American Burn Association Guidelines on the Management of Acute Pain in the Adult Burn Patient: A Review of the Literature, a Compilation of Expert Opinion, and Next Steps

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The ABA pain guidelines were developed 14 years ago and have not been revised despite evolution in the practice of burn care. A sub-committee of the American Burn Association's Committee on the Organization and Delivery of Burn Care was created to revise the adult pain guidelines. A MEDLINE search of English-language publications from 1968 to 2018 was conducted using the keywords "burn pain," "treatment," and "assessment." Selected references were also used from the greater pain literature. Studies were graded by two members of the committee using Oxford Centre for Evidence-based Medicine—Levels of Evidence. We then met as a group to determine expert consensus on a variety of topics related to treating pain in burn patients. Finally, we assessed gaps in the current knowledge and determined research questions that would aid in providing better recommendations for optimal pain management of the burn patient. The literature search produced 189 papers, 95 were found to be relevant to the assessment and treatment of burn pain. From the greater pain literature 151 references were included, totaling 246 papers being analyzed. Following this literature review, a meeting to establish expert consensus was held and 20 guidelines established in the areas of pain assessment, opioid medications, nonopioid medications, regional anesthesia, and nonpharmacologic treatments. There is increasing research on pain management modalities, but available studies are inadequate to create a true standard of care. We call for more burn specific research into modalities for burn pain control as well as research on multimodal pain control.

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Funding This project was supported by the National Center for Advancing Translational Sciences, National Institutes of Health, through grant number UL1 TR001860. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Conflict of interest statement. No competing financial interests exist.

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doi:10.1093/jbcr/iraa119

PURPOSE

The purpose of this guideline is to update the previous guideline by Drs Faucher and Furukawa.[1] To accomplish this, we review the principles of acute pain management in adult burn patients and present a reasonable approach to the management of the complex pain associated with burn injury based on a review of the literature and expert opinion. In addition, we provide suggestions for a research agenda that would yield evidence necessary for the next iteration of recommendations for the treatment of acute pain associated with burn injury.

STANDARDS

Despite examining 10 additional years of research there are insufficient data to fully support high-level evidence-based standards of care. Nevertheless, we combine the evidence available and expert opinion to put forth several guidelines for the assessment and management of pain during acute burn hospitalization.

RECOMMENDATIONS FOR THE MANAGEMENT OF ACUTE PAIN IN THE ADULT BURN PATIENT

Please see each section for more detailed explanations of the recommendations (see Table 1 for levels of recommendation).

Pain Assessment

1. Pain assessments should be performed several times a day and during various phases of care (Level A).
2. Pain assessments should be protocolized and recorded by the physician and the nursing staff during the various stages of care to ensure consistent language when discussing pain evaluation (Level B).
3. Pain assessment tools should use patient-reported scales when able (Level C).
4. The Burn Specific Pain Anxiety Scale (BSPAS) should be included as one of the pain assessments used during the course of an acute burn hospitalization as it is a validated tool for the burn patient population and includes evaluation of anxiety (Level C).
5. Critical Care Pain Observation Tool (CPOT) can be used when a patient is not able to interact or communicate their individual assessment of pain (Level D).

Opioid Pain Medications

6. When choosing opioid pain medications, decisions about choice of agent should be based on physiology, pharmacology, and physician experience given the limited amount of high-quality data available (Level C).
7. Opioid therapy should be individualized to each patient and continuously adjusted throughout their care due to the heterogeneity of individual responses, adverse effects, and the narrow therapeutic window of opioids (Level D).
8. Attempts should be made to use as few opiate equivalents as needed to achieve the desired level of pain control (Level C).
9. Opioid pain medications should not be used in isolation but in conjunction with nonopioid and nonpharmacological measures (Level C).
10. Patients should be educated about the role of opioids and other pain medications in their recovery from burn injury (Level D).

Nonopioid Pain Medications

11. Acetaminophen should be utilized on all burn patients, with care taken to monitor maximal daily dose (Level D).
12. nonsteroidal anti-inflammatory drugs (NSAIDs) should be considered in all patients due to their safety profile and efficacy in other settings; however, the patient's clinical picture including baseline comorbidities and kidney function as well as surgeon preference should be included in this decision (Level D).
13. Agents for the treatment of neuropathic pain (eg, gabapentin or pregabalin) should be considered as an adjunct to an opioid in patients who are having neuropathic pain or who are refractory to standard therapy (Level C).
14. Ketamine should be considered for procedural sedation, with appropriate training and monitoring for the physician and nursing staff who are administering (Level B).
15. Low-dose ketamine should be considered as an adjunct to opioid therapy in patients who could benefit from reduced opioid consumption, particularly in the postoperative period (Level D).
16. Dexmedetomidine and clonidine are recommended as pain management adjuncts, particularly in patients showing signs of withdrawal or prominent anxiety symptoms and dexmedetomidine as a first-line sedative in the intubated burn patient (Level D).
17. The use of IV lidocaine for burn pain management cannot be recommended at this time as a first-line agent, but it is a reasonable second- or third-line adjuvant agent (Level D).
18. Given the lack of evidence and the potential legal and political obstacles we are unable to make a recommendation for the use of cannabinoids in the treatment of acute burn pain (Level D).

Regional Anesthesia

19. Regional anesthesia for burn pain management has the potential to provide improved pain relief, patient satisfaction, and opioid use reduction without serious risks or complications (Level C).

Nonpharmacologic Treatments

20. Every patient should be offered a nonpharmacological pain control technique, at least as an adjunctive measure to their pain control regimen. When the expertise and/or equipment is available, cognitive-behavioral therapy, hypnosis, and virtual reality have the strongest evidence (Level A).

Table 1. Grades of recommendations

A	Consistent level 1 studies
B	Consistent level 2 or 3 studies *or* extrapolations from level 1 studies
C	Level 4 studies *or* extrapolations from level 2 or 3 studies
D	Level 5 evidence *or* troublingly inconsistent or inconclusive studies of any level

INTRODUCTION

Burn injury is widely considered one of the most painful injuries that a person can sustain. In addition to the intrinsic pain caused by the burn itself, the proper treatment of a burn injury requires painful procedures including debridement of the wound, daily wound care, and surgery, followed by aggressive physical and occupational therapy. Burn pain is especially complicated; it is multifaceted and frequently changes over time as the patient undergoes repeated procedures and treatments that require manipulation of their painful burn sites. Despite an understanding of the importance of pain

management in recovery from burn wounds there are numerous reports discussing the inadequacy of treatment of burn pain. Furthermore, inconsistency in practice standards has been well documented for almost three decades.[2–6]

TAXONOMY OF PAIN

The International Association for the Study of Pain (IASP) defines pain as "unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage."[7] Introduced in 1979, it is one of the most widely promulgated definitions for pain, including adoption by the World Health Organization. As our understanding of pain has advanced, there have been calls for an update to the original definition.[8–10] Nevertheless, the definition acknowledges that pain is a complex and multi-faceted phenomenon that includes subjective, psychosocial, and physiologic elements.

While the IASP definition of pain is widely utilized, there are several ways to categorize types of pain in neurological, physiological, and psychological domains. Published in 1965, Melzack and Wall's "Pain mechanisms: A new theory," introduced the Gate Theory of Pain.[11] Their work influenced subsequent pain research and provided neurophysiologic rationale and a mechanistic explanation for physical and psychologic aspects of pain and the development of chronic pain. Though many dispute specifics regarding the Gate Theory of Pain, the collective research on the neurophysiologic mechanisms of pain allow us to consider how pain signals are generated, promulgated, and perceived. Thus, pain can be described in terms of being somatogenic, nociceptive, neuropathic, and psychogenic as well as acute or chronic.

The pain caused by acute burn injury is first and foremost nociceptive in nature. The process by which the noxious burn stimulus is interpreted as what we describe as pain occurs in several stages: transduction, conduction, transmission, modulation, and perception. The initiation of this process involves the activation of nociceptors in the skin. These stimuli are converted, or transduced, into electrophysiologic signals. The nociceptors are the terminals endings of C fibers (unmyelinated) and/or A-delta fibers (myelinated) which conduct the signal from the peripheral nervous system centrally to the dorsal horn of the spinal cord. Transmission then occurs via the spinothalamic tracts to the brain. The processing of noxious stimuli occurs via both ascending and descending pathways and can be modulated by both excitatory and inhibitory mechanisms.

Several areas of the brain are involved in the perception of pain. These include the medulla, midbrain, and thalamus, then relayed to the somatosensory cortex, hypothalamus, hippocampus, and the amygdala. The involvement of these areas generates the different perceptions of pain such as intensity, urgency, cognitive, and emotional aspects of the pain response. Via complex biochemical and electrophysiological mechanisms utilizing numerous receptors, cells, fibers, and neurotransmitters the painful sensation is processed in the central nervous system. Nevertheless, having at least a conceptual understanding of the stages of this process leads us to consider the utility and importance of multi-modal approaches to pain management. Knowledge of specific pathways and players involved in the process leads us to consider potential pharmacologic and nonpharmacologic treatments.

Rather than considering pain from an etiologic or physiologic/affective approach, pain can also be described in terms of an individual's arc of recovery. Using this simpler taxonomy, pain can be described in terms of being background, breakthrough, or procedural in nature. Background (or baseline) pain exists while the patient is at rest and occurs from the burn injury itself. Breakthrough pain are instances when there is a transient exacerbation of pain. Procedural pain is pain associated with any therapeutic intervention with a patient, whether it is invasive (eg, arterial/venous access, wound debridement, and surgical) or noninvasive (eg, physical/occupational therapy).

Each of the approaches above provide a perspective to understanding the mechanisms and taxonomy of pain. They provide an important framework for the development and implementation of guidelines for pain management.

PROCESS

A sub-committee of the American Burn Association's Committee on the Organization and Delivery of Burn Care was created to revise the previously published pain guidelines.[1] A MEDLINE search of the English-language publications from 1968 to 2018 was conducted using the keywords "burn pain," "treatment," and "assessment" as was described in the previously published guidelines. This search produced 189 results, of which 95 were found to be relevant to the assessment and treatment of burn pain. Additional selected references were also used based on the committee's evaluation of the broader pain literature. Studies were sub-divided by topic and graded by two members of the committee per section using Oxford Centre for Evidence-based Medicine—Levels of Evidence.[12] When there was a disagreement about the grade of a particular study a third member of the committee was used to resolve the disagreement. These papers were compiled into an evidence-based review of current knowledge regarding treatment of burn-related pain. Please see Table 2 for all included papers and their level of evidence grading and Table 3 for a description of the level of evidence. The next step was an in-person meeting to determine expert consensus on a variety of topics related to the treatment of pain in burn-injured patients. The committee consisted of a wide range of burn care providers including burn surgeons, burn nurses, anesthesiologists, a pharmacist, and a psychologist. All members had significant interest and experience caring for burn injured patients. Finally, we assessed gaps in current knowledge and proposed research questions that would provide evidence for future recommendations. In this article, we address interventions used to ameliorate the profound and (at this point) inevitable pain patients experience in the course of acute burn care. Though outside the scope of this review, it should be noted that thoughtful wound management—prompt surgical coverage where indicated, preventing wound infection, and wound care approaches that reduce the frequency of dressing changes—play a crucial role in minimizing the pain that a patient experiences.

