Considerations for Pain Management in the Burn-Injured Patient

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1 Introduction

Pain has been defined as a "mutually recognizable somatic experience that reflects a person's apprehension of threat to their bodily or existential integrity." [1]. Under normal circumstances, pain helps the body to respond to a source of danger or tissue damage and facilitates protection for tissue repair. Acute pain arises from a range of noxious stimuli, including physical (heat, cold, electrical), mechanical, and chemical [2].

Burn pain has been investigated meticulously in the clinical and research field as the model to understand the intricate pathophysiology processes of pain. Burn pain combines features of nociceptive, neuropathic, and inflammatory mechanism together with peripheral and central components [2, 3].

The management of postburn pain is exceedingly complex, for once it depends on the patient factors such as physical, biological, and social status, but also the burn characteristics and mechanisms of injury. Furthermore, burn pain varies in the same individual throughout the different phases of recovery. Table 1 describes the effects of burns physiology on pain management.

Burn pain can be separated into four components—background pain, procedural pain, breakthrough pain, and neuropathic pain [4]—each of them requiring specific interventions.

Untreated or inadequately treated pain can lead to anxiety, fear, depression, and posttraumatic stress disorder. It can cause peripheral and central sensitization [5], resulting in chronic pain [6]. Lastly, pain can also impair the healing process due to multiple factors, including metabolic, humoral, endocrine, and immunological derangements.

Management of burn pain requires a multimodal management strategy. Despite the current "opioid crisis" and concerns about opioid tolerance, opioid-induced hyperalgesia, opioid abuse, misuse and diversion, intravenous opioids are the cornerstone of burn pain management [7, 8].This chapter will evaluate the pharmacological approach to burn pain. Non-pharmacological interventions, although important, are beyond the scope of this review.

2 Pain Pathways

After stimulation of local nociceptors, the impulse travels via Ad and C fibers to the dorsal horn of the spinal cord. Peripheral sensory nerves and descending influences from cortical areas can modulate the magnitude of the pain impulse. Pain is a conscious experience, an interpretation of the nociceptive input influenced by memories, emotional, pathological,

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Table 1 Effects of burns physiology on pain management

Physiologic state	Effect	Implications
Burn shock (0–48 h)	Plasma protein loss through burned skin Dilution of plasma proteins by resuscitation fluids decreased concentration of albumin Cardiac output decreases Increase pulmonary vascular resistance [39]	Increase in volume of distribution of medications. Elimination of some drugs by the kidney and liver is decreased [42]
Hypermetabolic state with increase blood flow to liver and kidney Generalized edema	Increase clearance and biotransformation of medications Decrease in albumin (binds acid and neutral drugs) Increase in alpha-1-acid glycoprotein (binds cationic drugs)	Increased analgesic clearance and pain [42] Doses and intervals are affected (usually increased doses and shorter intervals) Unpredictable absorption of IM medications Succinylcholine is contraindicated
Cytokine-mediated inflammatory response	Cascade of irritants that sensitize and stimulate pain fibers [3]	Wounds may become primarily hyperalgesic to mechanical or thermal stimuli

genetic, and cognitive factors. Resultant pain is therefore not always related linearly to the nociceptive drive or input, neither is it solely for vital protective functions [9].

Pain is a highly subjective experience affected not only by the burn wound itself but also by context, cognition, pharmacologic, mood, and other predisposing factors [10].

Figure 1 shows a representation of the substances involved in the transmission of noxious stimuli and the possible targets for pharmacological interventions [11].

3 Components of Burn Pain

Burn pain has four distinct components—background, procedural, breakthrough, and neuropathic pain. When pain persists for more than 6 months, it becomes chronic pain. Pharmacological and non-pharmacological interventions should be individualized to target each pain pattern [12].

Table 2 describes the most common pharmacologic interventions, intial doses, side effects, and target pain pattern.

3.1 Background Pain

It is a constant pain that is present while the patient is at rest. Background pain is the result of either direct injury or inflammation of the skin, subcutaneous tissue, muscle, or visceral tissue. This type of pain is typical of low to moderate intensity and long duration. It is best treated with mild-to-moderately potent analgesics administered so that plasma drug concentrations remain relatively constant throughout the day. Pain management strategies typically include regular acetaminophen, regular NSAIDs where appropriate, and the use of long-acting opioids.

