefe F, Smith A, et al. A biopsychosocial model of chronic pain for older adults. Pain Med. 2020;21(9):1793–805.
13. Shi Y, Hooten WM, Roberts RO, Warner DO. Modifiable risk factors for incidence of pain in older adults. Pain. 2010;151(2):366–71.
14. van Dijk JF, Zaslansky R, van Boekel RL, Cheuk-Alam JM, Baart SJ, Huygen FJ, et al. Postoperative pain and age: a retrospective cohort association study. Anesthesiology. 2021;135(6):1104–19.
15. Aubrun F, Marmion F. The elderly patient and postoperative pain treatment. Best Pract Res Clin Anaesthesiol. 2007;21(1):109–27.
16. Saraiva MD, Suzuki GS, Lin SM, de Andrade DC, Jacob-Filho W, Suemoto CK. Persistent pain is a risk factor for frailty: a systematic review and meta-analysis from prospective longitudinal studies. Age Ageing. 2018;47(6):785–93.
17. Dagnino APA, Campos MM. Chronic pain in the elderly: mechanisms and perspectives. Front Hum Neurosci. 2022;16:736688.
18. American Geriatrics Society Panel on Pharmacological Management of Persistent Pain in Older P. Pharmacological management of persistent pain in older persons. J Am Geriatr Soc. 2009;57(8):1331–46.
19. Gibson SJ, Farrell M. A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. Clin J Pain. 2004;20(4):227–39.
20. Lautenbacher S. Experimental approaches in the study of pain in the elderly. Pain Med. 2012;13(Suppl 2):S44–50.
21. Hadjistavropoulos T, Herr K, Prkachin KM, Craig KD, Gibson SJ, Lukas A, et al. Pain assessment in elderly adults with dementia. Lancet Neurol. 2014;13(12):1216–27.
22. Lautenbacher S, Peters JH, Heesen M, Scheel J, Kunz M. Age changes in pain perception: a systematic-review and meta-analysis of age effects on pain and tolerance thresholds. Neurosci Biobehav Rev. 2017;75:104–13.
23. Riley JL 3rd, King CD, Wong F, Fillingim RB, Mauderli AP. Lack of endogenous modulation and reduced decay of prolonged heat pain in older adults. Pain. 2010;150(1):153–60.
24. Tinnirello A, Mazzoleni S, Santi C. Chronic pain in the elderly: mechanisms and distinctive features. Biomolecules. 2021;11(8):1256.
25. Edwards RR, Fillingim RB. Age-associated differences in responses to noxious stimuli. J Gerontol A Biol Sci Med Sci. 2001;56(3):M180–5.
26. Gignac MA, Davis AM, Hawker G, Wright JG, Mahomed N, Fortin PR, et al. "What do you expect? You're just getting older": a comparison of perceived osteoarthritis-related and aging-related health experiences in middle- and older-age adults. Arthritis Rheum. 2006;55(6):905–12.
27. Forman WB, Stratton M. Current approaches to chronic pain in older patients. Geriatrics. 1991;46(7):47–52.
28. Igwe EO, Nealon J, O'Shaughnessy P, Bowden A, Chang HC, Ho MH, et al. Incidence of postoperative delirium in older adults undergoing surgical procedures: a systematic literature review and meta-analysis. Worldviews Evid-Based Nurs. 2023;20(3):220–37.
29. Barber JB, Gibson SJ. Treatment of chronic non-malignant pain in the elderly: safety considerations. Drug Saf. 2009;32(6):457–74.
30. Shellito AD, Dworsky JQ, Kirkland PJ, Rosenthal RA, Sarkisian CA, Ko CY, et al. Perioperative pain management issues unique to older adults undergoing surgery: a narrative review. Ann Surg Open. 2021;2(3):e072.
31. Drage MP, Schug SA. Analgesia in the elderly. Practical treatment recommendations. Drugs Aging. 1996;9(5):311–8.
32. Szeverenyi C, Kekecs Z, Johnson A, Elkins G, Csernatony Z, Varga K. The use of adjunct psychosocial interventions can decrease postoperative pain and improve the quality of clinical Care in Orthopedic Surgery: a systematic review and meta-analysis of randomized controlled trials. J Pain. 2018;19(11):1231–52.
33. Ramesh C, Nayak BS, Pai VB, Patil NT, George A, George LS, et al. Effect of preoperative education on postoperative outcomes among patients undergoing cardiac surgery: a systematic review and meta-analysis. J Perianesth Nurs. 2017;32(6):518–29 e2.
34. Kappesser J, Voit S, Lautenbacher S, Hermann C. Pain assessment for cognitively impaired older adults: do

items of available observer tools reflect pain-specific responses? Eur J Pain. 2020;24(4):851–62.
35. American Geriatrics Society. The management of chronic pain in older persons: AGS panel on chronic pain in older persons. J Am Geriatr Soc. 1998;46(5):635–51.
36. Schwan J, Sclafani J, Tawfik VL. Chronic pain Management in the Elderly. Anesthesiol Clin. 2019;37(3):547–60.
37. Jensen MC, Brant-Zawadzki MN, Obuchowski N, Modic MT, Malkasian D, Ross JS. Magnetic resonance imaging of the lumbar spine in people without back pain. N Engl J Med. 1994;331(2):69–73.
38. Tick H, Nielsen A, Pelletier KR, Bonakdar R, Simmons S, Glick R, et al. Evidence-based nonpharmacologic strategies for comprehensive pain care: the consortium pain task force white paper. Explore (NY). 2018;14(3):177–211.
39. Baumbauer KM, Young EE, Starkweather AR, Guite JW, Russell BS, Manworren RC. Managing chronic pain in special populations with emphasis on pediatric, geriatric, and drug abuser populations. Med Clin North Am. 2016;100(1):183–97.
40. Park CM, Inouye SK, Marcantonio ER, Metzger E, Bateman BT, Lie JJ, et al. Perioperative gabapentin use and in-hospital adverse clinical events among older adults after major surgery. JAMA Intern Med. 2022;182(11):1117–27.
41. Rajan J, Behrends M. Acute pain in older adults: recommendations for assessment and treatment. Anesthesiol Clin. 2019;37(3):507–20.
42. Turnheim K. When drug therapy gets old: pharmacokinetics and pharmacodynamics in the elderly. Exp Gerontol. 2003;38(8):843–53.
43. Sera L, Uritsky T. Pharmacokinetic and pharmacodynamic changes in older adults and implications for palliative care. Prog Palliative Care. 2016;24(5):255–61.
44. Drenth-van Maanen AC, Wilting I, Jansen PAF. Prescribing medicines to older people-how to consider the impact of ageing on human organ and body functions. Br J Clin Pharmacol. 2020;86(10):1921–30.
45. Aymanns C, Keller F, Maus S, Hartmann B, Czock D. Review on pharmacokinetics and pharmacodynamics and the aging kidney. Clin J Am Soc Nephrol. 2010;5(2):314–27.
46. Gupta D, Avram M. Rational opioid dosing in the elderly: dose and dosing interval when initiating opioid therapy. Clin Pharmacol Ther. 2012;91(2):339–43.
47. Wongrakpanich S, Wongrakpanich A, Melhado K, Rangaswami J. A comprehensive review of non-steroidal anti-inflammatory drug use in the elderly. Aging Dis. 2018;9(1):143.
48. McLean AJ, Le Couteur DG. Aging biology and geriatric clinical pharmacology. Pharmacol Rev. 2004;56(2):163–84.
49. Hilmer SN, Shenfield GM, Le Couteur DG. Clinical implications of changes in hepatic drug metabolism in older people. Ther Clin Risk Manag. 2005;1(2):151–6.
50. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. Br J Clin Pharmacol. 2004;57(1):6–14.
51. Johnston C, Hilmer SN, McLachlan AJ, Matthews ST, Carroll PR, Kirkpatrick CM. The impact of frailty on pharmacokinetics in older people: using gentamicin population pharmacokinetic modeling to investigate changes in renal drug clearance by glomerular filtration. Eur J Clin Pharmacol. 2014;70(5):549–55.
52. Papaleontiou M, Henderson CR Jr, Turner BJ, Moore AA, Olkhovskaya Y, Amanfo L, et al. Outcomes associated with opioid use in the treatment of chronic noncancer pain in older adults: a systematic review and meta-analysis. J Am Geriatr Soc. 2010;58(7):1353–69.
53. Prostran M, Vujovic KS, Vuckovic S, Medic B, Srebro D, Divac N, et al. Pharmacotherapy of pain in the older population: the place of opioids. Front Aging Neurosci. 2016;8:144.
54. Naples JG, Gellad WF, Hanlon JT. The role of opioid analgesics in geriatric pain management. Clin Geriatr Med. 2016;32(4):725–35.
55. Beyth RJ, Shorr RI. Epidemiology of adverse drug reactions in the elderly by drug class. Drugs Aging. 1999;14(3):231–9.
56. Kurisu K, Miyabe D, Furukawa Y, Shibayama O, Yoshiuchi K. Association between polypharmacy and the persistence of delirium: a retrospective cohort study. BioPsychoSocial Med. 2020;14:1–5.
57. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, et al. 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. J Pain. 2016;17(2):131–57.
58. American Society of Anesthesiologists Task Force on Acute Pain M. Practice guidelines for acute pain management in the perioperative setting: an updated report by the American Society of Anesthesiologists Task Force on Acute Pain Management. Anesthesiology. 2012;116(2):248–73.
59. Mohanty S, Rosenthal RA, Russell MM, Neuman MD, Ko CY, Esnaola NF. Optimal perioperative Management of the Geriatric Patient: a Best Practices Guideline from the American College of Surgeons NSQIP and the American Geriatrics Society. J Am Coll Surg. 2016;222(5):930–47.
60. Wang W, Gao X, Ma Y, Di X, Xiao K, Zhou L, et al. Regional vs general anesthesia for retrograde Intrarenal surgery: a systematic review and meta-analysis. J Endourol. 2020;34(11):1121–8.
61. Mufarrih SH, Qureshi NQ, Yunus RA, Katsiampoura A, Quraishi I, Sharkey A, et al. A systematic review and meta-analysis of general versus regional anesthesia for lower extremity amputation. J Vasc Surg. 2023;77(5):1542–52 e9.

62. Liu SS, Strodtbeck WM, Richman JM, Wu CL. A comparison of regional versus general anesthesia for ambulatory anesthesia: a meta-analysis of randomized controlled trials. Anesth Analg. 2005;101(6):1634–42.
63. Barreveld A, Witte J, Chahal H, Durieux ME, Strichartz G. Preventive analgesia by local anesthetics: the reduction of postoperative pain by peripheral nerve blocks and intravenous drugs. Anesth Analg. 2013;116(5):1141–61.
64. Yeung JH, Gates S, Naidu BV, Wilson MJ, Gao Smith F. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. Cochrane Database Syst Rev. 2016;2(2):CD009121.
65. Zhu X, Yang M, Mu J, Wang Z, Zhang L, Wang H, et al. The effect of general anesthesia vs. regional anesthesia on postoperative delirium-a systematic review and meta-analysis. Front Med (Lausanne). 2022;9:844371.
66. Liu S, Chen J, Shi H, Li J, Zeng G, Liu W, et al. Comparing perioperative outcomes between regional anesthesia and general anesthesia in patients undergoing hip fracture surgery: a systematic review and meta-analysis. Can J Anaesth. 2024;71:849.
67. Tsui BC, Wagner A, Finucane B. Regional anaesthesia in the elderly: a clinical guide. Drugs Aging. 2004;21(14):895–910.
68. Papadakis M, Sapkas G, Papadopoulos EC, Katonis P. Pathophysiology and biomechanics of the aging spine. Open Orthop J. 2011;5:335–42.
69. Hirabayashi Y, Shimizu R, Matsuda I, Inoue S. Effect of extradural compliance and resistance on spread of extradural analgesia. Br J Anaesth. 1990;65(4):508–13.
70. Corcoran E, Kinirons B. Regional anaesthesia in the elderly patient a current perspective. Curr Opin Anesthesiol. 2021;34(1):48–53.
71. Neal JM, Barrington MJ, Brull R, Hadzic A, Hebl JR, Horlocker TT, et al. The second ASRA practice advisory on neurologic complications associated with regional anesthesia and pain medicine: executive summary 2015. Reg Anesth Pain Med. 2015;40(5):401–30.
72. Paqueron X, Boccara G, Bendahou M, Coriat P, Riou B. Brachial plexus nerve block exhibits prolonged duration in the elderly. Anesthesiology. 2002;97(5):1245–9.
73. Hanks RK, Pietrobon R, Nielsen KC, Steele SM, Tucker M, Warner DS, et al. The effect of age on sciatic nerve block duration. Anesth Analg. 2006;102(2):588–92.
74. Horlocker TT, Vandermeuelen E, Kopp SL, Gogarten W, Leffert LR, Benzon HT. Regional anesthesia in the patient receiving antithrombotic or thrombolytic therapy: American Society of Regional Anesthesia and Pain Medicine evidence-based guidelines (Fourth Edition). Reg Anesth Pain Med. 2018;43(3):263–309.
75. Narouze S, Benzon HT, Provenzano D, Buvanendran A, De Andres J, Deer T, et al. Interventional Spine and Pain Procedures in Patients on Antiplatelet and Anticoagulant Medications (Second Edition): Guidelines From the American Society of Regional Anesthesia and Pain Medicine, the European Society of Regional Anaesthesia and Pain Therapy, the American Academy of Pain Medicine, the International Neuromodulation Society, the North American Neuromodulation Society, and the World Institute of Pain. Reg Anesth Pain Med. 2018;43(3):225–62.
76. Davis PJ, Cladis FP. Smith's anesthesia for infants and children e-book. Elsevier Health Sciences; 2016.
77. Vecchione TM, Agarwal R, Monitto CL. Error traps in acute pain management in children. Pediatr Anesth. 2022;32(9):982–92.
78. Pacifici GM, Allegaert K. Clinical pharmacology of paracetamol in neonates: a review. Curr Ther Res. 2015;77:24–30.
79. Coté CJ, Lerman J, Todres ID. A practice of anesthesia for infants and children E-book: expert consult: online and print. Elsevier Health Sciences; 2012.
80. Cravero JP, Agarwal R, Berde C, Birmingham P, Coté CJ, Galinkin J, et al. The Society for Pediatric Anesthesia recommendations for the use of opioids in children during the perioperative period. Pediatr Anesth. 2019;29(6):547–71.
81. Verghese ST, Hannallah RS. Acute pain management in children. J Pain Res. 2010;3:105–23.
82. Greeley WJ, de Bruijn NP. Changes in sufentanil pharmacokinetics within the neonatal period. Anesth Analg. 1988;67(1):86–90.
83. Gauntlett IS, Fisher DM, Hertzka RE, Kuhls E, Spellman MJ, Rudolph C. Pharmacokinetics of fentanyl in neonatal humans and lambs: effects of age. Anesthesiology. 1988;69(5):683–7.
84. Scierka AM, Davis PJ, Killian A, Stiller RL, Cook DR, Guthrie RD. Pharmacokinetics of alfentanil in newborn premature infants and older children. Dev Pharmacol Ther. 1989;13(1):21–7.
85. Gunter JB. Benefit and risks of local anesthetics in infants and children. Pediatr Drugs. 2002;4:649–72.
86. Dobereiner EF, Cox RG, Ewen A, Lardner DR. Evidence-based clinical update: which local anesthetic drug for pediatric caudal block provides optimal efficacy with the fewest side effects? Can J Anesth/J Can Anesth. 2010;57(12):1102–10.
87. Jacobs A, Price HN, Popenhagen MP. Blowing away the pain: a technique for pediatric pain management. Pediatr Dermatol. 2014;31(6):757–8.
88. Thrane SE, Wanless S, Cohen SM, Danford CA. The assessment and non-pharmacologic treatment of procedural pain from infancy to school age through a developmental lens: a synthesis of evidence with recommendations. J Pediatr Nurs. 2016;31(1):e23–32.
89. Gillum M, Huang S, Kuromaru Y, Dang J, Yenikomshian HA, Gillenwater TJ. Nonpharmacologic management of procedural pain in pediatric burn patients: a systematic review of randomized controlled trials. J Burn Care Res. 2022;43(2):368–73.
90. Srouji R, Ratnapalan S, Schneeweiss S. Pain in children: assessment and nonpharmacological management. Int J Pediatr. 2010;2010(1):474838.

25 Perioperative Management of Patients with Opioid Use Disorder

Kristy A. Fisher, Daiana A. Takashima, Sudheer Potru, and Olabisi Lane

Introduction

The opioid epidemic continues to be a significant issue facing healthcare providers, despite an overall decrease in opioid prescriptions since the height of the epidemic [1]. The CDC estimates 25% of patients on long-term opioid therapy suffer from opioid use disorder (OUD) [2]. The estimated prevalence of OUD in 2016 was 26.8 million people, with over 100,000 deaths by opioid overdose globally in 2017 [3]. Therefore, physicians are very likely to encounter OUD and other histories of opioid use in patients necessitating perioperative pain management. Chronic opioid use presents unique challenges during the perioperative period, with increased postoperative complications, delayed wound healing, prolonged recovery, increased healthcare utilization (i.e., length of stay and readmission), and increased postoperative mortality and morbidity; the latter includes higher levels of postoperative pain, with reduced function and satisfaction [2]. It is imperative that all pain physicians understand the expectations for management of postoperative pain with chronic opioid use.

K. A. Fisher (✉) · D. A. Takashima · S. Potru · O. Lane
Division of Pain Medicine, Department of Anesthesiology, Emory University, Atlanta, GA, USA
e-mail: fisherk@spineorthocenter.com

Background, Current Understanding, and Clinical Considerations

Diagnostic Criteria

See Table 25.1 for diagnostic criteria for OUD as per The Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM V):

A problematic pattern of opioid use leading to clinically significant impairment of distress, as manifested by at least two of the following, occurring within a 12-month period:

1. Opioids are often taken in larger amounts or over a longer period than was intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
3. A great deal or time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects.
4. Craving, or a strong desire or urge to use opioids.
5. Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued opioid use despite having persistent or recurrent social or inter-

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_25

personal problems caused or exacerbated by the effects of opioids.
7. Important social, occupational, or recreational activities are given up or reduced because of opioid use.
8. Recurrent opioid use in situations in which it is physically hazardous.
9. Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance.
10. Tolerance, as defined by either of the following:
   – A need for markedly increased amounts of opioids to achieve intoxication or desired effect.
   – A markedly diminished effect with continued use of the same amount of an opioid.
11. Withdrawal, as manifested by either of the following:
   – The characteristic opioid withdrawal syndrome (refer to Criteria A and B of the criteria set for opioid withdrawal).
   – Opioids (or a closely related substance) are taken to relieve or avoid withdrawal symptoms.

*Note: This criterion is not considered to be met for those taking opioids solely under appropriate medical supervision [4].

Table 25.1 Perioperative recommendations for medicinal treatment of OUD and chronic opioid users

Medication	Intraoperative recommendations	Postoperative recommendations
Long-acting oral opioid medications	Minimize intraoperative opioids [33]	Consider administration of full mu agonist or increased and/or divided doses of buprenorphine [20] Minimize duration of epidurals, PCAs, and IV opioids if possible [33] Close monitoring for uncontrolled pain if multimodal analgesia proves inadequate [20] Appropriate follow-up to ensure tapering off postoperative opioids once acute pain resolves [20] Maximize relapse prevention strategies [2]
Methadone oral	Continue [2] Consider adjunct nonopioid and short-acting opioids due to inadequate coverage of intraoperative pain with methadone alone (e.g., regional analgesia, PCA) [2] Avoid partial opioid agonists (e.g., butorphanol, buprenorphine) [2]	Continue [2] Provide last methadone dose verification letter [2]
Buprenorphine sublingual	Continue at preoperative dose [20]	Continue [20] *For mild/moderate pain*: Home dose can be split into 2-3x/day [20] *For severe pain*: Consider increasing home dose to 24–32 mg (in divided doses) or using buprenorphine IV 0.3 mg IV every 6 h prn [20] Provide taper plan to bring back down to home dose [20, 34, 35]

(continued)

Table 25.1 (continued)

Medication	Intraoperative recommendations	Postoperative recommendations
Buprenorphine buccal film	Continue at home dose [36]	Continue at home dose [36]
Buprenorphine + naloxone sublingual film	Continue at home dose [19, 20]	Continue at home dose [20] *For mild/moderate pain*: Home dose can be split into 2–3×/day [20] *For severe pain*: Consider increasing buprenorphine dose to 24–32 mg (in divided doses) or using buprenorphine IV 0.3 mg IV every 6 h prn [20] Provide taper plan [20, 34, 35]
Buprenorphine transdermal	Continue at home dose [36]	Continue at home dose [36]
Fentanyl patches	Remove Efficacy has been demonstrated, but best practice standard is to remove [37]	Restarting patch for acute postoperative pain is not recommended [37]
Naltrexone	*For elective surgeries where severe pain could be expected and where multimodal strategies may be insufficient*: Stop preoperatively: Oral >72 h IV >4 weeks (can transition to oral in the meantime) *For emergency surgeries*: Consider nonopioid strategies [2]	*If stopped prior to surgery*: Multidisciplinary approach. Coordinate with all providers for restarting; consider any acute pain medications used and indicated wait times prior to restarting [2] Caution: if naltrexone is no longer occupying receptors, opioids can elicit an exaggerated response due to receptor upregulation and increased sensitivity [2]. This could result in unexpected respiratory depression *If continued through surgery*: IM: may need higher doses of opioids [2]
In remission without medication treatment	Consider nonopioid medications and adjunct therapies [2]	If needed, opioid analgesics should be prescribed at lowest effective dose for limited period [2] Responsible support person involved to hold/dispense opioid analgesic medications [2]

Multimodal analgesia should be considered whenever possible (e.g., adjunctive medications, regional anesthesia techniques) [20]

Patient population is at high risk of relapse; use opioids with caution and individual discretion. Accommodate for risk of relapse upon discharge by discussing with prior addiction practitioner, new linkage to treatment, or initiation of medication therapy

Tolerance, Hyperalgesia, and Pain Perception

Pain perception and adequate pain management differ in individuals with history of chronic opioid use, with decreased pain tolerance, heightened pain sensitivity, and comorbid chronic pain as known potential consequences [5]. Tolerance and hyperalgesia are serious sequelae of chronic opioid use that can contribute to inadequately controlled pain, with resultant dose escalation. Tolerance is defined as the requirement of higher doses to achieve the same clinical effect, while hyperalgesia is a paradoxical effect of increased pain or hypersensitivity to painful stimuli with prolonged opioid use [6, 7]. Both tolerance and hyperalgesia can affect acute and perioperative pain management [8]. Many psychosocial barriers also stand in the way of optimal perioperative pain management. These include patient anticipation of suboptimal care due to previous negative encounters with the healthcare system, likely resulting from a mutual lack of trust between providers and patients with OUD or chronic opioid use, as well as the stigma often directed toward patients with substance use disorders [8].

Studies have indicated a higher utilization of opioids postoperatively in patients with a history of OUD and on opioid agonist pharmacotherapy postoperatively [9]. Preoperative use of opioids has also been correlated with a longer duration of postoperative use [10], as well as inability to reliably taper opioids after surgery, even when the surgery itself has likely improved the underlying pain generator [2]. Over 20% of patients receiving elective surgeries are chronic opioid users [10]. Therefore, assuring reasonable expectations of anticipated postoperative pain and opioid use perioperatively is essential to ensure appropriate medication administration and tapering postoperatively [2].

Clinical Applications

Patients with OUD are particularly vulnerable in the perioperative period as re-exposure to opioid medications predisposes them to an increased risk of misuse and overdose [11–14]. In fact, 64–77% of chronic opioid users continue to fill opioid prescriptions several months after surgery [10] and one in ten is still using opioids 1 year after discharge, despite expected recovery of pain within the first month postsurgery [15–17]. Additionally, OUD patients undergoing surgery were almost twice as likely to misuse medications as those who were not [11], with rates as high as 58% in OUD surgical patients 1-year postop [13]. Some noted risk factors for relapse include the induction period, positive urine drug screen within the last 20 months, cessation of medication for OUD and medication maintenance, as well as insufficient communication between discharge and outpatient follow-up [18–20].

At discharge, distinct and uncomplicated directions should be provided to the patient and their family and other support systems. Discharge instructions should include proper dosage, storage, tapering, and disposal, as well as any potential adverse effects [2]. There are no guidelines for specific tapering protocols available in the literature. One study implemented motivational interviewing, consisting of weekly phone calls, and found a 62% increase in the rate of baseline opioid use and a 53% increase in the rate of postoperative cessation of opioid medications [21].

Evidence-Based Practices

Postop IV Opioid Use

Evidence is conflicting regarding the use of intravenous (IV) opioids in OUD patients, with no current standardized protocol. However, literature agrees on the importance of managing acute postoperative pain to prevent relapse [2, 22–25], as uncontrolled pain is a major contributor in this vulnerable population [26, 27]. Given the heightened risk of relapse in OUD patients, efforts should ideally also be made to minimize IV opioids by utilizing alternative routes of administration (oral, transdermal, IM, epidural) or offering nonopioid analgesics whenever possible [2, 28]. Additionally, postoperative acute opioid use should be individually tailored around the history of opioid use, status of dependence/recovery, and severity and duration of the existing or expected pain [29]. Furthermore, the use of patient-controlled analgesia (PCA) programs with dose limits and lockout intervals, and careful monitoring with inclusion of nonopioids should be considered [22, 23].

Postoperative pain can vary significantly. Higher doses of opioids may be needed for increased pain sensitivity, tolerance (which is difficult to predict), and hyperalgesia [30–32]. Careful monitoring of increased pain, respiratory depression, sedation, and withdrawal symptoms is recommended [32]. Patient tolerance and organ function should determine the choice of opioid.

Perioperative Management

The table below lists the current recommendations for perioperative management of opioid

medications in those with chronic opioid use, as well as for the various available forms of chronic pharmacologic management of OUD.

Challenges and Considerations

Buprenorphine Inductions Postoperatively

Buprenorphine is a safer alternative to OUD due to its long half-life and partial agonism [20]. Liebschutz et al [38] and the Substance Abuse and Mental Health Service Administration (SAMHSA) [39] found a decreased rate of illicit opioid use at 6-months follow-up among hospitalized patients receiving buprenorphine induction postoperatively upon discharge.

Evidence also suggests a higher retention in OUD treatment programs. When clinically indicated, providers should consider the use of buprenorphine for postoperative analgesia with OUD upon discharge [20]. Confirmation of its indication can be performed using various screening tools, such as the Screener and Opioid Assessment for Patients with Pain, Opioid Risk Tool, Addiction Behaviors Checklist, and Current Opioid Misuse Measure [40]. Moreover, social work and additional services for assistance with establishing outpatient buprenorphine prescribers are recommended [20]. Of note, buprenorphine can be a very convenient medication for discharge because it can be legally given without concomitant adjuvant treatment, making it a good option for those without insurance or established outpatient follow-up care [20, 41]. Contraindications for buprenorphine initiation include elevated liver function greater than three times the normal level, active intoxication or impairment with other CNS depressants, and hypersensitivity to any listed ingredient. Initiating buprenorphine postoperatively should be a shared decision-making process between the patient and the physician [20].

Although no current standardized protocol for postoperative buprenorphine induction exists, literature recommends its initiation in small doses to lessen the risk of precipitating withdrawal [20]. Recommendations include buprenorphine induction within 4–6 h of the last short-acting, full-mu opioid agonist or within 1–2 h of IV full mu agonist opioids. If necessary to reduce withdrawal symptoms, adjuvant medications may also be used. Patients should be given 2 mg/0.5 mg of buprenorphine/naloxone sublingually as tolerated every 1 h as needed for pain or any feelings of withdrawal. The recommended daily maximum dose of buprenorphine is 16 mg, but if a greater dose is needed, it is strongly advised to consult with an addiction specialist. Patients should also schedule follow-up visits with a buprenorphine prescriber, addiction medicine specialist, or a treatment facility after being discharged [20].

Naltrexone: The Dangers of Rapid mu-Blockade and mu-Blockade-Reversal

Naltrexone, a competitive, long-acting, central opioid antagonist, is FDA-approved to decrease cravings and maintain abstinence in the treatment of opioid and alcohol dependence [42]. Through competitive displacement and reversal of mu-opioid agonists, naltrexone is highly effective in preventing repeated respiratory depression, but can precipitate withdrawals in those with recent opioid use [43], thus necessitating an opioid-free period of 7–10 days prior to administration [44, 45]. This may be particularly dangerous in opioid-dependent patients, leading to life-threatening withdrawal symptoms including ischemia, arrhythmias, pulmonary edema, and sudden death [46, 47]. When opioids are utilized for pain management, this blockade can be reversed using higher doses of opioids. However, there is an increased potential for opioid-induced respiratory depression, due to upregulation of receptors and increased sensitivity, thus necessitating provisions for respiratory support [43].

Fentanyl

Fentanyl is a very potent synthetic opioid with 50–100 times more potency than morphine. Fentanyl is a mu-selective opioid agonist, but also exhibits activation of other opioid receptors, including delta and potentially kappa. It has a strong effect on dopamine release within the reward system, leading to euphoria and relaxation, which substantially escalates its habit-forming potential. Indications and other uses include preoperative analgesia, general anesthesia, anesthesia adjunct, postoperative pain control, tolerance to opioids in chronic pain patients, and off-label for acute pain of moderate to severe intensity [48]. Of note, there is no data demonstrating an effect on postoperative opioid use with the use of fentanyl near the start of general anesthesia [2].

Fentanyl has been a concern within the illicit drug market, with its common addition to heroin [48], its false advertisement as commonly prescribed opioid pills [2], and its easily alterable chemical structure for detection avoidance [49]. The fact that users are typically unaware of its use and the unregulated and varying nature of its potency have given rise to substantial concern for unintentional overdose. Notably, there has been an increase in the percentage of deaths involving synthetic opioids, from 56% in 2019 to 82% in 2020 [49]. The average amount of fentanyl has increased from 1.3 mg/tablet in 2017 to 2.2 mg/tablet in 2022 [2]. Despite its very high potency and rapid onset, fentanyl remains naloxone sensitive. However, higher and possibly repeated doses may be needed [50].

Xylazine

Xylazine, a structural analog of clonidine often used as a nonopioid analgesic and sedative in veterinary medicine, has become an area of concern due to its rapid emergence within the US illicit drug supply [51]. A recent study from the CDC reports an increase of death percentage from illegal fentanyl laced with xylazine, from 3% in 2019 to 11% in 2022 [52]. As a CNS depressant acting via alpha-adrenergic agonism [51], xylazine is unresponsive to opioid antagonism and there are currently no FDA-approved treatments for reversal. However, if intoxication is suspected, current recommendations are to administer naloxone, due to its common combination with fentanyl [53]. It is also important to note that additional treatment and supportive measures may be warranted [51, 54–56].