Table 2. Evidence-based literature review of current knowledge regarding treatment of burn-related pain

Topic	Reference (numbers in italics are reference number from manuscript)	Data class
Pain Assessment	Ashburn MA. Burn pain: the management of procedure-related pain. J Burn Care Rehabil 1995;16(3 Pt 2):365–71. [13]	Level 5, grade D
	Browne AL et al. Persistent pain outcomes and patient satisfaction with pain management after burn injury. Clin J Pain 2001;27(2):136–45.	Level 4, grade C
	Carrougher GJ et al. Comparison of patient satisfaction and self-reports of pain in adult burn-injured patients. J Burn Care Rehab 2003;24(1):1–8. [2]	Level 2c, grade B
	Casser HR et al. Multidisciplinary assessment for multimodal pain therapy. Indications and range of performance. Schmerz 2013;27(4):363–70.	Level 5, grade D
	Choiniere M et al. The pain of burns: characteristics and correlates. J Trauma 1989;29:1531–9.[3]	Level 4, grade C
	Connor-Ballard PA. Understanding and managing burn pain: part 1. Am J Nurs 2009;109(4):48–56; quiz 57.	Level 5, grade D
	Connor-Ballard PA. Understanding and managing burn pain: Part 2. Am J Nurs 2009;109(5):54–62; quiz 63.	Level 5, grade D
	de Castro RJ et al. Pain management in burn patients. Braz J Anesthesiol 2013;63(1):149–53.[14]	Level 5, grade D
	de Jong AE et al. The visual analogue thermometer and the graphic numeric rating scale: a comparison of self-report instruments for pain measurement in adults with burns. Burns 2015;41(2):333–40.[15]	Level 2b, grade B
	de Jong AE et al. Pain in young children with burns: extent, course and influencing factors. Burns 2014;40(1):38–47.[16]	Level 2b, grade C
	de Jong A et al. Reliability, validity and clinical utility of three types of pain behavioral observation scales for young children with burns aged 0–5 years. Pain 2010;150(3):561–7.	Level 2b, grade C
	de Jong AE et al. Reliability and validity of the pain observation scale for young children and the visual analogue scale in children with burns. Burns 2005;31(2):198–204.[17]	Level 4, grade C
	Echevarria-Guanilo ME et al. Reliability and validity of the Brazilian-Portuguese version of the Burns Specific Pain Anxiety Scale (BSPAS). Int J Nurs Stud 2011;48(1): 47–55.	Level 2c, Grade B
	Esfahlan AJ et al. Burn pain and patients' responses. Burns 2010;36(7):1129–33.	Level 2b; grade C
	Gelinas C. Pain assessment in the critically ill adult: recent evidence and new trends. Intensive Crit Care Nurs 2016;34: 1–11.[18]	Level 5, grade D
	Griggs C et al. Sedation and pain management in burn patients. Clin Plast Surg 2017;44(3):535–40.	Level 5, grade D
	Gamst-Jensen H et al. Acute pain management in burn patients: appraisal and thematic analysis of four clinical guidelines. Burns 2014;40(8):1463–9.	Level 5 grade D
	Gordon M et al. Use of pain assessment tools: is there a preference? J Burn Care Rehabil 1998;19(5):451–4.[19]	Level 1b, grade B
	Jonsson CE et al. Background pain in burn patients: routine measurement and recording of pain intensity in a burn unit. Burns 1998;24(5):448–54.[20]	Level 2b, grade B
	Kohler H et al. Pain management in children: assessment and documentation in burn units. Eur J Pediatr Surg 2001;11(1):40–3.[21]	Level 2C grade C
	Mahar PD et al. Frequency and use of pain assessment tools implemented in randomized controlled trials in the adult burns population: a systematic review. Burns 2012;38(2):147–54.[22]	Level 2a, grade B
	Martin-Herz SP et al. Pediatric pain control practices of North American Burn Centers. J Burn Care Rehab 2003;24(1):26–36.	Level 2c grade C
	McGhee LL et al. The relationship of early pain scores and posttraumatic stress disorder in burned soldiers. J Burn Care Res 2011;32(1):46–51.	Level 3b, grade C
	Myers R et al. Sedation and analgesia for dressing change: a survey of American Burn Association Burn Centers. J Burn Care Res 2017;38(1):e48–54.	Level 2c, grade C
	Payen JF et al. Assessing pain in critically ill sedated patients by using a behavioral pain scale. Crit Care Med 2001;29(12):2258–63.[23]	Level 4, grade C
	Perez Boluda MT et al. The dynamic experience of pain in burn patients: a phenomenological study. Burns 2016;42(5):1097–04.[24]	Level 4, grade C

Table 2. Continued

Topic	Reference (numbers in italics are reference number from manuscript)	Data class
	Perry S et al. Assessment of pain by burn patients. J Burn Care Rehabil 1981;2:322–7.[4]	Level 4, grade C
	Ptacek J et al. Pain, coping and adjustment in patients with burns: preliminary findings from a prospective study. J Pain Symptom Manage 1995;10:446–55.[5]	Level 2b, grade B
	Radnovich R et al. Acute pain: effective management requires comprehensive assessment. Postgrad Med 2014;126(4):59–72.[25]	Level 5 grade D
	Rae CP et al. An audit of patient perception compared with medical and nursing staff estimation of pain during burn dressing changes." Eur J Anaesthesiol 2000;17(1):43–5.	Level 4, grade C
	Ratcliff SL et al. The effectiveness of a pain and anxiety protocol to treat the acute pediatric burn patient. Burns 2006;32(5):554–62.	Level 3b, grade C
	Richardson P, Mustard L. The management of pain in the burns unit. Burns 2009;35(7):921–36.	Level 5, grade D
	Robert R et al. Anxiety: current practices in assessment and treatment of anxiety of burn patients. Burns 2000;26(6):549–52.[26]	Level 4, grade C
	Shen J et al. Evaluation of nurse accuracy in rating procedural pain among pediatric burn patients using the Face, Legs, Activity, Cry, Consolability (FLACC) Scale. Burns 2017;43(1):114–20.[27]	Level 2b, grade B
	Singer AJ et al. Association between burn characteristics and pain severity. Am J Emerg Med 2015;33(9):1229–31.	Level 3b, grade C
	Springborg AD et al. Effects of target-controlled infusion of high-dose naloxone on pain and hyperalgesia in a human thermal injury model: a study protocol: a randomized, double-blind, placebo-controlled, crossover trial with an enriched design. Medicine 2016;95(46):e5336.	Level 1b, grade A
	Stites M. Observational pain scales in critically ill adults. Crit Care Nurse 2013;33: 68–78.	Level 5, grade D
	Stoddard FJ et al. Treatment of pain in acutely burned children. J Burn Care Rehabil 2002;23(2):135–56.	Level 5, grade D
	Summer GJ et al. Burn injury pain: the continuing challenge. J Pain 2007;8(7):533–48.	Level 5, grade D
	Taal LA, Faber AW. The burn specific pain anxiety scale: introduction of a reliable and valid measure. Burns 1997;23(2):147–50.[28]	Level 2b, grade B
	Taal LA et al. The abbreviated burn specific pain anxiety scale: a multicenter study. Burns 1999;25(6):493–7.[29]	Level 2b, grade C
	Taverner T, Prince J. Acute neuropathic pain assessment in burn injured patients: a retrospective review. J Wound Ostomy Continence Nurs 2016;43(1):51–5.[30]	Level 2b, grade C
	Topolovec-Vranic J et al. Validation and evaluation of two observational pain assessment tools in a trauma and neurosurgical intensive care unit. Pain Res Manag 2013;18(6):e107–14.	Level 5, grade D
	Turk DC et al. Analyzing multiple endpoints in clinical trials of pain treatments: IMMPACT recommendations. Initiative on methods, measurement, and pain assessment in clinical trials. Pain 2008;139(3):485–93.	Level 5, grade D
	Wasiak J et al. Inhaled methoxyflurane for pain and anxiety relief during burn wound care procedures: an Australian case series. Int Wound J 2014;11(1):74–8.	Level 4, grade C
	Weddell R. Improving pain management for patients in a hospital burns unit. Nurs Times 2004;100(11):38–40.	Level 5, grade D
	Weinberg K et al. Pain and anxiety with burn dressing changes: patient self-reports. J Burn Care Rehabil 2000;21:157–61.[6]	Level 4, grade C
	Wibbenmeyer L. et al. An evaluation of factors related to postoperative pain control in burn patients. J Burn Care Res 2015;36(5):580–6.[31]	Level 3b, grade C
	Wibbenmeyer L. et al. Evaluation of the usefulness of two established pain assessment tools in a burn population. J Burn Care Res 2011;32:52–60.	Level 3b, grade C
	Williams DA. The importance of psychological assessment in chronic pain. Curr Opin Urol 2013;23(6):554–9.	Level 5, grade D
	Yang CL, Wei ZR. Advances in the research of burn pain. Zhonghua Shao Shang Za Zhi 2017;33(1):61–4.	Level 5, grade D
	Yang HT et al. Improvement of burn pain management through routine pain monitoring and pain management protocol. Burns 2013;39(4):619–24.[32]	Level 1b, grade A

Table 2. Continued

Topic	Reference (numbers in italics are reference number from manuscript)	Data class
Pharmacologic Treatments		
Opioid Pain Medication	Altier N et al. Successful use of methadone in the treatment of chronic neuropathic pain arising from burn injuries: a case-study. Burns 2001;27(7):771–5.	Level 4, grade C
	Andrews RM. Predictors of patient satisfaction with pain management and improvement 3 months after burn injury. J Burn Care Res 2012;33(3):442–52.	Level 2b, grade B
	Borland ML et al. Intranasal fentanyl is an equivalent analgesic to oral morphine in pediatric burns patients for dressing changes: a randomized double blind crossover study. Burns 2005;31(7):831–7.[33]	Level 1b, grade B
	Chen L et al. Prediction of effect-site concentration of sufentanil by dose–response target controlled infusion of sufentanil and propofol for analgesic and sedation maintenance in burn dressing changes. Burns 2014;40(3):455–9.[34]	Level 2b, grade B
	Corkery JM et al. The effects of methadone and its role in fatalities. Hum Psychopharmacol 2004;19:565–76.	Level 5, grade D
	Cuignet O et al. Effects of gabapentin on morphine consumption and pain in severely burned patients. Burns 2007;33(1):81–6.	Level 3b, grade C
	Finn J et al. A randomized crossover trial of patient controlled intranasal fentanyl and oral morphine for procedural wound care in adult patients with burns. Burns 2004;30(3):262–8.[35]	Level 1b, grade B
	Foertsch CE et al. A quasi-experimental, dual-center study of morphine efficacy in patients with burns. J Burn Care Rehabil 1995;16(2 Pt 1):118–26.[36]	Level 1b, grade A
	Gallagher G et al. The use of a target-controlled infusion of alfentanil to provide analgesia for burn dressing changes a dose finding study. Anesthesia 2000;55: 1159–63.[37]	Level 4, grade C
	Grimsrud KN et al. Identification of cytochrome P450 polymorphisms in burn patients and impact on fentanyl pharmacokinetics: a pilot study. J Burn Care Res 2019;40(1):91–6.[38]	Level 4, grade C
	Holtman JR Jr., Jellish WS. Opioid-induced hyperalgesia and burn pain. J Burn Care Res 2012;33(6):692–701.	Level 5, grade D
	Inturrisi CE. Pharmacology of methadone and its isomers. Minerva Anestesiol 2005;71:435–7.	Level 5, grade D
	Jones GM et al. Impact of early methadone initiation in critically injured burn patients: a pilot study. J Burn Care Res 2013;34:342–8.[39]	Level 4, grade C
	Kim DE et al. A review of adjunctive therapies for burn injury pain during the opioid crisis. J Burn Care Res 2019;40(6):983–95.[40]	Level 5, grade D
	Latarjet J, Choinère M. Pain in burn patients. Burns 1995;21(5):344–8.	Level 5, grade D
	Layson-Wolf C et al. Clinical use of methadone. J Pain Palliat Care Pharmacother 2002;16:29–59.	Level 5, grade D
	Le Floch R et al. Use of remifentanil for analgesia during dressing change in spontaneously breathing non-intubated burn patients. Ann Burns Fire Disasters 2006;19:136–9.[41]	Level 4, grade C
	Lilleso J et al. Effect of peripheral morphine in a human model of acute inflammatory pain. Br J Anaesthe 2000;85(2):228–32.	Level 1b, grade B
	Linneman PK et al. The efficacy and safety of fentanyl for the management of severe procedural pain in patients with burn injuries. J Burn Care Rehabil 2000;216: 519–22.[42]	Level 1b, grade B
	Long TD et al. Morphine-infused silver sulfadiazine (MISS) cream for burn analgesia: a pilot study. J Burn Care Rehabili 2001;22(2):118–23.	Level 2b, grade B
	Lugo RA et al. Pharmacokinetics of methadone. J Pain Palliat Care Pharmacother 2005;19:13–24.	Level 5, grade D
	Martin-Herz SP et al. Pediatric pain control practices of North American Burn Centers. J Burn Care Rehabili 2003;24(1):26–36.	Level 5, grade D
	McIntyre MK et al. Progress of clinical practice on the management of burn-associated pain: lessons from animal models. Burns 2016;42(6):1161–72.	Level 5, grade D
	McSherry T et al. Randomized, crossover study of immersive virtual reality to decrease opioid use during painful wound care procedures in adults. J Burn Care Res 2018;39(2):278–85.	Level 2b, grade B