3.2 Procedural Pain

In contrast to background pain, procedural pain reaches quite intense levels for a brief period; therefore, analgesic regimens for procedural pain are best comprised of combinations of short-acting opioids, benzodiazepines, magnesium and lidocaine infusions, and subanesthetic doses of ketamine.

Among the short-acting opioids, sufentanil poses particular characteristics that make it the first choice. For once, its potency, solubility, and high affinity for mu receptors. This later characteristic is very important in the context of downregulation of mu and kappa receptors.

Procedural pain is generated by a myriad of interventions such as wound debridement, burn excision, donor skin harvesting, grafting, placement of central lines, dressing changes, and rehabilitation efforts.

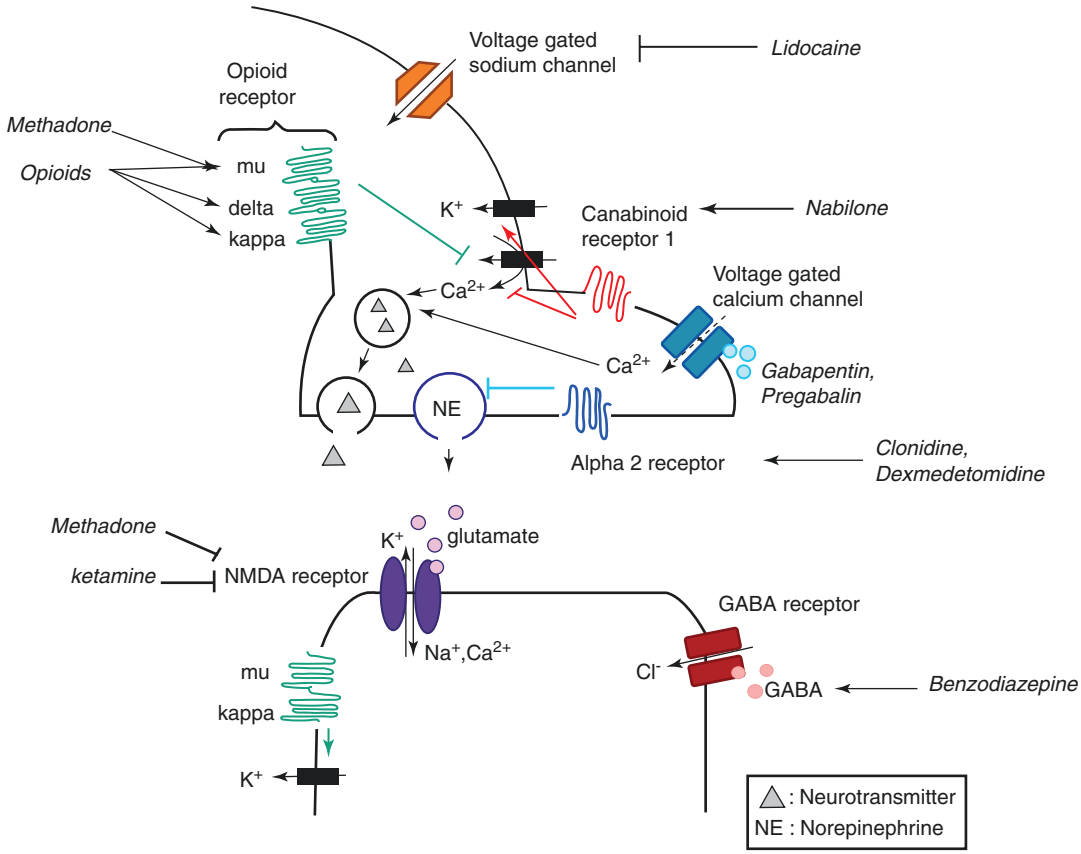

Fig. 1 Pain pathways. *GABA* γ-aminobutyric acid, *NMDA* N-methyl-D-aspartate. Reproduced with permission from Retrouvey H, Shahrokhi S. Pain and the Thermally Injured Patient—A Review of Current Therapies. *Journal of Burn Care & Research*. 2015;36(2):315–323

3.3 Breakthrough Pain

Breakthrough pain describes unexpected spikes of pain that occur when background analgesic effects are exceeded, either at rest, during procedures, or with stress [10]. It can be a result of inadequate doses of analgesics for background pain, or to changing mechanisms of pain over time [13].