Future Directions and Research

Kratom

Kratom is a psychoactive, plant-derived, Southeast Asian substance from the *Mitragyna speciosa* plant, with both stimulating (lower doses) and opioid-like effects (higher doses) [57]. The exact mechanism of action remains unknown, but four pharmacologically active compounds exist. 7-OH-mitragynine, an oxidized, hepatically metabolized metabolite of mitragynine, has 13 times more affinity for opioid receptors than morphine. Controversial evidence suggests that mitragynine agonizes the mu and delta receptors, while 7-OH-mitragynine agonizes the mu and kappa receptors. However, others suggest that both act on the mu and delta receptors as partial agonists [58]. Although both kratom and opioids initiate G-protein-coupled receptor (GPCR) signaling, kratom fails to activate the beta-arrestin pathway, which is responsible for adverse effects (sedation, constipation, and respiratory system depression) [59, 60]. This could provide promising potential with its use in pain management and OUD.

The most common use of kratom is for opioid dependence and withdrawal, as it offers a very inexpensive alternative to opioid agonism [61]. Although literature reveals therapeutic value in terms of acute and chronic pain management, morphine and ethanol withdrawals and dependence, and reduced pain sensitivity, its safety remains controversial, including concerning consequences of dependence and withdrawals [62]. Other concerns include its inability to be detected in routine screening and evaluation [57], its lack

of regulation with the Drug Enforcement Administration (DEA) [57, 63, 64], as well as its rapidly increasing recent use with concerns of unfamiliarity of appropriate care, as indicated by the amount of calls to poison control centers over the last 2 years [65].

Key Takeaways

- OUD remains at a high prevalence, despite increased awareness of the opioid epidemic and an overall decrease in opioid prescriptions. Chronic opioid use can significantly impact pain in the perioperative period.
- Perioperative management of chronic opioid use and OUD is complex due to altered pain perception from tolerance and hyperalgesia, and the risk for relapse.
- A standardized protocol for perioperative management fails to exist. However, consensus seems to favor the continuation of pharmacologic management of OUD, incorporating multimodal analgesia including regional anesthesia, and the implementation of a multidisciplinary team, to ensure adequate pain coverage and reduced risk of relapse.
- The use of IV and other forms of short-acting opioid medication for acute-postoperative on chronic pain remains controversial.
- Some challenges and future considerations include the potential of naltrexone for respiratory depression if the mu-blockade is overcome too rapidly, the dangerous nature of recreational fentanyl and xylazine, as well as the potential role of kratom in the treatment of OUD and associated pain.

References

1. Stoicea N, Costa A, Periel L, Uribe A, Weaver T, Bergese SD. Current perspectives on the opioid crisis in the US healthcare system: a comprehensive literature review. Medicine (Baltimore). 2019;98(20):e15425.
2. Abdelsayed A, Schroeder K (2024) The implications of the opioid epidemic on perioperative pain management. Cham, Springer Nature.
3. Strang J, Volkow ND, Degenhardt L, Hickman M, Johnson K, Koob GF, et al. Opioid use disorder. Nat Rev Dis Primers. 2020;6(1):3.
4. American Psychiatric Association. Diagnostic and statistical manual of mental disorders: DSM-5. 5th ed. Washington: American Psychiatric Association; 2013.
5. Ward EN, Quaye ANA, Wilens TE. Opioid use disorders: perioperative management of a special population. Anesth Analg. 2018;127(2):539–47.
6. Colvin LA, Bull F, Hales TG. Perioperative opioid analgesia-when is enough too much? A review of opioid-induced tolerance and hyperalgesia. Lancet (Lond Engl). 2019;393(10180):1558–68.
7. Mercadante S, Arcuri E, Santoni A. Opioid-induced tolerance and hyperalgesia. CNS Drugs. 2019;33(10):943–55.
8. Pavone K, Gorgol H, Rust V, Bronski M, Labelle C, Compton P. Exploring the postoperative pain experiences of individuals with opioid use disorder and the nurses providing care in the USA: a qualitative descriptive study protocol. BMJ Open. 2023;13(10):e072187.
9. Cobb J, Craig W, Richard J, Snow E, Turcotte H, Warters R, et al. A retrospective study of acute postoperative pain after cesarean delivery in patients with opioid use disorder treated with opioid agonist pharmacotherapy. J Addict Med. 2022;16(5):549–56.
10. Larach DB, Hah JM, Brummett CM. Perioperative opioids, the opioid crisis, and the anesthesiologist. Anesthesiology. 2022;136(4):594–608.
11. Namiranian K, Siglin J, Sorkin JD, Norris EJ, Aghevli M, Covington EC. Postoperative opioid misuse in patients with opioid use disorders maintained on opioid agonist treatment. J Subst Abus Treat. 2020;109:8–13.
12. Compton WM, Jones CM, Baldwin GT. Relationship between nonmedical prescription-opioid use and heroin use. N Engl J Med. 2016;374(2):154–63.
13. Brummett CM, Waljee JF, Goesling J, Moser S, Lin P, Englesbe MJ, et al. New persistent opioid use after minor and major surgical procedures in US adults. JAMA Surg. 2017;152(6):e170504.
14. Prabhakar NK, Chadwick AL, Nwaneshiudu C, Aggarwal A, Salmasi V, Lii TR, et al. Management of postoperative pain in patients following spine surgery: a narrative review. Int J Gen Med. 2022;15:4535–49.
15. Myers J, Compton P. Addressing the potential for perioperative relapse in those recovering from opioid use disorder. Pain Med Malden Mass. 2018;19(10):1908–15.
16. Wang MC. Calculating risks: the power and pitfalls of registry data. Spine J. 2013;13(10):1180–2.
17. Alam A, Gomes T, Zheng H, Mamdani MM, Juurlink DN, Bell CM. Long-term analgesic use after low-risk surgery: a retrospective cohort study. Arch Intern Med. 2012;172(5):425–30.
18. White SR, Bird SM, Merrall ELC, Hutchinson SJ. Drugs-related death soon after hospital-discharge among drug treatment clients in scotland: record link-

age, validation, and investigation of risk-factors Vrana KE, editor. PLoS One. 2015;10(11):e0141073.
19. Goel A, Azargive S, Weissman JS, Shanthanna H, Hanlon JG, Samman B, et al. Perioperative pain and addiction interdisciplinary network (PAIN) clinical practice advisory for perioperative management of buprenorphine: results of a modified Delphi process. Br J Anaesth. 2019;123(2):e333–42.
20. Kohan L, Potru S, Barreveld AM, Sprintz M, Lane O, Aryal A, et al. Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel. Reg Anesth Pain Med. 2021;46(10):840–59.
21. Hah JM, Trafton JA, Narasimhan B, Krishnamurthy P, Hilmoe H, Sharifzadeh Y, et al. Efficacy of motivational-interviewing and guided opioid tapering support for patients undergoing orthopedic surgery (MI-opioid taper): a prospective, assessor-blind, randomized controlled pilot trial. EClinicalMedicine. 2020;28:100596.
22. Thomas DA, Boominathan P, Goswami J, Mukherjee S, Vadivelu N. Perioperative management of patients with addiction to opioid and non-opioid medications. Curr Pain Headache Rep. 2018;22(7):52.
23. Mitra S, Sinatra RS. Perioperative management of acute pain in the opioid-dependent patient. Anesthesiology. 2004;101(1):212–27.
24. Curatolo C, Trinh M. Challenges in the perioperative management of the patient receiving extended-release naltrexone. Case Rep. 2014;3(11):142–4.
25. Israel JS, Poore SO. The clinical conundrum of perioperative pain Management in Patients with opioid dependence: lessons from two cases. Plast Reconstr Surg. 2013;131(4):657e–8e.
26. Kantor TG, Cantor R, Tom E. A study of hospitalized surgical patients on methadone maintenance. Drug Alcohol Depend. 1980;6(3):163–73.
27. Larson MJ, Paasche-Orlow M, Cheng DM, Lloyd-Travaglini C, Saitz R, Samet JH. Persistent pain is associated with substance use after detoxification: a prospective cohort analysis. Addiction (Abingdon Engl). 2007;102(5):752–60.
28. Clarke H, Soneji N, Ko DT, Yun L, Wijeysundera DN. Rates and risk factors for prolonged opioid use after major surgery: population based cohort study. BMJ. 2014;348(feb11 3):g1251.
29. Substance misuse: acute pain management | Faculty of Pain Medicine [Internet]. [cited 2024 Apr 25]. Available from: https://fpm.ac.uk/opioids-aware-opioids-addiction/substance-misuse-acute-pain-management
30. Alford DP, Compton P, Samet JH. Acute pain management for patients receiving maintenance methadone or buprenorphine therapy. Ann Intern Med. 2006;144(2):127–34.
31. Peng PWH, Tumber PS, Gourlay D. Review article: perioperative pain management of patients on methadone therapy. Can J Anaesth. 2005;52(5):513–23.
32. Anitescu M. The patient with substance use disorder. Curr Opin Anaesthesiol. 2019;32(3):427–37.
33. Hyland SJ, Brockhaus KK, Vincent WR, Spence NZ, Lucki MM, Howkins MJ, et al. Perioperative pain management and opioid stewardship: a practical guide. Healthcare. 2021;9(3):333.
34. Joo SS, Hunter OO, Tamboli M, Leng JC, Harrison TK, Kassab K, et al. Implementation of a patient-specific tapering protocol at discharge decreases total opioid dose prescribed for 6 weeks after elective primary spine surgery. Reg Anesth Pain Med. 2020;45(6):474–8.
35. Tamboli M, Mariano ER, Gustafson KE, Briones BL, Hunter OO, Wang RR, et al. A multidisciplinary patient-specific opioid prescribing and tapering protocol is associated with a decrease in Total opioid dose prescribed for six weeks after Total hip arthroplasty. Pain Med. 2020;21(7):1474–81.
36. Anderson TA, Quaye ANA, Ward EN, Wilens TE, Hilliard PE, Brummett CM. To stop or not, that is the question: acute pain Management for the patient on chronic buprenorphine. Anesthesiology. 2017;126(6):1180–6.
37. Kaye AD, Menard BL, Ehrhardt KP, Gennuso SA, Okereke EC, Tirumala SR, et al. Consensus perioperative management best practices for patients on transdermal fentanyl patches undergoing surgery. Curr Pain Headache Rep. 2019;23(7):50.
38. Liebschutz JM, Crooks D, Herman D, Anderson B, Tsui J, Meshesha LZ, et al. Buprenorphine treatment for hospitalized, opioid-dependent patients: a randomized clinical trial. JAMA Intern Med. 2014;174(8):1369–76.
39. Special Circumstances for Providing Buprenorphine | SAMHSA [Internet]. [cited 2024 Apr 25]. Available from: https://webarchive.library.unt.edu/web/20201218105154/https://www.samhsa.gov/medication-assisted-treatment/statutes-regulations-guidelines/special-circumstances
40. Duber HC, Barata IA, Cioè-Peña E, Liang SY, Ketcham E, Macias-Konstantopoulos W, et al. Identification, management, and transition of Care for Patients with Opioid use Disorder in the emergency department. Ann Emerg Med. 2018;72(4):420–31.
41. Federal Register [Internet]. 2021 [cited 2024 Apr 25]. Practice guidelines for the Administration of Buprenorphine for treating opioid use disorder. Available from: https://www.federalregister.gov/documents/2021/04/28/2021-08961/practice-guidelines-for-the-administration-of-buprenorphine-for-treating-opioid-use-disorder
42. Hall WD, Mattick RP. Oral substitution treatments for opioid dependence. Lancet. 2008;371(9631):2150–1.
43. Basic & Clinical Pharmacology, 15e | AccessMedicine | McGraw Hill Medical [Internet]. [cited 2024 Apr 25]. Available from: https://accessmedicine.mhmedical.com/book.aspx?bookID=2988
44. Bisaga A, Mannelli P, Yu M, Nangia N, Graham CE, Tompkins DA, et al. Outpatient transition to extended-release injectable naltrexone for patients with opioid use disorder: a phase 3 randomized trial. Drug Alcohol Depend. 2018;187:171–8.

45. McGraw Hill Medical [Internet]. [cited 2024 Apr 25]. Opioid Antagonists. Available from: https://accessemergencymedicine.mhmedical.com/content.aspx?sectionid=210262002&bookid=2569
46. Webster LR, Cochella S, Dasgupta N, Fakata KL, Fine PG, Fishman SM, et al. An analysis of the root causes for opioid-related Overdose deaths in the United States. Pain Med. 2011;12(suppl 2):S26–35.
47. Hassanian-Moghaddam H, Afzali S, Pooya A. Withdrawal syndrome caused by naltrexone in opioid abusers. Hum Exp Toxicol. 2014;33(6):561–7.
48. Ramos-Matos CF, Bistas KG, Lopez-Ojeda W. Fentanyl. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. [cited 2024 Apr 25]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK459275/.
49. Opioid Overdose | Drug Overdose | CDC Injury Center [Internet]. 2023 [cited 2024 Apr 25]. Available from: https://www.cdc.gov/drugoverdose/deaths/opioid-overdose.html
50. Moss RB, Carlo DJ. Higher doses of naloxone are needed in the synthetic opioid era. Subst Abuse Treat Prev Policy. 2019;14(1):6.
51. Solanki PK, Yellapragada S, Lynch B, Eibel M, Viscusi ER, Emerick T. Emergence of xylazine as a public health threat: what does the anesthesiologist need to know for perioperative care? Reg Anesth Pain Med. 2024; https://doi.org/10.1136/rapm-2023-105190.
52. What You Should Know About Xylazine | Drug Overdose | CDC Injury Center [Internet]. 2024 [cited 2024 Apr 25]. Available from: https://www.cdc.gov/drugoverdose/deaths/other-drugs/xylazine/faq.html
53. Abuse NI on D. Xylazine | National Institute on Drug Abuse (NIDA) [Internet]. 2022 [cited 2024 Apr 25]. Available from: https://nida.nih.gov/research-topics/xylazine
54. Thangada S, Clinton HA, Ali S, Nunez J, Gill JR, Lawlor RF, et al. Notes from the field: Xylazine, a veterinary tranquilizer, identified as an emerging novel substance in drug Overdose deaths – Connecticut, 2019–2020. MMWR Morb Mortal Wkly Rep. 2021;70(37):1303–4.
55. Capraro AJ, Wiley JF, Tucker JR. Severe intoxication from xylazine inhalation. Pediatr Emerg Care. 2001;17(6):447–8.
56. Ehrman-Dupre R, Kaigh C, Salzman M, Haroz R, Peterson LK, Schmidt R. Management of Xylazine Withdrawal in a hospitalized patient: a case report. J Addict Med. 2022;16(5):595–8.
57. Sethi R, Hoang N, Ravishankar DA, McCracken M, Manzardo AM. Kratom (Mitragyna speciosa): Friend or Foe? Prim Care Companion CNS Disord [Internet]. 2020 Jan 30 [cited 2024 Apr 25];22(1). Available from: https://www.psychiatrist.com/pcc/kratom-friend-or-foe
58. Jentsch MJ, Pippin MM. Kratom. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. [cited 2024 Apr 25]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK585120/.
59. Váradi A, Marrone GF, Palmer TC, Narayan A, Szabó MR, Le Rouzic V, et al. Mitragynine/corynantheidine pseudoindoxyls as opioid analgesics with mu Agonism and Delta antagonism, which do not recruit β-Arrestin-2. J Med Chem. 2016;59(18):8381–97.
60. Bohn LM, Lefkowitz RJ, Caron MG. Differential mechanisms of morphine Antinociceptive tolerance revealed in βArrestin-2 Knock-out mice. J Neurosci. 2002;22(23):10494–500.
61. Prevete E, Hupli A, Marrinan S, Singh D, Udine BD, Bersani G, et al. Exploring the use of Kratom (Mitragyna speciosa) via the YouTube data tool: a novel netnographic analysis. Emerging Trends Drugs Addict Health. 2021;1:100007.
62. Prevete E, Kuypers KPC, Theunissen EL, Corazza O, Bersani G, Ramaekers JG. A systematic review of (pre)clinical studies on the therapeutic potential and safety profile of kratom in humans. Hum Psychopharmacol Clin Exp. 2022;37(1):e2805.
63. Eastlack SC, Cornett EM, Kaye AD. Kratom-pharmacology, clinical implications, and outlook: a comprehensive review. Pain Ther. 2020;9(1):55–69.
64. Tobacyk J, Parks BJ, Lovelady N, Brents LK. Qualitative content analysis of public responses to an FDA inquiry on the impact of scheduling changes to kratom. Int J Drug Policy. 2022;108:103817.
65. Post S, Spiller HA, Chounthirath T, Smith GA. Kratom exposures reported to United States poison control centers: 2011–2017. Clin Toxicol. 2019;57(10):847–54.

Cultural and Ethical Challenges in Pain Management

26

Vinita Singh and Rupa Nallamothu

Introduction

The International Association for the Study of Pain (IASP) describes pain as an unpleasant experience with both sensory and emotional components that is associated with tissue damage [1]. During the postoperative period, poor pain control is associated with an increased incidence of nausea and vomiting, cardiac and pulmonary stress, psychological stress, delayed ambulation and return of function, higher readmission rate, overall cost of care, and length of hospital stay. In the United States (US), opioid analgesics are commonly used for postoperative pain. Due to the involvement of a variety of social, cultural, and medical factors, managing and evaluating pain is complex [2].

The cultural background of the patient influences how the patient describes and experiences pain. Pain is subjective and can be challenging for the patient to describe to their provider. Therefore, effective communication and the relationship between the provider and patient are important in the management of pain. Practicing in an ethically and culturally diverse society requires physicians to have an understanding and respect for the cultures of their patients. Also, physicians must consider these cultures in the treatment of pain to provide effective pain management [3].

There are several ethical components in the management of pain. The ethical questions involved in pain management include: "What importance does pain have in medicine? What role does pain management play in the clinical care of patients? What duties do health care professionals have concerning the pain of their patients? What other duties must be balanced against the duty to provide adequate analgesia?" [4]. Physicians have an ethical responsibility to relieve pain and act in the best interests of their patients [4].

Background and Current Understanding

Both the patient and provider introduce their own beliefs about pain to the clinical situation. These beliefs can have a significant impact on care. Cultural factors influence patients' language of pain and distress. Some cultural groups expect a large display of emotion in the presence of pain, but other groups value stoicism, restraint, and playing down the pain. These expectations influence whether pain is seen as a clinical problem that needs a clinical solution. For example, in the

V. Singh (✉)
Department of Anesthesiology, Emory University School of Medicine, Atlanta, GA, USA
e-mail: vinita.singh@emory.edu

R. Nallamothu
Lake Erie College of Osteopathic Medicine, Erie, PA, USA

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_26

population of Australian aborigines, one-third of men and half of the women reported back pain when asked, but they did not see it as a health problem. Unless they were asked, the patients did not report symptoms, display pain behavior, or seek medical treatment for their pain. Similarly, in rural Nepal, back pain is common, but no one sought medical help for their symptoms [5]. Therefore, cultural influences have a significant impact on the treatment of pain.

From the perspective of the provider, there are cultural barriers in the treatment of pain. There are disparities in the treatment of pain based on the patient's racial or ethnic background. For example, a review found that Black and Hispanic patients were more likely to be undertreated for their pain across multiple types of healthcare settings. Although Black patients recorded higher back pain scores on a 10-point scale in comparison to White patients, providers considered Black patients less likely to have disc disease and to have less pain than White patients. This disparity can be a result of stereotyped perceptions of race and ethnicity, language barriers, socioeconomic status, communication between the doctor and patient, and the clinical assessment of pain [5]. Therefore, the cultural beliefs of providers can influence pain management.

Also, ethical considerations influence the treatment of pain. Twenty years ago, Cassel reported that medicine's focus on purely treating the diseases of the body prevented it from addressing the suffering of individuals. Through separating physical or biological pain from other types of pain, medicine can avoid the responsibility of acknowledging all types of pain that result from the patient's experience of disease or illness. To provide ethical care to the patient, this delineation must be resolved. Through integrating care-based ethics in pain management with a focus on the provider-patient relationship, the approach to pain management can be changed to focus on the person, not the disease, as the main concern [4]. This approach can improve the management of pain.

The opioid crisis has introduced ethical dilemmas in the management of pain. Overall, drug overdose deaths increased from 2019 to 2022 with 107,941 drug overdose deaths reported in 2022. Deaths that involved synthetic opioids other than methadone (primarily fentanyl) continued to rise with 73,838 overdose deaths reported in 2022 [6]. Postsurgical pain management was an important contributor to the opioid crisis [7]. As a result, in anesthesiology, there has been a drive toward opioid reduction in surgical pain management and reduced intraoperative opioid usage during general anesthesia [8]. Since persistent opioid use after surgery may lead to misuse, abuse, addiction, and diversion, providers must optimize postoperative pain management and limit opioid use after surgery [7]. An ethical approach to pain management must balance these two considerations.

Additionally, cultural implications are involved in the opioid crisis. People who identified as non-Hispanic white were more likely to receive an opioid prescription, so the risk of opioid addiction is higher in this group. Disparities in healthcare for pain often cause pain to be untreated in racial and ethnic minorities. Race impacts access to treatment, so the access to treatment in racial minorities is lower. Access to medications for opioid use disorder is lower in communities with a higher amount of African American and Hispanic populations [9]. Providers must consider the different effects of the opioid epidemic in different cultural groups when treating pain.

Clinical Applications and Techniques

To integrate ethical principles and cultural sensitivity into clinical practice, physicians should be educated about the importance of communication skills and techniques to improve their communication skills. In Carvalho et al. [4], the authors proposed an ethical framework that emphasizes the use of a variety of ethical theories, such as ethics of care and virtues, and principle-based ethics, to improve communication between providers and patients [4]. Also, the American Medical Association's Institute for Ethics created a curriculum to educate practicing physicians on

end-of-life care for patients. The name of the curriculum is Education for Physicians on End-of-Life Care (EPEC). This curriculum includes a module with suggestions regarding body language to optimize communication. This framework could serve as a model for the creation of a curriculum for healthcare professionals who treat patients for pain and could be used for the integration of ethical principles and cultural sensitivity [10]. Through being educated about these frameworks, physicians can apply these principles in pain management.

Evidence-Based Practices

Cultural competence training for providers is one mechanism for reducing racial and ethnic disparities in healthcare. This training can have a beneficial effect on the knowledge, attitudes, and skills of providers. Due to this training, patients experience more satisfaction with their providers. Through teaching providers to be able to apply a patient-centered approach and have better communication skills with their patients, cultural competence training allows providers to provide better care to patients. Providers who have received this training might have more skills in obtaining histories from patients and making appropriate diagnoses [11]. Therefore, cultural competency training is an important tool in providing care to patients.

Also, Kaldjian's framework for shared decision-making (SDM) is a useful strategy for applying cultural and ethical considerations in healthcare (see Fig. 26.1). SDM prioritizes respect for the autonomy of patients in treatment because the patient can assume responsibility for their role in the provider-patient relationship. Kaldjian's framework reframes SDM as purpose-oriented dialogue that allows patients and healthcare providers to have conversations about medical facts, beliefs, and values. Both the provider and the patient can intentionally work toward specific goals that result from these discussions. These goals connect treatments and tests to the patient's ideal goal of the improvement of their health [12]. Since culture influences the patient's values, this framework considers both cultural and ethical values.

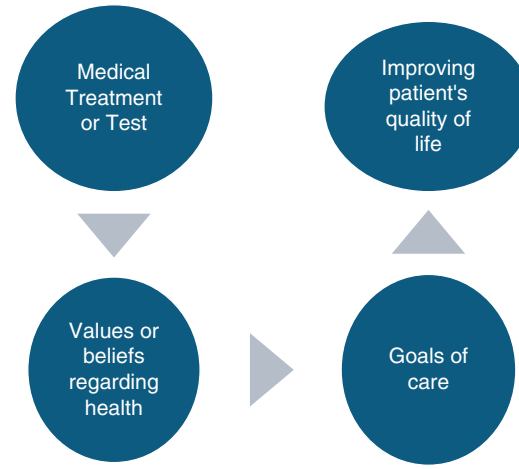


Fig. 26.1 Main points of the chapter

Challenges and Considerations

Health disparities among minority groups are a significant concern in implementing culturally competent care for pain management. Since ethnic minorities are less likely to become involved in medical decisions about their treatment than nonminority groups, healthcare providers must be aware of the challenges that these groups experience. Also, providers need to engage in personal reflexivity to be aware of the impact of their own values and beliefs in the healthcare setting. Health professionals should be aware that their personal biases influence their responses to the management of pain. Reflexivity can help providers avoid ethnocentrism, which is the belief that their culture is superior to other cultures [5]. Through thinking about how their own experiences have shaped their beliefs, health professionals can become more cognizant about how they communicate with patients. The adoption of a multifaceted approach to pain management can help providers consider the influences of multiple factors on cultural competency.

Also, there are limitations in providing ethically competent care in pain management. Since the experience of pain is subjective and depends

on an individual's experiences, culture, and beliefs, narrative medicine is an important tool in pain management. It is difficult to develop policies based on narrative medicine because it depends significantly on an individual's experience. The ethical principle of justice is important in pain management because people who experience pain are a vulnerable group. Currently, financial interests can make it difficult in healthcare to provide the appropriate amount of monitoring to patients. Therefore, there are challenges in providing an ethical approach in assessing, managing, and controlling pain. Access to treatment for pain control is inequitable [4]. These limitations must be considered in the management of pain.

Case Studies or Clinical Scenarios

Culture and ethnicity influence an individual's experience of pain. In South Asian communities in the UK, patients and family carers experience concerns about taking pain medication, home pain management, and communication about pain with healthcare professionals. These patients report that they value personal resilience, privacy, and self-management. To improve the experiences of these individuals, healthcare providers should have greater awareness around people's fears and concerns about pain medication, the potential use of alternative pain management strategies, and cultural issues, such as resilience, privacy, dignity, and gender roles [13]. Similarly, a survey found that South African patients in Cape Town, South Africa, reported that they had difficulties communicating with their physicians. Since women in this culture are allowed to express their pain verbally more than men, physicians sometimes erroneously conclude that a female patient is in more severe pain than a male patient [14]. To provide culturally competent care to patients, providers should be aware of the needs and values of their cultural group.

Future Directions and Research

Further research into cultural and ethical considerations in pain management should explore the variety of factors involved in both areas. Due to the large number of factors in providing culturally competent care, healthcare providers must be aware of the need to apply a comprehensive strategy in the management of pain. Factors such as gender, language, acculturation, socioeconomic factors, family involvement, and interactions with the health care system influence the cultural considerations in healthcare. Therefore, these factors must be further considered in the management of pain [5]. The use of opioids in the management of pain is a significant ethical concern in pain management. Providers must simultaneously optimize postoperative pain management and limit opioid use after surgery. There is a need for evidence-based strategies for opioid tapering to be developed that complement the guidelines and expert opinions advocating for postoperative opioid tapering to maximize patient success, limit underprescribing of opioids to patients, and prevent the misuse and diversion of opioids [7]. To effectively manage pain while integrating ethics and culture, more research is needed in these areas.

Key Takeaways

1. The cultural background of the patient influences how the patient describes and experiences pain.
2. The opioid crisis has introduced ethical dilemmas in the management of pain.
3. To integrate ethical principles and cultural competency into clinical practice, physicians should be educated about the importance of communication skills and techniques to improve their communication skills.
4. Health disparities among minority groups are a significant concern in implementing culturally competent care for pain management.

5. Kaldjian's framework for SDM is a useful strategy for applying cultural and ethical considerations in healthcare.

References

1. Raja SN, Carr DB, Cohen M, et al. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020;161(9):1976–82. https://doi.org/10.1097/j.pain.0000000000001939.
2. Chen Q, Chen E, Qian X. A narrative review on perioperative pain management strategies in enhanced recovery pathways-the past, present and future. J Clin Med. 2021;10(12):2568. https://doi.org/10.3390/jcm10122568. Published 2021 Jun 10.
3. Givler A, Bhatt H, Maani-Fogelman PA. The importance of cultural competence in pain and palliative care. [Updated 2023 May 22]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. https://www.ncbi.nlm.nih.gov/books/NBK493154/.
4. Carvalho AS, Martins Pereira S, Jácomo A, et al. Ethical decision making in pain management: a conceptual framework. J Pain Res. 2018;11:967–76. https://doi.org/10.2147/JPR.S162926. Published 2018 May 15.
5. Peacock S, Patel S. Cultural influences on pain. Rev Pain. 2008;1(2):6–9. https://doi.org/10.1177/204946370800100203.
6. U.S. Department of Health and Human Services. Drug overdose death rates. National Institutes of Health; 2024. https://nida.nih.gov/research-topics/trends-statistics/overdose-death-rates
7. Hah JM, Bateman BT, Ratliff J, Curtin C, Sun E. Chronic opioid use after surgery: implications for perioperative management in the face of the opioid epidemic. Anesth Analg. 2017;125(5):1733–40. https://doi.org/10.1213/ANE.0000000000002458.
8. Santa Cruz Mercado LA, Liu R, Bharadwaj KM, et al. Association of intraoperative opioid administration with postoperative pain and opioid use. JAMA Surg. 2023;158(8):854–64. https://doi.org/10.1001/jamasurg.2023.2009.
9. Jalali MS, Botticelli M, Hwang RC, et al. The opioid crisis: a contextual, social-ecological framework. Health Res Policy Syst. 2020;18:87. https://doi.org/10.1186/s12961-020-00596-8.
10. Blacksher E. Hearing from pain: using ethics to reframe, prevent, and resolve the problem of unrelieved pain. Pain Med. 2001;2(2):169–75. https://doi.org/10.1046/j.1526-4637.2001.002002169.x.
11. Beach MC, Price EG, Gary TL, et al. Cultural competence: a systematic review of health care provider educational interventions. Med Care. 2005;43(4):356–73. https://doi.org/10.1097/01.mlr.0000156861.58905.96.
12. Dinoff BL. Ethical treatment of people with chronic pain: an application of Kaldjian's framework for shared decision-making. Br J Anaesth. 2019;123(2):e179–82. https://doi.org/10.1016/j.bja.2019.04.042.
13. Clarke G, Crooks J, Bennett MI, et al. Experiences of pain and pain management in advanced disease and serious illness for people from South Asian communities in Leeds and Bradford: a qualitative interview study. BMC Palliat Care. 2023;22(1):90. https://doi.org/10.1186/s12904-023-01208-2. Published 2023 Jul 19.
14. Nortjé N, Albertyn R. The cultural language of pain: a South African study. S Afr Fam Pract. 2015;57(1):24–7. https://doi.org/10.1080/20786190.2014.977034.

Part VIII

Complications and Adverse Effects

Opioid-Induced Hyperalgesia and Other Complications

27

Alisa Wilkinson, Amrutha Bindu Nagella, and Bhavana Yalamuru

Introduction

The incidence of moderate to severe postoperative pain is prevalent and ranges from 31% to 58% in the first 2 weeks after surgery [1]. Poorly controlled pain results in significant suffering and increased morbidity in addition to increased economic burden in the form of readmissions, emergency room visits, lost work days, and stress on caregivers. It is paramount to adequately treat postoperative pain and balance adequate analgesia with the side effects of analgesics.

Opioids have been the cornerstone of the management of acute perioperative pain. Use of opioids is associated with many well-known side effects including decreased gastric motility, respiratory depression, sedation, nausea, vomiting, and dizziness [3]. Over the years, other nonopioid medications and regional anesthetic techniques have been developed and incorporated into perioperative pain regimens to minimize the side effects of opioids and reduce the risk of development of opioid dependence and abuse.