Table 2. Continued

Topic	Reference (numbers in italics are reference number from manuscript)	Data class
	Ng JWG et al. Management of the lower gastrointestinal system in burn: a comprehensive review. Burns 2016;42(4):728–37.	Level 5, grade D
	Nilsson A et al. Patient controlled sedation using a standard protocol for dressing changes in burns: patients' preference, procedural details and a preliminary safety evaluation. Burns 2008;34(7):929–34.[43]	Level 2b, grade B
	Okie S. A flood of opioids, a rising tide of deaths. N Engl J Med 2010;363(21): 1981–5.	Level 5, grade D
	Pardesi O et al. Pain Management in pediatric burn patients: review of recent literature and future directions. J Burn Care Res 2017;38(6):335–47.	Level 5, grade D
	Patterson DR et al. Baseline pain as a moderator of hypnotic analgesia for burn injury treatment. J Consul Clin Psychol 1997;65(1):60–7.	Level 2b, grade B
	Patterson DR et al. The 2002 Lindberg Award. PRN vs regularly scheduled opioid analgesics in pediatric burn patients. J Burn Care Rehabili 2002;23(6):424–30.	Level 3A, grade B
	Prakash S et al. Patient-controlled analgesia with fentanyl for burn dressing changes. Anesth Analg 2004;99(2):552–5.	Level 1b, grade B
	Ratcliff SL et al. The effectiveness of a pain and anxiety protocol to treat the acute pediatric burn patient. Burns 2006;32(5):554–62.	Level 4, grade C
	Retrouvey H, Shahrokhi S. Pain and the thermally injured patient-a review of current therapies. J Burn Care Res 2015;36(2):315–23.[44]	Level 5, grade D
	Richardson P, Mustard L. The management of pain in the burns unit. Burns 2009;35(7):921–36.	Level 5, grade D
	Rittner HL et al. The clinical (ir)relevance of opioid-induced immune suppression. Curr Opin Anaesthesiol 2010;23(5):588–92.	Level 4, grade C
	Robert R et al. A double-blind study of the analgesic efficacy of oral transmucosal fentanyl citrate and oral morphine in pediatric patients undergoing burn dressing change and tubbing. J Burn Care Rehabili 2003;24:351–5.[45]	Level 2b, grade C
	Schulte H et al. The synergistic effect of combined treatment with systemic ketamine and morphine on experimentally induced windup-like pain in humans. Anesth Analg 2004;98(6):1574–80.	Level 2b, grade B
	Shah H et al. Factors in the choice of oral transmucosal fentanyl citrate dose for adult burns dressings. Burns 2009;35(6):798–801.[46]	Level 3b, grade C
	Sharar SR et al. A comparison of oral transmucosal fentanyl citrate and oral oxycodone for pediatric outpatient wound care. J Burn Care Rehabili 2002;23(1):27–31.[47]	Level 2b, grade B
	Sharar SR et al. A comparison of oral transmucosal fentanyl citrate and oral hydromorphone for inpatient pediatric burn wound care analgesia. J Burn Care Rehabili 1998;19(6):516–21.	Level 2b, grade B
	Shelley K, Paech MJ. The clinical applications of intranasal opioids. Curr Drug Deliv 2008;5(1):55–8.	Level 5, grade D
	Sheridan R et al. Multi-center benchmarking study. Long-term posttraumatic stress symptoms vary inversely with early opiate dosing in children recovering from serious burns: effects durable at 4 years. J Trauma Acute Care Surg 2014;76(3):828–32.[48]	Level 2b, grade B
	Seol TK et al. Propofol–ketamine or propofol-remifentanil for deep sedation and analgesia in pediatric patients undergoing burn dressing changes: a randomized clinical trial. Paediatr Anaesth 2015;25(6):560–6.[49]	Level 2b, grade C
	Stein C, Küchler S. Non-analgesic effects of opioids: peripheral opioid effects on inflammation and wound healing. Curr Pharm Des 2012;18(37):6053–69.	Level 5, grade D
	Sullivan SR et al. "Opioid creep" is real and may be the cause of "fluid creep. Burns 2014;30(6):583–90.	Level 2b, grade C
	Thompson EM et al. Efficacy and safety of procedural sedation and analgesia for burn wound care. J Burn Care Res 2012;33(4):504–9.	Level 3b, grade C
	Trupkovic T et al. Analgesia and sedation in the intensive care of burn patients: results of a European survey. J Intensive Care Med 2011;26:397–407.	Level 5, grade D
	Webster LR. Risk factors for opioid-use disorder and overdose. Anesth Analg 2017;125(5):1741–8.	Level 5, grade D
	Welling A. A randomized controlled trial to test the analgesic efficacy of topical morphine on minor superficial and partial thickness burns in accident and emergency departments. Emerg Med J 2007;24(6):408–12.	Level 2a, grade B

Table 2. Continued

Topic	Reference (numbers in italics are reference number from manuscript)	Data class
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	Williams PI et al. Use of methadone in the morphine-tolerant burned paediatric patient. Br J Anaesth 1998;80:92–5.[50]	Level 4, grade C
	Yang C et al. Efficacy and feasibility of opioids for burn analgesia: an evidence-based qualitative review of randomized controlled trials. Burns 2018;44(2):241–8.	Level 3b, grade C
	Zor F et al. Pain relief during dressing changes of major adult burns: ideal analgesic combination with ketamine. Burns 2010;36(4):501–5.	Level 3b, grade C
Non-Opioid Medication	Asmussen S et al. A meta-analysis of analgesic and sedative effects of dexmedetomidine in burn patients. Burns 2013;39(4):625–31.	Level 2a, grade B
	Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Practice 2011;11:353–68.[51]	Level 4, grade C
	Canpolat DG et al. Ketamine-propofol vs ketamine-dexmedetomidine combinations in pediatric patients undergoing burn dressing changes. J Burn Care Res 2012;33(6):718–22.[52]	Level 2b, grade B
	Carstensen M, Moller AM. Adding ketamine to morphine for intravenous patient-controlled analgesia for acute postoperative pain: a qualitative review of randomized trials. Br J Anaesth 2010;104(4):401–6.	Level 2a, grade B
	Cashman JN. The mechanisms of action of NSAIDs in analgesia. Drugs 1996;52(Suppl 5):13–23.[53]	Level 5, grade D
	Coimbra C et al. Patient-controlled sedation using propofol for dressing changes in burn patients: a dose-finding study. Anesth Analg 2003;97(3):839–42.	Level 4, grade C
	Cuignet O et al. Effects of gabapentin on morphine consumption and pain in severely burned patients. Burns 2007;33(1):81–86.[54]	Level 3b, grade C
	Davis KD et al. Cutaneous pretreatment with the capsaicin analog NE-21610 prevents the pain to a burn and subsequent hyperalgesia. Pain 1995;62(3):373–8.	Level 4, grade C
	Desai C et al. Effectiveness of a topical local anesthetic spray as analgesia for dressing changes: a double-blinded randomized pilot trial comparing an emulsion with an aqueous lidocaine formulation. Burns 2014;40(1):106–12.	Level 1b, grade B
	Dworkin RH et al. Pharmacologic management of neuropathic pain: evidence-based recommendations. Pain 2007;132(3):237.	Level 5, grade D
	Edrich T et al. Ketamine for long-term sedation and analgesia of a burn patient. Anesth Analg 2004;99(3):893–5.[55]	Level 5 grade D
	Everett JJ et al. Adjunctive interventions for burn pain control: comparison of hypnosis and ativan: the 1993 Clinical Research Award. J Burn Care Rehabili 1993;14(6):676–83.	Level 4, grade C
	Frank B et al. Comparison of analgesic effects and patient tolerability of nabilone and dihydrocodeine for chronic neuropathic pain: randomized, crossover, double blind study. BMJ 2008;336:199–201.[56]	Level 1b, grade B
	Graham GG, Scott KF. Mechanisms of action of paracetamol. Am J Ther 2006;12: 46–55.[57]	Level 5, grade D
	Gray P et al. Pregabalin in severe burn injury pain: a double-blind, randomized placebo-controlled trial. Pain 2011;152(6):1279–88.[58]	Level 1b, grade B
	Gray P et al. Successful use of gabapentin in acute pain management following burn injury: a case series. Pain Med 2008;9(3):371–6.[59]	Level 4, grade C
	Green DP et al. Role of endogenous TRPV1 agonists in a postburn pain model of partial-thickness injury. Pain 2013;154(11):2512–20.	Level 2b, grade B
	Hansen SL et al. A retrospective study on the effectiveness of intranasal midazolam in pediatric burn patients. J Burn Care Rehabili 2001;22(1):6–8.	Level 4, grade C
	Heinrich M et al. Conscious sedation: off-label use of rectal S(+)-ketamine and midazolam for wound dressing changes in paediatric heat injuries. Eur J Pedia Surg 2004;14(4):235–9.	Level 4, grade C
	Jonsson A et al. Inhibition of burn pain by intravenous lignocaine infusion. Lancet 1991;338(8760):151–2.	Level 4, grade C
	Kariya N et al. Oral clonidine for sedation and analgesia in a burn patient. J Clin Anesth 1998;10(6):514–7.	Level 4, grade C