3.4 Neuropathic Pain

Neuropathic pain is caused by the direct injury or inflammation to neural tissue or vasum-nevorums in the peripheral and central nervous system. As neurons regenerate, abnormal excitability at or near the site of nerve injury can occur. It often persists after burn wounds have healed. It may be experienced as numbness and tingling in the burned areas, which may progress to painful paresthesias [14].

Since limited options are available for the management of neuropathic pain, gabapentinoids, and laser therapy should be considered as potential treatment options [15].

4 Pain Management

4.1 Pharmacological

4.1.1 Opioids

Opioids mimic the effects of endogenous opioid peptides by interacting with the mu, delta, and kappa receptors. Each opioid has a different

Table 2 Pharmacological options for treatment of burn pain

Medication	Receptor/Mechanism	Dose	Effect	Side Effects	Component of pain target
Opioids	mu, delta, and kappa opioid receptors		Analgesia	Nausea, vomiting, constipation, gastric dysmotility, dependence, and tolerance. Opioid-induced hyperalgesia	Background Procedural Breakthrough
Morphine		IV PCA 1–2 mg Q 5–10 min			
Hydromorphone		PO: 2–4 mg Q2h IV PCA 0.1–0.4 mg Q5–10 min			
Fentanyl		IV PCA 20–50 mcg Q5–10 min			
Sufentanil		IV PCA 2–6 mcg Q5–10 min			
Methadone [17]	Mu opioid (agonist) *NMDA* (antagonist)	15 mg PO OD	Inhibits opioid tolerance and reduces central sensitization	Long half-life (8–59 h)	Background
Oxycodone		10–20 mg POQID			
Codeine		60 mg PO QID			
NSAIDs	Inhibition Cyclo-oxygenase (COX-1 and COX-2).		Antipyretic, anti-inflammatory, and analgesic effects	GI bleeding, decreased platelet activity, and AKI	Background Breakthrough
Acetaminophen	Inhibition of central prostaglandin synthesis	1 g PO QID	Decreases opioid consumption Synergistic effects with opioids		Background Breakthrough

Antidepressants [15]	Interference with serotonin uptake, interaction with alpha-receptors, opioidergic effect, blockade of NMDA receptor, sodium and calcium channel. Inhibition of histaminic, cholinergic, muscarinic, and nicotinic receptors			Anticholinergic effects (tachycardia, dry mouth, urinary retention), sedation	
Amitriptyline		10–50 mg PO QHS			Neuropatic
Duloxetine	SNRIs	30–120 mg PO OD			Neuropatic
Dexmedetomidine [24]	α-2 agonist (2A subtype)	0.2–0.7 mcg/kg/h	Minimal to no risk of respiratory depression	Bradycardia and hypotension	Procedural
Clonidine [22]	α-2 agonist	0.1 mg PO BID		Bradycardia and hypotension	Procedural
Lidocaine [34]	Voltage-gated sodium channels	1 mg/kg/H	Inhibiting nerve conduction in afferent nerves that signal pain	Seizures, arrhythmias, bradycardia	Procedural Background
Cannabinoids	CB1 (responsible for most side effects) CB2 (responsible for non-psychotropic effects)		Anti-inflammatory and anti-hyperalgesia	Dependence, tolerance, headache, dizziness, anxiety, memory impairment, speech impediment, and sedation	Neuropathic
Nabilone [30]	CB 1 agonist	0.5–1 mg PO BID			
Gabapentinoids [25]	α2δ-1 subunit of voltage-gated calcium channels (dorsal horn and dorsal root ganglia)		Inhibits the sensitization of the central nervous system by reducing neurotransmitter release Reduce postburn pruritus	Dizziness, somnolence, dry mouth, and edema	Neuropathic
Pregabalin		25–200 mg PO TID			
Gabapentin		100–1200 mg PO TID			
Benzodiazepines	GABA receptor		No analgesic properties	Sedation, respiratory depression, addiction, and tolerance	Procedural Background
Lorazepam		1–2 mg PO			