This chapter will review the adverse effects of analgesics used in the management of acute postoperative pain including—opioids, nonopioid medications like NSAIDs (nonsteroidal antiinflammatory medications), acetaminophen, gabapentinoids, ketamine, local anesthetics as well as regional anesthetic techniques.

Background and Current Understanding

Opioids have been used for thousands of years starting with naturally derived analgesics from opium poppy. Later, morphine was able to be extracted for use, and in the early 1900s, synthetic opioid derivatives were developed [4]. Opioids play an important role in pain management in the perioperative setting. While they are an effective tool for acute pain, they are associated with a plethora of side effects like sedation, nausea, vomiting, dizziness, pruritus, and respiratory depression [4].

Opioids bind opioid receptors which are G-protein couple receptors. These receptors are further subclassified into mu (MOP), delta (DOP), kappa (KOP), as well as nonclassical nociception (NOP). The mu opioid receptor is the dominant receptor for analgesia. Mu receptors which are expressed in pain pathways, the GI tract, respiratory centers of the brain, and chemoreceptor trigger zone of the brain. Use of opioids activates these various mu receptors resulting in both analgesia and side effects [5]. Mu receptor

A. Wilkinson · B. Yalamuru (✉)
Department of Anesthesiology, University of Virginia, Charlottesville, VA, USA
e-mail: by2g@uvahealth.org

A. B. Nagella
School of Public Health and Health Professions, University at Buffalo, Buffalo, NY, USA

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_27

activation can result in activation of hedonic reward centers and is responsible for addiction, dependence behaviors, as well as the development of tolerance. The mu opioid receptor activation in the gut by opioids results in constipation [6].

Development of opioid tolerance is a complex process involving opioid receptors and neural circuits. Tolerance is the process when a patient requires increasing doses of opioids to maintain the same analgesic effect [5].

There is a developing understanding of the paradoxical worsening of pain despite opioid administration, referred to as opioid-induced hyperalgesia (OIH) where patients have increased pain after exposure to increasing doses of opioids [7]. Hyperalgesia is hypothesized to be a sensitization process as opposed to a tolerance process, whereby continued administration of opioids after a certain point can induce higher levels of pain response.

The pathophysiology of OIH is complex and multifactorial. There is dysregulation of pain pathways at both central and peripheral levels, leading to heightened pain sensitivity. When opioids are administered, their effects initially lead to a blunting or delay in these pronociceptive systems, but as administration of opioids continues, there is a sensitization of pronociceptive systems leading to increased pain response [8]..

Any opioid can be linked to opioid hyperalgesia, although certain opioids have significant evidence to suggest their use can induce opioid hyperalgesia, including fentanyl and remifentanil [9, 10] and increasing doses pose a higher risk of development of OIH [11].

The prevailing theory is that pain response is a balance of pronociceptive and antinociceptive systems. Continued administration of opioids can lead to sensitization of pronociceptive systems [8]. These pronociceptive systems include multiple proposed biochemical mechanisms.

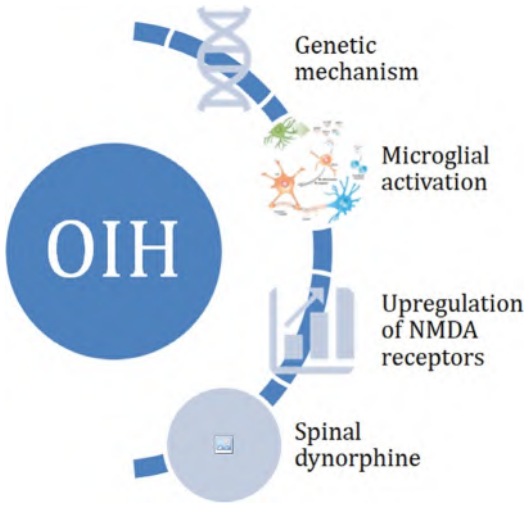
At the central level, the descending pain modulatory system, particularly the rostral ventral medulla (RVM), plays a pivotal role in inducing OIH. Under normal conditions, the RVM exerts both inhibitory and facilitatory control over nociception; however, chronic opioid exposure disrupts this balance leading to facilitation of the pain. This process is mediated by opioid-induced disinhibition of GABAergic interneurons, which reduces endogenous pain suppression while simultaneously enhancing excitatory ON-cell activity, resulting in increased nociceptive transmission [12, 13].

In addition to the descending pathway dysfunction, there is also upregulation of NMDA receptors following chronic opioid exposure leads to central sensitization and hyperalgesia. NMDA receptor overexpression leads to increased calcium influx, wind-up of nociceptive neurons, and long-term potentiation of pain transmission [14]. Chronic opioid exposure also leads to a state of neuroinflammation. Prolonged use of opioids triggers microglial activation in the spinal dorsal horn. Proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 induce nociceptive neuron hyperexcitability, exacerbating pain sensitivity [15, 16]. The spinal dynorphin levels rise, which release neuropeptides like CGRP, increasing the nociceptive inputs at the spinal cord level. Collectively, this results in a hyperexcitable state that not only counteracts opioid-induced analgesia but also promotes persistent pain that is refractory to opioid escalation [17].

At the peripheral level, opioid receptor activation modulates nociceptive signaling through prostaglandin synthesis and transient receptor potential (TRP) channel alterations. Chronic opioid exposure primes TRPV1 and TRPA1 channels, leading to increased peripheral sensitization and exacerbation of inflammatory pain [18]. Opioid-induced activation of cyclooxygenase-2 (COX-2) results in enhanced prostaglandin production, which further amplifies nociceptive signaling [19].

In addition to all the above mechanisms, genetic and epigenetic factors influence susceptibility to OIH, with polymorphisms in opioid receptors, NMDA receptors, and inflammatory mediators. The complex interplay between these factors leads to OIH.

Commonly cited possible pathways of opioid-induced hyperalgesia include genetic mechanisms, decreased reuptake and enhanced nociceptive response, spinal dynorphin, descending facilitations, and central glutaminergic system mechanisms [2].



Clinical Implications of Adverse Effects of Opioids and Nonopioid Techniques of Pain Management

1. *Opioids*
   A. *Respiratory Depression:* MOP receptor activation results in decreased cellular signal transduction and depression of the respiratory neurons in the pre-Bot zinger complex in the ventrolateral medulla. This results in respiratory depression. Risk factors for opioid-induced respiratory depression are male sex, sleep apnea, age, sleep apnea, heart failure, and concomitant use of sedatives and respiratory depressants. In addition, at higher doses, the phrenic nerve motor output is affected and is depressed. Naloxone is the first line of treatment for respiratory depression secondary to opioids in addition to supportive measures [20].
   B. *Tolerance:* Tolerance to opioid administration develops with repeated administration and results in decreased efficacy of the medication. This primarily occurs due to the increase in the number of inactive mu receptors on the cell membrane due to cellular trafficking as well as desensitization. Clinical management requires the use of adjuvants in pain management in combination with opioids, as well as opioid rotation [6].
   C. *Addiction and Physical Dependence:* In addition to tolerance, long-term opioid therapy can result in physical dependence and addiction. This occurs secondary to upregulation of cyclic AMP and increased signaling at the locus coeruleus. Opioid binding at the MOP in the brain results in increased dopaminergic release and activates the nucleus accumbens and induces pleasure. As the reward and pleasure centers of the brain are activated by opioid administration, it can result in addiction and physical dependence [21]. Pain management guidelines recommend opioid sparing techniques and use of small, incremental doses as needed and avoiding large doses and rapid escalation [6].
   D. *Constipation*: This occurs due to the activation of the MOP in the enteric neurons leading to delayed gastrointestinal transit times as well as stimulation of the sphincters. In addition, there is increased water absorption in the gut due to increased levels of serotonin and aquaporin channels. Constipation affects 40% of patients on long-term opioid therapy. Patients on opioids require a bowel regimen with laxatives as well as increased hydration and a fiber-rich diet. In addition, opioid antagonists like naloxone and/or methylnaltrexone can be used [22].
   E. *Nausea and Vomiting:* Opioid receptors are present in the chemoreceptor trigger zone, vestibular apparatus, and in the gastrointestinal tract. Activation of these receptors can result in nausea and vomiting. About 20% of the patients on opioid

therapy experience nausea and vomiting. Blocking the serotonergic and neurokinin receptors in the area postrema of the brain stem can be attempted to help minimize the nausea and vomiting secondary to opioids [23].

F. *Other adverse effects* include drowsiness, lethargy, urinary retention, and pruritus. Long-term use has also been associated with hypogonadism.

Pruritus is more common with neuraxial opioids that are hydrophilic (morphine). It is likely secondary to mast cell activation and histamine release, as well as the activation of itch pathways by the mu opioid receptors in the spinal cord [24].

2. *Nonsteroidal Antiinflammatory Medications (NSAIDs)*

NSAIDs inhibit COX enzymes, decrease prostaglandin production, and act peripherally and centrally to decrease generation and transmission of nociceptive signals. The inhibition of COX enzymes is also responsible for the adverse effects of this class of medications. A decrease in prostaglandin levels is responsible for the loss of cytoprotective layer of gastric mucosa leading to increased gastrointestinal ulcers. Alteration in renal blood flow can result in impaired renal function [25]. Inhibition of prostacyclin formation and increased thromboxane A2 levels by NSAIDS lead to increased risk of vasoconstriction and adverse cardiac events. There is some literature that suggests that postoperative use of NSAIDS is associated with an increased risk of anastomotic leakage following colonic resections [26, 27]. Additionally, NSAIDs can cause delayed bone healing or nonunion [28]. This risk is lower for lower doses or shorter duration of treatment, but should still be considered as an important risk, especially in the context of orthopedic surgeries.

3. *Acetaminophen* is a commonly used antipyretic and antiinflammatory medication that reduces COX activity and is used for analgesia in the acute postoperative period. Commonly associated side effects include hypersensitivity, rash, hepatic and renal injury, Acetaminophen is associated with hepatic and renal injury, allergic reaction, and hematological abnormalities like anemia, leukopenia, and even electrolyte abnormalities It should be used with caution in patients with liver disease [29].

4. *Gabapentinoids:*

Gabapentinoids are anticonvulsants that have analgesic properties and are especially effective in the treatment of neuropathic pain. Over the past decade, these medications were increasingly used in the acute postoperative period as well as part of enhanced recovery pathways in the perioperative period. Common side effects include somnolence, development of dependence, ataxia, dizziness, confusion, vision changes, and hypoventilation [30]. Current evidence is mixed on whether gabapentinoids provide significant postoperative pain relief, with a recent meta-analysis [31] showing that postoperative pain scores with the use of gabapentinoids were not clinically improved.

5. *Ketamine:*

Ketamine is a phencyclidine derivative which is an anesthetic and analgesic medication. It exerts its analgesic action primarily through reversible NMDA and glutamate receptor antagonism. It is also a partial Mu receptor agonist. Ketamine can cause psychotomimetic reactions at high doses as well as dizziness, nausea, and sedation [32]. Some of the side effects observed with ketamine include tachycardia, increased blood pressure, anorexia, nausea, vomiting, diplopia, nystagmus, increased intraocular pressure, anxiety, dissociative states, hallucinations, hepatotoxicity, and increased intracranial pressure. It should be used with caution in pregnant and lactating women, and avoided in patients with schizophrenia, hemodynamic instability, and increased intracranial pressure [33].

6. *Regional Anesthesia*

Regional anesthesia techniques and use of local anesthetics are common and effective tools to manage postoperative pain whilst reducing opioid use [34]. This includes spinal

and epidural anesthesia, peripheral nerve blocks, and infiltration of local anesthetics at surgical sites. In addition, infusions of local anesthetics (specifically lidocaine) have been shown to have antiinflammatory and antinociceptive effects [35].

Each type of regional technique has its own side effect and complication profile. Neuraxial blockade through spinal or epidural anesthesia can cause spinal hematoma, infection or abscess, permanent neurological injury through direct trauma or spinal cord ischemia, local anesthetic toxicity, and postdural puncture headache [36]. Any peripheral nerve blockade can cause local nerve injury through direct trauma, and all include the risk of damage to nearby structures, for example, pneumothorax after supraclavicular block [37].

Local anesthetic medications provide analgesia via blockade of voltage-gated sodium channels and subsequent interruption of impulse transmission. In addition to hypersensitivity and allergic reactions, there is a significant risk of systemic toxicity with increasing concentrations as well as systemic administration of local anesthetics. This manifests in the form of metallic taste in the mouth, ringing in the ears, circumoral numbness, seizures followed by hypotension, dysrhythmias, heart block, and subsequent cardiovascular compromise [38]. All regional techniques that involve injection of local anesthetic have a risk of local anesthetic systemic toxicity (LAST) which can cause life-threatening CNS and cardiovascular toxicity [39].

7. *Peripheral Nerve Stimulation and Cryoanalgesia:*

Peripheral nerve stimulation and cryoablation are both forms of pain management that are newer techniques that can be used in the perioperative setting to manage neuropathic pain. Placement of a peripheral nerve stimulator involves placing small electrodes along the sensory nerves that are connected to a pulse generator or communicate with a wireless generator that uses electrical signals to modulate pain pathways. This technique has a risk of bleeding, infection, nerve injury, migration of leads, or lead fracture [40]. Cryoablation can be used to target neuropathic pain that can be localized to a peripheral nerve. It has risks including skin changes (hyper or hypo pigmentation), hair loss at the site of cryoablation, pain, or damage to nearby structures [41].

Evidence-Based Practice

Mitigating Adverse Effects of Opioids and Opioid-Induced Hyperalgesia

Owing to the complex overlapping mechanisms between OIH, opioid tolerance, and opioid dependence, adopting an opioid-sparing strategy is critical to optimizing long-term pain management while reducing the risk of OIH and other opioid-associated side effects. Given the evidence to support opioids causing opioid-induced hyperalgesia in a dose-dependent manner, it is critical to use a multimodal approach for effective and safe perioperative pain management that limits opioid use. Using lower doses of opioids should be targeted [42], with additional use of analgesics from other classes, including those discussed above. Specifically, the use of NMDA antagonists may be associated with a lower incidence of opioid-induced hyperalgesia [9, 43, 44].

Acetaminophen and NSAIDs should be used in appropriate patient populations (based on comorbidities) as opioid-sparing medications and as part of multimodal pain regimens. Preemptively administering acetaminophen prior to surgery and initiation of painful stimuli can reduce the postoperative need for opioid use [45]. Additionally, the use of neuraxial analgesia and regional anesthetic techniques when applicable may be associated with decreased need for perioperative opioid use, as well as ultimately decreased incidence of chronic postsurgical pain [46].

The most effective approach to OIH is prevention. A multimodal perioperative pain management strategy is essential to prevent the risk of OIH.

- Preoperatively, identifying at-risk patients before surgery is essential, as individuals with chronic opioid use, central sensitization syndromes, or heightened pain sensitivity are more likely to develop OIH. Preoperative risk stratification should include opioid history assessment and screening for chronic pain conditions, enabling individualized pain management plans [2]. It is important to educate patients about opioid-sparing techniques, multimodal analgesia, and realistic pain expectations. Preoperative opioid tapering in chronic opioid users may reduce the risk of developing hyperalgesia, supporting the rationale for preoperative opioid optimization programs (26816103).
- Intraoperatively, minimizing intraoperative opioid exposure is crucial to preventing OIH.
  - High-dose remifentanil infusions, particularly those exceeding 0.2 μg/kg/min, have been strongly associated with postoperative hyperalgesia [47]. A gradual tapering approach when discontinuing opioid infusions may reduce the risk of withdrawal-induced hyperalgesia.
  - Multimodal analgesia targeting multiple pain pathways may reduce opioid dependence. NMDA receptor antagonists, such as ketamine and dextromethorphan, help counteract opioid-induced neuroplastic changes. Low-dose ketamine, administered as a 0.5 mg/kg bolus followed by a 0.1–0.2 mg/kg/h infusion, has been shown to effectively prevent OIH and reduce postoperative opioid consumption [48].
  - Alpha2-adrenergic agonists, such as dexmedetomidine and clonidine, methadone, and COX-2 inhibitors have shown potential to reduce postoperative opioid requirements and thereby attenuate hyperalgesia.
- Postoperatively, opioid-sparing regimens including NSAIDs, acetaminophen, gabapentinoids, and regional anesthesia techniques whenever possible are ideal. Duloxetine, a serotonin-norepinephrine reuptake inhibitor (SNRI), and Melatonin, due to its antiinflammatory and neuroprotective properties, may also play a role in reducing hyperalgesia associated with prolonged opioid exposure [49].

As our understanding of the risks involved with different forms of analgesics evolve, guidelines to direct the best multimodal pain control regimens are evolving. The data regarding the best multimodal pain management approach in certain types of surgery is being organized into guidelines, specifically Enhanced Recovery After Surgery (ERAS) guidelines. Use of these guidelines to create more uniform use of multimodal pain management approaches has the potential to improve the administration of perioperative analgesics going forward [50].

Challenges and Considerations

A challenge for effective perioperative analgesia comes from the need for further research into opioid hyperalgesia and the need for better data on regional anesthetic techniques. Currently, the most conclusive data on opioid hyperalgesia is in animal models [9]. There is data to suggest that the phenomenon of opioid-induced hyperalgesia is a real risk, although more large-scale clinical trials to understand the specifics are needed. Additionally, most of the current data regarding the development of OIH is on remifentanil, and more data is needed on other types of opioids [11].

While regional anesthetic techniques provide a promising alternative that may limit the need for opioids, there is a need for more standardized outcome metrics in the research to assess the efficacy of regional techniques [51] as an adjunct for reducing perioperative pain. A review of the current literature shows that some studies use a numerical 1–10 pain score, some use opioid requirement, and some use a visual analogue scale, and the time points at which pain scores were measured postoperatively had wide variation.

Finally, there is likely difficulty in establishing uniform guidelines for multimodal analgesia

approaches across systems due to limitations or variance in resources or practice models.

Future Directions and Research

To develop a more complete understanding of opioid-induced hyperalgesia, future large-scale clinical trials are needed. Specifically, more data is needed on OIH from the use of opioids other than remifentanil. With further research into the types and dosing of opioids that cause OIH, this can help inform clinicians of the best approach for multimodal analgesia techniques that most safely use opioids as an adjunct. As this data evolves, it can help to inform updated ERAS guidelines for optimal perioperative pain control.

References

1. Park R, Mohiuddin M, Arellano R, Pogatzki-Zahn E, Klar G, Gilron I. Prevalence of postoperative pain after hospital discharge: systematic review and meta-analysis. Pain Rep. 2023;8(3):e1075.
2. Lee M, Silverman SM, Hansen H, Patel VB, Manchikanti L. A comprehensive review of opioid-induced hyperalgesia. Pain Physician. 2011;14(2):145–61.
3. Benyamin R, Trescot AM, Datta S, Buenaventura R, Adlaka R, Sehgal N, et al. Opioid complications and side effects. Pain Physician. 2008;11(2 Suppl):S105–20.
4. Duarte DF. Opium and opioids: a brief history. Rev Bras Anestesiol. 2005;55(1):135–46.
5. Williams JT, Ingram SL, Henderson G, Chavkin C, von Zastrow M, Schulz S, et al. Regulation of mu-opioid receptors: desensitization, phosphorylation, internalization, and tolerance. Pharmacol Rev. 2013;65(1):223–54.
6. Paul AK, Smith CM, Rahmatullah M, Nissapatorn V, Wilairatana P, Spetea M, et al. Opioid analgesia and opioid-induced adverse effects: a review. Pharmaceuticals (Basel). 2021;14(11):1091.
7. Hayhurst CJ, Durieux ME. Differential opioid tolerance and opioid-induced hyperalgesia: a clinical reality. Anesthesiology. 2016;124(2):483–8.
8. Celerier E, Laulin JP, Corcuff JB, Le Moal M, Simonnet G. Progressive enhancement of delayed hyperalgesia induced by repeated heroin administration: a sensitization process. J Neurosci. 2001;21(11):4074–80.
9. Celerier E, Rivat C, Jun Y, Laulin JP, Larcher A, Reynier P, Simonnet G. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. Anesthesiology. 2000;92(2):465–72.
10. Salengros JC, Huybrechts I, Ducart A, Faraoni D, Marsala C, Barvais L, et al. Different anesthetic techniques associated with different incidences of chronic post-thoracotomy pain: low-dose remifentanil plus presurgical epidural analgesia is preferable to high-dose remifentanil with postsurgical epidural analgesia. J Cardiothorac Vasc Anesth. 2010;24(4):608–16.
11. Fletcher D, Martinez V. Opioid-induced hyperalgesia in patients after surgery: a systematic review and a meta-analysis. Br J Anaesth. 2014;112(6):991–1004.
12. Heinricher MM, Neubert MJ, Martenson ME, Goncalves L. Prostaglandin E2 in the medial preoptic area produces hyperalgesia and activates pain-modulating circuitry in the rostral ventromedial medulla. Neuroscience. 2004;128(2):389–98.
13. Ossipov MH, Porreca F. Challenges in the development of novel treatment strategies for neuropathic pain. NeuroRx. 2005;2(4):650–61.
14. Mao J, Price DD, Mayer DJ. Thermal hyperalgesia in association with the development of morphine tolerance in rats: roles of excitatory amino acid receptors and protein kinase C. J Neurosci. 1994;14(4):2301–12.
15. Ferrini F, Trang T, Mattioli TA, Laffray S, Del'Guidice T, Lorenzo LE, et al. Morphine hyperalgesia gated through microglia-mediated disruption of neuronal Cl(-) homeostasis. Nat Neurosci. 2013;16(2):183–92.
16. Watkins LR, Maier SF. Immune regulation of central nervous system functions: from sickness responses to pathological pain. J Intern Med. 2005;257(2):139–55.
17. Trujillo KA, Akil H. Opiate tolerance and dependence: recent findings and synthesis. New Biol. 1991;3(10):915–23.
18. Berta T, Qadri Y, Tan PH, Ji RR. Targeting dorsal root ganglia and primary sensory neurons for the treatment of chronic pain. Expert Opin Ther Targets. 2017;21(7):695–703.
19. Hutchinson MR, Zhang Y, Brown K, Coats BD, Shridhar M, Sholar PW, et al. Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of toll-like receptor 4 (TLR4). Eur J Neurosci. 2008;28(1):20–9.
20. Jansen SC, Dahan A. Opioid-induced respiratory depression. BJA Educ. 2024;24(3):100–6.
21. Kosten TR, George TP. The neurobiology of opioid dependence: implications for treatment. Sci Pract Perspect. 2002;1(1):13–20.
22. Prichard D, Norton C, Bharucha AE. Management of opioid-induced constipation. Br J Nurs. 2016;25(10):S4–S5, S8–11.
23. Imam MZ, Kuo A, Ghassabian S, Smith MT. Progress in understanding mechanisms of opioid-induced gastrointestinal adverse effects and respiratory depression. Neuropharmacology. 2018;131:238–55.
24. Nguyen E, Lim G, Ross SE. Evaluation of therapies for peripheral and Neuraxial opioid-induced pruritus based on molecular and cellular discoveries. Anesthesiology. 2021;135(2):350–65.

25. Gupta A, Bah M. NSAIDs in the treatment of postoperative pain. Curr Pain Headache Rep. 2016;20(11):62.
26. Klein M, Andersen LP, Harvald T, Rosenberg J, Gogenur I. Increased risk of anastomotic leakage with diclofenac treatment after laparoscopic colorectal surgery. Dig Surg. 2009;26(1):27–30.
27. Holte K, Andersen J, Jakobsen DH, Kehlet H. Cyclooxygenase 2 inhibitors and the risk of anastomotic leakage after fast-track colonic surgery. Br J Surg. 2009;96(6):650–4.
28. Wheatley BM, Nappo KE, Christensen DL, Holman AM, Brooks DI, Potter BK. Effect of NSAIDs on bone healing rates: a meta-analysis. J Am Acad Orthop Surg. 2019;27(7):e330–e6.
29. Gerriets V, Anderson J, Patel P, Nappe TM. Acetaminophen. In: StatPearls. Treasure Island (FL); 2025.
30. Quintero GC. Review about gabapentin misuse, interactions, contraindications and side effects. J Exp Pharmacol. 2017;9:13–21.
31. Verret M, Lauzier F, Zarychanski R, Perron C, Savard X, Pinard AM, et al. Perioperative use of Gabapentinoids for the management of postoperative acute pain: a systematic review and meta-analysis. Anesthesiology. 2020;133(2):265–79.
32. Bell RF, Kalso EA. Ketamine for pain management. Pain Rep. 2018;3(5):e674.
33. Rosenbaum SB, Gupta V, Patel P, Palacios JL. Ketamine. In: StatPearls. Treasure Island (FL); 2025.
34. Kessler J, Marhofer P, Hopkins PM, Hollmann MW. Peripheral regional anaesthesia and outcome: lessons learned from the last 10 years. Br J Anaesth. 2015;114(5):728–45.
35. Chu R, Umukoro N, Greer T, Roberts J, Adekoya P, Odonkor CA, et al. Intravenous lidocaine infusion for the management of early postoperative pain: a comprehensive review of controlled trials. Psychopharmacol Bull. 2020;50(4 Suppl 1):216–59.
36. Horlocker TT. Complications of spinal and epidural anesthesia. Anesthesiol Clin North Am. 2000;18(2):461–85.
37. Gupta K, Bhandari S, Singhal D, Bhatia PS. Pneumothorax following ultrasound guided supraclavicular brachial plexus block. J Anaesthesiol Clin Pharmacol. 2012;28(4):543–4.
38. Garmon EH, Huecker MR. Topical, local, and regional anesthesia and anesthetics. In: StatPearls. Treasure Island (FL); 2025.
39. El-Boghdadly K, Pawa A, Chin KJ. Local anesthetic systemic toxicity: current perspectives. Local Reg Anesth. 2018;11:35–44.
40. Eldabe S, Buchser E, Duarte RV. Complications of spinal cord stimulation and peripheral nerve stimulation techniques: a review of the literature. Pain Med. 2016;17(2):325–36.
41. Trescot AM. Cryoanalgesia in interventional pain management. Pain Physician. 2003;6(3):345–60.
42. Shin SW, Cho AR, Lee HJ, Kim HJ, Byeon GJ, Yoon JW, et al. Maintenance anaesthetics during remifentanil-based anaesthesia might affect postoperative pain control after breast cancer surgery. Br J Anaesth. 2010;105(5):661–7.
43. Wu L, Huang X, Sun L. The efficacy of N-methyl-D-aspartate receptor antagonists on improving the postoperative pain intensity and satisfaction after remifentanil-based anesthesia in adults: a meta-analysis. J Clin Anesth. 2015;27(4):311–24.
44. Lee SJ, Lee JN. The effect of perioperative esmolol infusion on the postoperative nausea, vomiting and pain after laparoscopic appendectomy. Korean J Anesthesiol. 2010;59(3):179–84.
45. Xuan C, Yan W, Wang D, Mueller A, Ma H, Wang J. Effect of preemptive acetaminophen on opioid consumption: a meta-analysis. Pain Physician. 2021;24(2):E153–E60.
46. Chen YK, Boden KA, Schreiber KL. The role of regional anaesthesia and multimodal analgesia in the prevention of chronic postoperative pain: a narrative review. Anaesthesia. 2021;76(Suppl 1):8–17.
47. Guignard B, Bossard AE, Coste C, Sessler DI, Lebrault C, Alfonsi P, et al. Acute opioid tolerance: intraoperative remifentanil increases postoperative pain and morphine requirement. Anesthesiology. 2000;93(2):409–17.
48. Koppert W, Sittl R, Scheuber K, Alsheimer M, Schmelz M, Schuttler J. Differential modulation of remifentanil-induced analgesia and postinfusion hyperalgesia by S-ketamine and clonidine in humans. Anesthesiology. 2003;99(1):152–9.
49. Song L, Wu C, Zuo Y. Melatonin prevents morphine-induced hyperalgesia and tolerance in rats: role of protein kinase C and N-methyl-D-aspartate receptors. BMC Anesthesiol. 2015;15:12.
50. Adamina M, Kehlet H, Tomlinson GA, Senagore AJ, Delaney CP. Enhanced recovery pathways optimize health outcomes and resource utilization: a meta-analysis of randomized controlled trials in colorectal surgery. Surgery. 2011;149(6):830–40.
51. Pushpanathan E, Setty T, Carvalho B, Sultan P. A systematic review of postoperative pain outcome measurements utilised in regional anesthesia randomized controlled trials. Anesthesiol Res Pract. 2018;2018:9050239.

28 Managing Side Effects of Analgesic Medications in Perioperative Pain Management

Geoffrey D. Panjeton and Hess Panjeton

Introduction

The perioperative period poses a significant challenge for patients, primarily due to the anticipation of postoperative pain, which approximately 80% of patients experience [1]. This prevalent issue has driven extensive research into optimizing perioperative pain management strategies. The cornerstone of these strategies is the administration of a multimodal regimen that employs a combination of medications, each acting through different mechanisms to provide effective pain relief. This approach aims not only to enhance the efficacy of pain control but also to minimize the side effects and potential adverse reactions associated with any single class of medications.

Effective pain management is paramount in perioperative care as it significantly influences the patient's comfort and recovery trajectory. While analgesic medications are potent in alleviating pain, their use is often accompanied by a spectrum of side effects that can compromise patient outcomes. These range from mild discomforts, such as nausea and dizziness, to more severe complications, including organ damage and dependency risks, which underscore the critical need for meticulous management of these medications.

To address these challenges, it is crucial to recognize and proactively consider the potential side effects of analgesic drugs. This involves a comprehensive approach that starts with a thorough assessment of the patient's medical history and specific health conditions that might amplify the risk of adverse effects. Tailoring the analgesic regimen not only to the surgical procedure but also to the individual's unique health profile is a strategy that can significantly mitigate the risk of complications.

Furthermore, ongoing monitoring throughout the perioperative period is essential to adjust treatment plans promptly and effectively based on the patient's response to medications. Education and communication with patients about the potential side effects of their pain management plan are equally important to ensure they are well-informed and engaged in their care process.

By integrating these strategies, healthcare providers can optimize pain management protocols that enhance patient comfort and facilitate quicker recoveries while minimizing the side effects associated with pain medications. This chapter delves deeper into the various types of analgesics used in perioperative care, their mechanisms of action, potential side effects, and strategies for managing these effects to ensure comprehensive patient care.

G. D. Panjeton (✉)
Department of Anesthesiology and Critical Care, Saint Louis University, St. Louis, MO, USA

H. Panjeton
Department of Anesthesiology, Washington University in Saint Louis, St. Louis, MO, USA

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_28

Background and Current Understanding

Analgesics, from opioids to nonsteroidal antiinflammatory drugs (NSAIDs), play a pivotal role in pain management. The growing understanding of the implications of higher doses and prolonged use of analgesic medications has shifted the focus toward balanced multimodal pain management. Current understanding underscores a need for judicious use of analgesics, balancing efficacy with safety.