Table 2. Continued

Topic	Reference (numbers in italics are reference number from manuscript)	Data class
	Kaul I et al. Use of gabapentin and pregabalin for pruritus and neuropathic pain associated with major burn injury: a retrospective chart review. Burns 2018;44(2): 414–22.	Level 4, grade C
	Kaur S et al. Effect of intraoperative infusion of low-dose ketamine on management of postoperative analgesia. J Nat Sci Biol Med 2015;6:378–82.[60]	Level 2b, grade B
	Kundra P et al. Oral ketamine and dexmedetomidine in adults' burns wound dressing—A randomized double blind cross over study. Burns 2013;39(6): 1150–6.[61]	Level 1b, grade B
	Lee JJ et al. Effectiveness of nalbuphine for relief of burn debridement pain. J Burn Care Rehabili 1989;10(3):241–6.	Level 2b, grade B
	Lu S et al. A double blind placebo control pilot study on the safety and tolerability of Nabilone in marijuana users. Mental Health Subs Use 2013;6:133–9.	Level 2b, grade B
	Loftus RW et al. Intraoperative ketamine reduces perioperative opiate consumption in opiate-dependent patients with chronic back pain undergoing back surgery. Anesthesiology 2010;113:639–46. [62]	Level 1b, grade B
	Lyons B et al. Pain relief with low-dose intravenous clonidine in a child with severe burns. Intensive Care Med 1996;22(3):249–51.[63]	Level 5, grade D
	Maani CV et al. Combining ketamine and virtual reality pain control during severe burn wound care: one military and one civilian patient. Pain Med 2011;12(4):673–8.	Level 5, grade D
	MacPherson RD et al. Ketamine and midazolam delivered by patient-controlled analgesia in relieving pain associated with burns dressings. Clin J Pain 2008;24(7): 568–71.[64]	Level 4, grade C
	Marinangeli F et al. Clonidine for treatment of postoperative pain: a dose-finding study. Eur J Pain 2002;6:35–42.[65]	Level 1b, grade B
	Martin E et al. The role of the alpha2-adrenoceptor agonist dexmedetomidine in postsurgical sedation in the intensive care unit. J Intensive Care Med 2003;18: 29–41.[66]	Level 1b, grade A
	McGuinness SK et al. A systematic review of ketamine as an analgesic agent in adult burn injuries. Pain Med 2011;12(10):1551–8.[67]	Level 2a, grade B
	Meyer WJ, 3rd et al. Acetaminophen in the management of background pain in children post-burn. J Pain Symptom Manage 1997;13(1):50–5.[68]	Level 4, grade C
	Nauta M et al. Codeine-acetaminophen versus nonsteroidal anti-inflammatory drugs in the treatment of post-abdominal surgery pain: a systematic review of randomized trials. Am J Surg 2009;198(2):256–61.[69]	Level 1a, grade A
	Norambuena C et al. Oral ketamine and midazolam for pediatric burn patients: a prospective, randomized, double-blind study. J Pediatr Surg 2013;48(3):629–34.	Level 1b, grade A
	Orrey DC et al. Results of a pilot multicenter genotype-based randomized placebo-controlled trial of propranolol to reduce pain after major thermal burn injury. Clin J Pain 2015;31(1):21–9.	Level 1a, grade A
	Owens VF et al. Ketamine: a safe and effective agent for painful procedures in the pediatric burn patient. J Burn Care Res 2006;27(2):211–6.[70]	Level 4, grade C
	Pal SK et al. Adjunctive methods of pain control in burns. Burns 1997;23:404–12.[71]	Level 5, grade D
	Pedersen JL et al. Topical glucocorticoid has no antinociceptive or anti-inflammatory effect in thermal injury. Br J Anaesth 1994;72(4):379–82.	Level 1b, grade B
	Pichot C et al. Dexmedetomidine and clonidine: from second- to first-line sedative agents in the critical care setting? J Intensive Care Med 2012;27:219–37.[72]	Level 5, grade D
	Promes JT et al. A prospective, multicenter, randomized, double-blind trial of IV ibuprofen for treatment of fever and pain in burn patients. J Burn Care Res 2011;32(1):79–90.[73]	Level 2b, grade B
	Retrouvey H, Shahrokhi S. Pain and the thermally injured patient-a review of current therapies. J Burn Care Res 2015;36(2):315–23.[44]	Level 5, grade D
	Shank ES et al. Hemodynamic responses to dexmedetomidine in critically injured intubated pediatric burned patients: a preliminary study. J Burn Care Res 2013;34(3):311–17.[74]	Level 4, grade C
	Springborg AD et al. Effects of target-controlled infusion of high-dose naloxone on pain and hyperalgesia in a human thermal injury model: a study protocol: a randomized, double-blind, placebo-controlled, crossover trial with an enriched design. Medicine 2016;95(46):e5336.	Level 1b, grade B

Table 2. Continued

Topic	Reference (numbers in italics are reference number from manuscript)	Data class
	Tran HT et al. Intravenous ketorolac for pain management in a ventilator-dependent patient with thermal injury. Pharmacotherapy 1996;16(1):75–8.[75]	Level 5, grade D
	Tryba M, Gehling M. Clonidine—a potent analgesic adjuvant. Curr Opin Anaesthesiol 2002;15:511–7. [76]	Level 5, grade D
	Turcotte D et al. Examining the roles of cannabinoids in pain and other therapeutic indications: a review. Expert Opin Pharmaco 2010;11:17–31.[77]	Level 2a, grade B
	Wasiak J et al. Intravenous lidocaine for the treatment of background or procedural burn pain. Cochr Datab Syst Rev 2012;6:CD005622.[78]	Level 1a, grade A
	Webb AR et al. The addition of a small-dose ketamine infusion to tramadol for postoperative analgesia: a double-blinded, placebo-controlled, randomized trial after abdominal surgery. Anesth Analg 2007;104:912–7.[79]	Level 1b, grade B
	Werner MU et al. Analgesic effects of dexamethasone in burn injury. Reg Anesth Pain Med 2002;27(3):254–60.	Level 1b, grade B
	Wibbenmeyer L et al. Gabapentin is ineffective as an analgesic adjunct in the immediate postburn period. J Burn Care Res 2014;35(2):136–42. [80]	Level 1b, grade B
	Wong L, Turner L. Treatment of post-burn neuropathic pain: evaluation of pregablin. Burns 2010;36:769–72.[81]	Level 4, grade C
	Zhang J et al. Effects of puerarin on the inflammatory role of burn-related procedural pain mediated by P2X(7) receptors. Burns 2013;39(4):610–8.	Level 3b, grade C
	Zor F. et al. Pain Relief during dressing changes of major adult burns: ideal analgesic combination with Ketamine. Burns 2010;36(4): 501–5.[82]	Level 2b, grade B
Regional Anesthesia	Ashburn MA. Burn pain: the management of procedure-related pain. J Burn Care Rehabil 1995;16(3 pt 2):365–71.	Level 5, grade D
	Burd A, Ahmed K. Staged serial debridement and one stage grafting under local anesthesia. a bed side procedure. Burns 2010;36(4):588–9.	Level 5, grade D
	Bussolin L et al. Tumescent local anesthesia for the surgical treatment of burns and postburn sequelae in pediatric patients. Anesthesiology 2003;99(6):1371–5. [83]	Level 2b, grade B
	Bussolin L et al. Plasma levels of lignocaine during tumescent local anesthesia in children with burns. Anaesth Intens Care 2010;38(6):1008–12.[84]	Level 3b, grade C
	Cuignet O et al. The efficacy of continuous fascia iliaca compartment block for pain management in burn patients undergoing skin grafting procedures. Anesth Analg 2004;98(4):1077–81.[85]	Level 1b, grade B
	Cuignet O et al. The long-term analgesic efficacy of a single-shot fascia iliaca compartment block in burn patients undergoing skin-grafting procedures. J Burn Care Rehabil 2005;26(5):409–15.[86]	Level 1b, grade B
	Dahl JB et al. The effect of pre- versus postinjury infiltration with lidocaine on thermal and mechanical hyperalgesia after heat injury to the skin. Pain 1993;53(1):43–51.	Level 3b, grade C
	Gupta A et al. A study of regional nerve blocks and local anesthetic creams (Prilox) for donor sites in burn patients. Burns 2007;33(1):87–91.	Level 3b, grade C
	Harbin KR, Norris TE. Anesthetic management of patients with major burn injury. AANA J 2012;80(6):430–9.	Level 5, grade D
	Janezic TF. Skin grafting of full thickness burns under local anesthesia with EMLA cream. Burns 1998;24(3):259–63.[87]	Level 5, grade D
	Jellish WS et al. Effect of topical local anesthetic application to skin harvest sites for pain management in burn patients undergoing skin-grafting procedures. Ann Surg 1999;229(1):115–20. [88]	Level 2b, grade B
	Kestenbaum AD et al. Doppler-guided axillary block in a burn patient. Anesthesiology 1990;73(3):586–7.	Level 5, grade D
	Mago V, Prasad M. Tumescent local anesthesia for release of postburn neck contractures. J Burn Care Res 2009;30(6):1049.	Level 5, grade D
	Mora AG et al. En route use of analgesics in nonintubated, critically ill patients transported by U.S. Air Force critical care air transport teams. Mil Med 2016; 181(5 Suppl):145–51.	Level 4, grade C
	Pardesi O, Fuzaylov G. Pain management in pediatric burn patients: review of recent literature and future directions. J Burn Care Res 2017;38(6):335–47.	Level 4, grade C
	Pedersen JL et al. Effect of preemptive nerve block on inflammation and hyperalgesia after human thermal injury. Anesthesiology 1996;84(5):1020–6. [89]	Level 4, grade C

Table 2. Continued

Topic	Reference (numbers in italics are reference number from manuscript)	Data class
	Prasad MK et al. Severe post-burn neck contracture release and skin graft harvest using tumescent local anesthesia as the sole anesthetic technique. J Anesth 2012;26(1):97–99.[90]	Level 5, grade D
	Prasetyono TO, Koswara AF. Linear hand burn contracture release under local anesthesia without tourniquet. Hand Surg 2015;20(3):484–7.	Level 5, grade D
	Randalls B. Continuous brachial plexus blockade. a technique that uses an axillary catheter to allow successful skin grafting. Anaesthesia 1990;45(2):143–4.	Level 5, grade D
	Shank ES et al. Ultrasound-guided regional anesthesia for pediatric burn reconstructive surgery: a prospective study. J Burn Care Res 2016;37(3):e213–7.[91]	Level 5, grade D
	Shick V et al. The benefits of ultrasound-guided continuous sensory nerve blockade in the setting of burn injury: a case report of bilateral continuous superficial peroneal nerve blockade in a patient with severe sleep apnea. J Clin Anesth 2017;36:62–6.	Level 5, grade D
	Shteynberg A et al. Ultrasound guided lateral femoral cutaneous nerve (LFCN) block: safe and simple anesthesia for harvesting skin grafts. Burns 2013;39(1):146–9.[92]	Level 3b, grade C
	Wasiak J et al. Adjuvant use of intravenous lidocaine for procedural burn pain relief: a randomized double blind, placebo-controlled, crossover trial." Burns 2011;37: 951–7.[77]	Level 1b, grade B
Non-Pharmacologic Treatments		
General	de Jong AEE et al. Nonpharmacological nursing interventions for procedural pain relief in adults with burns: a systematic literature review. Burns 2007;33:811–27.[93]	Level 3a, grade B
	Everett JJ et al. Cognitive and behavioral treatments for burn pain. Pain Clin 1990;3:133–45.	Level 5, grade D
	Fauerbach JA et al. Coping with the stress of a painful medical procedure. Behav Res Ther 2002;40(9):1003–15.[94]	Level 1b, grade A
	Hanson MD et al. Nonpharmacological interventions for acute wound care distress in pediatric patients with burn injury: a systematic review. J Burn Care Res 2008;29:730–41.[95]	Level 2b, grade B
	Martin-Herz SP et al. Psychological principles of burn wound pain in children: part II: treatment applications. J Burn Care Rehabil 2000;21(5):458–72.	Level 5, grade D
	Scheffler M et al. Efficacy of non-pharmacological interventions for procedural pain relief in adults undergoing burn wound care: a systematic review and meta-analysis of randomized controlled trials. Burns 2018;44(7):1709–20.[96]	Level 1a, grade A
	Thurber CA et al. Psychological principles of burn wound pain in children: part I: theoretical framework. J Burn Care Rehabil 2000; 21(4):376–87.	Level 5, grade D
Hypnosis	Askay SW et al. A randomized controlled trial of hypnosis for burn wound care. Rehabili Psychol 2007;52:247–53.	Level 1b, Grade A
	Berger MM et al. Impact of a pain protocol including hypnosis in major burns. Burns 2010;36(5):639–46.[97]	Level 2c, Grade B
	Chester SJ et al. Effectiveness of medical hypnosis for pain reduction and faster wound healing in pediatric acute burn injury: study protocol for a randomized controlled trial. Trials 2016;17(1):223.[98]	Level 5, grade D
	Everett JJ et al. Adjunctive interventions for burn pain control: comparison of hypnosis and ativan: the 1993 Clinical Research Award. J Burn Care Rehabili 1993;14(6):676–83.	Level 2b, grade B
	Frenay MC et al. Psychological approaches during dressing changes of burned patients: a prospective randomized study comparing hypnosis against stress reducing strategy. Burns 2001;27(8):793–9.	Level 1b, grade B
	Patterson DR et al. Hypnotherapy as a treatment for pain in patients with burns: research and clinical considerations. J Burn Care Rehabil 1987;8:263–8.	Level 3a, grade B
	Patterson DR et al. Hypnosis for the treatment of burn pain. J Consul Clin Psychol 1992;60:713–7.[99]	Level 2b, grade B
	Patterson DR, Ptacek JT. Baseline pain as a moderator of hypnotic analgesia for burn injury treatment. J Consul Clin Psychol. 1997;65:60–7.	Level 2b, grade B
	Patterson DR, Jensen M. Hypnosis and Clinical Pain. Psychol Bull 2003;129:495–521.	Level 5, grade D
	Patterson DR et al. Factors predicting hypnotic analgesia in clinical burn pain. Int J Clin Exper Hypn 1997;45:377–95.	Level 5, grade D