Clinical Applications and Techniques

Managing side effects involves a multifaceted approach:

1. Patient Assessment: Detailed assessment to identify risks related to comorbid conditions, such as chronic kidney disease, obstructive sleep apnea, liver disease, etc.
2. Choice of Analgesics: Selecting appropriate medication based on patient history and type of surgery.
3. Dosing Strategies: Implementing the lowest effective dose for the shortest duration.
4. Monitoring: Regular monitoring for efficacy and early detection and management of side effects.

NSAIDs

NSAIDs often constitute the foundation of multimodal pain management strategies due to their effectiveness in reducing inflammation and pain by antagonizing the production of prostaglandins via inhibition of cyclooxygenase (COX) enzymes [2]. However, they must be used cautiously due to potential side effects such as gastrointestinal bleeding and nephrotoxicity [2]. Interestingly, despite the theoretical risk of increased bleeding associated with NSAID use, extensive reviews have not corroborated this concern, underscoring the importance of evidence-based practice. There is some evidence that reflects patients taking NSAIDs in the perioperative period experienced a higher incidence of pseudarthrosis, hardware failure, and revision surgery in spine and orthopedic surgeries requiring the implantation of hardware [3].

Gabapentinoids

Gabapentin and pregabalin, initially developed as anticonvulsants, are mainstays of managing chronic neuropathic pain, and more recently, their use in the management of acute neuropathic and nociceptive pain in the postoperative setting has increased [4]. Their potential effectiveness in reducing postoperative nausea and vomiting and slight opioid-sparing effects offers a benefit, yet further investigation is needed to clarify a precise dosing regimen and identify particular patient groups that would benefit the most [4]. Additionally, the potential benefits of gabapentinoids must be weighed against possible side effects such as dizziness and visual disturbances, which can affect patient recovery [4].

Duloxetine

Duloxetine, primarily known for its use in managing depression and anxiety, plays a role in controlling chronic musculoskeletal and neuropathic pain conditions like fibromyalgia and diabetic neuropathy. As a selective serotonin and norepinephrine reuptake inhibitor (SNRI), it acts centrally at the dorsal horn of the spinal cord to increase reuptake of norepinephrine, dopamine, and serotonin, which in turn enhances inhibition of pain transmission [5]. There are also additional mechanisms proposed, such as central pain modulation at the prefrontal cortex and peripheral blocking of the Neuronal Nav1.7 Na + channel to reduce hyperalgesia [5]. Meta-analysis has reflected improved postoperative pain scores and reduced opioid consumption; however, patients did report increased dry mouth, headache, and somnolence [5].

Common Analgesics: Mechanism, Site of Metabolism, and Side Effects [6]

1. Acetaminophen
   - Mechanism of Action: Inhibits prostaglandin synthesis in the central nervous system (CNS) and peripherally blocks pain impulse generation
   - Metabolism: Liver
   - Side Effects: Liver damage, nausea, rash, and rare allergic reactions
2. Baclofen
   - Mechanism of Action: Acts on GABA receptors in the spinal cord, inhibiting nerve reflexes
   - Metabolism: Primarily in the liver
   - Side Effects: Drowsiness, dizziness, weakness, fatigue
3. Buprenorphine
   - Mechanism of Action: Partial opioid agonist at mu receptors; antagonist at kappa receptors
   - Metabolism: Liver (CYP3A4)
   - Side Effects: Nausea, dizziness, respiratory depression, dependency
4. Carisoprodol
   - Mechanism of Action: Blocks interneuronal activity and depresses polysynaptic neurons in the spinal cord and brain
   - Metabolism: Liver
   - Side Effects: Drowsiness, dizziness, headache, and dependency
5. Celecoxib
   - Mechanism of Action: Selective COX-2 inhibitor, reduces prostaglandins synthesis
   - Metabolism: Liver (CYP2C9)
   - Side Effects: Gastrointestinal upset, cardiovascular risk, renal impairment
6. Corticosteroids (e.g., Dexamethasone, Betamethasone)
   - Mechanism of Action: Modulates gene expression to produce antiinflammatory and immunosuppressive effects
   - Metabolism: Liver
   - Side Effects: Immunosuppression, hyperglycemia, osteoporosis, mood changes
7. Cyclobenzaprine
   - Mechanism of Action: Acts at the brain stem to reduce tonic somatic motor activity
   - Metabolism: Liver
   - Side Effects: Drowsiness, dry mouth, dizziness
8. Gabapentin
   - Mechanism of Action: Binds to voltage-gated calcium channels, reducing excitatory neurotransmitter release
   - Metabolism: Not metabolized, excreted unchanged by kidneys
   - Side Effects: Dizziness, fatigue, peripheral edema
9. Ketamine
   - Mechanism of Action: NMDA receptor antagonist
   - Metabolism: Liver
   - Side Effects: Dissociation, hallucinations, increased blood pressure, nausea
10. Ketorolac
    - Mechanism of Action: Non-selective COX inhibitor, reducing prostaglandin synthesis
    - Metabolism: Liver
    - Side Effects: Gastrointestinal bleeding, renal impairment, dizziness
11. Lidocaine
    - Mechanism of Action: Sodium channel blocker, inhibits nerve impulse conduction
    - Metabolism: Liver
    - Side Effects: Numbness, tingling, cardiovascular and CNS disturbances
12. Metaxalone
    - Mechanism of Action: Unknown, thought to involve central nervous system depression
    - Metabolism: Liver
    - Side Effects: Drowsiness, dizziness, headache, nausea
13. Methocarbamol
    - Mechanism of Action: Central muscle relaxant with unknown mechanism
    - Metabolism: Liver
    - Side Effects: Drowsiness, dizziness, lightheadedness, nausea

14. Naloxone
    - Mechanism of Action: Opioid antagonist, competitively binds to opioid receptors
    - Metabolism: Liver
    - Side Effects: Withdrawal symptoms in opioid-dependent individuals
15. NSAIDs (e.g., Ibuprofen, Aspirin, Naproxen)
    - Mechanism of Action: Non-selective COX inhibitors, reducing prostaglandin synthesis
    - Metabolism: Liver
    - Side Effects: Gastrointestinal bleeding, renal impairment, increased cardiovascular risk
16. Opioids (e.g., Fentanyl, Hydrocodone, Oxycodone)
    - Mechanism of Action: Agonists at opioid receptors in the brain, altering the perception of and response to pain
    - Metabolism: Primarily in the liver
    - Side Effects: Nausea, vomiting, constipation, respiratory depression, dependency, and tolerance
17. Pregabalin
    - Mechanism of Action: Binds to calcium channels reducing neurotransmitter release
    - Metabolism: Minimal; excreted largely unchanged by kidneys
    - Side Effects: Dizziness, sleepiness, blurred vision, weight gain
18. Tizanidine
    - Mechanism of Action: Agonist at alpha-2 adrenergic receptors, likely reducing nociceptive neurotransmitters
    - Metabolism: Liver
    - Side Effects: Hypotension, dry mouth, drowsiness, dizziness
19. Tramadol
    - Mechanism of Action: Weak opioid receptor agonist and inhibitor of serotonin and norepinephrine reuptake
    - Metabolism: Liver (CYP2D6 and CYP3A4)
    - Side Effects: Nausea, dizziness, constipation, dependency, seizure risk

Evidence-Based Practices

Recent research highlights strategies like multimodal analgesia, which combines different classes of analgesics to reduce individual drug doses, thereby minimizing side effects. Studies also emphasize the role of non-pharmacological methods like cold therapy and relaxation techniques in adjunct to pharmacotherapy.

Challenges and Considerations

Challenges include:

- Varied Patient Responses: Individual differences in metabolism and sensitivity.
- Opioid-Related Side Effects: Constipation, nausea, respiratory depression, and addiction potential.
- NSAID-Related Issues: Gastrointestinal complications and renal impairment.
- Special considerations involve managing chronic pain patients and those with a history of substance abuse.

Case Studies or Clinical Scenarios

Case 1: Patient with Chronic Kidney Disease Unable to Take NSAIDs

- Background: A 58-year-old patient with chronic kidney disease (CKD) stage 3 requires pain management for osteoarthritis.
- Challenge: NSAIDs, commonly used for arthritis pain, are contraindicated due to their nephrotoxic potential, which could exacerbate kidney dysfunction.
- Approach: The treatment plan focuses on acetaminophen for pain relief, complemented by physical therapy and local treatments like capsaicin cream to avoid systemic side effects. Additional interventional-based approaches utilizing common regional anesthesia procedures can be beneficial as well.

Case 2: Patient with Obstructive Sleep Apnea and Limited Opioid Tolerance

- Background: A 45-year-old patient with obstructive sleep apnea (OSA) is postoperative from abdominal surgery, requiring pain management.
- Challenge: Opioids may cause sedation and further depress respiration, which can be severe in OSA patients.
- Approach: Utilize a multimodal analgesia approach, including low-dose opioids combined with acetaminophen, NSAIDs, and nonpharmacological interventions like ice application and relaxation techniques to minimize opioid use. Additional interventional-based approaches utilizing common regional anesthesia procedures can be beneficial as well.

Case 3: Elderly Patient with Increased Sensitivity to Muscle Relaxants

- Background: An 82-year-old patient needs pain management for acute back spasms.
- Challenge: Elderly patients are often sensitive to medications like muscle relaxants and gabapentin, which can cause excessive sedation and increase the risk of falls.
- Approach: Start with a very low dose of a muscle relaxant, closely monitor for side effects, and prioritize safer alternatives such as physical therapy and localized heat therapy to manage pain and muscle tension without heavy reliance on pharmacological interventions.

Case 4: Postoperative Pain Management in a Patient with History of Substance Use Disorder

- Background: A 37-year-old patient is recovering from knee replacement surgery and has a history of opioid addiction, now in remission.
- Challenge: Managing postoperative pain effectively while minimizing the risk of relapse into substance use.
- Approach: Implement a nonopioid-based pain management strategy, including NSAIDs, acetaminophen, and local anesthetics including continuous peripheral nerve block infusions.

Future Directions and Research

- Non-Pharmacological Interventions: Exploring the role of alternative therapies in pain management—incorporating acupuncture, for example, intra and postoperatively.
- Studying efficacy—increasing focus on patient-reported outcomes as opposed to more subjective pain scores in studying pain management efficacy.
- Personalized pain care—exploring the role of pharmacogenomics in optimizing pain medication management.

Key Takeaways

- Balancing pain relief while managing side effects is integral to optimizing perioperative care.
- Multimodal analgesia offers an effective approach to minimize side effects.
- Patient-specific strategies are essential, considering individual risk factors and responses.
- Regular monitoring and patient education are vital in managing side effects.
- Further developing ongoing research and innovative approaches will further improve analgesic use in perioperative care.

References

1. Gan TJ, Habib AS, Miller TE, White W, Apfelbaum JL. Incidence, patient satisfaction, and perceptions of post-surgical pain: results from a US national survey. Curr Med Res Opin. 2014;30(1):149–60.
2. Martinez L, Ekman E, Nakhla N. Perioperative opioid-sparing strategies: utility of conventional NSAIDs in adults. Clin Ther. 2019;41(12):2612–28.

3. Lindsay SE, Philipp T, Ryu WHA, Wright C, Yoo J. Nonsteroidal anti-inflammatory drugs in the acute post-operative period are associated with an increased incidence of Pseudarthrosis, hardware failure, and revision surgery following single-level spinal fusion. Spine (Phila Pa 1976). 2023;48(15):1057–63.
4. Verret M, Lauzier F, Zarychanski R, Perron C, Savard X, Pinard AM, et al. Perioperative use of Gabapentinoids for the Management of Postoperative Acute Pain: a systematic review and meta-analysis. Anesthesiology. 2020;133(2):265–79.
5. Govil N, Arora P, Parag K, Tripathi M, Garg PK, Goyal T. Postoperative acute pain management with duloxetine as compared to placebo: a systematic review with meta-analysis of randomized clinical trials. Pain Pract. 2023;23(7):818–37.
6. Brenner G, Rathmell JP, Massachusetts General Hospital. The Massachusetts General Hospital handbook of pain management. 4th ed. Philadelphia: Wolters Kluwer; 2021. p. 643.

Further Reading

1. Acute Postoperative Pain Management. British Journal of Surgery, Oxford Academic, https://academic.oup.com/bjs/article/107/2/e70/6120927.
2. Chen Q, Chen E, Qian X. A narrative review on perioperative pain management strategies in enhanced recovery pathways—the past, present and future. J Clin Med. 2021;10(12) https://doi.org/10.3390/jcm10122568.

29

Nerve Injuries and Neuropathic Pain: Focuses on the Identification and Treatment of Nerve-Related Pain Issues

Rene Przkora and Daniel Jose Lopez

Introduction

Nerve injuries are a significant source of both acute and chronic pain syndromes, often leading to debilitating conditions that severely impact patients' quality of life. Acute pain is typically a direct result of tissue damage, resolving as the injury heals. However, chronic pain persists beyond the normal healing period, often due to maladaptive neural changes following the injury. Nerve injuries can result from various etiologies, including trauma, surgery, or diseases affecting the nervous system, with chronic pain syndromes like neuropathic pain frequently emerging postinjury. According to the International Association for the Study of Pain (IASP), "neuropathic pain is caused by a lesion or disease of the somatosensory nervous system" [1].

Background and Current Understanding

The understanding and medical management of nerve injuries and their consequent pain syndromes require a comprehensive approach. These injuries can occur due to a wide range of causes, including mechanical compression, laceration, or chemical damage. In addition to traumatic events, iatrogenic injuries ranging from regional anesthesia techniques to surgical procedures are also significant contributors [2]. For instance, surgical procedures, especially those involving the spine, joints, or peripheral nerves, can inadvertently damage nerves, leading to acute pain in the postoperative setting or persisting chronically, resulting in various pain syndromes. One such syndrome, neuropathic pain, will be covered in this chapter.

The earliest classification of nerve injuries by Seddon and Sunderland remains widely used, dividing injuries into neuropraxia, axonotmesis, and neurotmesis [3]. Neuropraxia is a mild injury with temporary myelin loss but intact axons, common in entrapment neuropathies, and usually resolves within weeks. Axonotmesis involves axonal damage but preserved connective tissues, allowing for regeneration, typically seen in crush and stretch injuries. Neurotmesis, the most severe, involves extensive damage to axons, myelin, and connective tissues, often from severe trauma, and requires surgical repair for recovery.

The pathophysiology of acute and chronic pain following nerve injury involves complex mechanisms. In a normal state of pain processing, pain signals are transmitted from the periphery to the central nervous system (CNS) via nociceptors. It includes signal transduction at peripheral recep-

R. Przkora (✉) · D. J. Lopez
Division of Pain Medicine, Department of Anesthesiology, University of Florida College of Medicine, Gainesville, FL, USA
e-mail: rprzkora@anest.ufl.edu

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_29

tors, signal conduction along peripheral nerves, modulation of pain at the spinal cord, perception of pain at the supraspinal level, and the accompanying sensations, emotional responses, and affective state [4]. After nerve injury, however, there is a notable increase in spontaneous activity from damaged neurons, abnormal excitability, and sensitization of pain pathways both at the site of injury and in the CNS. Central sensitization refers to an increased responsiveness of neurons within the CNS, which leads to an amplification of pain signals. Peripheral sensitization involves changes in the primary afferent neurons, making them more responsive to stimuli. Additionally, inflammatory responses and immune cell activation at the injury site can exacerbate pain by releasing proinflammatory cytokines and other mediators that sensitize nociceptors.

Clinical Applications

Accurately diagnosing peripheral nerve injuries relies on a thorough patient history and physical examination. Patients often present with sensory disturbances (e.g., numbness, tingling), motor deficits (e.g., weakness, paralysis), or neuropathic pain (e.g., burning, shooting pain) localized to the distribution of the affected nerve. These objective and subjective findings apply to both acute and chronic pain following nerve injury; however, this may be difficult to identify postoperatively as patients are recovering from anesthetics and with continued analgesics [5]. Furthermore, typical postoperative inflammation and healing can produce similar symptoms, highlighting the importance of distinguishing between these physical findings. Physical examination may reveal changes in muscle tone, reflexes, and strength. Specific clinical tests, such as Tinel's sign (tapping over the nerve to elicit tingling) or Phalen's test (maintaining wrist flexion to reproduce symptoms), can help localize the injury.

To confirm a diagnosis of nerve injury, various diagnostic studies can be employed. Electromyography and nerve conduction studies are commonly used to assess the electrical activity of muscles and the speed of nerve signal transmission, respectively. Imaging studies, such as magnetic resonance imaging (MRI) or high-resolution ultrasound, can visualize structural abnormalities in nerves and surrounding tissues [5]. It should be noted, however, that these diagnostic tests have limitations and criticisms regarding their precision in diagnosing peripheral nerve injuries. Additionally, quantitative sensory testing assesses sensory nerve function and can detect changes in pain thresholds indicative of neuropathic pain.

Treatment for neuropathic pain syndromes secondary to nerve injury includes both conservative and interventional approaches. Conservative treatments involve pharmacologic therapies such as nonsteroidal antiinflammatory drugs, anticonvulsants (e.g., gabapentin, pregabalin), and antidepressants (e.g., amitriptyline, duloxetine) which target neuropathic pain mechanisms. Interventional options include nerve blocks, epidural injections, and neuromodulation techniques like spinal cord stimulation (SCS) and peripheral nerve stimulation (PNS). The US Food and Drug Administration has approved several devices for neuromodulation, such as SCS systems, which deliver electrical impulses to the spinal cord to modulate pain signals [6]. While these treatments are effective in providing analgesia for patients with neuropathic pain, they are palliative and do not address the underlying nerve regeneration.

Evidence-Based Practices

The effectiveness of various treatment approaches for postnerve injury analgesia and rehabilitation has been evaluated in numerous studies. Multimodal pain treatment algorithms, which combine pharmacologic, interventional, and physical therapies, are often recommended to address the multifaceted nature of neuropathic pain. Evidence suggests that combining these modalities can provide synergistic pain relief and improve functional outcomes. For instance, the combination of pharmacologic agents targeting different pain pathways has been shown to

enhance pain control and minimize side effects compared to monotherapy.

Neuromodulation strategies have gained significant attention for treating neuropathic pain. SCS and PNS are well-documented techniques that involve the use of electrical impulses to modulate pain pathways. SCS has been particularly effective in patients with chronic pain conditions like postsurgical chronic neuropathic pain and complex regional pain syndrome [6]. Clinical studies have demonstrated significant pain reduction and improved quality of life in patients undergoing SCS. Similarly, PNS has shown promise in treating pain syndromes by directly targeting peripheral nerves, with evidence supporting its efficacy in reducing pain intensity and improving functional outcomes.

Challenges and Considerations

Preventing nerve injuries in the perioperative setting poses significant challenges. Iatrogenic nerve injuries can result from direct trauma during surgery, compression from improper positioning, or ischemia due to prolonged tourniquet use. Implementing preventive measures such as careful surgical techniques, appropriate patient positioning, and intraoperative neuromonitoring, can reduce the incidence of nerve injuries [7]. However, these measures can be difficult to implement consistently and may involve additional costs and logistical challenges.

Delayed diagnosis of nerve injuries can lead to prolonged pain, disability, and poor clinical outcomes. Early identification and intervention are crucial for preventing chronic pain syndromes and facilitating recovery. Delays can occur due to a lack of awareness among healthcare providers, variability in the presentation of nerve injuries, and the absence of definitive diagnostic tests. Prompt and accurate diagnosis is essential for initiating appropriate treatment and minimizing the risk of chronic neuropathic pain.

Intraoperative neuromonitoring involves the use of electrophysiological techniques to monitor the functional integrity of neural structures during surgery. This can help detect and prevent iatrogenic nerve injuries in real time [8]. Intraoperative neuromonitoring techniques include somatosensory evoked potentials (SSEPs), motor evoked potentials (MEPs), and electromyography [9]. While intraoperative neuromonitoring has been shown to reduce the risk of nerve injuries, its implementation can be challenging due to factors such as the cost of equipment, the need for specialized personnel, and the potential for interference with the surgical field. Despite these challenges, it remains a valuable tool for enhancing patient safety during high-risk surgical procedures.

Future Direction and Research

Drug repurposing involves finding new therapeutic uses for existing medications [10]. This approach can expedite the availability of treatments for neuropathic pain by leveraging the known safety profiles of these drugs. Several medications are currently being investigated for their potential to alleviate neuropathic pain, including ketamine, botulinum toxin, and cannabinoids. Ketamine, an N-methyl-D-aspartate receptor antagonist, has shown efficacy in treating refractory neuropathic pain by modulating glutamatergic transmission and reducing central sensitization. Botulinum toxin, traditionally used for muscle spasticity, has been found to alleviate pain by inhibiting the release of pain mediators from nerve endings. Cannabinoids, derived from cannabis, are being explored for their analgesic properties in neuropathic pain, targeting both peripheral and central pain pathways.

Clinical trials investigating neuromodulation for spinal cord injury (SCI) patients are ongoing, exploring the potential of these techniques to alleviate pain and improve neurological function [11]. Studies are also examining the combination of neuromodulation with regenerative therapies, such as stem cell transplantation, to further enhance functional recovery.

Epidural electrical stimulation (EES) is an emerging therapeutic approach for SCI patients [11]. EES involves the application of electrical currents to the spinal cord to facilitate functional

recovery and pain relief. Recent studies have demonstrated that EES can promote motor recovery, improve autonomic functions, and reduce pain in SCI patients. Research is ongoing to optimize stimulation protocols, understand the underlying mechanisms, and evaluate long-term outcomes. EES represents a promising avenue for enhancing the quality of life and functional independence of SCI patients.

References

1. IASP: IASP Terminology. Neuropathic pain. https://www.iasp-pain.org (2011). Accessed 1 June 2024.
2. Hogan QH. Pathophysiology of peripheral nerve injury during regional anesthesia. Reg Anesth Pain Med. 2008;33(5):435–41. https://doi.org/10.1016/j.rapm.2008.03.002.
3. Seddon HJ. A classification of nerve injuries. Br Med J. 1942;2(4260):237–9.
4. Kitahata LM. Pain pathways and transmission. Yale J Biol Med. 1993;66:437–42.
5. John A, Rossettie S, Rafael J, Cox C, Ducic I, Mackay B. Assessment of motor function in peripheral nerve injury and recovery. Orthop Rev (Pavia). 2022;14(3):37578. https://doi.org/10.52965/001c.37578.
6. Bates D, Schultheis BC, Hanes MC, Jolly SM, Chakravarthy KV, Deer TR, et al. A comprehensive algorithm for management of neuropathic pain. Pain Med. 2019;20(suppl 1):S2–S12. https://doi.org/10.1093/pm/pnz075.
7. Bouyer-Ferullo S. Preventing perioperative peripheral nerve injuries. AORN J. 2013;97(1):110–24.e9. https://doi.org/10.1016/j.aorn.2012.10.013.
8. Gonzalez AA, Jeyanandarajan D, Hansen C, Zada G, Hsieh PC. Intraoperative neurophysiological monitoring during spine surgery: a review. Neurosurg Focus. 2009;27(4):E6. https://doi.org/10.3171/2009.8.FOCUS09150.
9. Wong AK, Shils JL, Sani SB, Byrne RW. Intraoperative neuromonitoring. Neurol Clin. 2022;40(2):375–89. https://doi.org/10.1016/j.ncl.2021.11.010.
10. Attal N, Bouhassira D, Colvin L. Advances and challenges in neuropathic pain: a narrative review and future directions. Br J Anaesth. 2023;131(1):79–92. https://doi.org/10.1016/j.bja.2023.04.021.
11. Lam CM, Latif U, Sack A, Govindan S, Sanderson M, Vu DT, et al. Advances in spinal cord stimulation. Bioengineering (Basel). 2023;10(2):185. https://doi.org/10.3390/bioengineering10020185.

Part IX

Future Perspectives in Perioperative Pain Management

30 Advances in Pharmacology: Looks at Emerging Pharmaceutical Approaches to Pain Management

Anjali H. Patel, Mathew Warth, and Vinita Singh

Introduction

Advances in perioperative pain management increasingly focus on minimizing opioid exposure while maintaining effective analgesia. Rising rates of opioid-related adverse events, particularly in older adults and patients with multiple comorbidities, underscore the need for safer pharmacologic strategies. Recent developments—such as the FDA approval of suzetrigine, a selective NaV1.8 inhibitor that delivers targeted peripheral analgesia without central nervous system side effects, and the expanded perioperative use of buprenorphine, a partial μ-opioid receptor agonist with a ceiling effect on respiratory depression—represent important steps forward. Investigational agents like biased μ-opioid receptor ligands offer the potential to preserve analgesia while further reducing sedation and respiratory depression, though widespread clinical adoption is pending.

This chapter reviews the pharmacologic profiles, clinical evidence, and perioperative roles of these agents, with the goal of informing more individualized, safer, and evidence-based pain management pathways.

Background and Current Understanding

Pain management has evolved from the use of herbal remedies in ancient civilizations to complex multimodal regimens shaped by pharmacologic innovation, societal change, and clinical observation. Opioids remain a cornerstone for moderate-to-severe perioperative pain but are increasingly limited by risks of sedation, respiratory depression, tolerance, and dependence. In older adults, these adverse effects can be particularly pronounced, with sedation adding to fall risk and postoperative delirium. Nonopioid agents—such as nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen—are effective in many contexts and have favorable safety profiles, but they may not provide sufficient analgesia for high-intensity surgical pain.

The limitations of traditional options have prompted the search for analgesics that maintain efficacy while reducing harm. Buprenorphine, widely used in opioid use disorder and chronic pain management, offers sustained analgesia with a lower risk of respiratory compromise [1,

A. H. Patel
Mercer University, Macon, GA, USA
e-mail: Anjali.H.Patel@live.mercer.edu

M. Warth
Medical College of Georgia, Augusta, GA, USA
e-mail: MWARTH@augusta.edu

V. Singh (✉)
Department of Anesthesiology, Emory University School of Medicine, Atlanta, GA, USA
e-mail: Vinita.singh@emory.edu

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6_30

2]. Suzetrigine, recently FDA-approved, provides peripherally selective sodium channel blockade, potentially avoiding central opioid-related side effects altogether [3]. Biased μ-opioid receptor ligands, though still investigational, aim to selectively activate G-protein signaling while minimizing β-arrestin–mediated adverse events [4]. Together, these agents represent a shift toward mechanism-driven, opioid-sparing strategies in perioperative care.

Understanding the pharmacologic properties of these emerging agents is essential before considering their clinical application. The following section reviews the mechanisms of action, pharmacokinetic profiles, and dosing parameters for suzetrigine, buprenorphine, and oliceridine, providing a foundation for interpreting subsequent clinical evidence.

Pharmacology: Suzetrigine, Buprenorphine, and Oliceridine

Suzetrigine (Journavx, VX548): NaV1.8 Inhibitor

Mechanism of Action

Suzetrigine is a peripherally acting, selective NaV1.8 voltage-gated sodium channel inhibitor. NaV1.8 channels are expressed predominantly in nociceptive sensory neurons, where they play a key role in pain signal transmission [5]. By selectively blocking these channels, suzetrigine reduces nociceptive signaling without affecting motor or central nervous system sodium channels, thereby avoiding sedation, respiratory depression, and addiction risk associated with μ-opioid receptor activation [5]. It is approved by the Food and Drug Administration to treat moderate-to-severe acute pain in adults with up to 14 days of treatment [6, 7].

Pharmacokinetics

- *Onset of Action*: ~2 h (oral) [8].
- *Maximum Concentration/Time to Reach Maximum Concentration (Tmax/Cmax:)*: Reached within 2–4 h after a 100 milligram (mg) loading dose (0.62 micrograms per milliliter) [8]
- *Duration of Action*: ~12 h; dosed every 12 h for continued effect
- *Metabolism/Elimination*: Hepatically metabolized via cytochrome P (CYP) 3A; avoid use with strong CYP3A inhibitors (e.g., ketoconazole, grapefruit juice) [8]
- *Dosing Recommendations*:
  - Loading dose: 100 mg orally once (fasted)
  - Maintenance: 50 mg every 12 h
  - May reduce to 50 mg once daily after 4 doses if needed
  - FDA-approved only for short-term use (≤14 days) [8]

Clinical Summary

Suzetrigine offers an opioid-sparing analgesic option for postoperative patients, particularly those at risk for respiratory depression or central side effects. Its peripherally selective action makes it attractive for elderly and medically complex patients, though its role is currently limited to short-term pain control [7–9].

Buprenorphine: Partial μ-Opioid Receptor Agonist/κ-Antagonist

Mechanism of Action

Buprenorphine is a high-affinity partial agonist at the μ-opioid receptor and antagonist at the κ-opioid receptor. This profile provides potent analgesia with a ceiling effect on respiratory depression, reducing overdose risk [10]. Its slow dissociation from μ-receptors and long elimination half-life prolong analgesic duration. Antagonism at κ-receptors may also contribute to mood stabilization and reduction of dysphoria and thereby reduce the risk of misuse compared to full agonists. Buprenorphine's high receptor affinity can competitively block full μ-opioid agonists, necessitating careful perioperative opioid planning (Fig. 30.1).

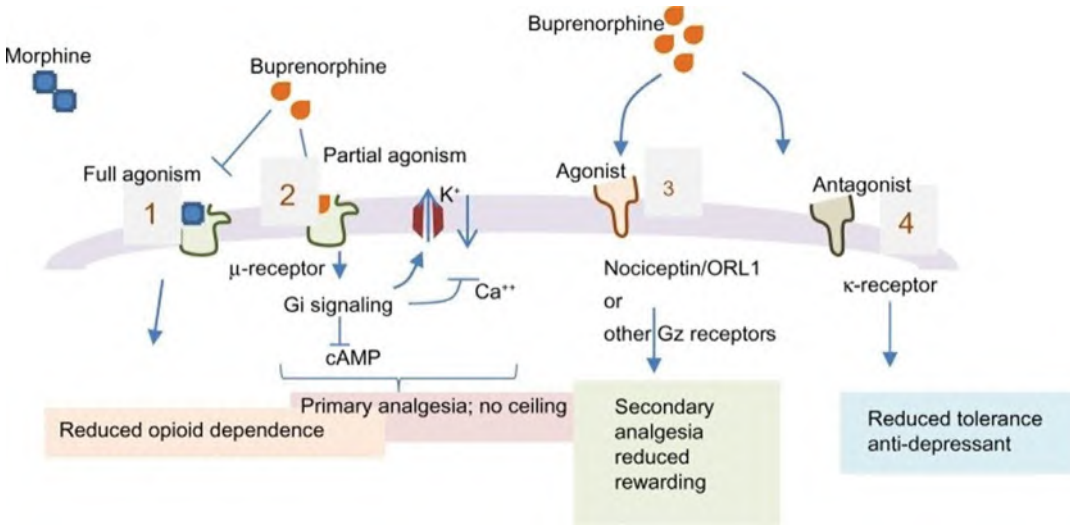


Fig. 30.1 Mechanism of action for buprenorphine [21]. (Originally published by and used with permission from Dove Medical Press Ltd) [11]

Pharmacokinetics

- *Onset*:
  - *Sublingual (SL)*: ~30 min
  - *Transdermal*: ~12–24 h (transdermal)
  - *IV/IM*: ~15 min
- *Peak Bioavailability with Oral/Transdermal*: Up to 65% (buccal), 100% (transdermal)
- *Tmax/Cmax*:
  - Sublingual: Tmax ~45 min, Cmax levels consistent with effective analgesia
  - Intravenous (IV)/intramuscular (IM): Cmax ~14 nanograms/mL at ~4 h
- *Half-life*: Elimination half-life averages 37 h (range 20–70 h)
- *Duration*: Up to 24 h of analgesia per dose
- *Metabolism*: Primarily hepatic via CYP3A4 and CYP2C8 to norbuprenorphine; norbuprenorphine undergoes glucuronidation by UDP-glucuronosyltransferases (UGT); excreted in bile and urine
- *Dosing*:
  - *Sublingual film*: 75 micrograms (mcg), 150 mcg, 300 mcg, 450 mcg, 600 mcg, 750 mcg, and 900 mcg doses for chronic pain/sublingual maintenance. Frequency: every 8–12 h
  - *Sublingual tablets*: 2 mg and 8 mg strengths, available in combination with naloxone, 0.5 and 2 mg respectively, (suboxone = buprenorphine with naloxone in 4 to 1 ratio)
  - *Transdermal patch*: 5 mcg/h, 7.5 mcg/h, 10 mcg/h, 15 mcg/h, and 20 mcg/h doses, comes as extended release, replaced every 7 days
  - *IV/IM (acute pain)*: 0.3 mg/mL injection solution for IM use. Titrate cautiously; consider existing formulation strengths and patient tolerance
  - *Other parenteral*: 100 mg/0.5 mL and 300 mg/1.5 mL-extended-release subcutaneous injection [2, 12, 12]
- *Perioperative dosing guidance*—Kohan et al. [13]
  - *≤4 mg/day sublingual*: Continue without dose change; supplemental opioids are usually effective at standard doses
  - *4–12 mg/day*: Continue; consider dividing total daily dose into 2–3 doses for improved analgesic coverage
  - *>12 mg/day*: Continue; if high analgesic needs are anticipated, reduce to 12–16 mg/day 2–3 days preoperatively or split into 3–4 doses daily
  - *Acute postoperative pain*: Supplement with high-affinity full μ-opioid agonists (e.g.,

hydromorphone, fentanyl); anticipate higher opioid requirements due to receptor competition
  - *Multimodal analgesia*: Strongly recommended—incorporate regional anesthesia, acetaminophen, NSAIDs, gabapentinoids, ketamine, and other adjuvants when possible
- *Key Clinical Considerations*:
  - High μ-receptor affinity may diminish the analgesic effect of concurrently administered full opioid agonists.
  - Dividing the buprenorphine dose can improve its shorter-duration analgesic component without compromising stability in patients with opioid use disorder (OUD).
  - Routine perioperative discontinuation is discouraged due to increased risk of withdrawal, uncontrolled pain, and OUD relapse.
  - Sedation remains a potential concern in older adults, especially when combined with other CNS depressants.

Clinical Summary

Buprenorphine offers safe and prolonged analgesia for patients with opioid tolerance, OUD, or chronic pain, with lower risk of respiratory compromise. For most patients, particularly those on ≤16 mg/day, perioperative continuation of buprenorphine with a multimodal analgesic approach provides safe, stable pain control while mitigating withdrawal and relapse risk. Its high μ-receptor affinity and unique pharmacology necessitate thoughtful perioperative planning, including strategies to address receptor competition. Supplemental opioids, if required, should be carefully selected and monitored [1, 12, 13].

Oliceridine (Olinvyk, TRV130): G-Protein Biased μ-Opioid Receptor Agonist

Mechanism of Action

Oliceridine is a μ-opioid receptor agonist that preferentially activates the G-protein signaling pathway over the β-arrestin 2 pathway. Activation of the G-protein pathway reduces neuronal excitability, producing potent analgesia. The biased signaling profile reduces recruitment of β-arrestin 2, which is implicated in opioid-related adverse effects such as respiratory depression, constipation, and tolerance [4]. Additionally, reduced β-arrestin activation appears to limit Toll-like receptor 4 (TLR4) activation in microglial cells, thereby decreasing neuroinflammation and potentially lowering the incidence of neurocognitive side effects compared with traditional opioids [14]. While this mechanistic bias is associated with an improved safety profile, the exact molecular basis for reduced adverse effects remains incompletely understood.

Pharmacokinetics

- *Onset of Action*: Rapid—within 1–2 min post IV administration
- *Tmax/Cmax*: Tmax ~2 min post-IV dose; rapid attainment of peak plasma concentration
- *Duration*: Analgesic effects last approximately 3–4 h
- *Metabolism/Elimination*: Primarily hepatic oxidation and glucuronidation via CYP3A4 and CYP2D6; metabolites excreted renally and hepatobiliary
- *Dosing Recommendations*:
  - Initial: 1.5 mg IV bolus
  - Supplemental: 0.1–0.5 mg IV as needed
  - Max: 27 mg in 24 h
  - Restricted to hospital use for acute pain when alternatives are inadequate [4, 14, 15]

Clinical Summary

Oliceridine offers potent IV analgesia with potentially fewer respiratory and gastrointestinal side effects than conventional μ-opioid agonists, making it a valuable hospital-based analgesic for moderate-to-severe acute pain. It was FDA approved on August 7, 2020, for intravenous use in hospitals or monitored clinical settings only [16]. Its short duration of action necessitates careful titration and monitoring, particularly in patients with high analgesic needs [4, 14] (Table 30.1).

Table 30.1 Pharmacokinetic and mechanistic profiles of newer perioperative analgesics

Feature	Suzetrigine	Buprenorphine	Oliceridine
Mechanism of action	Selective NaV1.8 channel inhibitor; blocks peripheral nociceptive signaling without CNS or motor side effects	High-affinity partial μ-opioid receptor agonist; κ-antagonist; ceiling effect on respiratory depression; displaces full μ-agonists	G-protein biased μ-opioid receptor agonist; reduces β-arrestin 2 recruitment and TLR4 activation, lowering respiratory and neuroinflammatory risk
Onset	~2 h (oral)	~30 min (SL), ~15 min (IV/IM)	1–2 min (IV)
Tmax/Cmax	2–4 h post-dose	SL ~45 min; IV Cmax ~14 ng/mL at ~4 h	Tmax ~2 min; Cmax in minutes after IV bolus
Half-life	Data limited; dosing supports 12 h intervals	Avg ~37 h (range 20–70 h)	~3–4 h
Duration	~12 h per dose	Up to 24 h per dose	3–4 h per dose
Metabolism	CYP3A; avoid strong CYP3A inhibitors (e.g., grapefruit juice)	CYP3A4/2C8; glucuronidation via UGTs; biliary and renal excretion	Hepatic oxidation and glucuronidation; renal and biliary excretion
Dosing	100 mg oral load, then 50 mg q12h (max 14 days)	SL 0.15–0.8 mg; transdermal q7 days; IV/IM for acute pain	Initial 1.5 mg IV bolus; 0.1–0.5 mg PRN; max 27 mg/day
Clinical use notes	FDA-approved for short-term use in moderate–severe acute pain; avoids opioid receptor pathways	Preferred to continue perioperatively for ≤16 mg/day; multimodal analgesia essential; plan for receptor competition	FDA-approved Aug 7, 2020, for IV use in hospital/monitored settings only; titrate for acute pain; monitor closely
Perioperative dosing recommendations	Continue per standard short-course dosing; not used chronically	≤4 mg/day: Continue unchanged; 4–12 mg/day: continue, divide into 2–3 doses; >12 mg/day: Continue, consider reducing to 12–16 mg/day or divide into 3–4 doses; supplement with high-affinity opioids if needed	Hospital or monitored setting only; titrate to effect for acute postoperative pain; no outpatient use

SL sublingual, *IV* intravenous, *h* hours

Clinical Applications and Techniques

Suzetrigine (Journavx™, VX-548): NaV1.8 Inhibitor

Suzetrigine is a first-in-class, FDA-approved NaV1.8 channel inhibitor indicated for the treatment of acute postoperative pain in adults. The FDA-approved suzetrigine in January 2025, making it the first NaV1.8-targeting analgesic available for clinical use. By selectively targeting voltage-gated sodium channels on peripheral nociceptors, it attenuates pain signal propagation without engaging central μ-opioid pathways, thereby avoiding common opioid-related adverse effects such as sedation, respiratory depression, and constipation.

Evidence Base: Phase 3 randomized trials in abdominoplasty and bunionectomy models have demonstrated significant pain score reductions and opioid-sparing benefits with a favorable safety profile [17].

Clinical Role: Particularly valuable for opioid-naïve surgical patients, those at high risk for opioid-induced side effects, and as a core component of opioid-sparing multimodal perioperative pain protocols [7, 9].

Technique and Administration

- Initiate with *100 mg oral loading dose* (fasted)
- Follow with *50 mg every 12 h*
- Reduce to *50 mg once daily* after four doses if needed
- Limit to ≤*14 days* per FDA guidelines
- Avoid with strong CYP3A inhibitors (e.g., grapefruit juice) [8]

Buprenorphine: Partial μ-Agonist/κ-Antagonist

Buprenorphine's high μ-receptor affinity, partial agonism, and κ-antagonism provide potent, long-acting analgesia with a ceiling effect on respiratory depression, making it a key agent for perioperative management of patients with chronic pain, opioid tolerance, or opioid use disorder (OUD).

Continuation Versus Initiation

- *Continuation*: For most surgical patients—especially those on ≤16 mg/day—perioperative continuation is preferred to avoid withdrawal, destabilized pain control, and relapse risk [18].
- *Initiation*: In OUD patients requiring surgery, buprenorphine may be initiated perioperatively to stabilize analgesia and prevent opioid misuse relapse [19].

According to the University of California, San Francisco medical center, dosage of buprenorphine can be continued at the maintenance dose or adjusted depending on the pain levels of the patient as well as the requirements of the surgery.

Perioperative Dosing Techniques [13]

- ≤*4 mg/day SL*: Continue unchanged; supplemental opioids generally effective
- *4–12 mg/day SL*: Continue; consider splitting into 2–3 doses/day for enhanced perioperative coverage
- >*12 mg/day SL*: Continue; consider reducing to 12–16 mg/day 2–3 days preop or divide into 3–4 doses/day.

Supplementation: High-affinity opioids (hydromorphone, fentanyl) if needed, combined with multimodal agents (acetaminophen, NSAIDs, gabapentinoids, ketamine, regional anesthesia).

Receptor Affinity Note: Due to its high μ-receptor binding, buprenorphine may blunt the effects of full agonists; plan supplemental analgesia accordingly.

Oliceridine (Olinvyk®): G-Protein Biased μ-Opioid Agonist

Oliceridine is a μ-opioid receptor agonist with *preferential activation of the G-protein pathway* over the β-arrestin pathway, aiming to maintain potent analgesia while mitigating common opioid-related adverse effects. Reduced β-arrestin recruitment is associated with lower rates of respiratory depression, constipation, and tolerance, and decreased Toll-like receptor 4 activation in microglia may contribute to reduced neuroinflammation.

Evidence Base: Phase 3 trials demonstrated effective analgesia with lower incidence of sedation and respiratory compromise compared with morphine, though adverse effects remain possible [4].

Clinical Role: Short-term use in monitored inpatient settings where rapid-onset analgesia is needed and minimization of opioid-related side effects is a priority. Current use, mostly in clinical trials.

Technique and Administration

- Initial dose: *1.5 mg IV bolus*
- Supplemental: *0.1–0.5 mg as needed*
- Maximum: *27 mg in 24 h*
- Monitor for respiratory depression, particularly in older adults and those with comorbidities [15]

Summary of Clinical Use Patterns

- *Suzetrigine*: Opioid-sparing, peripherally acting analgesic; ideal for acute postoperative pain in opioid-naïve or high-risk patients.

- *Buprenorphine*: Continue perioperatively for most patients; may initiate in OUD patients; tailor dosing to pain intensity and surgical complexity.
- *Oliceridine*: Hospital-only IV opioid option with rapid onset and potentially fewer adverse effects than traditional opioids; best for closely monitored acute pain management.

Evidence-Based Practices

Optimizing perioperative pain management with newer pharmacologic agents requires integrating the best available evidence with patient-specific factors, surgical context, and institutional protocols.

Suzetrigine (VX-548)

- *Phase 3 Randomized Controlled Trials*: In abdominoplasty and bunionectomy populations, suzetrigine significantly reduced numeric pain scores and opioid consumption compared with placebo, with a tolerability profile similar to non-opioid comparators [7].
- *Safety*: Across trials, no signal of respiratory depression or CNS impairment was observed, underscoring its role in *opioid-sparing protocols* for acute postoperative pain.
- *Guideline Positioning*: While formal guideline integration is pending, emerging consensus supports its inclusion in multimodal analgesia, especially in opioid-naïve or opioid-sensitive patients.

Buprenorphine

- *Continuation Benefits*: Multisociety expert consensus [13] supports *continuing buprenorphine perioperatively* for most patients, particularly those on ≤16 mg/day, to maintain receptor stability, avoid withdrawal, and reduce relapse risk [13].
- *Dose Adjustment Strategies*: Evidence supports splitting higher daily doses into multiple administrations to optimize receptor availability for supplemental analgesics.
- *Initiation in OUD*: Perioperative initiation in untreated OUD patients improves pain control and reduces postoperative opioid misuse risk.
- *Safety*: Ceiling effect on respiratory depression provides safety margin, but vigilance for sedation—especially in older adults—is warranted.

Oliceridine (Olinvyk®)

- *Efficacy Data*: Phase 3 trials in orthopedic and abdominal surgeries demonstrated rapid analgesia onset (<2 min post-IV bolus) and effective pain control with fewer respiratory safety events compared to morphine, although overall opioid-related adverse effects were still present [14]. Clinical data also suggest a reduced risk of sedation and gastrointestinal side effects, supporting its role as a hospital-based analgesic for monitored use only.
- In a recent randomized controlled trial, *Dahan et al.* evaluated neurocognitive outcomes using a "utility function" approach (probability of benefit minus probability of harm) based on *saccadic peak velocity* (marker of sedation) and *body sway* (marker of motor instability). Within clinical concentration ranges, oliceridine demonstrated a *positive utility score* for both measures, indicating preserved neurocognitive performance, while morphine's utility ranged from zero to negative.
- *Approved Use and Limitations*: Oliceridine is *FDA-approved (August 7, 2020)* for *intravenous use in hospitals or monitored clinical settings only*. It is not recommended for outpatient or chronic pain use and should be reserved for cases requiring rapid-onset IV opioid therapy with close monitoring.

Key Principles for Practice Integration

1. *Match Mechanism to Patient Profile*:
   (a) Use suzetrigine for opioid-naïve or opioid-sensitive patients requiring short-term, peripherally acting analgesia.
   (b) Continue buprenorphine in OUD/chronic pain patients; initiate if indicated in untreated OUD during surgical admission.
   (c) Reserve oliceridine for monitored inpatient use when rapid-onset IV opioid analgesia is required.
2. *Adopt a Multimodal Analgesic Approach*:
   (a) Combine newer agents with acetaminophen, NSAIDs, gabapentinoids, NMDA antagonists, and regional anesthesia to maximize efficacy and minimize opioid load.
3. *Plan for Transitions of Care*:
   (a) Develop perioperative-to-postdischarge analgesia plans that account for each agent's pharmacokinetics, dosing limitations, and regulatory constraints.

While the clinical evidence for suzetrigine, buprenorphine, and oliceridine highlights meaningful advances in efficacy and safety, translating these findings into routine perioperative care requires careful consideration of real-world challenges. Patient variability, the evolving opioid crisis, and the limitations of existing analgesic strategies all influence how—and in whom—these agents should be used.

Challenges and Considerations

The urgency for new directions in pain management is underscored by the limitations and unintended consequences of current analgesic strategies. Foremost among these is the ongoing opioid crisis, which began in the United States in the mid-1990s and has claimed more than 500,000 lives over the past two decades [20]. Multiple factors—including socioeconomic pressures, prescribing practices, and limited availability of effective non-opioid analgesics—have contributed to this crisis.

Another complicating factor in pain management is the subjective and personal experience of pain itself. Demographic, genetic, and psychosocial variables each play a role in our perception of pain. A biological example of this concept would be the varying haplotypes of the gene encoding catechol-O-methyl-transferase (*COMT*) [21], an enzyme responsible for the metabolism of catecholamines. *COMT* has been linked to pain-related mu-opioid receptor binding in the central nervous system [22], as well as global pain sensitivity [23]. Differences in the expression of *COMT* among the population are one of many examples that highlight the challenging nature of pain perception.

Age further shapes analgesic decision-making. Geriatric patients, increasingly common in perioperative practice due to rising life expectancy, often present with multiple comorbidities that complicate dosing and increase vulnerability to adverse effects [24]. Sedation—particularly from opioids—can increase the risk of falls, delirium, and prolonged hospitalization in older adults, reinforcing the value of opioid-sparing or selectively targeted agents such as suzetrigine and investigational biased opioid ligands. At the other end of the age spectrum, pediatric pain management is challenged by the difficulty of accurately assessing pain, which can result in underestimation and undertreatment [25]. These patient-specific considerations underscore the need for individualized, evidence-based approaches that integrate novel pharmacologic options into multimodal analgesic plans.

Case Studies or Clinical Scenarios

Real-world experiences highlight the clinical implications of continuing versus discontinuing novel analgesics in the perioperative setting. A case published in *Journal of Pain & Palliative Care Pharmacotherapy* illustrates buprenorphine's potential advantages over full μ-opioid agonists for both chronic and perioperative pain control [26].

Two years later, he underwent right total knee arthroplasty. Buprenorphine was discontinued on the day of surgery (rather than the more traditional 48–72 h prior), and the patient reported satisfactory pain control during hospitalization. In contrast, when he underwent left total knee arthroplasty after being switched to hydrocodone/acetaminophen (10 mg/325 mg, eight tablets daily), he experienced poorly controlled postoperative pain despite higher morphine-equivalent dosing. This case underscores the potential benefits of perioperative buprenorphine continuation, as supported by recent expert consensus guidelines.

Future Directions and Research

Opioid-sparing strategies—such as Enhanced Recovery After Surgery (ERAS) protocols and multimodal analgesia—have substantially reduced perioperative opioid exposure and associated adverse events. Future advances will likely build on these frameworks by incorporating novel agents like suzetrigine, buprenorphine, and biased μ-opioid receptor ligands into individualized, evidence-based regimens [27]. Future advances will likely build on these frameworks by incorporating novel agents like suzetrigine, buprenorphine, and biased μ-opioid receptor ligands into individualized, evidence-based regimens [28].

Suzetrigine, FDA-approved in January 2025 as the first NaV1.8-targeting analgesic, offers peripheral nociceptive blockade without the sedation, respiratory depression, or dependency risk associated with opioids. Ongoing research will clarify its role beyond initial postoperative applications, including in high-risk populations such as the elderly.

Buprenorphine continues to gain traction in perioperative planning for patients with opioid tolerance, chronic pain, or opioid use disorder. Ongoing studies are exploring its use in transitioning patients from full opioid agonists to partial agonist/antagonist therapy, including buprenorphine/naltrexone combinations, though optimal dosing and initiation protocols require further investigation [2].

Biased μ-opioid receptor ligands like oliceridine hold promise for delivering potent analgesia with fewer respiratory and cognitive side effects. However, their use remains limited to monitored inpatient settings, and additional Phase 4 safety data are needed to support broader adoption.

Finally, advances in *pharmacogenomics* may enable analgesic regimens tailored to individual genetic profiles, accounting for variations in metabolism, receptor binding, and pain sensitivity. Further research in this area could allow truly personalized perioperative pain management strategies that optimize efficacy while minimizing risk [29].

Conclusion

As the field moves toward more individualized, multimodal approaches, integrating emerging pharmacologic agents with established protocols will be key to achieving effective analgesia while minimizing harm—setting the stage for the next evolution in perioperative pain management.

References

1. Quaye ANA, Zhang Y. Perioperative Management of Buprenorphine: solving the conundrum. Pain Med. 2019;20(7):1395–408. https://doi.org/10.1093/pm/pny217.
2. Vu PD, Bansal V, Chitneni A, et al. Buprenorphine for chronic pain management: a narrative review. Curr Pain Headache Rep. 2023;27(12):811–20. https://doi.org/10.1007/s11916-023-01185-4.
3. Commissioner O of the. FDA approves novel non-opioid treatment for moderate to severe acute pain. FDA January 30, 2025. https://www.fda.gov/news-events/press-announcements/fda-approves-novel-non-opioid-treatment-moderate-severe-acute-pain. Accessed 4 Aug 2025.
4. Che T, Dwivedi-Agnihotri H, Shukla AK, Roth BL. Biased ligands at opioid receptors: current status and future directions. Sci Signal. 2021;14(677):eaav0320. https://doi.org/10.1126/scisignal.aav0320.
5. Osteen JD, Immani S, Tapley TL, et al. Pharmacology and mechanism of action of Suzetrigine, a potent

and selective NaV1.8 pain signal inhibitor for the treatment of moderate to severe pain. Pain Ther. 2025;14(2):655–74. https://doi.org/10.1007/s40122-024-00697-0.
6. Keam SJ. Suzetrigine: First Approval. Drugs. 2025;85(6):845–51. https://doi.org/10.1007/s40265-025-02178-w.
7. McCoun J, Winkle P, Solanki D, et al. Suzetrigine, a non-opioid $Na_V1.8$ inhibitor with broad applicability for moderate-to-severe acute pain: a phase 3 single-arm study for surgical or non-surgical acute pain. JPR. 2025;18:1569–76. https://doi.org/10.2147/JPR.S509144.
8. Suzetrigine Prescribing Information. https://pi.vrtx.com/files/uspi_suzetrigine.pdf. Accessed 4 Aug 2025.
9. Bertoch T, D'Aunno D, McCoun J, et al. Suzetrigine, a nonopioid Na V 1.8 inhibitor for treatment of moderate-to-severe acute pain: two phase 3 randomized clinical trials. Anesthesiology. 2025;142(6):1085–99. https://doi.org/10.1097/ALN.0000000000005460.
10. Dahan A, Yassen A, Romberg R, et al. Buprenorphine induces ceiling in respiratory depression but not in analgesia. Br J Anaesth. 2006;96(5):627–32. https://doi.org/10.1093/bja/ael051.
11. Khanna IK, Pillarisetti S. Buprenorphine—an attractive opioid with underutilized potential in treatment of chronic pain. J Pain Res. 2015;8:859–70. https://doi.org/10.2147/JPR.S85951.
12. Kumar R, Viswanath O, Saadabadi A. Buprenorphine. In: StatPearls. StatPearls Publishing; 2025. http://www.ncbi.nlm.nih.gov/books/NBK459126/. Accessed 8 Aug 2025.
13. Kohan L, Potru S, Barreveld AM, et al. Buprenorphine management in the perioperative period: educational review and recommendations from a multisociety expert panel. Reg Anesth Pain Med. 2021;46(10):840–59. https://doi.org/10.1136/rapm-2021-103007.
14. Moss L, Hijma H, Demitrack M, et al. Neurocognitive effect of biased μ-opioid receptor agonist Oliceridine, a utility function analysis and comparison with morphine. Anesthesiology. 2023;139(6):746–56. https://doi.org/10.1097/ALN.0000000000004758.
15. Yi K, Sun W, Yu W, Chen S. Overview and prospects of the clinical application of Oliceridine. Drug Des Devel Ther. 2025;19:5415–30. https://doi.org/10.2147/DDDT.S525471.
16. Schedules of Controlled Substances: Placement of Oliceridine in Schedule II. Federal Register. June 10, 2021. https://www.federalregister.gov/documents/2021/06/10/2021-11981/schedules-of-controlled-substances-placement-of-oliceridine-in-schedule-ii. Accessed 8 Aug 2025.
17. Singla NK, Skobieranda F, Soergel DG, et al. APOLLO-2: a randomized, placebo and active-controlled phase III Study Investigating Oliceridine (TRV130), a G protein–biased ligand at the μ-opioid receptor, for management of moderate to severe acute pain following abdominoplasty. Pain Pract. 2019;19(7):715–31. https://doi.org/10.1111/papr.12801.
18. Buprenorphine. Pain Management Education at UCSF. https://pain.ucsf.edu/opioid-analgesics/buprenorphine. Accessed 4 Aug 2025.
19. Hurley RW, Adams MCB, Barad M, et al. Consensus practice guidelines on interventions for cervical spine (facet) joint pain from a multispecialty international working group. Reg Anesth Pain Med. 2022;47(1):3–59. https://doi.org/10.1136/rapm-2021-103031.
20. Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain – United States, 2016. MMWR Recomm Rep. 2016;65(1):1–49. https://doi.org/10.15585/mmwr.rr6501e1.
21. Fillingim RB. Individual differences in pain: understanding the mosaic that makes pain personal. Pain. 2017;158(Suppl 1):S11–8. https://doi.org/10.1097/j.pain.0000000000000775.
22. Zubieta JK, Heitzeg MM, Smith YR, et al. COMT val158met genotype affects mu-opioid neurotransmitter responses to a pain stressor. Science. 2003;299(5610):1240–3. https://doi.org/10.1126/science.1078546.
23. Diatchenko L, Slade GD, Nackley AG, et al. Genetic basis for individual variations in pain perception and the development of a chronic pain condition. Hum Mol Genet. 2005;14(1):135–43. https://doi.org/10.1093/hmg/ddi013.
24. Rajput K, Ng J, Zwolinski N, Chow RM. Pain Management in the Elderly: a narrative review. Anesthesiol Clin. 2023;41(3):671–91. https://doi.org/10.1016/j.anclin.2023.03.003.
25. Di Sarno L, Gatto A, Korn D, et al. Pain management in pediatric age. An update. Acta Biomed. 2023;94(4):e2023174. https://doi.org/10.23750/abm.v94i4.14289.
26. Silva MJ, Rubinstein A. Continuous perioperative sublingual buprenorphine. J Pain Palliat Care Pharmacother. 2016;30(4):289–93. https://doi.org/10.1080/15360288.2016.1231734.
27. Chen Q, Chen E, Qian X. A narrative review on perioperative pain management strategies in enhanced recovery pathways-the past, present and future. J Clin Med. 2021;10(12):2568. https://doi.org/10.3390/jcm10122568.
28. Rathert C, Wyrwich MD, Boren SA. Patient-centered care and outcomes: a systematic review of the literature. Med Care Res Rev. 2013;70(4):351–79. https://doi.org/10.1177/1077558712465774.
29. Alorfi NM. Pharmacological methods of pain management: narrative review of medication used. Int J Gen Med. 2023;16:3247–56. https://doi.org/10.2147/IJGM.S419239.

Technology and Pain Management

31

G. Taylor Patterson, Chiamaka Ohanu, and Anna Woodbury

Introduction

In the evolving landscape of perioperative pain management, this chapter explores the transformative impact of new technologies as innovative alternatives to traditional pharmacotherapy and invasive procedures. From preoperative preparation to postoperative care, this chapter delves into cutting-edge advancements that have the potential to enhance patient outcomes and reduce the drawbacks associated with conventional pain management strategies. Through the lens of diverse technological modalities, ranging from wearable devices to neurostimulation and virtual reality (VR), we examine the potential role these interventions have in alleviating perioperative pain. By elucidating the multifaceted applications of these technologies in various settings, this chapter aims to contribute valuable insights to the evolving landscape of perioperative care.

G. Taylor Patterson · C. Ohanu
Division of Pain Medicine, Department of Anesthesiology, Emory University School of Medicine, Atlanta, GA, USA

A. Woodbury (✉)
Division of Pain Medicine, Department of Anesthesiology, Emory University School of Medicine, Atlanta, GA, USA

Atlanta Veterans Affairs Healthcare System, Atlanta, GA, USA
e-mail: awoodbu@emory.edu

Background and Information

Device utilization for pain management can be traced back to the Roman physician Scribonius Largus in 153 AD [1]. Largus recognized the analgesic properties of electrical current when patients, suffering from acute gout attacks, immersed themselves in the sea alongside electric black torpedo fish resulting in quick resolution of pain [1]. The American scientist Benjamin Franklin built on this foundation by employing electrical therapy to alleviate the suffering of individuals grappling with palsies and paralysis [2]. However, it was the groundbreaking work of American neurosurgeon Clyde Norman Shealy in the 1970s that marked a transformative milestone in the evolution of pain management technologies. Shealy's ingenuity led to the development and subsequent refinement of the transcutaneous electrical nerve stimulation (TENS) unit, a seminal invention that paved the way for a diverse array of innovative devices tailored to address both acute and chronic pain [3].

This field of technologies has expanded into a myriad of shapes, forms, and sizes, with some already integrated into clinical practices while others remain in early clinical trials. Among those utilizing techniques that precisely target acute pain at its source include peripheral nerve stimulation, noninvasive brain stimulation devices, and high-frequency focused ultrasound. Beyond these neuro-targeted approaches,

P. Gulur et al. (eds.), *Perioperative Pain Management*,
https://doi.org/10.1007/978-3-032-11484-6_31

psychological and biofeedback-based methods, including virtual reality, wearable devices such as Apple Watches, and health applications, have demonstrated promising potential as complementary tools in the intricate management of pain. The ongoing exploration and integration of these diverse technologies underscore the dynamic and ever-evolving nature of pain management modalities, highlighting the shift toward personalized, safe, and minimally/noninvasive approaches to perioperative pain management.

Clinical Applications and Techniques

Wearable Technologies

In perioperative pain management, the development of everyday wearable technology has ushered in a new era of personalized, data-driven care. Such examples include Apple™ watch and Fitbit©, which provide a noninvasive means to continuously monitor heart rate variability, offering insight into patients' physiological responses to stress and pain [4, 5]. The seamless collection of biofeedback data presents an opportunity for both physicians to tailor pain management strategies based on individualized needs, as well as patients themselves to evaluate their self-management of pain by controlling their physiological parameters through breathing exercises, improving sleep, and increasing activity. On another front, devices like Quell™, a calf-worn stimulator designed for individuals with fibromyalgia, exemplify the potential for multiple use cases seen with wearable technology [6]. Not only does Quell utilize electrical pulsations to alleviate fibromyalgia pain acutely, but it also captures crucial data on treatment utilization, sleep quality, and pain severity for fine tuning of treatment [7]. The benefits of such wearable technologies lie in their capacity to provide real-time information to both healthcare providers and patients, leading to further personalization of care, insights into treatment response, and higher patient satisfaction.

Virtual Reality

Advancements in virtual reality (VR), exemplified by META's Quest™ and Apple's Vision Pro™, have spurred extensive exploration in practical use cases for the technology including its efficacy in managing pain and anxiety in the perioperative setting. Ongoing research has shown that VR can be utilized as a cost-effective, feasible way to help reduce preoperative anxiety and reduce sedative administration by providing enhanced educational experiences about the surgical process and utilizing distractive techniques during the preoperative period [8, 9]. In a similar fashion, VR has demonstrated positive effects in minimizing pain while reducing opioid reliance in the postoperative period [10]. The aforementioned benefits result in improved efficiency, reduction in sedation-related adverse events, decreased hospital expenses, and overall improved patient satisfaction [8–10].