Table 2. Continued

Topic	Reference (numbers in italics are reference number from manuscript)	Data class
	Patterson DR et al. Hypnotherapy as an adjunct to narcotic analgesia for the treatment of pain for burn debridement. Amer J Clin Hypn 1989;31:156–63.	Level 3b, grade C
	Patterson DR et al. Virtual reality hypnosis: a case report. Int J Clin Exp Hypn 2004;52:27–38.	Level 4, grade C
	Patterson D et al. Hypnosis delivered through immersive virtual reality for burn pain. Int J Clin Exp Hypn 2006;54(2):130–42.	Level 3b, grade B
	Shakibaei F et al. Hypnotherapy in managemnet of pain and reexperiencing of trauma in burn patients. Int J Clin Exp Hypn 2008;56(2):185–97.	Level 1b, grade B
	Van der Does AJ et al. Hypnosis and pain in patients with severe burns: a pilot study. Burns 1988;14(5):399–404.[100]	Level 4, grade C
Distraction Techniques/ Virtual Reality	Brown NJ et al. Efficacy of a children's procedural preparation and distraction device on healing in acute burn wound care procedures: study protocol for a randomized controlled trial. Trials 2012;13:238. [101]	Level 5, grade D
	Brown NJ et al. Play and heal: randomized controlled trial of DittoTM intervention efficacy on improving re-epithelialization in pediatric burns. Burns 2014;40(2): 204–13.[102]	Level 2b, grade B
	Carrougher GJ et al. The effect of virtual reality on pain and range of motion in adults with burn injuries. J Burn Care Rehabil 2009;30(5):785–91. [103]	Level 1b, grade A
	Chan E et al. Application of a virtual reality prototype for pain relief of pediatric burn in Taiwan. J Clin Nurs 2007;16(4):786–93.[104]	Level 4, grade C
	Das DA et al. The efficacy of playing a virtual reality game in modulating pain for children with acute burn injuries: a randomized controlled trial. BMC Pediat 1995;5(1):1.[105]	Level 2b, grade B
	Eccleston C, Crombez G. Pain demands attention: a cognitive-affective model of the interruptive function of pain. Psychol Bull 1999;125:356–66.[106]	Level 5, grade D
	Hoffman H et al. Virtual reality pain control during burn wound debridement in the hydrotank. Clin J Pain 2008;24(4):299–304.[107]	Level 3b, grade B
	Hoffman HG et al. Water-friendly virtual reality pain control during wound care. J Clin Psychol 2004;60(2):189–95.[108]	Level 4, grade C
	Hoffman HG et al. Use of virtual reality for adjunctive treatment of adult burn pain during physical therapy: a controlled study. Clin J Pain 2000;16: 244–50.[109]	Level 3b, grade B
	Hoffman HG et al. Virtual reality as an adjunctive pain control during burn wound care in adolescent patients. Pain 2000;85(1–2):305–9.[110]	Level 4, grade C
	Konstantatos AH et al. Predicting the effectiveness of virtual reality relaxation on pain and anxiety when added to PCA morphine in patients having burns dressings changes. Burns 2009;35(4):491–9.	Level 1b, grade A
	Maani C et al. Pain control during wound care for combat-related burn injuries using custom, articulated arm-mounted virtual reality goggles. J Cyberther Rehabil 2008;1(2):193–8.[111]	Level 4, grade C
	Miller AC et al. A distraction technique for control of burn pain. J Burn Care Rehabili 1992;22(2):144–9.[112]	Level 2b, grade B
	Miller K et al. Multi-modal distraction. Using technology to combat pain in young children with burn injuries. Burns 2010;36(5):647–58. [113]	Level 2b, grade B
	Morris LD et al. The effectiveness of virtual reality on reducing pain and anxiety in burn injury patients. Clin J Pain 2009;25(9):815–26.[114]	Level 2a, grade B
	Morris LD et al. Feasibility and potential effect of a low-cost virtual reality system on reducing pain and anxiety in adult burn injury patients during physiotherapy in a developing country. Burns 2010;36(5):659–64.[115]	Level 4, grade C
	Mott J et al. The efficacy of an augmented virtual reality system to alleviate pain in children undergoing burns dressing changes: a randomized controlled trial. Burns 2008;34(6):803–8.[116]	Level 1b, grade A
	Park E et al. The effects of relaxation breathing on procedural pain and anxiety during burn care. Burns 2013;39(6):1101–6.	Level 2c, grade B
	Schmitt YS et al. A randomized, controlled trial of immersive virtual reality analgesia, during physical therapy for pediatric burns. Burns 2011;37(1):61–8.[117]	Level 1b, grade A

Table 2. Continued

Topic	Reference (numbers in italics are reference number from manuscript)	Data class
	Sharar S et al. Factors influencing the efficacy of virtual reality distraction analgesia during postburn physical therapy: preliminary results from 3 ongoing studies. Arch Phys Med Rehabili 200788(12 Suppl 2):S43–9.[118]	Level 3b, grade B
	Slater M,Wibur S. A framework for immersive virtual environments (FIVE): speculations on the role of presence in virtual environments. Presence 1997;6:603–16.[119]	Level 5, grade D
	Small C et al. Virtual restorative environment therapy as an adjunct to pain control during burn dressing changes: study protocol for a randomized controlled trial. Trials 2015;16:329.	Level 4, grade C
	van Twillert B et al. Computer-generated virtual reality to control pain and anxiety in pediatric and adult burn patients during wound dressing changes. J Burn Care Res 2007;28(5):694–702.[120]	Level 1b, grade B
Music	Ferguson SL, Voll KV. Burn pain and anxiety: the use of music relaxation during rehabilitation. J Burn Care Rehabili 2004;25(1):8–14.	Level 3b, grade B
	Fratianne RB et al. The effect of music-based imagery and musical alternate engagement on the burn debriedement process. J Burn Care Rehabil 2001;22(1):47–53.	Level 2c, grade B
	Hsu KC et al. Effect of music intervention on burn patients' pain and anxiety during dressing changes. Burns 2016;42(8):1789–96.[121]	Level 2b, grade B
	Presner JD et al. Music therapy for assistance with pain and anxiety management in burn treatment. J Burn Care Rehabil 2001;22(1):83–8.	Level 5, grade D
	Tan X et al. The efficacy of music therapy protocols for decreasing pain, anxiety, and muscle tension levels during burn dressing changes: a prospective randomized crossover trial. J Burn Care Res 2010;31(4):590–7.[122]	Level 2b, grade B
	Whitehead-Pleaux AM et al. The effects of music therapy on pediatric patients' pain and anxiety during donor site dressing change. J Music Ther 2006;43(2):136–53.	Level 2b, grade C
	Whitehead-Pleaux AM et al. Exploring the effects of music therapy on pediatric pain: phase 1. J Music Ther 2007;44(3):217–41.	Level 2c, grade C
Relaxation	Choi J et al. Aromatherapy for the relief of symptoms in burn patients: a systematic review of randomized controlled trials. Burns 2017;44(6):1395–402.[123]	Level 3a, grade B
	Knudson-Cooper MS. Relaxation and biofeedback training in the treatment of severely burned children. J Burn Care Rehabil 1981;2(2):102–110.	Level 2b, grade C
	Wernick RL et al. Pain management in severely burned adults: a test of stress inoculation. J Behav Med 1981;4(1):103–9.	Level 2c, grade C
Massage	Field T et al. Post-burn itching, pain, and psychological symptoms are reduced with massage therapy. J Burn Care Rehabil 2000;21(3):189–93.	Level 2b, grade C
	Field T et al. Burn injuries benefit from massage therapy. J Burn Care Rehabil 1998;19(3):241–4.	Level 2b, grade C
	Hernandez-Reif M et al. Childrens' distress during burn treatment is reduced by massage therapy. J Burn Care Rehabili 2011;22:191–5.[124]	Level 2b, grade C
	Parlak Gurol A et al. Itching, pain, and anxiety levels are reduced with massage therapy in burned adolescents." J Burn Care Res 2010;31(3):429–32.[125]	Level 2c, grade B
	Seyyed-Rasooli A et al. Comparing the effects of aromatherapy massage and inhalation aromatherapy on anxiety and pain in burn patients: a single-blind randomized clinical trial. Burns 2016;42(8):1774–80.[126]	Level 1b, grade B

PAIN ASSESSMENT IN THE ADULT BURN PATIENT

Guideline 1: Pain assessments should be done repeatedly during the day during different activities. This would allow assessment of pain during all phases of care and capture fluctuations that occur throughout the day. Attempting to capture assessments at different time points would help with identifying acute pain needs as well as determine the degree of background pain[13,14,32] (Level A).

Guideline 2: Pain assessments should be protocolized and recorded by the physician and the nursing staff during various stages of care to ensure consistent language when discussing pain evaluation. Protocolized burn pain assessment strategies were effective for capturing and treating pain during a patient's hospital care[21] (Level B).

Guideline 3: Pain assessment tools should use patient-reported scales when able. Burn pain is an experience of the individual patient and observation-based pain assessments correlated poorly with patient assessments of pain[24] (Level C).

Table 3. Levels of evidence

1a	Systematic Review of Randomized Control Trials
1b	Individual randomized control trials (with narrow confidence interval)
1c	All or none case-series
2a	Systematic review of cohort studies
2b	Individual cohort study (including low quality RCT; eg, <80% follow-up)
2c	Outcomes research or ecological studies
3a	Systematic review of case–control studies
3b	Individual case–control Study
4	Case-series (and poor quality cohort and case–control studies)
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

Guideline 4: The Burn Specific Pain Anxiety Scale (BSPAS) should be included as one of the pain assessments used during the course of an acute burn hospitalization as it is a validated tool for the burn patient population and includes evaluation of anxiety. This scale had high correlation with patient pain assessments and captures the impact of anxiety on the patient's pain experience[28,29] (Level C).
Guideline 5: Critical Care Pain Observation Tool CPOT can be used when a patient is not able to interact with care providers or communicate their individual assessment of pain. While this tool has not been extensively tested in a burn population there are no other assessment tools available for critically ill patients (Level D).

Rationale

Assessment of pain is a cornerstone to pain management in patient care though there are many nuances to accurately evaluate an individual's experience of pain. The measurement of pain is especially difficult with the critically ill patient who is intubated, sedated, and/or delirious. Current tools for this patient population demonstrate poor interrater reliability or poor correlation with the patient's reported pain. An additional challenge in burn patients is that multiple types of pain (background pain, procedural pain associated with wound care, or rehabilitative pain) temporally intersect but require different assessment tools and different treatment strategies.[16,20] In short, acute, perioperative and chronic pain warrant different approaches. Finally, the assessment of pain is further complicated by the patient's anxiety and its impact on the experience of pain before, during and after wound care.[28,29] The evaluation of tools that exclusively assess anxiety was beyond the scope of this review. However, standard practice should include a concurrent assessment of anxiety and pain.