Applications

Proliferation of mobile applications designed to facilitate pain management can be attributed to their potential capacity to curtail healthcare costs, diminish complication rates, and elevate both patient and clinician satisfaction. Notable applications like the Panda App™, Lumina™ and Branch Health™ empower users to monitor pain, mood, sleep, and daily medication usage, with built-in reminders [11, 12]. The collected data is seamlessly transmitted to healthcare providers, enabling ongoing monitoring and personalized adjustments. Other applications such as Calm™ and Headspace™ target the psychological dimensions of chronic pain. By leveraging mindfulness meditation techniques, these apps aim to mitigate perceived pain and alleviate detrimental psychological features, including depression and pain catastrophizing [13]. Physicians and researchers find particular encouragement in the cost-effectiveness of these technologies, leveraging the widespread accessibility of smartphones among the general population.

Noninvasive Brain Stimulation

Research in noninvasive brain stimulation (nIBS) has intensified in recent years, focusing on its potential to modulate pain perception within the CNS by delivering electrical current to specific regions of the brain. Techniques like transcranial direct current stimulation (tDCS) and transcranial alternating current stimulation (tACS) utilize different characteristics of electrical current to achieve the aforementioned goal of reducing perceived pain (Fig. 31.1) [14–16]. In caveat, noninvasive vagus nerve stimulation (nVNS) differs in that it indirectly alters the central nervous system by way of direct vagus nerve stimulation. For example, trans-auricular vagus nerve stimulation (taVNS) utilizes electrodes placed at the tragus of the ear to stimulate the vagus nerve [17, 18], while trans-cervical vagus nerve stimulation (tcVNS) achieves a similar result but at the level of the neck [19]. nVNS devices have shown promise in their ability to modulate areas of the brain, effecting changes in perceived pain and anxiety. Lastly, repetitive transcranial magnetic stimulation (rTMS) employs electromagnetic current to generate neuronal changes directly within the CNS, ultimately resulting in analgesia and anxiolysis (Fig. 31.1) [20]. In addition to its ability to target deeper cortical regions relative to other therapies described above, recent advances in the technology have allowed the device to be more portable and user friendly, increasing its ability to be utilized in a perioperative or home-based setting. Overall, nIBS devices have shown promise in reducing pain in a variety of acute and chronic conditions, with broad applications for the perioperative period [14, 15, 17, 20].

Peripheral Nerve Stimulation

Peripheral nerve stimulation (PNS) can be used to target localized postoperative and acute pain, as opposed to targeting the CNS. The gate control theory of pain posits a mechanism by which direct electrical stimulation of the peripheral nervous system activates inhibitory neural pathways within the spinal cord, thus reducing transmission of pain signals to the brain [21, 22]. Studies have shown that implanted electrodes, also called peripheral nerve stimulators, can lead to decreased postoperative pain, reduced postoperative opioids and longer lasting analgesia without affecting motor function, as seen with traditional anesthetic blocks [21]. Another form of PNS includes percutaneous electrical nerve stimulation (PENS) or electroacupuncture (EA), which involves percutaneously inserted needles attached to electrical stimulation to produce a neuromodulatory response. Transcutaneous electrical nerve stimulation devices (TENS) are similar in effect without the need for needle sticks or invasive procedures, though potentially less potent. By transcutaneous administration of low-intensity, high-frequency, and small-pulse electrical waves, studies have shown reductions in postsurgical pain and increased therapy and rehabilitation engagement [23]. Similarly, noninvasive magnetic peripheral nerve stimulation (mPNS) devices, like Neuralace™, derived from rTMS but acting at the periphery, have shown promise in modulating pain and curtailing opioid use in the postoperative period [24].

Therapeutic Ultrasound

High-intensity focused ultrasound (HIFUS) harnesses high-energy, concentrated ultrasound waves in order to ablate nerves identified as damaged or persistently overactive, thereby diminishing the propagation of pain signals from the PNS to the CNS [25]. The technology works by inducing both thermal and mechanical damage via the cavitation effect to desired neuronal tissues. Current studies have shown its efficacy in treating palliative cancer pain and other chronic pain conditions such as chronic neuropathic pain and osteoarthritic pain resulting in a reduction of overall systemic opioid use [25, 26]. However, few studies have investigated its role in the perioperative pain setting directly. Transcranial focused ultrasound (tFUS) can also modulate neural activity through facilitation or suppression without an ablative effect, much like other forms of nIBS, and can stimulate deep structures of the

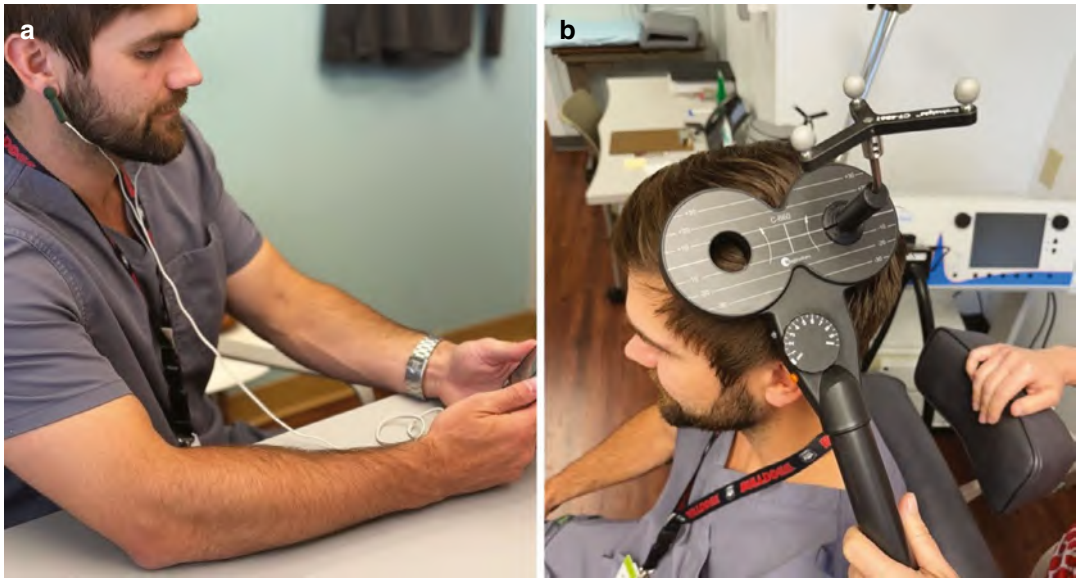


Fig. 31.1 Noninvasive brain stimulation technologies used for pain. (**a**) Dr. Patterson demonstrates the utilization of the Alpha-Stim™ cranial electrotherapy stimulation (CES) device, which employs self-delivered transcranial alternating current stimulation (tACS) to reduce anxiety, insomnia, depression, and pain. The device is low-risk, portable, noninvasive, and can be utilized in a variety of settings. (**b**) Dr. Woodbury demonstrates the placement of a repetitive transcranial magnetic stimulation (rTMS) coil over Dr. Patterson's skull to deliver an electromagnetic current, targeting deep brain structures such as the left motor cortex or dorsolateral prefrontal cortex to reduce pain. Magnetic stimulation can also be applied to peripheral nerves to reduce pain through a noninvasive, neuromodulatory effect

brain [27]. Given HIFUS's analgesic effects, noninvasiveness, and absence of nonionizing radiation, it remains a useful tool in the chronic pain setting, but also a promising technology for potential utilization in the perioperative period.

Evidence-Based Practices

Perioperative VR

Currently, there are a multitude of ongoing investigations regarding the benefits of VR in the perioperative setting. We will highlight only two recent publications, noting that this is a rapidly expanding field of research. At Oregon Health & Sciences University, the department of otolaryngology used VR to specifically assess its efficacy in postoperative pain management of patients after undergoing head and neck surgery [28]. Twenty-nine patients who rated their pain score at least three out of ten were randomized into either the 3D VR treatment group using an Oculus Quest™ or the control group using a 2D smartphone. The intervention involved participants undergoing a 15-minute gaming experience on their respective devices, with changes in pain score, quantified by an 11-point numeric rating scale taken before and after surgery, being evaluated as the primary outcome. In addition, changes in opioid use and patient satisfaction were evaluated as the secondary outcomes. When compared to the control group, patients utilizing VR had a clinically meaningful reduction in self-reported postoperative pain at one-, two-, three-, and four-hour post-intervention checks. Additionally, at four- and eight-hour postintervention, the VR group had a meaningful reduction in opioid use by 9.10 MME and 14.00 MME, respectively, when compared to the control group [28]. These findings further support the use of VR in pain management in the perioperative setting.

A clinical study conducted in Seoul, South Korea, aimed to assess the efficacy of VR in reducing perioperative anxiety among children undergoing elective procedures [29]. Sixty-nine children were divided into either the intervention group, where they viewed a brief video via VR featuring the popular animated penguin character, Pororo, that provided surgical information, or the control group, which received conventional information about the surgery without using VR [29, 30]. Anxiety levels for all participants were measured using the Yale Preoperative Anxiety Scale (m-YPAS) before entering the operating room. The study revealed significantly lower m-YPAS scores in the VR group compared to the control group (median 31.7 vs. 51.7, respectively; $P < 0.001$). Consequently, the researchers concluded that VR serves as an effective tool for alleviating perioperative anxiety among adolescents undergoing elective procedures [29].

Apps

As discussed earlier, mobile health applications are becoming a more commonly used tool in the perioperative setting. Another app often utilized by patients is The Patient Journey App™.

It allows individuals with musculoskeletal disorders to receive a comprehensive conveyance of information regarding their operations, from preoperative medical instructions to the postoperative rehabilitation process [31]. A recent cross-sectional study evaluated questionnaires to over 526 users, and concluded that the vast majority found the application extremely usable, informative, and a presentable tool for those suffering from MSK disorders [31]. Yet another example of how mobile apps can improve multiple processes within the perioperative setting is CommunicatOR™. The application, developed by anesthesiologists at Thomas Jefferson University Hospital, allows non-native English speakers the ability to communicate with providers in the operating room [32]. The application translates commonly used phrases, such as "open your eyes" to the patient's preferred language. When surveyed about the experience of the app, 88% of the participants felt more relaxed when receiving information in their native language [32]. As there is robust literature on the effects of relaxation on reduced postoperative pain [33], the use of applications in the perioperative environment may be associated with improved pain outcomes.

TENS

A 2003 meta-analysis of twenty-one RCTs studied the effectiveness of TENS in controlling acute postoperative pain and lowering opioid consumption in patients [38]. Data showed that TENS usage was effective in alleviating pain at both immediate and 24-hour postoperative periods in addition to showing a significant reduction in opioid consumption of 26.5% when compared to the control group [38]. Given that postoperative pain and increased postoperative opioid consumption contribute to poorer patient outcomes and longer hospital stays, the implementation of effective solutions is needed [37]. Given the robust data for postoperative pain, portability, cost-effectiveness, and ease of use of TENS units, it is surprising that the use of the device in postoperative settings has not been more widely implemented. While there may be concerns with TENS and other electrical stimulation devices in the context of interfering with implanted pacemakers, insulin pumps, or other implanted devices, there are otherwise few contraindications and side effects.

tDCS

Similar to TENS, recent advances in tDCS have allowed portable devices to be utilized in a home-based setting. A pilot randomized controlled trial (RCT) conducted at the Medical University of South Carolina explored the use of tDCS in controlling patient-controlled analgesia (PCA) opioid usage in individuals receiving lumbar spinal surgery [34]. Twenty-seven participants were split into either the tDCS intervention group or control group receiving a sham treatment. tCDS

or sham treatments were delivered at the 30 minute, 4-hour, ~24-hour, ~28-hour postoperative intervals, with amounts of PCA hydromorphone administered being measured. Results showed that patients undergoing true tDCS treatment, on average, had a 23% reduction of PCA usage when compared to the control group [34]. Thus, researchers concluded that tDCS is an effective, nonpharmacologic, noninvasive modality for pain management in patients undergoing spinal surgery.

Challenges and Considerations

Technology in healthcare is a vastly growing endeavor, while most of the methods used in clinical settings provide many benefits to overall patient care, there still exist several challenges to implementing these practices into everyday use. In the setting of wearable devices, lack of clinical validity and contextual consideration poses challenges to sole reliance on this technology. For example, the differences in types of sensors used and differences in locations of wearable devices worn on patients, such as smart watches or ingestible smart implants, may make it difficult to amass consistent, reproducible quality data collection [35, 36]. On the other hand, different indications for use, such as fitness tracking versus postoperative surgery tracking, carry different degrees of importance in terms of reliability [36]. Regarding nIBS devices, questions regarding optimal dosing parameters for different pain conditions remain. Recommendations to alleviate these challenges include the use of research and regulation to ensure equal data quality and context-specific standardization [36].

TENS has been in widespread use for decades and is portable and affordable. Some of the best evidence for TENS use is in the perioperative setting [37–39], and yet this therapy is still not widely used in hospital systems for acute pain. It is unclear why TENS is not found in many hospital units, despite a large amount of research supporting its efficacy for postoperative pain. There is a possibility that the lack of utilization is solely due to a knowledge deficit amongst providers. Despite this, research is needed to assess the various stakeholders and their reasons for not implementing TENS so that it can be addressed in the future.

A challenge facing widespread use of VR devices relates to upfront costs required. Virtual reality is accessible through several mediums, and cost is likely to depend on the medium used. Since many healthcare facilities in the United States already use computers to assist with electronic medical records, providing patients with the technology of viewing calming images as a form of VR does not pose a significant challenge. However, the challenge comes from VR requiring specialized headset devices, which are currently not commonly found in healthcare facilities. According to the NY Times, wireless VR headsets range from $200–$800 per headset [40], and the full cost to run a device with the appropriate computer software system is approximately $2500 [41]. Implementation would require upfront monetary and employee-training investments that could be difficult for hospital systems to justify.

Similar challenges apply to the other device-based technologies discussed, which would require an investment of time for training, monetary costs for device acquisition, and space for device storage. However, these challenges are not insurmountable as hospital systems have previously invested in new technologies with high upfront costs, such as the portable ultrasound machine, deemed to dramatically enhance patient care. These investments would likely be worthwhile in order to reduce in-hospital recovery time and the long-term socioeconomic costs related to pain and potential for opioid addiction and overdose.

Future Directions and Research

While several VR, HIFU and PNS devices, such as the TENS unit, have been given FDA approval for the treatment of specific pain indications, many others discussed above have only obtained FDA clearance, given the relatively low risk and noninvasive nature of the devices. The agency

has fallen short of granting FDA approval to many due to the rigorous process required to obtain approval status and the lack of quality trial data needed. Thus, moving forward, carefully structured randomized control trials specifically utilizing the devices in the perioperative setting are needed in order to gain insight into the effectiveness of devices in real-world settings.

While the inherent mechanism of pain is standardized across populations, achieving optimal outcomes demands a personalized approach to treatment. Ultimately, continued research and innovation in this field will result in the expansion of the arsenal used for perioperative pain management beyond traditional pharmacotherapy and invasive procedures. Doing so will allow for more personalization of therapy in the hopes of greater overall outcomes.

Clinical Scenario

A 65-year-old man with a past medical history of substance use disorder in remission for two years presents to the preoperative clinic for a scheduled hip arthroplasty after breaking his hip during a ground-level fall. The patient is very anxious about his surgery because the last time he had surgery for an inguinal hernia repair several decades ago, he had severe postoperative nausea/vomiting as well as ilioinguinal neuralgia. He also does not want to take opioids after surgery, and he is worried about how he will manage his perioperative pain. Two days before his surgery, he downloads an app his surgeon recommends. The app details information about what to expect from surgery and how quickly he can expect to recover after his hip replacement. After further discussion with his anesthesiologist about postoperative pain and a multimodal pain regimen, he agrees to TENS treatment. His surgery goes successfully without any complications, and he receives TENS 30 minutes after emerging from anesthesia in addition to antiemetics. Once fully recovered in the PACU, the patient receives another treatment of TENS before being transported to his inpatient room for further management. The next day, the patient is surprised at how few pain medications he requested overnight. He is even more surprised at the lack of nausea he experienced compared to his previous surgery. Approximately 24 hours after surgery, the patient has a moderate amount of pain but does not want opioids. Instead, he opts to control his pain with a VR game and an additional TENS treatment, applied to the skin near the surgical incision. At the 48-hour postoperative mark, the patient feels well and meets all criteria for discharge. He is discharged with a TENS unit for home use, which he is instructed to apply perincisionally (not directly over the incision) 2–3 times per day, for 20 minutes, as needed to reduce pain. He also downloads a pain tracking app that teaches him meditative techniques and other methods for further reducing pain. The app also provides feedback to his surgeon regarding his pain scores over time.

Key Takeaways

1. The field of perioperative pain management is rapidly expanding and variably dynamic.
2. The end goal for novel therapies should revolve around limiting reliance on addictive substances.
3. By achieving the above goal, a plethora of positives, including better patient outcomes, reduced expenses, and increased patient/physician satisfaction, ultimately result.
4. Future studies are required for many of the technologies to elucidate the effectiveness and role they have in perioperative pain management.
5. Additionally, more data is needed in order for hospitals to justify the high up-front costs that accompany the implementation of several of the technologies discussed.

References

1. Francis J, Dingley J. Electroanaesthesia – from torpedo fish to TENS. Anaesthesia. 2015;70(1):93–103. https://doi.org/10.1111/anae.12887.
2. Gensel L. The medical world of Benjamin Franklin. J R Soc Med. 2005;98(12):534–8.

3. Teoli D, An J. Transcutaneous Electrical Nerve Stimulation. In: StatPearls. StatPearls Publishing; 2024. http://www.ncbi.nlm.nih.gov/books/NBK537188/. Accessed 4 Feb 2024.
4. Lee J, Mawla I, Kim J, et al. Machine learning-based prediction of clinical pain using multimodal neuroimaging and autonomic metrics. Pain. 2019;160(3):550–60. https://doi.org/10.1097/j.pain.0000000000001417.
5. Stojancic RS, Subramaniam A, Vuong C, et al. Predicting pain in people with sickle cell disease in the day hospital using the commercial wearable apple watch: feasibility study. JMIR Form Res. 2023;7:e45355. https://doi.org/10.2196/45355.
6. Jamison RN, Edwards RR, Curran S, et al. Effects of wearable transcutaneous electrical nerve stimulation on fibromyalgia: a randomized controlled trial. J Pain Res. 2021;14:2265–82. https://doi.org/10.2147/JPR.S316371.
7. How it Works. Quell Fibromyalgia. https://quellfibromyalgia.com/how-it-works/. Accessed 9 Mar 2024.
8. Using Virtual Reality to Treat Real Pain | NIH HEAL Initiative. Published December 22, 2020. https://heal.nih.gov/news/stories/virtual-reality. Accessed 4 Feb 2024.
9. Flores A, Hoffman HG, Navarro-Haro MV, et al. Using immersive virtual reality distraction to reduce fear and anxiety before surgery. Healthcare. 2023;11(19):2697. https://doi.org/10.3390/healthcare11192697.
10. Payne O, Smith V, Rolnik DL, et al. Virtual reality and its use in post-operative pain following laparoscopy: a feasibility study. Sci Rep. 2022;12:13137. https://doi.org/10.1038/s41598-022-17183-2.
11. Dunsmuir D, Wu H, Sun T, et al. A postoperative pain management mobile app (Panda) for children at home after discharge: usability and feasibility. JMIR Perioper Med. 2019;2(2):e12305. https://doi.org/10.2196/12305.
12. Branch Health on the App Store. https://apps.apple.com/us/app/branch-health/id1065632442. Accessed 4 Mar 2024.
13. Mascaro JS, Singh V, Wehrmeyer K, et al. Randomized, wait-list–controlled pilot study of app-delivered mindfulness for patients reporting chronic pain. Pain Rep. 2021;6(1):e924. https://doi.org/10.1097/PR9.0000000000000924.
14. Pacheco-Barrios K, Cardenas-Rojas A, Thibaut A, et al. Methods and strategies of tDCS for the treatment of pain: current status and future directions. Expert Rev Med Devices. 2020;17(9):879–98. https://doi.org/10.1080/17434440.2020.1816168.
15. Chang MC, Briand MM, Boudier-Revéret M, Yang S. Effectiveness of transcranial alternating current stimulation for controlling chronic pain: a systematic review. Front Neurol. 2023;14:1323520. https://doi.org/10.3389/fneur.2023.1323520.
16. Park BS, Jin S, Kim WY, Kang DS, Choi YJ, Lee YS. Comparison of the effects of cranial electrotherapy stimulation and midazolam as preoperative treatment in geriatric patients: A CONSORT-compliant randomized controlled trial. Medicine (Baltimore). 2022;101(35):e30336. https://doi.org/10.1097/MD.0000000000030336.
17. Kim AY, Marduy A, de Melo PS, et al. Safety of transcutaneous auricular vagus nerve stimulation (taVNS): a systematic review and meta-analysis. Sci Rep. 2022;12:22055. https://doi.org/10.1038/s41598-022-25864-1.
18. Wang L, Wang Y, Wang Y, et al. Transcutaneous auricular vagus nerve stimulators: a review of past, present, and future devices. Expert Rev Med Devices. 2022;19(1):43–61. https://doi.org/10.1080/17434440.2022.2020095.
19. Gazi AH, Harrison AB, Lambert TP, et al. Pain is reduced by transcutaneous cervical vagus nerve stimulation and correlated with cardiorespiratory variability measures in the context of opioid withdrawal. Front Pain Res Lausanne Switz. 2022;3:1031368. https://doi.org/10.3389/fpain.2022.1031368.
20. Lefaucheur JP, Antal A, Ayache SS, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol Off J Int Fed Clin Neurophysiol. 2017;128(1):56–92. https://doi.org/10.1016/j.clinph.2016.10.087.
21. Trent AR, Chopra P, Jain A. Peripheral nerve stimulator. In: StatPearls. StatPearls Publishing; 2024. http://www.ncbi.nlm.nih.gov/books/NBK539703/. Accessed 9 Mar 2024.
22. Ong Sio LC, Hom B, Garg S, Abd-Elsayed A. Mechanism of action of peripheral nerve stimulation for chronic pain: a narrative review. Int J Mol Sci. 2023;24(5):4540. https://doi.org/10.3390/ijms24054540.
23. Martimbianco ALC, Porfírio GJ, Pacheco RL, Torloni MR, Riera R. Transcutaneous electrical nerve stimulation (TENS) for chronic neck pain. Cochrane Database Syst Rev. 2019;2019(12):CD011927. https://doi.org/10.1002/14651858.CD011927.pub2
24. Bedder M, Parker L. Magnetic peripheral nerve stimulation (mPNS) for chronic pain. J Pain Res. 2023;16:2365–73. https://doi.org/10.2147/JPR.S409331.
25. Dababou S, Marrocchio C, Scipione R, et al. High-intensity focused ultrasound for pain management in patients with cancer. RadioGraphics. 2018;38(2):603–23. https://doi.org/10.1148/rg.2018170129.
26. Yeo SY, Bratke G, Grüll H. High intensity focused ultrasound for treatment of bone malignancies—20 years of history. Cancers. 2022;15(1):108. https://doi.org/10.3390/cancers15010108.
27. di Biase L, Falato E, Caminiti ML, Pecoraro PM, Narducci F, Di Lazzaro V. Focused ultrasound (FUS) for chronic pain management: approved and potential applications. Neurol Res Int. 2021;2021:8438498. https://doi.org/10.1155/2021/8438498.
28. Pandrangi VC, Shah SN, Bruening JD, et al. Effect of virtual reality on pain management and opioid use among hospitalized patients after head and neck sur-

gery: a randomized clinical trial. JAMA Otolaryngol. 2022;148(8):724–30. https://doi.org/10.1001/jamaoto.2022.1121.
29. Ryu JH, Park SJ, Park JW, et al. Randomized clinical trial of immersive virtual reality tour of the operating theatre in children before anaesthesia. Br J Surg. 2017;104(12):1628–33. https://doi.org/10.1002/bjs.10684.
30. Kain ZN, Caldwell-Andrews AA, Maranets I, et al. Preoperative anxiety and emergence delirium and postoperative maladaptive behaviors. Anesth Analg. 2004;99(6):1648–54. https://doi.org/10.1213/01.ANE.0000136471.36680.97.
31. Willems SJ, Coppieters MW, Pronk Y, et al. A clinical journey mobile health app for perioperative patients: cross-sectional study. JMIR Hum Factors. 2021;8(1):e20694. https://doi.org/10.2196/20694.
32. Taicher BM, Alam RI, Berman J, Epstein RH. Design, implementation, and evaluation of a computerized system to communicate with patients with limited native language proficiency in the perioperative period. Anesth Analg. 2011;112(1):106–12. https://doi.org/10.1213/ANE.0b013e3182009cd1.
33. Roykulcharoen V, Good M. Systematic relaxation to relieve postoperative pain. J Adv Nurs. 2004;48(2):140–8. https://doi.org/10.1111/j.1365-2648.2004.03181.x.
34. Glaser J, Reeves ST, Stoll WD, et al. Motor/prefrontal transcranial direct current stimulation (tDCS) following lumbar surgery reduces postoperative analgesia use. Spine. 2016;41(10):835. https://doi.org/10.1097/BRS.0000000000001525.
35. Aliverti A. Wearable technology: role in respiratory health and disease. Breathe Sheff Engl. 2017;13(2):e27–36. https://doi.org/10.1183/20734735.008417.
36. Canali S, Schiaffonati V, Aliverti A. Challenges and recommendations for wearable devices in digital health: Data quality, interoperability, health equity, fairness. PLOS Digit Health. 2022;1(10):e0000104. https://doi.org/10.1371/journal.pdig.0000104.
37. Viderman D, Nabidollayeva F, Aubakirova M, et al. The impact of transcutaneous electrical nerve stimulation (TENS) on acute pain and other postoperative outcomes: a systematic review with meta-analysis. J Clin Med. 2024;13(2):427. https://doi.org/10.3390/jcm13020427.
38. Rakel BA, Zimmerman BM, Geasland K, et al. Transcutaneous electrical nerve stimulation for the control of pain during rehabilitation after total knee arthroplasty: A randomized, blinded, placebo-controlled trial. Pain. 2014;155(12):2599–611. https://doi.org/10.1016/j.pain.2014.09.025.
39. Elboim-Gabyzon M, Andrawus Najjar S, Shtarker H. Effects of transcutaneous electrical nerve stimulation (TENS) on acute postoperative pain intensity and mobility after hip fracture: A double-blinded, randomized trial. Clin Interv Aging. 2019;14:1841–50. https://doi.org/10.2147/CIA.S203658.
40. The 3 Best VR Headsets for 2024. Reviews by wirecutter. https://www.nytimes.com/wirecutter/reviews/best-standalone-vr-headset/. Accessed 12 May 2024.
41. Garrett B, Taverner T, Gromala D, Tao G, Cordingley E, Sun C. Virtual reality clinical research: Promises and challenges. JMIR Serious Games. 2018;6(4):e10839. https://doi.org/10.2196/10839.

The Role of Integrative Medicine and Alternative Therapies

32

Sahrudh Dharanendra, Shawn Shoham, and Anna Woodbury

Introduction

Traditional perioperative pain management often relies heavily on pharmacological interventions, which may be effective, but come with their own set of limitations and side effects. In recent years, the integration of non-conventional approaches, or integrative medicine, has gained traction in the medical community. Integrative approaches offer an expanded range of nonpharmacological and noninvasive or minimally invasive treatment options. These options may be appropriate for those who have either maximized pharmacotherapy or do not wish to pursue invasive or pharmacologic therapies. Moreover, they can serve as an adjunct to conventional perioperative pain therapies and improve treatment response. This chapter delves into the relevance and efficacy of integrative medicine in perioperative pain management [1].

S. Dharanendra · A. Woodbury (✉)
Division of Pain Medicine, Department of Anesthesiology, Emory University School of Medicine, Atlanta, GA, USA

Atlanta Veterans Affairs Healthcare System, Atlanta, GA, USA
e-mail: awoodbu@emory.edu

S. Shoham
Division of Pain Medicine, Department of Anesthesiology, University of Miami, Miami, FL, USA

Definition of Integrative Medicine

Integrative medicine combines allopathic medical practices with alternative, evidence-based methods to enhance patient care and outcomes. It moves beyond the conventional separation of complementary/alternative medicine, embracing a more inclusive model that integrates a variety of both pharmacological and nonpharmacological treatments. In the context of perioperative pain management, integrative approaches can serve as adjuncts to conventional therapies, potentially improving the overall treatment response and patient satisfaction [1].

Background and Current Understanding

Historically, the adoption of integrative therapies in clinical practice has faced challenges due to varying levels of acceptance and understanding within the medical community. However, recent data from the National Health Interview Survey Census on the usage of integrative therapies highlighted a growing acceptance and application in various medical fields, including the management of chronic pain. From 2002 to 2022, the use of integrative and complementary therapies grew from 19.2% to 36.7% in US adults [2]. Despite this progress, common misconceptions persist. On one hand, some skeptics dismiss

P. Gulur et al. (eds.), *Perioperative Pain Management*,
https://doi.org/10.1007/978-3-032-11484-6_32

integrative medicine due to a perceived lack of evidence or efficacy. On the other hand, proponents may overestimate its benefits, viewing it as a panacea and underestimating potential risks.

A balanced approach lies in evidence-based evaluation, where each integrative therapy is scrutinized for its efficacy, safety, and role in patient care. Integrative medicine is not a one-size-fits-all solution, nor is it devoid of risks. Like any medical intervention, it requires careful consideration of its applications and limitations [3–5].

Manipulative Therapies

Manipulative therapies involve hands-on techniques to align the body's structure and improve physical function (Table 32.1). These therapies, including osteopathic manipulative treatment (OMT), massage, and chiropractic care, are grounded in the understanding that the body's systems are interconnected and can be manipulated to promote healing, alleviate pain, and enhance overall well-being.

Osteopathic Medicine

Osteopathic medicine was founded by Dr. Andrew Taylor Still in the late nineteenth century. It is a form of alternative medicine emphasizing physical manipulation of the body's muscle tissue and bones. Osteopathic medicine focuses on the body's interconnectedness and utilizes its innate healing capacity. Numerous studies have shown that OMT leads to significant pain relief, enhanced and quicker bowel function, and shorter hospital stays [20]. Further detail can be found in Table 32.1.

Chiropractic Medicine

Chiropractic medicine, established by D.D. Palmer in the late nineteenth century, focuses on diagnosing and treating musculoskeletal disorders, primarily of the spine. Chiropractors use manual adjustments and manipulations to correct alignment issues, relieve pain, and improve function, with the intent of contributing to pain management and injury recovery. In retrospective studies, certain chiropractic maneuvers have been associated with improved pain relief following lumbar surgery (Table 32.1).

Massage Therapy

Massage therapy involves manipulating the body's soft tissues through varying pressure and movement. It's renowned for reducing stress, pain, and muscle tension. Massage is known to enhance blood circulation, promote relaxation, relieve pain, and improve overall well-being, making it a popular choice for people seeking relief from various physical ailments, and has been shown to provide benefit in peri-operative care (Table 32.1).