Many different pain scales are available for the evaluation of acute pain including a scale for critical care populations. These various pain assessment tools attempt to assess pain at rest/background, procedural pain, pediatric pain, critical care, and pain in association with anxiety. Burn patients have complex interactions of different types of pain as they progress through their burn care and recovery. There is background pain associated with open wounds, pain associated with daily wound care and procedures, and breakthrough pain that occurs both at rest and with activity. Ideally, the pain control requirements of patients decrease as their wound burden decreases and as mobility increases but there are patients who go on to develop chronic pain. These complex interactions as well as the current physiologic status of the patient make pain assessment both difficult and dynamic, thereby requiring frequent reassessment.[14]

A multitude of pain assessment tools are available: Visual Analog Scale (VAS),[127] Faces Pain Rating (FBR)/Wong-Baker FACES,[128] Burn Specific Pain Anxiety Scale (BSPAS),[28] Behavioral Pain Scale (BPS),[23] Critical Care Pain Observation Tool (CPOT),[18] Numerical Rating Scale (NRS),[129] McGill Pain Scale,[130] Color Scales for pain,[131] and Face, Legs, Activity, Cry, Consolability scale (FLACC).[132] Each of these tools has their strengths, weaknesses, and specific clinical scenarios when they perform the best. Some of these tools can only be used on patients who are alert as they require the patient to choose a number or a face (VAS or FPR), whereas others are meant to be used in critically ill populations (CPOT). However, these scales have not been validated in the burn population. Some of these tools are specific for pediatric versus adult populations and some incorporate other factors that impact pain such as anxiety and anticipatory pain. Most of these tools have only been evaluated and validated in small, single institution studies. The final conclusion is that no one scale is interchangeable or universally used by majority of burn centers. They each have their strengths and weaknesses and are more specific to patients in certain phases of care. The nursing observation scales typically show poor correlation with individual reports of pain and therefore should be abandoned in favor of more objective pain rating scales or patient-reported scales.[15,17,19,27]

The majority of the tools are unidimensional and may not accurately assess the various types of pain encountered by burn patients. Given burn pain's dynamic and complex nature, there is a need to develop tools that are more comprehensive incorporating, for example, anxiety, pruritus and neuropathic pain.[22,25,28–30] Perez Boluda et al noted that in order to create a thorough assessment tool both the patients' and staff's assessment of pain should be considered.[24]

Recording daily and activity-based assessment of pain and relief is necessary to capture the dynamic needs of the patient and understand that pain is an experience unique to that individual. Therefore, multiple assessments would be required to adequately address background and acute pain. In addition to the multiple assessments per day of pain and anxiety in burn patients in a variety of settings, the medications used for the management of pain should also be assessed on a daily basis to ensure that we are minimizing medications where we are able and avoiding prescribing multiple medications from the same class. This would ideally be done with the assistance of a clinical pharmacist. Patient expectations of acceptable levels of pain relief should be established when individualizing pain treatment plans. The clinician should also understand a patient's prior experience with pain medications, which may influence their response to the pain treatment.[21,32] It is imperative that burn centers understand the dynamic nature of pain and that there are many factors that influence the individual's response to pain such as: prior exposure to pain medication,

history of prior traumatic events, poor coping mechanisms, as well as a fluctuating medical condition.

Future Research

We call for the burn community to investigate the creation of an approach to pain assessment that allows consistency with assessments and would facilitate a data driven decision by the clinician which is responsive to the fluctuating needs of the patient and fosters individualized care. BSPAS and CPOT should be considered as possible pain assessments for generalized use in burn centers. The assessment scale that is ultimately chosen should be able to be used in the critically ill patient and the patient who is able to participate in their care. The pain assessment scales that are developed should then be validated and the implementation across a variety of diverse burn centers should be studied as well. Additionally, the use of common data elements for data collection about pain assessment would allow for comparisons between scales.

PHARMACOLOGIC THERAPY

Opioid Pain Medications

Guideline 6: When choosing opioid pain medications, decisions about choice of agent should be based on physiology, pharmacology, and physician experience given the limited amount of high-quality data available regarding their use in burn pain management (Level C).
Guideline 7: Opioid therapy should be individualized to each patient and continuously adjusted throughout their care due to the heterogeneity of individual responses, adverse effects, and the narrow therapeutic window of opioids (Level D).
Guideline 8: While we certainly support the responsible use of opioids to alleviate severe pain, attempts should be made to use as few opiate equivalents as needed to achieve the desired level of pain control. This can be accomplished by the use of non-opioid medications and nonpharmacologic adjuncts to opioid pharmacological therapies. While data on dosing and scheduling strategies is limited, principles of pharmacology and behavioral science support the use of long-acting opioid agents for background pain, where feasible, to minimize the frequency and individual doses of short acting agents needed for "breakthrough pain" (Level C).
Guideline 9: Opioid pain medications should not be used in isolation but in conjunction with nonopioid and nonpharmacological measures (Level C).
Guideline 10: Patients should be educated about the role of opioids and other pain medications in their recovery from burn injury (Level D).

Rationale Opioid pain medications have for many years been considered the standard of care for the treatment of acute burn pain. However, the superiority of opioid (vs. nonopioid) therapy for management of burn pain has never been demonstrated in a randomized control trial. A "quasi-controlled" study was performed by comparing patient-reported pain scores at two nearby burn centers—one with a conventional opioid-based analgesic regimen and the other with a strict no opioid-policy. At multiple time points, pain and anxiety levels were similar or lower in patients treated at the center *not* utilizing opioids.[36] While thought-provoking, the failure of this study to control for potential differences in patient populations and other treatment differences between the two centers limit our ability to interpret the results.

The overwhelming consensus remains that opioid therapy is an essential tool for pain management in thermal injuries. Sheridan et al demonstrated in a retrospective, multi-institutional study that increased opioid utilization in the early phases of acute burn care was associated with lower pain levels and rates of PTSD symptoms at mid- and long-term follow-up.[48]

The protracted course of burn pain places burn patients at high risk for tolerance, which can markedly compromise the efficacy of opiates in this population over time. Wibbenmeyer et al demonstrated that increased use of opiates preoperatively was associated with increased pain and opiate requirement, even after controlling for burn size, preoperative pain scores and other relevant variables.[31] The authors concluded that this reflected a tolerance effect. In extreme cases, many have described a phenomenon of opioid-induced hyperalgesia in burn patients, wherein patients develop a discernible increase in pain sensitivity over time when exposed to sustained course of opiates. Unfortunately, there is a little documentation in the burn literature of this phenomenon, largely due to the lack of discreetly defined objective measures.[31]

Anecdotally, many providers use methadone to counter tolerance and/or hyperalgesia. However, the only data supporting this practice is limited to two relatively small case-series reporting the successful use of methadone to restore pain control in patients showing progressive difficulty with pain control despite aggressive escalation of opioid therapy.[39,40,50]

The literature clearly demonstrates the dosing of opioids requires a careful consideration of patient tolerance and an ongoing titration of these agents as they show remarkably inconsistent dose–responses in different patients. As in other populations, pharmacogenetic polymorphisms are clearly correlated with different dosing requirements for opioids in burn patients.[38] Furthermore, acute metabolic changes and fluid shifts associated with large thermal injuries create significant shifts in the volume of distribution and pharmacokinetics of opioids and burn patients.[133] Given these unpredictable variables and these agents limited therapeutic windows, opioid agents require ongoing adjustment for safe and effective pain control in this population.[46]

The vast majority of data available on the efficacy and safety of opioid therapy in burn patients comes from studies looking at utilization of opioids for procedural pain during dressing changes. Opioid analgesia is the standard practice for management of procedural pain in the majority of burn centers in North America and Europe, though there is tremendous variability among centers regarding which agents are typically used and how.

Fentanyl has been shown to be a safe and effective agent for pain control and burn dressing changes both in adults and children. Intravenous (IV) fentanyl infusions are generally used in the context of close monitoring (conscious sedation). Dosing should be carefully titrated for each patient, as IV fentanyl requirements show marked inter-patient variability, and are not reliably predicted by objective patient factors such as burn size or age.[42] Intranasal and oral transmucosal

formulations of fentanyl both demonstrated similar safety and similar or increased analgesic efficacy when compared to oral/enteral formulations of other narcotics including codeine, oxycodone, morphine, and hydromorphone.[33,35,45,47]

To accommodate for the rapid escalations of pain associated with burn wound care multiple alternative intravenous opioids have been utilized to achieve more rapidly titratable analgesia. Safe and effective burn dressing change analgesia in nonintubated patients using a combination of Propofol and sufentanil has been delivered in a targeted-infusion system.[34] Remifentanil has been shown to be safe and effective both as an adjunct to Propofol and as a monotherapy.[41,49] Alfentanil has been demonstrated to be effective in multiple studies either as a target infusion, titrated by a nurse, or as a patient controlled.[37,43]

Future Research As we move forward in treating burn pain, we highly encourage further work looking into the relative efficacy and adverse effects of different agents. There is a tremendous gap in research into opioid weaning strategies in burn care, which represents a critical need given the prolonged opioid exposure so frequent in burn care. We would specifically encourage study of methadone that might help corroborate the anecdotal reports shared by many burn care providers.

Further work is needed to explore the physiology and management of opioid tolerance and opioid-induced hyperalgesia in burn patients. For such research to move forward, there is a need for a more sophisticated definition of the pathophysiology leading to these phenomena. Finally, in the context of the national opioid epidemic, there is a dire need to identify the relationship between opioid therapy for acute pain and the development of chronic pain and/or opioid use disorder. Strategies must be developed to prevent the devastating complications that can occur from a well-intended therapy.

Burn care providers have a unique opportunity to follow patients from their initial exposure to opioid therapy all the way through to multiple years post injury. Efforts to make the most of this opportunity by thorough, thoughtful, and prospective study could prove to be immensely beneficial to burn patients and other patients treated with opioids.

Nonopioid Pain Medication

Acetaminophen Guideline 11: Acetaminophen should be utilized on all burn patients, with care taken to monitor maximal daily dose. While acetaminophen has an excellent safety profile, maximal doses should be monitored to decrease the risk of hepatotoxicity (Level D).

Rationale Acetaminophen has both analgesic and antipyretic effects, although its exact mechanism of action is not known. Acetaminophen is thought to weakly inhibit prostaglandin synthesis, sharing many similar characteristics to cyclooxygenase-2 inhibitors without the adverse effects of platelet inhibition or gastrointestinal toxicities.[57] It is available in oral, rectal, and intravenous (IV) dosage forms. While acetaminophen has been regularly used in the treatment of burn-related pain,[44,71] there are few studies in this population. Meyer et al described the use of acetaminophen for background pain in pediatric patients and found it to be effective and safe, though efficacy was measured indirectly in terms of need for additional medications.[68] To date, there are no studies that have investigated the efficacy of IV acetaminophen in the burn population.

Future Research As we move forward in treating pain associated with burn care, we highly encourage further investigation into the efficacy of acetaminophen. We would specifically recommend examining the ideal dose, timing, and route of administration for acetaminophen in the acute burn patient.

Nonsteroidal Anti-inflammatory Drugs Guideline 12: nonsteroidal anti-inflammatory drugs (NSAIDs) should be considered in all patients due to their safety profile and efficacy in other settings; however, the patient's clinical picture including baseline comorbidities and kidney function as well as surgeon preference should be included in this decision. This recommendation is made through weighing the likely analgesic benefits against patient-specific risk factors such as renal insufficiency, coagulopathy, gastritis, or other complications. Given the paucity of data addressing the impact of NSAID use on skin graft hematoma and graft take, the patient's surgeon should be involved in this decision process (Level D).

Rationale Nonsteroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen, naproxen, and ketorolac, have analgesic, antipyretic, and anti-inflammatory properties.[53] NSAIDs reversibly inhibit cyclooxygenase by inhibiting prostaglandin production.[53] Their use has been limited in burn patients due to serious safety concerns, including gastrointestinal toxicity and bleeding, renal dysfunction, risk of cardiovascular events, and platelet dysfunction.[44,71]

There are few studies that have investigated the use of NSAIDs in the burn population for the treatment of pain. Tran et al described a case of ketorolac use in a burn patient to assist with ventilator weaning by decreasing the use of opioids.[75] The patient had completed all necessary grafting surgeries, and his wounds were closed when ketorolac was initiated. Treatment with ketorolac was limited after a rise in serum creatinine was noted, but the patient was able to be weaned from opioid medications and was liberated from the ventilator. In 2011, Promes et al. investigated the use of IV ibuprofen in 61 burn patients compared to placebo,[73] assessing for safety. No adverse effects with regards to bleeding were noted in either group. The study was not designed to assess analgesic efficacy (opioid treatments were not controlled or quantified). Outside of the burn literature, the safety and efficacy of NSAID therapy in broader trauma surgical populations has been documented extensively.[69]

Future Research Future research on the use of NSAIDS in acute burn patients is needed. Specifically, research on NSAIDs should focus on their safety profile in burn patients with care being given to concerns about renal insufficiency, gastritis, coagulopathy, skin graft hematoma, and skin graft take.