Table 32.1 Evidence-based manipulative therapies

Integrative therapy	Author (year)	Study type	Sample size	Outcome of study
Osteopathic	Barral et al. (2020) [6]	Clinical trial (CT)	70	Significantly less pain at rest and while walking one-month post-TKA ($p = 0.00001$ and $p= 0.0001$, respectively). Reduced opioid consumption in the first postoperative week ($p = 0.0001$)
	Roncada (2020) [7]	Randomized controlled trial (RCT)	82	OMT led to significant reductions in chronic thoracic pain postcoronary artery bypass graft surgery ($p < 0.05$), providing evidence for its use in managing postoperative pain
	Probst et al. (2016) [8]	RCT	20	OMT was feasible and safe in postoperative patients after bowel resection. It showed a trend towards lower postoperative morbidity and reduced pain. Specifically, the comprehensive complication index was lower for patients receiving OMT (30.8 vs. 37.1), and pain scores decreased significantly by an average of 2 points on the numeric rating scale for the OMT group, while there was no change for the control group. Larger RCTs are needed to evaluate its effectiveness
	Kim (2015) [9]	RCT	33	OMT showed more improvement in postsurgical physical disability and residual pain compared to exercise, with statistically significant differences ($p < 0.05$)
	Baltazar et al. (2015) [10]	Retrospective cohort study	55	OMT applied after major gastrointestinal operations was associated with a significant reduction in time to first postoperative flatus (mean time of 3.1 days in OMT group vs. 4.7 days in non-OMT group, $p = 0.035$) and postoperative hospital length of stay (mean LOS of 6.1 days in OMT group vs. 11.5 days in non-OMT group, $p = 0.006$), indicating its efficacy in enhancing postoperative recovery
	Goldstein et al. (2005) [11]	RCT	39	Administration of postoperative OMT enhanced pre- and postoperative morphine analgesia in the immediate 48-hour period following elective total abdominal hysterectomy, with significant reduction in morphine use and blood concentrations ($p \leq 0.04$)
Chiropractic	Chu and Trager (2022) [12]	Retrospective chart review	31	A retrospective chart review showed chiropractic spinal manipulation (CSMT) significantly reduced pain and disability in adults with persistent spinal pain syndrome type 2 (PSPS-2) following lumbar surgery. Average baseline Numeric Pain Rating Scale (NPRS) scores fell from 6.6 to 0.6, and Oswestry Disability Index (ODI) scores dropped from 43.8% to 2.4% posttreatment. Predictors of better outcomes included younger age, shorter symptom duration, and higher baseline pain or disability levels ($p < 0.05$)
	Coulis & Lisi (2013) [13]	Case study	3	This case series described chiropractic treatment outcomes for three patients with postoperative spine pain. Treatment modalities included spinal manipulation and flexion-distraction mobilization. Patient-reported outcomes indicated subjective improvements in pain, with numeric pain scores decreasing notably. Specifically, pain levels were reported to decrease by at least 2 points on the Numeric Pain Scale, reflecting clinically significant pain relief. All treatments were tolerated with one report of transient benign soreness, indicating a favorable safety profile

(continued)

Table 32.1 (continued)

Integrative therapy	Author (year)	Study type	Sample size	Outcome of study
	Hurwitz et al. (2006) [14]	RCT	681	Study followed 610 patients for 18 months, finding minimal difference between chiropractic and medical care in improving pain and disability (adjusted RR of remission = 1.29; 95% CI = 0.80–2.07). Physical therapy combined with medical care was more effective (adjusted RR = 1.69; 95% CI = 1.08–2.66). Perceived improvement was higher in chiropractic patients, yet less than 20% were pain-free at 18 months
	Kruse and Cambron (2011) [15]	Retrospective study	32	In this retrospective study, patients with postsurgical lumbar spine pain experienced significant pain relief following chiropractic care using the Cox flexion distraction technique. The average pain score decreased from 6.4 to 2.3 after an average of 14 treatments. The most significant improvement was seen in patients who had combination surgeries (discectomy, fusion, and/or laminectomy), with an average pain reduction of 5.7 out of 10. No adverse events were reported
Massage	Mitchinson et al. (2007) [16]	RCT	605	This study utilized back massage as adjuvant therapy for acute postoperative pain. In the massage group ($N = 200$), short-term decreases in pain intensity and unpleasantness were 0.34 and 0.41 points more (on a 10-point scale) than the control group ($N = 203$), respectively ($p < 0.001$ for both). Anxiety reduction was 0.48 points greater in the massage group compared to controls ($p < 0.001$). Long-term, pain intensity and unpleasantness declined faster in the massage group by 0.22 and 0.25 points per day, respectively ($p = 0.02$ and $p = 0.01$), over the first four postoperative days
	Cutshall et al. (2010) [17]	RCT	58	In the massage group ($N = 30$), there were significant reductions in pain (mean change: −2.3, $p < 0.001$), anxiety (mean change: −1.7, $p< 0.001$), and tension (mean change: −3.1, $p < 0.001$) compared with the control group ($N = 28$), which received standard care. The study highlighted the feasibility of massage in a cardiac surgical setting, with positive patient feedback and no reported adverse events
	McRee et al. (2007) [18]		105	Preoperative massage (30 minutes) in female subjects undergoing laparoscopic gynecologic surgery led to significantly reduced intraoperative narcotics use (2.2 ± 1.1 mcg of fentanyl/kg/hour in the massage group vs. 2.8 ± 2.0 mcg/kg/hour in the control group) and lower postoperative anxiety (9.83 ± 2.9 in the massage group vs. 11.24 ± 3.6 in the control group). The study indicates that preoperative massage may help in decreasing narcotic requirements and anxiety levels postsurgery
	Liu et al. (2022) [19]	Meta-analysis	3243	The comprehensive meta-analysis revealed that massage therapy significantly reduced postoperative pain with a standardized mean difference (SMD) of −1.32 (95% CI, −2.01 to −0.63; $p = 0.0002$) and high heterogeneity (I2 = 98.67%). The analysis included short-term (immediate assessment) and long-term (4–6 weeks post-treatment) effects, both showing significant pain relief. In subgroup analyses, the effectiveness of massage therapy was consistent across various surgical types, with notable pain reduction for cesarean section and heart surgery. No significant adverse effects were reported, indicating a favorable safety profile for massage therapy in postoperative pain management

Energy Therapies

Energy therapies focus on the belief that the body is encompassed by a vital life force or energy field (Table 32.2). These therapies aim to balance and heal the energy flow within the body to enhance physical, mental, and emotional health. Energy healing encompasses various practices that aim to manipulate the energy fields around the body to promote health and healing. Practitioners use their hands to clear, energize, and balance the body's energy pathways, or meridians, to support healing and foster physical and emotional well-being. Some of these therapies may also fall into other categories. For example Qigong can also be considered a mind-body therapy, and acupuncture can be considered a manipulative therapy.

Reiki

Reiki is a Japanese form of energy healing where practitioners channel universal energy through their hands to the recipient, promoting healing, relaxation, and stress reduction. This noninvasive therapy is believed to improve the flow and balance of energy in the body, facilitating the body's natural healing processes. Studies to date have provided equivocal results for perioperative pain management (Table 32.2).

Table 32.2 Evidence-based energy therapies

Integrative therapy	Author (year)	Study type	Sample size	Outcome of study
Acupuncture	Usichenko et al. (2007) [21]	RCT	120	In this randomized trial, patients receiving auricular acupuncture required significantly less ibuprofen (median 200 mg, interquartile range 0–600 mg) after ambulatory knee surgery than the control group receiving an invasive needle technique (median 600 mg, interquartile range 200–800 mg), with $p = 0.012$. Pain intensity was similar across groups, highlighting auricular acupuncture's analgesic benefit postoperatively
	Han et al. (2024) [22]	CT	41	This clinical trial demonstrated that angiopuncture significantly decreased pain levels postoperatively at various time points (6, 12, 24, 48, and 72 hours) with statistical significance ($p < 0.05$), indicating its potential as an effective pain management technique after surgery
	Taghavi et al. (2013) [23]	RCT	90	Electro-acupuncture significantly reduced postoperative pain with lower VAS scores by 1–2 points ($p < 0.05$) and reduced morphine use by 1.9 mg in the first 6 hours post-operation compared to controls. The time to first analgesic request was extended by about 8 minutes in the acupuncture group. Fewer acupuncture patients experienced dizziness as well
Energy Healing	Mcneil et al. (2021) [24]	RCT	50	EH therapy showed a decrease in preoperative anxiety in patients undergoing posterior surgical correction for AIS. No significant difference in pain reduction or hospital stay length compared to controls (pain: $p < 0.001$ postoperative increase, anxiety decrease: $p < 0.001$, oral medication transition: $p = 0.11$, hospital stay: $p = 0.07$)
	Aslan & Özkan (2019) [25]	RCT	210	In this study, abdominal surgery patients treated with bioenergy showed a significant decrease in postoperative pain compared to those not treated with bioenergy. Pain severity scores were lower at 60, 90, and 120 minutes post-treatment in the bioenergy group, indicating its effectiveness in pain management

(continued)

Table 32.2 (continued)

Integrative therapy	Author (year)	Study type	Sample size	Outcome of study
Qigong	Quixadá et al. (2022) [26]	CT	21	The study found that Qigong training significantly impacted posture and mood in breast cancer survivors with persistent postsurgical pain. Improvements in vertical head and spine angles correlated with reductions in fatigue, anxiety, and pain severity. Specifically, a moderate to strong correlation was observed between improved posture and reduced fatigue and anxiety in different conditions (EO, EOR, EC). This supports the embodied cognition framework, suggesting that Qigong can be an effective integrative treatment for biopsychosocial conditions like PPSP
	Osypiuk et al. (2020) [27]	Pilot Study	21	In breast cancer survivors with persistent postsurgical pain, significant improvements were observed at 12 weeks in pain severity and interference, fatigue, anxiety, depression, perceived stress, self-esteem, pain catastrophizing, several subdomains of quality of life, interoceptive awareness, and shoulder range of motion. Postintervention effects sustained at 6 months. No serious adverse events were reported
Reiki	Midilli et al. (2016) [28]	RCT	45	In patients undergoing cesarean section, 15 minutes of Reiki applied to the incision area significantly reduced pain and decreased the need for analgesics compared to sham Reiki and control groups. Pain reduction in the Reiki group was 76.06% between the first and second day posttreatment. Reiki did not significantly affect vital signs but extended the time before the need for additional analgesics
	Bourque et al. (2012) [29]	RCT	30	In patients undergoing screening colonoscopy, Reiki did not significantly reduce the amount of meperidine needed compared to control, but 16% of Reiki recipients required less than 50 mg of meperidine, compared to all patients in the control group requiring more than 50 mg. This suggests a potential for decreased pain medication needs during colonoscopy when Reiki is used, warranting further study
	vanderVaart et al. (2011) [30]	RCT	80	In women undergoing elective C-section, distant Reiki did not significantly affect pain levels, opioid consumption, or rate of healing compared to usual care. However, the Reiki group showed significantly lower heart rate and blood pressure postsurgery
	Shaybak et al. (2017) [31]	RCT	40	Study on patients undergoing CABG showed Reiki energy healing reduced chest pain severity caused by coughing and deep breathing. The study suggests Reiki as an effective nonmedical method for pain relief post-CABG, recommending further research on its efficacy compared to drug therapy and other complementary medicine methods
	Şişman & Arslan (2023) [32]	RCT	93	This study targeted patients undergoing abdominal surgeries. Reiki significantly reduced surgical fear, anxiety, and pain levels, and increased oxygen saturation levels in the Reiki group compared to the control and sham Reiki groups. The differences were statistically significant ($p < 0.005$), suggesting Reiki's effectiveness as a noninvasive, costefficient method for patient care in abdominal surgery

Qigong

Qigong is a traditional Chinese mind-body practice combining movement, meditation, and controlled breathing to enhance the flow of Qi (vital energy) in the body. Regular practice is thought to improve mental and physical health by enhancing balance, flexibility, and the body's innate healing abilities.

Acupuncture

Acupuncture, a traditional Chinese medical practice, involves inserting thin needles at specific body points to alleviate pain and promote healing. Widely recognized for its effectiveness in treating various conditions, acupuncture is particularly noted for its success in managing chronic low back pain, offering a less invasive alternative to conventional medical treatments. Battlefield acupuncture (BFA), a form of auricular acupuncture that targets points in the ear utilizing semi-permanent needles, was developed specifically to address acute pain and can be used in the peri-operative setting. Table 32.2 provides a non-exhaustive list of acupuncture studies for postoperative pain management, highlighting several forms of acupuncture, including auricular acupuncture, angiopuncture, and electroacupuncture. Other forms of acupuncture include Japanese scalp acupuncture and Korean hand acupuncture.

Whole Medical Systems

Whole medical systems offer potential avenues for the management of perioperative pain. Evidence exists to support Traditional Chinese Medicine, Ayurveda, Homeopathy, and Naturopathy as being beneficial in reducing both acute and chronic pain (Table 32.3). These health systems usually involve a holistic approach, often rooted in herbal medicine with an emphasis on whole body treatment. The evidence is more robust for these systems having a role in the management of chronic pain and disability. However, there remains a need to further investigate the role of these systems in alleviating the burden of acute pain in a perioperative setting. The aspects of these health systems that may play the largest role in the improvement of acute pain include interventions such as acupuncture, aromatherapy, or nutritional supplementation with herbal remedies. There may be a predictive role for Ayurvedic medicine as to which patients will have greater pain tolerance (Table 32.3). Overall, these medical systems may be most utilized as adjunctive measures. It should be noted that many of the therapies already discussed are components of some of these whole medical systems.

Mind-Body Therapies

Mind-body therapies include approaches to health centered around building a stronger connection between the mind and the body to promote improved wellness (Table 32.4). Current therapies include guided imagery, biofeedback, hypnosis, mindfulness, meditation, yoga, and tai chi. These therapies remain intriguing due to their low adverse effect risk as well as their ability to affect health outcomes across broad patient categories. Technology may allow for augmentation of benefits seen in these therapies, such as EMG biofeedback and app-based meditation and hypnosis. Emerging therapies may include virtual reality-based versions of these mind-body therapies.

Table 32.3 Evidence-based whole medical systems

Systems	Author (year)	Type	Intervention	Study population and sample size	Results	Adverse effects
Traditional Chinese Medicine	Liu et al. (2024) [33]	RCT	Effect of acupressure medicine on perioperative nursing of children with trichiasis surgery	Children ($n = 52$) per group	Significantly decreased pain scores, decreased incidence of crying, and increased overall satisfaction	None reported
	Zhang et al. (2014) [34]	Animal study	Defhyrocorybulbine synthesis and investigation of antinociceptive capabilities in dopamine knockout mice	Knockout mice ($n = 9$–24)	Antinociceptive effect in neuropathic mouse model, lack of development of tolerance	None reported
Ayurvedic	Hegana et al. (2016) [35]	RCT	Effect of Karamardadi yoga 500 mg vs. diclofenac sodium 50 mg in postop management of patients undergoing hemorrhoidectomy	Adults ($n = 30$) per group	Reduced time to first analgesic dose in experimental group vs. control group	None reported
	Lim et al. (2017) [36]	Animal study	Ashwagandha (*Withania somnifera* root extract) activity in rat model of postoperative and neuropathic pain	Rats ($n = 9$) per group dosage	Hyperalgesia and cytokine levels were alleviated after 15 days of treatment with 100 mg/kg and 300 mg/kg	None reported
	Shindhe et al. (2017) [37]	Observational	30 individuals who underwent hemorrhoidectomy under spinal anesthesia were selected and prakriti was assessed along with pain	Adults ($n = 30$)	Patients demonstrated significantly different wipeout periods	None reported
Homeopathy	Barlow et al. (2013) [38]	Systematic review	Multimodal therapies to improve pain after ambulatory knee surgery.	Adults ($n = 565$) receiving intervention	Reduced pain with acupoint pressure, Arnica demonstrated reduced swelling but not reduced pain	None reported
	Stevinson et al. (2003) [39]	RCT	30C, 6C, or placebo of homeopathic arnica given to patients undergoing elective carpal tunnel surgery	Adults ($n = 62$) across groups	No significant difference between Arnica and placebo groups	No significant difference between Arnica and placebo groups
Naturopathy	Lederer et al. (2018) [40]	Systematic review/ meta-analysis	Treatments for typical postoperative problems with a variety of naturopathic medicines	Mixed ($n = 16{,}490$)	Some reports of reduced pain in acupuncture, aromatherapy, and music therapy	None reported in studies included

Table 32.4 Evidence-based mind-body therapies

Mind-body therapy	Author (year)	Type	Intervention	Study population and sample size	Results	Adverse effects
Guided Imagery	Jacobson et al. (2016) [41]	RCT	Guided imagery pre-, intra-, and postoperative periods for total knee replacement	Adults (n = 29) per group	Lower Western Ontario and McMaster Universities Arthritis Index (WOMAC) Pain scores at 3 weeks postsurgery	None reported
	Vagnoli et al. (2019) [42]	RCT	Relaxation guided imagery preminor surgery	Children 6–12 years old (n = 30) per group	Face, Legs, Activity, Cry, Consolability Scale—significantly reduced in experimental group	None reported
Virtual reality	Haisley et al. (2020) [43]	RCT	VR meditation/mindfulness sessions post-operatively for minimally invasive foregut surgery	Adults (n = 26) per group	Similar postoperative pain scores and overall satisfaction	None reported
	Orgil et al. (2023) [44, 45]	RCT	VR biofeedback postoperatively and during pain	Children and adolescents (n = 35) per group	Questionnaire responses indicate patients received pain benefit	None reported
Biofeedback	Wang et al. (2015) [46]	RCT	Biofeedback + continuous passive motion vs. control post total knee arthroplasty	Adults (n = 66) total	Numerical pain score significantly reduced	None reported
	Xie et al. (2021) [47]	Systematic review/ meta-analysis	Electromyography (EMG) biofeedback post any knee surgery across three trials	Adults (n = 222) total	No statistically significant pain reduction	None reported
Hypnosis	Awaludin et al. (2022) [48]	Cross-sectional	Smartphone-based perioperative nursing intervention for patients	Adults (n = 86)	Reduced pain and anxiety levels	None reported
	Gupta et al. (2022) [49]	RCT	Hypnosis session vs. hypnosis education for patients undergoing total knee arthroplasty	Adults (n = 64) total	Reduced opioid usage and pain in opioid-experienced patients	None reported
	Rosenbloom et al. (2024) [50]	RCT	Pre and postoperative hypnosis for major oncologic surgery	Adults (n = 92) total	Reduced opioid usage	None reported
	Potie et al. (2016) [51]	Review	Pre, peri, and postoperative hypnosis in breast cancer surgery patients	Adults (n unlisted)	Reduced pain perception and pain scores	None reported
	Lacroix et al. (2019) [52]	Nonrandomized study	Postoperative hypnosis in mastectomy patients	Adults (n = 21) per group	Reduced acute pain, reduced opioid dosage	None reported

(continued)

Table 32.4 (continued)

Mind-body therapy	Author (year)	Type	Intervention	Study population and sample size	Results	Adverse effects
Mindfulness/ Meditation	Gurram et al. (2021) [53]	RCT	Heartfulness meditation before impacted third molar surgery	Adults (n = 60) total	Reduced anxiety scores, no difference in pain scores	None reported
	Canfield et al. (2021) [54]	Intervention	Self-guided mindfulness pre- and postoperatively for total knee arthroplasty	Adults (n = 189) in treatment group	Significantly reduced sleep disturbance, no difference in pain scores	None reported
	Roberts et al. (2022) [55]	Review	Pre-, intra-, and postoperative mindfulness	Adults (n = 1324)	Reduced opioid usage and pain severity	None reported
Yoga	Sohl et al. (2016) [56]	Single arm	1 pre- and 2 postoperative yoga sessions for patients undergoing exploratory laparotomies for suspected gynecologic malignancies	Adults (n = 10)	Decreases in acute pain distress and increased satisfaction	None reported
	Chandrababu et al. (2023) [57]	Systematic review/ meta-analysis	Yoga interventions in patients undergoing coronary artery bypass graft	Adults (n = 1227)	Decreased pain, stress, inflammatory markers	None reported
Tai Chi Chuan/ Qi gong	Li et al. (2019) [58]	RCT	Tai Chi exercises in the weeks post total knee arthroplasty	Adults (n = 107) total	Improved WOMAC Physical function, no difference in pain	None reported
	Osypiuk et al. (2020) [27]	Single-arm pilot	12-week Qigong mind-body exercise for breast cancer patients with persistent postsurgical pain	Adults (n = 18)	Statistically significant improvements were observed in pain severity and interference, fatigue, anxiety, depression, perceived stress, and self-esteem	None reported
Multifactorial	Garland et al. (2020) [59]	Systematic review/ meta-analysis	Meditation/guided imagery/relaxation/ hypnosis in reducing opiate-treated pain postoperative	Adults (n = 6404)	Significant moderate reductions in pain, small reduction in opiate usage	2/29 studies reported worsening opioid dosages

Biologically Based Therapies

As previously noted, biologically based medicine forms an underpinning of many holistic medical systems. However, many of these remedies have been investigated independently of their traditional systems, highlighting the potential for more individualized therapeutic effects tied to dosage or extraction of active ingredients. In the peri- and postoperative setting, herbal remedies may have anticoagulatory, antiinflammatory, and antinociceptive effects (Table 32.5). While there is evidence to suggest numerous supplements may have potentially harmful effects, these effects seemed to be tied more to interactions with medications rather than inherent harms.

Vitamins and other dietary supplements have been investigated in different dosages and concentrations for their effect on pain reduction, both in an acute and chronic setting. While vitamin deficiencies have well-known roles in health outcomes, current evidence suggests that augmentation may be beneficial even in patients without severe deficiencies. We highlight B, C, D, and E vitamins, along with magnesium and fish oil, in this section for their use in pain control (Table 32.6). Compared to herbal remedies, these nutritionally based treatments may be associated with a lower risk of adverse effects.

While supplementation with specific nutritional agents may provide benefit, there may also be a role for overall dietary patterns in the management of perioperative pain. Evidence remains more limited due to the difficulty of capturing the nuances within and between different dietary patterns. The current globalized diet landscape includes numerous options ranging from fully meat based to vegan. Vegan, vegetarian, Mediterranean, ketogenic, and others may have positive effects in pain control in the perioperative setting (Table 32.7).

Table 32.5 Evidence-based herbal supplements

Herbal medicine	Author (year)	Type	Intervention	Study population and sample size	Results	Adverse effects
Gingko/Ginseng/ Green Tea	Kellermann et al. (2012) [60]	Meta-analysis	Standardized *Gingko biloba* leaf extract	Adults with dementia, peripheral arterial disease, or diabetes mellitus (n = 1985) between groups	No increased bleeding risk	None reported
	Tan et al. (2020) [61]	Meta-analysis	Gingko/green tea use concurrently with warfarin	Adults receiving warfarin (n unlisted)	Possible increased risk of warfarin potentiation	Increased bleeding risk
	Choi et al. (2019) [62]	Review	Ginseng therapy or ginseng combination therapy	In vitro and in vivo studies; adults receiving antiplatelet or anticoagulation (n unlisted)	Potential antiplatelet effects, lower risk of interaction with warfarin	Potentially increased bleeding
	Choi et al. (2017) [63]	Review	Analysis of warfarin interaction with American Ginseng, Korean red ginseng, ginkgo preparations of patients	Adults (n = 160) between studies	Possible interaction of American ginseng, other herbs unclear	Low rate of adverse effects
Bromelain	Pereira et al. (2023) [64]	Systematic review	Effect of 99.9–1200 mg/day dosage of bromelain on inflammatory markers	Adults (n = 192) between studies	Showed positive effects on inflammatory markers, including IFN-γ and IL-5, some variance	Very few adverse effects reported, occasional GI symptoms
	Leelakanok et al. (2023) [65]	Systematic review and meta-analysis	Effect of oral and topical bromelain on various measures, including sinusitis, burn pain, and wound healing	Adults (n= 1375) treatment group	Some slight benefit of oral bromelain in pain scores, not extremely strong	Very few reported including headache, nausea, flatulence
Boswellia serrata/ *Curcuma longa*	Merolla et al. (2015) [66]	RCT	Assess the analgesic effect of supplement in patients undergoing supraspinatus repair	Adults	Significantly lower overall pain scores in group T versus group P at 1 week (p = 0.0477)	None reported
Topical cinnamon ointment	Mohammadi et al. (2014) [67]	RCT	Effect of cinnamon on perineal pain and healing in postpartum women following episiotomy incision repair	Adults (n = 144) between groups	Significantly decreased VAS pain scores at 1 week vs. placebo Decreased VAS pain score at 4 hours and 10–11 days after procedure	None reported

Topical nutmeg extract	Motilal et al. (2013) [68]	RCT	Effect of topical nutmeg extract on symptoms of painful diabetic neuropathy	Adults ($n = 74$) between groups	No statistical difference between trial and placebo groups	None reported
Oral turmeric therapy	Paultre et al. (2021) [69]	Systematic review	Effect of turmeric therapy on pain and function in patients with knee osteoarthritis	Adults ($n = 1174$) across studies	Improvement from baseline in placebo studies; no difference in studies while comparing to NSAIDs	No severe adverse events, mild GI symptoms
Oral kava	Savage et al. (2023) [70]	RCT	Effect on kava on dorsal anterior cingulate GABA levels in patients with generalized anxiety disorder	Adults ($n = 37$) between groups	Reduction of central GABA levels, no significant relation to treatment	No severe adverse effects
Passiflora incarnata, *Erythrina mulungu*, midazolam	da Cunha et al. (2021) [71]	RCT	Effect of oral preparations of *Passiflora incarnata*, *Erythrina mulungu*, midazolam on anxiety in patients undergoing extraction of third mandibular molars	Adults ($n = 200$) total	Similar reduction in measures of anxiety for *Passiflora* and midazolam, compared to placebo and *mulungu*	No severe adverse effects
Valerian root extract (VRE)	Roh et al. (2019) [72]	RCT	Effect of 100 mg 3 times a day of VRE on resting-state connectivity changes via EEG in patients with stress	Adults ($n = 64$) between groups	No significant difference in improved anxiety between VRE and placebo	No severe adverse effects

Table 32.6 Evidence-based vitamin/supplement therapies

Vitamin/ supplements	Author (year)	Type	Intervention	Study population and sample size	Results	Adverse effects
Vitamin D	Helde-Frankling et al. (2021) [73]	RCT	12 weeks of cholecalciferol (vitamin D3) 4000 IU/day or placebo	Adult palliative cancer patients with 25-hydroxy vitamin D levels <50 nmol/L (n = 150) total	Per-protocol analysis showed less usage of opioids in the vitamin D group compared to in the placebo group −0.56 (95% CI −1.07; −0.05; p = 0.03)	No major adverse effects, two cases of mild hypercalcemia
	Zadro et al. (2017) [74]	Systematic review and meta-analysis	Measuring association of vitamin D deficiency with lower back pain	Adults with lower back pain (n = 21,742) total	Individuals with LBP were more likely to have vitamin D deficiency (pooled OR = 1.60, 95% CI: 1.20–2.12, p = 0.001, n = 19), severe deficiency (pooled OR = 2.08, 95% CI: 1.19–3.64, p = 0.010, n = 7), compared to those without LBP	N/A
Magnesium	Albrecht et al. (2013) [75]	Meta-analysis	Effect of perioperative administration of varying doses of magnesium on opioid consumption and pain scores	Adult surgical patients (n = 1461) total	Average 24.4% reduction of IV morphine consumption at 24 hours post op; $p < 0.00001$, mean pain scores reduced by 4.2, $p < 0.0001$	Hypotension, bradycardia, sedation
	Azimi et al. (2023) [76]	Systematic review and meta-analysis	Effect of intraoperative adjunctive magnesium sulfate on pain and opioid usage	Adult patients undergoing total knee arthroplasty (n = 536) total	Significantly reduced opioid consumption during the first 24 hours after operation (SMD: −1.88, 95% confidence interval (CI): [−3.66 to −0.10]; p = 0.038), lower pain scores at rest 24 hours after surgery (SMD: −1.53, 95% CI: [−2.70 to −0.37]; p = 0.010)	No significant adverse effects
	Shi et al. (2021) [77]	Meta-analysis	Effect of intraarticular magnesium on pain and opioid usage	Adult patients undergoing arthroscopic knee surgery (n = 677) total	Mg was associated with significantly less opioid consumption within postoperative 24 h (MD = − 4.23, 95% CI: − 4.64 to − 3.82; p = 0.21; I2 = 27%), significantly reduced VAS pain scores at rest and with movement at various times within 24 hours	No significant adverse effects

Vitamin C	Jain et al. (2019) [78]	RCT	Effect of vitamin C tablet on pain score, analgesia requirement, and functional outcome	Patients with closed fracture of the foot/ankle who had received surgery under spinal anesthesia ($n = 60$) between groups	The VAS score at second and sixth week follow-up was 3.13 ± 1.74 and 0.63 ± 0.93 in group A and 1.83 ± 1.91 and 0.07 ± 0.254 in group B, respectively ($p < 0.008$) The mean amount of analgesia used at the end of 6 weeks, in group A (placebo) was 5.70 ± 1.06 (3–8.2) g and in group B (vitamin C) was 3.41 ± 1.05 (1.3–6.1) g ($p < 0.002$)	No significant adverse effects noted
	Aïm et al. (2017) [79]	Systematic review and meta-analysis	Effect of various dosages of vitamin C supplementation post injury for 50 days on pain and development of complex regional pain syndrome 1	Patients with various degrees of wrist fractures ($n = 875$) across studies	No significant difference between treatment and control groups	No significant adverse effects noted
	Chen et al. (2016) [80]	Systematic review and meta-analysis	Effect of perioperative vitamin C supplementation on postoperative pain and development of complex regional pain syndrome 1	Patients undergoing various surgical procedures ($n = 1598$) across studies	3 applicable CRPS I studies showed a decrease in postoperative CRPS I after perioperative vitamin C supplementation (relative risk = 2.25; τ 2 = 0, inconclusive evidence for pain reduction	No significant adverse effects noted
Boswellia serrata and/or high EPA supplement vs. placebo	Pérez-Piñero et al. (2023) [81]	RCT	Effect of *Boswellia serrata* and/or high EPA supplement on pain and function in knee pain	Patients above age 40 with persistent knee pain ($n = 120$) across groups	Decreases of WOMAC overall score were only statistically significant for the group of Boswellia + AvailOm® as compared with placebo (mean − 8.327 ± 2.788, $p = 0.021$). Analysis showed statistically significant differences in VAS scores of the three groups of Boswellia, AvailOm®, and Boswellia + AvailOm® as compared to placebo, with mean differences of −1.784 ± 0.499 ($p = 0.003$), −1.779 ± 0.490 ($p = 0.003$), and − 1.695 ± 0.495 ($p < 0.005$), respectively	No significant adverse effects noted

(continued)

Table 32.6 (continued)

Vitamin/ supplements	Author (year)	Type	Intervention	Study population and sample size	Results	Adverse effects
Omega-3-fatty acids	Bernabe-Garcia et al. (2016) [82]	RCT	Effect of enteral Docosahexaneoic acid (DHA) administered on reduction of analgesic requirement	Neonates undergoing cardiovascular surgery ($n = 35$) across groups	Compared with the control group, the DHA group received lower cumulative dose (14.6 ± 2.2 vs. 25.2 ± 4.8 μg/kg, $p = 0.029$) and shorter duration of buprenorphine (2 days (1–8) vs. 4.5 days (1–12); $p = 0.053$).	No significant adverse effects noted
	Ruiz-Tovar et al. (2019) [83]	RCT	Effect of nutritional supplementation with omega-3-fatty acids on postoperative pain	Adults receiving laparoscopic roux-en-Y gastric bypass ($n = 40$) across groups	Mean postoperative pain was 25 ± 9.2 mm in control group and 10.9 ± 4.4 mm in experimental group ($p = 0.015$)	No significant adverse effects noted
Vitamin B and E in combination with diclofenac	Dehghan et al. (2015) [84]	RCT	Effect of oral B/E vitamins with diclofenac compared to placebo plus diclofenac on pain	Adult patients with knee osteoarthritis ($n = 120$) total	Knee pain VAS, total pain severity, knee joint stiffness, and the past 48-hour function changed differently in the three groups so that decrease in knee pain VAS and the past 48-hour function was reported higher in the vitamin B group than in the diclofenac and vitamin E groups ($p = 0.008$)	No significant adverse effects
Vitamin B complex	Khezri et al. (2017) [85]	RCT	Effect of vitamin B complex plus gabapentin vs. gabapentin alone on postoperative pain	Woman who underwent cesarean section under spinal anesthesia ($n = 128$) between groups	The pain intensity in the gabapentin plus vitamin B complex group was lower than gabapentin group during 12 hours after surgery (95% CI: 1.4–2.2; $p < 0.001$). Total analgesic consumption in this group was less than gabapentin alone (95% CI: 1.07–1.24; $p = 0.034$)	No significant adverse effects
Eicosapentaenoic acid, docosahexaenoic acid, oleic acid, folic acid, vitamins A, B-6, D, E	Carrero et al. (2005) [86]	RCT	Effect of multiplex supplement vs. vitamin A and D supplement on various parameters in peripheral vascular disease	Male patients with peripheral vascular disease ($n = 60$) between groups	PFWD (pain-free walking distance) increased by up to 3.5 times in the S group. This increase was progressive from 3–12 months. Increases in PFWD directly correlated with the increases in plasma eicosapentaenoic acid (EPA) ($r = 0.37$; $p = 0.006$) and RBC folate concentrations ($r = 0.28$; $p = 0.040$), but showed only a trend with plasma oleic acid concentration ($r = 0.24$; $p = 0.083$).	No significant adverse effects
Topical vitamin E ointment	Ruiz-Tovar et al. (2016) [87]	RCT	Effect of topical vitamin E ointment vs. Vaseline ointment on pain	Adult patients undergoing hemorrhoidectomy ($n = 30$) per group	Median pain by VAS post-operative day (POD) 1 was 1.5 vs. 5 in control group ($p < 0.001$), POD 3 3.5 vs. 8.5 in control group ($p < 0.001$), POD 7 0.5 vs. 5 in control group	No significant adverse effects

Table 32.7 Evidence-based dietary therapies

Diet	Author (year)	Type	Intervention	Study population and sample size	Results	Adverse effects
Vegetarian/vegan	Nadal-Nicolas et al. (2021) [88]	Systematic review	Clinical trials/cohort studies with various types of vegan/vegetarian diets	Patients with fibromyalgia and healthy volunteers ($n = 255$) between studies	Inconsistent; some studies report statistically significant decreases in pain, more report no difference	No major adverse effects noted
Mediterranean, vegetarian, vegan, ketogenic	Schonenberger et al. (2021) [89]	Systematic review	Effect of dietary modification in RCTs on pain	Adults with rheumatoid arthritis ($n = 326$) across studies	Antiinflammatory diets resulted in significantly lower pain than ordinary diets (−9.22 mm; 95% CI −14.15 to −4.29; $p = 0.0002$; 7 RCTs, 326 participants)	No significant adverse effects noted
Ketogenic	Abboud et al. (2021) [90]	Systematic review	Effect of ketogenic dietary modifications in RCTs on quality of life in adults with chronic disease	Adults with various chronic diseases including obesity, diabetes, cancer ($n = 479$) across studies	No major statistically significant impact on pain was noted	No significant adverse effects
Various dietary modifications, supplements including ketogenic diet, Mediterranean diet	Xu Lou et al. (2022) [91]	Systematic review	Effect of dietary modification	Adults with noncancer chronic pain ($n = 9154$) across studies	In studies with a focus on dietary modification, greater decrease in pain was found, according to WOMAC, at 18 months in diet and exercise group when compared to exercise group only ($p = 0.004$) and D ($p = 0.001$)	No major adverse effects noted

Challenges and Considerations in Integrative Pain Management

Integrative pain management approaches, particularly manipulative and energy therapies, face challenges and special considerations. One significant hurdle is the difficulty in conducting placebo-controlled trials for therapies that require active participant interaction, such as OMT, chiropractic care, and Reiki. This makes it challenging to achieve the highest level of evidence for their efficacy. The subjective nature of these therapies and the personal experience of the practitioner and patient can introduce biases and misconceptions, affecting study outcomes and public perception. However, this individualized approach to therapy may also be a benefit of these practices, aligning closely with patient-centered care and potentially enhancing engagement, self-efficacy, and satisfaction. The challenge for the field is to develop research designs that respect this complexity while still providing rigorous, interpretable evidence about when, for whom, and under what conditions these therapies are most beneficial.

Biologically based alternative therapies must be rigorously investigated for quality of ingredients, as different sourcing may affect potency and side effect profile. Other considerations in the evaluation of alternative medical therapies for perioperative pain is the value of including multiple aspects from one medical system compared to that of picking and choosing from diverse options. Many systems may work best in a synergistic manner; this may influence the accuracy of current evidence, as separating aspects of different systems may affect their effectiveness.

Another consideration is the availability of trained professionals who can administer these therapies in a perioperative setting. Acquiring the necessary skills for specialized treatments like acupuncture or hypnotherapy demands extensive training, which may not be accessible or prioritized in all healthcare settings. Additionally, hospital administrators may be hesitant to integrate these therapies due to the costs associated with training and facility use, compounded by the typically low reimbursement rates for these treatments. However, initiatives like the Veterans Affairs' (VA) "Whole Health" programs and widespread training of clinicians in Battlefield Acupuncture demonstrate a move towards increasing access to integrative pain management techniques.

Example Case Studies

Consider an acrobat with a history of opioid abuse needing orthopedic surgery for a torn rotator cuff. He is adamant about avoiding opioids and midazolam due to fear of relapse. In such a scenario, nonpharmacological approaches like acupuncture, Reiki, or mindfulness-based stress reduction could be employed to manage his pain and anxiety effectively. He may also benefit from supplements such as magnesium and vitamin C, administered intraoperatively, and further supplementation of B-complex vitamins postoperatively, in combination with continued acupuncture sessions and medical massage to reduce his postoperative pain.

In another case, a patient post-spine surgery experiences unmanageable pain, despite numerous interventions including trigger point injections and patient-controlled analgesia (PCA). The surgical team is having difficulty with managing the patient's pain inpatient. Introducing electroacupuncture (EA) into their treatment plan provides the necessary pain relief to facilitate discharge.

Future Directions and Research

Emerging research is exploring the development of adequate sham controls for therapies that inherently involve touch and personal interaction, which could enhance the quality of randomized controlled trials (RCTs). There is a clear need for larger, pragmatic, multisite clinical trials to ascertain the effectiveness, safety, and cost-efficiency of these integrative therapies in various clinical settings. Technology may affect the method of application of many alternative medical therapies. Future directions may further leverage smartphone, virtual reality, and biofeedback

mechanisms to augment mindfulness and body-based treatments.

Key Takeaways

1. Integrative pain management represents a holistic approach, combining physical, emotional, and spiritual aspects to treat pain.
2. Challenges in integrative pain management include difficulties in conducting placebo-controlled trials and biases related to personal experience.
3. Training and availability of professionals for specialized therapies like acupuncture are significant considerations.
4. Integrative approaches provide additional tools to address complex pain management scenarios effectively.
5. Future research should focus on developing better sham controls and conducting extensive large, pragmatic clinical trials, as well as evaluating facilitators and barriers for integration of therapies into healthcare systems.

References

1. National Center for Complementary and Integrative Health. How integrative health research tackles the pain management crisis. MedlinePlus Magazine [Internet]. Available from: https://magazine.medlineplus.gov/article/how-integrative-health-research-tackles-the-pain-management-crisis. Accessed March 29, 2024.
2. National Center for Complementary and Integrative Health. Statistics on complementary and integrative health approaches [Internet]. Available from: https://www.nccih.nih.gov/research/statistics-on-complementary-and-integrative-health-approaches. Accessed March 29, 2024.
3. National Center for Complementary and Integrative Health. Know the science: how medications and supplements can interact [Internet]. Available from: https://www.nccih.nih.gov/health/know-science/how-medications-and-supplements-can-interact/introduction. Accessed March 29, 2024.
4. National Center for Complementary and Integrative Health. Natural doesn't always mean better [Internet]. Available from: https://www.nccih.nih.gov/health/know-science/natural-doesnt-mean-better. Accessed March 29, 2024.
5. National Center for Complementary and Integrative Health. Know the science [Internet]. Available from: https://www.nccih.nih.gov/health/know-science/quiz. Accessed March 29, 2024.
6. Barral P, et al. Preoperative osteopathic manipulative therapy improves postoperative pain and reduces opioid consumption after total knee arthroplasty: a prospective comparative study. J Osteopath Med. 2020;120(7):436–45. Available from: https://www.degruyter.com/document/doi/10.7556/jaoa.2020.071/html. Accessed March 29, 2024.
7. Roncada G. Osteopathic treatment leads to significantly greater reductions in chronic thoracic pain after CABG surgery: a randomised controlled trial. J Bodyw Mov Ther. 2020;24(3):202–11. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1360859220300565. Accessed March 29, 2024.
8. Probst P, et al. Randomised controlled pilot trial on feasibility, safety and effectiveness of osteopathic MANipulative treatment following major abdominal surgery (OMANT pilot trial). Int J Osteopath Med. 2016;20:31–40. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1746068916300049. Accessed March 29, 2024.
9. Kim BJ, et al. Rehabilitation with osteopathic manipulative treatment after lumbar disc surgery: a randomised, controlled pilot study. Int J Osteopath Med. 2015;18(3):181–8. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1746068914001205. Accessed March 29, 2024.
10. Baltazar GA, et al. Effect of osteopathic manipulative treatment on incidence of postoperative ileus and hospital length of stay in general surgical patients. J Osteopath Med. 2013;113(3):204–9. Available from: https://www.degruyter.com/document/doi/10.7556/jaoa.2013.113.3.204/html. Accessed March 29, 2024.
11. Goldstein FJ, et al. Preoperative intravenous morphine sulfate with postoperative osteopathic manipulative treatment reduces patient analgesic use after total abdominal hysterectomy. J Osteopath Med. 2005;105(6):273–9. Available from: https://www.degruyter.com/document/doi/10.7556/jaoa.2005.105.6.273/html. Accessed March 29, 2024.
12. Chu EC, Trager RJ. Effectiveness of multimodal chiropractic care featuring spinal manipulation for persistent spinal pain syndrome following lumbar spine surgery: retrospective chart review of 31 adults in Hong Kong. Med Sci Monit. 2022;28. Available from: https://www.medscimonit.com/abstract/index/idArt/937640. Accessed March 29, 2024.
13. Coulis CM, Lisi AJ. Chiropractic Management of Postoperative Spine Pain: a report of 3 cases. J Chiropr Med. 2013;12(3):168–75. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1556370713002228. Accessed March 29, 2024.
14. Hurwitz EL, et al. A randomized trial of chiropractic and medical care for patients with low back pain: eighteen-month follow-up outcomes from the UCLA low back pain study. Spine. 2006;31(6):611–21.

Available from: http://journals.lww.com/00007632-200603150-00002. Accessed March 29, 2024.
15. Kruse RA, Cambron J. Chiropractic Management of Postsurgical Lumbar Spine Pain: a retrospective study of 32 cases. J Manip Physiol Ther. 2011;34(6):408–12.
16. Mitchinson AR, et al. Acute postoperative pain management using massage as an adjuvant therapy: a randomized trial. Arch Surg. 2007;142(12):1158–67; discussion 1167.
17. Cutshall SM, et al. Effect of massage therapy on pain, anxiety, and tension in cardiac surgical patients: a pilot study. Complement Ther Clin Pract. 2010;16(2):92–5. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1744388109001091. Accessed March 29, 2024.
18. McRee L, et al. Effects of preoperative massage on intra- and postoperative outcomes. J Gynecol Surg. 2007;23(3):97–104. Available from: http://www.liebertpub.com/doi/10.1089/gyn.2007.B-02276-1. Accessed March 29, 2024.
19. Liu C, Chen X, Wu S. The effect of massage therapy on pain after surgery: a comprehensive meta-analysis. Complement Ther Med. 2022;71:102892. Available from: https://linkinghub.elsevier.com/retrieve/pii/S0965229922000942. Accessed March 29, 2024.
20. Randall CG, Paul HA, Lumley H, Ortega A, Rowley J, Brown B, Mohan S, et al. Osteopathic manipulative treatment during post-operative recovery: a scoping review. Cureus [Internet]. 2024 Feb 15. Available from: https://www.cureus.com/articles/210973-osteopathic-manipulative-treatment-during-post-operative-recovery-a-scoping-review. Accessed April 29, 2024.
21. Usichenko TI, et al. Auricular acupuncture for pain relief after ambulatory knee surgery: a randomized trial. CMAJ. 2007;176(2):179–83. Available from: http://www.cmaj.ca/cgi/doi/10.1503/cmaj.060875. Accessed March 29, 2024.
22. Han R, et al. Pain relief effect of angiopuncture therapy on patients with postoperative pain: a clinical trial. Medicine (Baltimore). 2024;103(2). Available from: https://journals.lww.com/10.1097/MD.0000000000036847. Accessed March 19, 2024.
23. Taghavi R, et al. The effect of acupuncture on relieving pain after inguinal surgeries. Korean J Pain. 2013;26(1):46–50. Available from: http://www.epain.org/journal/view.html?doi=10.3344/kjp.2013.26.1.46. Accessed March 29, 2024.
24. McNeil N, et al. Randomized controlled trial of energy healing effects on pain and anxiety in AIS posterior surgery: a pilot study. Spine Deform. 2021;9(4):1029–34.
25. Aslan B, Özkan M. The effect of bioenergy on postoperative pain in patients experienced abdominal surgery: a nonpharmacological approach. Complement Ther Clin Pract. 2019;36:158–63.
26. Quixadá AP, et al. Qigong training positively impacts both posture and mood in breast cancer survivors with persistent post-surgical pain: support for an embodied cognition paradigm. Front Psychol. 2022;13:800727. Available from: https://www.frontiersin.org/articles/10.3389/fpsyg.2022.800727/full. Accessed March 29, 2024.
27. Osypiuk K, et al. Qigong mind-body exercise as a biopsychosocial therapy for persistent post-surgical pain in breast cancer: a pilot study. Integr Cancer Ther. 2020;19:153473541989376. Available from: http://journals.sagepub.com/doi/10.1177/1534735419893766. Accessed March 29, 2024.
28. Midilli TS, Gunduzoglu NC. Effects of reiki on pain and vital signs when applied to the incision area of the body after cesarean section surgery: a single-blinded, randomized, double-controlled study. Holist Nurs Pract. 2016;30(6):368–78. Available from: https://journals.lww.com/00004650-201611000-00009. Accessed March 29, 2024.
29. Bourque AL, Sullivan ME, Winter MR. Reiki as a pain management adjunct in screening colonoscopy. Gastroenterol Nurs. 2012;35(5):308–12. Available from: https://journals.lww.com/00001610-201209000-00002. Accessed March 29, 2024.
30. vanderVaart S, et al. The effect of distant Reiki on pain in women after elective caesarean section: a double-blinded randomised controlled trial. BMJ Open. 2011;1(1). Available from: https://bmjopen.bmj.com/lookup/doi/10.1136/bmjopen-2010-000021. Accessed March 29, 2024.
31. Shaybak E, et al. The effect of reiki energy healing on CABG postoperative chest pain caused by coughing and deep breathing. Indian J Public Health Res Dev. 2017;8(2):305. Available from: http://www.indianjournals.com/ijor.aspx?target=ijor:ijphrd&volume=8&issue=2&article=06. Accessed March 29, 2024.
32. Şişman H, Arslan S. The effect of Reiki on anxiety, fear, pain, and oxygen saturation in abdominal surgery patients: a randomized controlled trial. Explore (NY). 2023;19(4):578–86. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1550830722002105. Accessed March 29, 2024.
33. Liu X, et al. Effect of traditional Chinese medicine characteristic nursing on perioperative nursing of children with Trichiasis correction under general anesthesia. Altern Ther Health Med. 2024;30(11):434–9.
34. Zhang Y, et al. A novel analgesic isolated from a traditional Chinese medicine. Curr Biol. 2014;24(2):117–23. https://doi.org/10.1016/j.cub.2013.11.039.
35. Hegana R, et al. Effect of Karamardādi Yoga versus diclofenac sodium in post-operative pain management: a randomized comparative clinical trial. Anc Sci Life. 2016;35(4):217–21. https://doi.org/10.4103/0257-7941.188174.
36. Lim DW, et al. Antihyperalgesic effects of ashwagandha (Withania Somnifera root extract) in rat models of postoperative and neuropathic pain. Inflammopharmacology. 2018;26(1):207–15. https://doi.org/10.1007/s10787-017-0389-1.
37. Shindhe PS, et al. Wipeout period of spinal anesthesia in hemorrhoidectomy in relation to Prakriti: an obser-

vational study. Ayu. 2017;38(3–4):113–6. https://doi.org/10.4103/ayu.AYU_43_17.
38. Barlow T, et al. The effect of complementary therapies on post-operative pain control in ambulatory knee surgery: a systematic review. Complement Ther Med. 2013;21(5):529–34. https://doi.org/10.1016/j.ctim.2013.06.008.
39. Stevinson C, et al. Homeopathic arnica for prevention of pain and bruising: randomized placebo-controlled trial in hand surgery. J R Soc Med. 2003;96(2):60–5. https://doi.org/10.1177/014107680309600203.
40. Lederer AK, et al. Naturopathic treatment and complementary medicine in surgical practice. Dtsch Arztebl Int. 2018;115(49):815–21. https://doi.org/10.3238/arztebl.2018.0815.
41. Jacobson AF, et al. Guided imagery for Total knee replacement: a randomized, placebo-controlled pilot study. J Altern Complement Med. 2016;22(7):563–75. https://doi.org/10.1089/acm.2016.0038.
42. Vagnoli L, et al. Relaxation-guided imagery reduces perioperative anxiety and pain in children: a randomized study. Eur J Pediatr. 2019;178(6):913–21. https://doi.org/10.1007/s00431-019-03376-x.
43. Haisley KR, et al. Feasibility of implementing a virtual reality program as an adjuvant tool for perioperative pain control; results of a randomized controlled trial in minimally invasive foregut surgery. Complement Ther Med. 2020;49:102356. https://doi.org/10.1016/j.ctim.2020.102356.
44. Orgil Z, et al. Dataset used to refine a treatment protocol of a biofeedback-based virtual reality intervention for pain and anxiety in children and adolescents undergoing surgery. Data Brief. 2023a;49:109331. https://doi.org/10.1016/j.dib.2023.109331.
45. Orgil Z, et al. Feasibility and acceptability of perioperative application of biofeedback-based virtual reality versus active control for pain and anxiety in children and adolescents undergoing surgery: protocol for a pilot randomised controlled trial. BMJ Open. 2023b;13(1):e071274. https://doi.org/10.1136/bmjopen-2022-071274.
46. Wang TJ, et al. Biofeedback relaxation for pain associated with continuous passive motion in Taiwanese patients after total knee arthroplasty. Res Nurs Health. 2015;38(1):39–50. https://doi.org/10.1002/nur.21633.
47. Xie YJ, et al. Effects of electromyography biofeedback for patients after knee surgery: a systematic review and meta-analysis. J Biomech. 2021;120:110386. https://doi.org/10.1016/j.jbiomech.2021.110386.
48. Awaludin S, et al. The effect of a smartphone-based perioperative nursing intervention: prayer, education, exercise therapy, hypnosis, and music toward pain, anxiety, and early mobilization on cardiac surgery. J Public Health Res. 2021;11(2):2742. https://doi.org/10.4081/jphr.2021.2742.
49. Gupta RK, et al. Effects of hypnosis versus enhanced standard of care on postoperative opioid use after total knee arthroplasty: the HYPNO-TKA randomised clinical trial-an infographic. Reg Anesth Pain Med, rapm-2022-103892. 2022. https://doi.org/10.1136/rapm-2022-103892.
50. Rosenbloom BN, et al. A randomized controlled trial of clinical hypnosis as an opioid-sparing adjunct treatment for pain relief in adults undergoing major oncologic surgery. J Pain Res. 2024;17:45–59. https://doi.org/10.2147/JPR.S424639.
51. Potié A, et al. Hypnosis in the perioperative management of breast cancer surgery: clinical benefits and potential implications. Anesthesiol Res Pract. 2016;2016:2942416. https://doi.org/10.1155/2016/2942416.
52. Lacroix C, et al. Impact of perioperative hypnosedation on postmastectomy chronic pain: preliminary results. Integr Cancer Ther. 2019;18:1534735419869494. https://doi.org/10.1177/1534735419869494.
53. Gurram P, et al. Effect of heartfulness meditation on anxiety and perceived pain in patients undergoing impacted third molar surgery. J Oral Maxillofac Surg. 2021;79(10):2060.e1–7. https://doi.org/10.1016/j.joms.2021.04.027.
54. Canfield MJ, et al. Evaluating the success of perioperative self-guided meditation in reducing sleep disturbance after total knee arthroplasty. J Arthroplasty. 2021;36(7S):e2. https://doi.org/10.1016/j.arth.2021.01.070.
55. Roberts RL, et al. Mindfulness-based interventions for perioperative pain management and opioid risk reduction following surgery: a stepped care approach. Am Surg. 2024;90(5):939–46. https://doi.org/10.1177/00031348221114019.
56. Sohl SJ, et al. Feasibility of a brief yoga intervention for improving acute pain and distress post gynecologic surgery. Int J Yoga Ther. 2016;26(1):43–7. https://doi.org/10.17761/1531-2054-26.1.43.
57. Chandrababu R, et al. Effects of yoga on anxiety, pain, inflammatory and stress biomarkers in patients undergoing cardiac surgery: a systematic review and meta-analysis. Complement Ther Clin Pract. 2023;53:101798. https://doi.org/10.1016/j.ctcp.2023.101798.
58. Li L, et al. Tai Chi Chuan exercises improve functional outcomes and quality of life in patients with primary total knee arthroplasty due to knee osteoarthritis. Complement Ther Clin Pract. 2019;35:121–5. https://doi.org/10.1016/j.ctcp.2019.02.003.
59. Garland EL, Hudak J, Hanley AW, Nakamura Y. Mindfulness-oriented recovery enhancement reduces opioid dose in primary care by strengthening autonomic regulation during meditation. Am Psychol., PMID: 32915027; PMCID: PMC7490853. 2020;75(6):840–52. https://doi.org/10.1037/amp0000638.
60. Kellermann AJ, Kloft C. Is there a risk of bleeding associated with standardized ginkgo biloba extract therapy? A systematic review and meta-analysis. Pharmacotherapy. 2011;31(5):490–502. https://doi.org/10.1592/phco.31.5.490.

61. Tan CS, Lee SW. Warfarin and food, herbal or dietary supplement interactions: a systematic review. Br J Clin Pharmacol. 2021;87(2):352–74. https://doi.org/10.1111/bcp.14404.
62. Choi MK, Song IS. Interactions of ginseng with therapeutic drugs. Arch Pharm Res. 2019;42(10):862–78. https://doi.org/10.1007/s12272-019-01184-3.
63. Choi S, et al. A systematic review of the pharmacokinetic and pharmacodynamic interactions of herbal medicine with warfarin. PLoS One. 2017;12(8). https://doi.org/10.1371/journal.pone.0182794.
64. Pereira IC, et al. Bromelain supplementation and inflammatory markers: a systematic review of clinical trials. Clin Nutr ESPEN. 2023;55:116–27. https://doi.org/10.1016/j.clnesp.2023.02.028.
65. Leelakanok N, et al. Efficacy and safety of bromelain: a systematic review and meta-analysis. Nutr Health. 2023;29(3):479–503. https://doi.org/10.1177/02601060231173732.
66. Merolla G, et al. Co-analgesic therapy for arthroscopic supraspinatus tendon repair pain using a dietary supplement containing Boswellia serrata and Curcuma longa: a prospective randomized placebo-controlled study. Musculoskelet Surg. 2015;99(Suppl 1). https://doi.org/10.1007/s12306-015-0364-1.
67. Mohammadi A, et al. Effects of cinnamon on perineal pain and healing of episiotomy: a randomized placebo-controlled trial. J Integr Med. 2014;12(4):359–66. https://doi.org/10.1016/S2095-4964(14)60025-X.
68. Motilal S, Maharaj RG. Nutmeg extracts for painful diabetic neuropathy: a randomized, double-blind, controlled study. J Altern Complement Med. 2013;19(4):347–52. https://doi.org/10.1089/acm.2012.0016.
69. Paultre K, et al. Therapeutic effects of turmeric or curcumin extract on pain and function for individuals with knee osteoarthritis: a systematic review. BMJ Open Sport Exerc Med. 2021;7(1). https://doi.org/10.1136/bmjsem-2020-000935.
70. Savage K, et al. Neuroimaging insights: Kava's (Piper Methysticum) effect on dorsal anterior cingulate cortex GABA in generalized anxiety disorder. Nutrients. 2023;15(21):4586. https://doi.org/10.3390/nu15214586.
71. da Cunha RS, et al. Herbal medicines as anxiolytics prior to third molar surgical extraction. A randomized controlled clinical trial. Clin Oral Investig. 2021;25(3):1579–86. https://doi.org/10.1007/s00784-020-03468-1.
72. Roh D, et al. Valerian extract alters functional brain connectivity: a randomized double-blind placebo-controlled trial. Phytother Res. 2019;33(4):939–48. https://doi.org/10.1002/ptr.6286.
73. Helde Frankling M, et al. Palliative-D'-Vitamin D supplementation to palliative cancer patients: a double blind, randomized placebo-controlled multicenter trial. Cancers (Basel). 2021;13(15):3707. https://doi.org/10.3390/cancers13153707.
74. Zadro J, et al. Mapping the association between vitamin D and low back pain: a systematic review and meta-analysis of observational studies. Pain Physician. 2017;20(7):611–40.
75. Albrecht E, et al. Peri-operative intravenous administration of magnesium sulphate and postoperative pain: a meta-analysis. Anaesthesia. 2013;68(1):79–90. https://doi.org/10.1111/j.1365-2044.2012.07335.x.
76. Azimi A, et al. Intra-operative adjunctive magnesium sulfate in pain management of total knee arthroplasty; a systematic review and meta-analysis. Arch Acad Emerg Med. 2023;11(1):e58. https://doi.org/10.22037/aaem.v11i1.2058.
77. Shi L, et al. Intra-articular magnesium to alleviate postoperative pain after arthroscopic knee surgery: a meta-analysis of randomized controlled trials. J Orthop Surg Res. 2021;16(1):111. https://doi.org/10.1186/s13018-021-02264-1.
78. Jain SK, et al. Role of anti-oxidant (vitamin-C) in post-operative pain relief in foot and ankle trauma surgery: a prospective randomized trial. Foot Ankle Surg. 2019;25(4):542–5. https://doi.org/10.1016/j.fas.2018.05.001.
79. Aïm F, et al. Efficacy of vitamin C in preventing complex regional pain syndrome after wrist fracture: a systematic review and meta-analysis. Orthop Traumatol Surg Res. 2017;103(3):465–70. https://doi.org/10.1016/j.otsr.2016.12.021.
80. Chen S, et al. Effect of perioperative vitamin C supplementation on postoperative pain and the incidence of chronic regional pain syndrome: a systematic review and meta-analysis. Clin J Pain. 2016;32(2):179–85. https://doi.org/10.1097/AJP.0000000000000218.
81. Pérez-Piñero S, et al. Efficacy of Boswellia Serrata extract and/or an omega-3-based product for improving pain and function in people older than 40 years with persistent knee pain: a randomized double-blind controlled clinical trial. Nutrients. 2023;15(17):3848. https://doi.org/10.3390/nu15173848.
82. Bernabe-Garcia M, et al. Enteral docosahexaenoic acid reduces analgesic administration in neonates undergoing cardiovascular surgery. Ann Nutr Metab. 2016;69(2):150–60. https://doi.org/10.1159/000452227.
83. Ruiz-Tovar J, Blanca M, et al. Preoperative administration of Omega-3 fatty acids on postoperative pain and acute-phase reactants in patients undergoing Roux-En-Y gastric bypass: a randomized clinical trial. Clin Nutr. 2019;38(4):1588–93. https://doi.org/10.1016/j.clnu.2018.07.026.
84. Dehghan M. Comparative effectiveness of B and E vitamins with diclofenac in reducing pain due to osteoarthritis of the knee. Med Arch. 2015;69(2):103–6. https://doi.org/10.5455/medarh.2015.69.103-106.
85. Khezri MB, et al. The comparative preemptive analgesic efficacy of addition of vitamin B complex to gabapentin versus gabapentin alone in women undergoing cesarean section under spinal anesthesia: a prospective randomized double-blind study. Medicine (Baltimore). 2017;96(15). https://doi.org/10.1097/MD.0000000000006545.

86. Carrero JJ, et al. Daily supplementation with (n-3) PUFAs, oleic acid, folic acid, and vitamins B-6 and E increases pain-free walking distance and improves risk factors in men with peripheral vascular disease. J Nutr. 2005;135(6):1393–9. https://doi.org/10.1093/jn/135.6.1393.
87. Ruiz-Tovar J, Duran M, et al. Reduction of postoperative pain and improvement of patients' comfort after Milligan-Morgan hemorrhoidectomy using topical application of vitamin E ointment. Int J Color Dis. 2016;31(7):1371–2. https://doi.org/10.1007/s00384-015-2483-4.
88. Nadal-Nicolás Y, et al. Vegetarian and vegan diet in fibromyalgia: a systematic review. Int J Environ Res Public Health. 2021;18(9):4955. https://doi.org/10.3390/ijerph18094955.
89. Schönenberger KA, et al. Effect of anti-inflammatory diets on pain in rheumatoid arthritis: a systematic review and meta-analysis. Nutrients. 2021;13(12):4221. https://doi.org/10.3390/nu13124221.
90. Abboud M, et al. Effect of ketogenic diet on quality of life in adults with chronic disease: a systematic review of randomized controlled trials. Nutrients. 2021;13(12):4463. https://doi.org/10.3390/nu13124463.
91. Xu L, et al. Nutritional aspects in chronic non-cancer pain: a systematic review. Front Nutr. 2022;9:931090. https://doi.org/10.3389/fnut.2022.931090.

Index

P. Gulur et al. (eds.), *Perioperative Pain Management*, https://doi.org/10.1007/978-3-032-11484-6