Gabapentin and Pregabalin Guideline 13: We suggest agents for the treatment of neuropathic pain(eg, gabapentin or pregabalin)should be considered as an adjunct to an opioid in patients who are having neuropathic pain or who

are refractory to standard therapy. In patients without neuropathic complaints, a trial of such agents is appropriate in patients with pain proving resistant or refractory to standard therapy. Providers and patients should be aware of potential adverse effects, which may become more profound with dose escalation (Level C).

Rationale Neuropathic pain is defined as pain arising as a direct consequence of a lesion or disease affecting the somatosensory system.[59] Neuropathic pain can be classified based on location(central vs. peripheral), etiology or signs and symptoms and common symptoms include paresthesia, dysesthesia, hypesthesia, hyperesthesia, hypoalgesia, hyperalgesia, and allodynia.[134] Diagnosis of neuropathic pain begins with a thorough history and physical. If the patient's pain distribution is neuroanatomically plausible and the history suggests a relevant lesion or disease then confirmatory testing should be considered with a bedside sensory examination to determine the presence of negative or positive sensory signs, confined to the innervation territory of the lesioned nervous structure.[59]

Gabapentin, a structural analog of γ-aminobutyric acid (GABA), has been used to treat postburn neuropathic pain and pruritus. Gabapentin's exact mechanism is not known, as it does not bind to GABA receptors or influence the uptake or degradation of GABA.

Studies to date have shown mixed results with gabapentin's effect on burn pain. Gray et al first described a series of six cases of neuropathic pain that was successfully treated with gabapentin.[59] Burn sizes ranged from 5% total body surface area (TBSA) to 40%, with daily doses ranging from 900 to 1800 mg/day. Cuignet et al showed similar results with their case–control study with 10 patients receiving gabapentin, demonstrating a reduction in opioid consumption and decreased pain scores when gabapentin was used.[134] They used a regimen of 800 mg three times daily (2400 mg/day) in patients with an average burn size of 25% TBSA for 21 days. However, when Wibbenmeyer et al studied gabapentin in a randomized, placebo-controlled study for acute postburn pain in 49 patients, they did not see a decrease in opioid requirements.[135] Their patient population had an average TBSA burn size of 15%, and approximately 85% of the patients reached a daily gabapentin dosage of 1800 mg/day or more.

Like gabapentin, pregabalin is structurally related to GABA but it does not bind to GABA receptors. Pregabalin is currently approved for the treatment of neuropathic pain secondary to diabetes and spinal cord injury, as well as fibromyalgia. Studies are limited on pregabalin and its effect on burn pain. A retrospective chart review of 13 patients was completed by Wong and Turner and found 69% of their patients had a reduction in pain scores.[54] Gray et al completed a randomized, placebo-controlled study with pregabalin, and they found a decrease in neuropathic pain in the pregabalin group.[80] Itch and procedural pain were also decreased in the treatment group, but there was no difference in opioid consumption, length of stay, or pain at 6 months.

The available evidence clearly indicates a benefit for gabapentin or pregabalin in patients with neuropathic pain, though the efficacy in non-neuropathic burn pain is far less certain. The efficacy of gabapentin in neuropathic pain is well established,[81] and neuropathic pain is a common problem in burn patients. It is entirely possible that the initial positive analgesic effects detected in the earlier studies of gabapentin in burn patients were reflecting the subset of patients with neuropathic pain.

Future Research For both gabapentin and pregabalin, large, multicenter studies are needed to determine whether either agent has a role in the treatment of neuropathic and non-neuropathic burn pain. Ideally a study comparing the two drugs would be conducted to determine whether gabapentin or pregabalin is a better medication for burn-related pain. Additionally, studies examining the maximum dose of gabapentin for burn patients and the weaning of the medication would be useful in helping practitioners make more informed decisions.

Ketamine Guideline 14: Ketamine should be considered for procedural sedation, utilizing appropriate training and monitoring for the physician and nursing staff who are administering (Level B).
Guideline 15: Low-dose ketamine should be considered as an adjunct to opioid therapy in patients who could benefit from reduced opioid consumption, particularly in the postoperative period (Level D).

Rationale Ketamine, a noncompetitive *N*-methyl d-aspartate (NMDA) receptor antagonist, has been used for treatment of pain as a primary and adjuvant analgesic in a variety of postoperative patient populations and has been shown to reduce pain scores and opioid requirements in other surgical populations.[58,62,136] However, data are limited in the burn population. Only one systematic review has been published to date, which reviewed 67 healthy volunteers in four studies,[79] suggesting a reduction in secondary hyperalgesia. One case report has been published by Edrich et al in which a patient's daily opioid requirements were decreased substantially once a ketamine infusion at 2.7 mg/kg/h was started and continued for 24 days while in the hospital.[60] No adverse events were reported.

Ketamine has also been shown to be useful for procedural sedation. While large, multicenter studies investigating ketamine in the treatment of burn pain are limited, several single centers have published their experiences with using ketamine for dressing changes.[52,55,61,64,67] MacPherson et al used patient-controlled analgesia in the form of a combination of intravenous ketamine and midazolam for adult patients undergoing dressing changes.[52] The average dose of ketamine was 94 mg and midazolam 4.7 mg for each dressing change, with 44% of the patients experiencing an adverse reaction. Hallucinations were the most common complication. Overall, both patients and staff perceived that the combination worked well for dressing changes. Owens et al also described a ketamine protocol for procedural sedation in pediatric patients in combination with midazolam. Out of 347 sedation events, they found 17 events (4.9%) had a potentially adverse outcome with 10 of those events (2.9%) requiring further intervention.[61] When used intramuscularly (IM) for dressing changes in adult patients, Zor et al found that pain scores improved when ketamine was used in combination with IM tramadol plus IM

dexmedetomidine or IM midazolam compared to ketamine IM alone.[64]

Future Research We encourage further research exploring the role of low-dose ketamine infusions as an adjunct therapy for background pain control, including the safety profile and opioid-sparing effects of low dose ketamine. Weaning parameters and adverse effects should also be examined Additionally, larger, multicenter studies are needed to determine the efficacy and full safety profile of ketamine for procedural sedation in acute burn patients. These studies should focus on dosing, appropriate monitoring, and recovery/rescue procedures.

Alpha-2 Agonists Guideline 16: Dexmedetomidine and clonidine are recommended as pain management adjuncts, particularly in patients showing signs of withdrawal or prominent anxiety symptoms and dexmedetomidine as a first-line sedative in the intubated burn patient (Level D).

Rationale Dexmedetomidine is an alpha-2 agonist with powerful sedative effects and moderate analgesic effects. This agent is frequently used in the intensive care unit setting as a sedative that is more conducive to wakefulness than benzodiazepines, and with reduced delirium effects.[70] The drug is administered as a continuous infusion. In burn care, it is often used as a sedative in intubated patients to facilitate participation in therapy and preserve respiratory drive. Additionally, dexmedetomidine has been shown to be a good adjunct to ketamine as it reduces hallucinations and delirium associated with ketamine use. Reports in postsurgical burn patients showed that dexmedetomidine can decrease opioid and propofol requirements by >50% in intubated intensive care patients.[82] Dexmedetomidine has generally been shown to have an acceptable safety profile but has been found to be associated with hypotension, bradycardia and sinus arrest on rare occasions.

Clonidine has similar, but weaker sedative and analgesic effects compared to dexmedetomidine. It is nonetheless commonly used as an oral option when weaning dexmedetomidine.[66] Clonidine can be used as a single agent for analgesia in most conditions; however, single agent use in burn pain management has not been shown to be effective. It is an excellent oral adjunct to opioid analgesia.[74] Several studies have shown decreased opioid requirements when used as an intravenous adjunct. Two reports demonstrated that clonidine was able to prolong local anesthesia activity.[66,76]

Both clonidine and dexmedetomidine can be administered in the management of alcohol, opiate and nicotine withdrawal.[65] This is a potential benefit in the burn trauma population where substance abuse is common. Although, hypotension and symptomatic bradycardia are infrequently associated with these medications, serious complications are rare. In critical care settings, both agents have been shown to preserve respiratory drive, reduce delirium and potentially preserve renal function.[65,70]

Future Research We encourage further research efforts to consolidate and expand our current understanding of the use of alpha-2 agonists for pain, withdrawal, sedation, and anxiety in acute burn patients. Through larger scale multi-institutional studies of these agents, we suggest examining optimal dosing, side effect profiles, effect on opioid requirements and control of withdrawal or anxiety for both dexmedetomidine and clonidine. Additionally, dexmedetomidine should be studied as a sedative in intubated patients. The dosage, optimal duration, adverse effects and weaning of dexmedetomidine as a sedative should be examined.

Lidocaine (Intravenous) Guideline 17: The use of IV lidocaine for burn pain management cannot be recommended at this time as a first-line agent, but it is a reasonable second- or third-line adjuvant agent (Level D).

Rationale Lidocaine is an anesthetic that can be administered locally, topically and by the intravenous route. (See regional pain management section or discussion topical and local applications). In the broader (ie, nonburn) acute pain literature, there is growing evidence that continuous lidocaine is effective as an adjunct analgesic. In a single-center prospective, randomized study, intravenous lidocaine was shown to reduce burn patient-reported pain scores when compared with placebo.[63] This is the only substantive study available for the use of intravenous lidocaine in burn pain management. However, no substantive effects on opioid consumption or patient-reported anxiety levels were noted in the study. A Cochrane review corroborates these results and demonstrated great potential in other medical conditions and nonburn trauma.[72] The Cochrane review recommended additional studies before a general recommendation could be given.

Future Research Further clinical study is encouraged to better document the efficacy and safety of intravenous lidocaine for pain control in the burn population. Specifically, future research should focus on determining the appropriate dose to reduce burn patient-reported pain scores and opioid consumption. Additionally, the effects of intravenous lidocaine on patient-reported anxiety levels should be examined.

Cannabinoids Recommendation 18: Given the lack of evidence and the potential legal and political obstacles we cannot offer a recommendation for the use of cannabinoids in the treatment of acute burn pain (Level D).

Rationale Cannabinoids are a diverse group of chemical compounds that act on the cannabinoid receptors in cells that modulate neurotransmitter release in the brain. Endocannabinoids (endogenously produced), phytocannabinoids (derived from plants) and synthetic cannabinoids may act as ligands on these receptors. These agents have notable anxiolytic, anti-emetic, anti-pruritic and analgesic effects that are not completely understood.[137] Unfortunately, the classification of most cannabinoids as prohibited schedule I drugs has limited formal study of these agents.

Dronabinol is synthetic variant of tetrahydrocannabinol (THC) is used primarily as an anti-emetic and appetite stimulant.[137] It is known to have mild analgesic effects. No reliable data are available for its use in pain management. It is currently listed as a schedule III drug.

Nabilone is a synthetic cannabinoid that is active on the cannabinoid receptor-1 (CBR-1). This medication has been used successfully to control neuropathic pain in oncology patients receiving chemotherapy.[78] Bestard et al showed that nabilone had similar effectiveness when compared with gabapentin in controlling neuropathic pain.[77] The medication is also an effective anti-emetic in cancer patients. This medication is currently listed as a schedule II drug.

Neither of the two available cannabinoid medications can be recommended for routine adjunct use in burn pain management. However, the authors note multiple anecdotes of burn patients who use cannabis as a treatment of their burn pain with incredible individual success. In states where legally permitted, we believe that they should be considered in difficult cases where other medications are ineffective, particularly in burn patients with a significant history of recreational cannabis use.

Future Research Despite persistent legal and political obstacles, there has been a recent resurgence in interest in medical research into these agents as several states and localities in the United States have legalized their use. Cannabinoids represent a great potential reservoir of new pain and anxiety treatments. We believe research into this class of compounds and the receptors is warranted.

Regional Anesthesia

Guideline 19: Regional anesthesia for burn pain management has the potential to provide improved pain relief, patient satisfaction, and opioid use reduction without serious risks or complications. Given the limited amount of good quality evidence we cannot at this time make specific recommendations about either the timing or dosing of regional anesthesia techniques, or the potential long-term benefits of early regional anesthesia use in this population (Level C).

Rationale The goal of regional anesthesia is to reduce sensation in a specific part of the body to facilitate a surgical procedure or to relieve pain. To accomplish this goal, local anesthetic drugs may be placed centrally in the epidural or intrathecal spaces (neuraxial anesthesia), near major peripheral nerves (peripheral nerve block) or infiltrated or placed topically for smaller areas of surface anesthesia. Peripheral nerve blocks have been described using both landmark-based and electric stimulation techniques to locate the target nerve. However, the use of ultrasound for more precise identification of anatomical structures and for live needle guidance has mostly superseded these methods. For neuraxial and peripheral nerve blocks, a catheter may be placed in order to provide a continuous infusion of local anesthetic for longer lasting anesthesia or analgesia. Regional anesthesia can be used alone or in combination with other anesthetic or analgesic modalities, including systemic analgesics and nonpharmacologic techniques.

There is a large body of evidence supporting regional analgesia in the perioperative acute pain literature, but there are limited data for its specific use in alleviating burn pain. Upon review of the literature, 10 studies were found that deserve brief emphasis for their potential relevance and benefit to burn pain management.

Topical anesthesia may provide meaningful pain relief for up to 24 h after skin graft harvesting, and has been shown to be effective using either a lidocaine/bupivacaine mix or a prilocaine/lidocaine cream.[51,56]

Tumescent local anesthesia (TLA) is a technique based upon the direct infiltration of large-volumes of a dilute solution of local anesthetic (typically lidocaine) into the subcutaneous fat, resulting in anesthesia over relatively wide areas of the skin and the subcutaneous tissue.[88] TLA is helpful[84,87] and safe, but it is generally limited by maximum dose that targets a limited area of skin, for example, 150 cm.[51,88] Additionally, it also does not allow for a catheter to be placed for long-term analgesia.

For anesthesia of larger surface areas, neuraxial anesthesia or peripheral nerve blockade may be more helpful as burn injuries often cover large areas and donor sites can be large surface areas as well. However, we found no studies looking at neuraxial anesthesia use in burn pain management, and only a limited number of small studies using peripheral nerve blocks.

One randomized controlled trial demonstrated successful preoperative analgesic block of the lateral thigh for split-thickness skin graft harvesting using ultrasound-guided lateral femoral cutaneous nerve (LFCN) block in 16 consecutive patients, with success being defined as avoidance of general anesthesia for the subsequent graft harvest or no analgesic requirement for 4 h postharvest.[83]

Shank et al performed a prospective comparison of three regional anesthesia techniques—single-shot injection, peripheral nerve catheter (PNC) infusion, and surgical infiltration of local anesthesia—for split-thickness skin graft harvesting on the thigh.[90] Compared to surgical infiltration with local anesthetic, they reported improved pain scores with a single-shot LFCN block on postoperative days 0 and 1 and with a fascia iliaca compartment block (FICB) PNC on postoperative days 1 and 2, although there was no significant reduction in opioid use between any of the treatment groups. A separate randomized controlled trial supports the effectiveness of a continuous FICB using a PNC, reporting a reduction in both opioid use and visual analogue pain score (VAS) for 72 h after split-thickness skin grafting.[92] However, a later study comparing single-shot and PNC FICBs in 81 patients demonstrated similar magnitudes of pain reduction and opioid sparing over 72 h, but with better outcomes (less residual paresthesia and higher patient satisfaction scores) in the single-shot group.[91]

There is a suggestion that early, postinjury nerve block can reduce hyperalgesia that develops after thermal injury. Pedersen et al placed a saphenous nerve block in healthy volunteers prior to experimental thermal injury.[85] Subjects who had a nerve block placed before the burn reported reduced primary and secondary hyperalgesia once the effect of the block had worn off, when compared to their contralateral burned and unblocked leg.

Future Research The evidence supports more widespread use and further investigation of regional anesthesia in the acute burn patient. Specifically, future research should focus on either the timing or dosing of regional anesthesia techniques, or the potential long-term benefits of early regional anesthesia use in the acute burn population.

Nonpharmacologic Treatments

Guideline 20: We recommend that every patient be offered a nonpharmacological pain control technique, at least as an adjunctive measure to their pain control regimen. When the

expertise and/or equipment is available, cognitive-behavioral therapy, hypnosis and virtual reality have the strongest evidence (Level A).

Rationale While pharmacologic modalities are central to the management of pain, non-pharmacologic therapies have been shown to be critical adjuncts in a comprehensive pain management plan. Various nonpharmacologic interventions have been studied as "alternative methods" of pain control and reported in the literature. Several literature reviews have been performed evaluating techniques and efficacy.[40]

A review of the nonpharmacological pain control literature for burns is wrought with challenges, given the expected procedural differences in study formats, data collection, and reporting. Ultimately, we identified 56 manuscripts that addressed and reviewed nonpharmacological acute pain techniques. The nonpharmacological techniques fell into four broad categories; cognitive-behavioral Therapy, Hypnosis, Distraction (Virtual Reality), and Relaxation (Breathing, Music, Stress Inoculation, Aromatherapy, massage). Of the 56 studies, 10 were rated at the highest level (Level 1) according to the Oxford criteria. There was one meta-analysis and two systematic reviews. Specifically, in 2007, de Jong et al reported on 26 studies that were published on interventions such as active hypnosis, rapid induction analgesia, and distraction/relaxation techniques.[86] Of those 26 articles, 17 showed that the interventions listed had a positive effect on patient-reported discomfort during acute wound care procedures, and, perhaps more importantly, no adverse effects were noted. They also concluded that the lack of any standardized methodology makes it difficult to draw definitive conclusions regarding efficacy of nonpharmacologic procedures. More recently, Scheffler et al published a systematic review of 21 randomized controlled trials (RCTs), comprising 660 patients in total.[89] They likewise conclude that while the trials showed significant positive effects of nonpharmacological interventions on pain outcomes, the degree of study heterogeneity and lack of reliable internal validity of the studies make broad generalizations about the use of any one specific intervention challenging. Finally, another review article evaluated similar methods of pain relief in the pediatric population, ultimately evaluating 12 studies.[93] They too, found significant methodological issues with the 12 papers they reviewed, specifically citing poor "internal validity" in 5 of the 12 studies deemed suitable for inclusion.

Of the remaining studies that we identified, the strongest evidence for efficacy of acute procedural pain is for hypnosis, virtual reality distraction and cognitive-behavioral therapy techniques.[86,95,96] Hypnosis was most effective when the affective component of pain was targeted in posthypnotic suggestions and for patients who had high pain. Although the success of this technique may also be dependent in some part upon patient factors, such as past pain experiences, memory, understanding of pain, cultural conditioning, substance abuse, coping style and/ or sensitivity to hypnotic suggestions,[86,99,112] there has been some degree of promise in both adult and pediatric populations.[96,98,100,105] Cognitive-behavioral therapy was most effective when decatastrophizing and reinterpreting pain signals were targeted. There was Level 2 and 3 evidence for the use of music therapy, aromatherapy and massage and other forms of distraction. Although we found limited and underpowered studies regarding massage and aromatherapy, results were positive when used as complementary to pharmacologic modalities.[93,94,97,124,125]

Several nonpharmacologic pain interventions center around the distraction principle, the concept that subjective pain can be decreased by redirecting the patient's focus away from pain sensation. The efficacy of distraction techniques relies on the gate control theory of pain, first described by Melzack and Wall.[11,126] The theory asserts that higher order thought processes can alter the interpretation of pain signals such that nonnoxious stimuli can suppress pain. Since pain requires attention, the greater the degree of distraction, the greater the potential for decreased pain as a result.[116,123]

Virtual reality is probably the distraction-based nonpharmacologic pain intervention with the most robust literature documenting its use and efficacy.[103,104,106,107,110–114,116,118,120,126] With virtual reality techniques, distraction is achieved by a sense of immersion and the concept of "presence" which is described as the experience of going "into" the virtual environment.[103,106,107,111,113–115,118,120] The stronger the sense of presence, the more attention is drawn to the virtual world, and the less attention available to the perception of pain.[107,120] Studies have shown that those patients that feel more "present" in the virtual world have lower pain scores during wound care and physiotherapy.[104,106,107,110,112,113,116–118,120,126]

Though ultimately targeting pain, many of the nonpharmacologic therapies used to mitigate burn pain do so indirectly by addressing underlying anxiety processes associated with pain. Uncontrolled anxiety can intensify pain as well as decrease the effectiveness of pain medication.[105,107,119,125] Furthermore, the distinction between pain and anxiety may not be easily discernible, as uncontrolled anxiety may be reported as pain and vice versa.[103] Multiple interventions that have proven successful (with varying levels of evidence) focus on allaying patient anxiety by restoring the patient's sense of control. Such techniques generally provide the patient with discreet set of options within their control and or a set of achievable tasks, that is, patient participation in wound care,[86] active engagement in music therapy,[109] and activities or goals within a virtual reality system[121,122] which can be interpreted as positive affect (eg, fun).[101,110,113,116,118]

It is important to note that in all of the studies reviewed, none reported significant negative adverse effects or patient harm. In light of the opioid crisis and the challenge of controlling high acute pain levels while minimizing opioid addiction and overdose, it is important to find and incorporate nonpharmacological options for managing anxiety and pain. Hypnosis and cognitive-behavioral therapy require some specialized training while virtual reality requires purchasing special equipment, and hospitals should be encouraged to invest in appropriately trained providers and equipment. But there is also efficacy for the less resource intensive techniques that most providers may be relatively easily trained to administer (eg, distraction, breathing, aromatherapy and music). nonpharmacological techniques can be an important and beneficial aspect of the multimodal treatment of burn-related pain.

Future Research Unfortunately, given the difficulty in standardizing methodology and/or randomization, as well

as the small sample sizes in many of these studies, most of the data reported in the current literature are limited in scope and/or generalizability. There is an urgent need for a set of common technical elements and descriptors to precisely define the various elements of nonpharmacologic pain interventions, so that data from various clinical trials can be better contextualized. In addition, future studies need to be more complex in identifying mediators and moderators of various techniques—how does the technique work and for whom does it work. These studies require collaborative, multi-institutional trials, rather than small, single-center studies that predominate in the existing literature. We would also encourage investigators to move beyond a focus on study of modalities (virtual reality therapy, cognitive therapy etc.), and toward a narrower focus on specific technical components of therapy—for example, virtual reality content features, specific cognitive or distraction techniques, well defined behavioral interventions etc. Finally, we would like to see studies that compare these various nonpharmacological interventions. These recommendations will allow providers to make more educated decisions about which interventions would best fit their institution and/or identify those interventions most likely to benefit a particular patient.

CONCLUSIONS

The management of pain following a burn is extremely complex and the various phases of care must be considered in pain assessments as well as when choosing which treatment modalities to use. All of the various modalities of pain control discussed above have a role in pain control for the burn injured patient and can be used to create an individualized multimodal analgesic plan for each patient. While there is increasing research on all of these modalities, the available studies are inadequate to support a true standard of care. Moving forward we call for more burn specific research into all modalities for burn pain control as well as research on multimodal pain control. Additionally, we call for the use of common data elements in burn pain research studies so studies and protocols created can be reliably compared.

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