(continued)

Table 2 (continued)

Medication	Receptor/Mechanism	Dose	Effect	Side Effects	Component of pain target
Midazolam		1–3 mg IV			
Ketamine [20]	NMDA (antagonist)	IV: 0.1–0.3 mg/kg/h PO 30–90 mg QID	Blocks pain transmission by inhibiting central sensitization Reduce primary and secondary hyperalgesia [21] Increases thermal injury-induced mechanical pain thresholds	Nausea, vomiting, hallucinations, mood alteration, bizarre dreams, emergence delirium Sympathetic activation causes tachycardia, hypertension, and salivation	Background Procedural Breakthrough
Nitrous Oxide [41]	Promotes the release of endogenous opioids that activate GABA Supraspinal GABA inhibition Spinal GABA activation	50–65% N_2O		Nausea, vomiting, hypoxia, vit B12 deficiency	Procedural
Magnesium		20–50 mcg/kg/h (max 2 g/h/max 24 h)			Neuropathic

AKI acute kidney injury, *GABA* γ-aminobutyric acid, *GI* gastrointestinal, *NMDA N*-methyl-D-aspartate receptor antagonist, *CB* Cannabinoid, *PCA* Patient-controlled analgesia, *SNRIs* Serotonin and norepinephrine receptor inhibitors, *OD* once a day, *QHS* once at night, *BID* twice a day, *TID* three times a day, *QID* four times a day, *PO* oral

effect on these subtypes of receptors, but mostly activate the mu receptor. The wide spectrum of opioids available for clinical use provides dosing flexibility (i.e., variable routes of administration, variable duration of action, variable potency) [13, 16].

For hospitalized burn patients, opioids are the cornerstone of pharmacologic pain control, in part because they are potent, inexpensive, widely available, and familiar to the majority of health care providers [12].

Side effects of opioids are significant and include respiratory depression, constipation, sedation, pruritus, sleep cycle interference, nausea, hallucinations, and vomiting. Additionally, opioids have been associated with dependence, tolerance, and hyperalgesia.

The opioid agonist-antagonist drugs (e.g., nalbuphine, butorphanol) produce analgesia (agonist property) with lesser side effects (antagonist properties), but also exhibit ceiling effects, limiting its use to mild burn pain.

Opioids are not effective at treating neuropathic burn pain.

Range doses for the most commonly used opioids are detailed in Table 2. Suggested starting doses are:

- Morphine: PCA 1 mg lockout 10 min.
- Hydromorphone: PCA 0.1 mg lockout 10 min. PO 2 mg Q2H.
- Fentanyl: PCA 25 mcg lockout 10 min.
- Sufentanil: PCA 2 mcg lockout 10 min.
- Oxycodone: 20 mg PO Q6H.
- Codeine: 60 mg PO Q6H.

Methadone

Methadone is a mu opioid receptor agonist with a weak NMDA receptor antagonist. Methadone is a moderate analgesic that has been used as an alternative analgesic in opioid-tolerant patients and to treat opioid dependence [17].

- The suggested starting dose is 15 mg PO once a day.

4.1.2 Adjuvants

NSAIDs

NSAIDs cause analgesia and anti-inflammatory effects by inhibition of prostaglandin synthesis by the cyclo-oxygenase (COX-1 and COX-2) [18].

NSAIDs are mild analgesics that exhibit a ceiling effect in their dose–response relationship. They are useful as adjuncts to opioids treating minor burns, usually in the outpatient setting. NSAIDs had shown to decrease central hyperalgesia, have a synergistic effect, and are opioid-sparing.

The widespread inhibition of cyclo-oxygenase is responsible for many of the adverse effects of these NSAIDs. Bleeding risk, gastrointestinal complications, and renal toxicity are the most feared side effects; making these agents generally unsuitable for the treatment of the typical, severe burn pain [10].

The suggested starting dose is:

- Celecoxib: 200 mg PO loading dose, followed by 100 mg PO Q12H (maximum 4 days).
- Ketorolac: 15 mg IV loading dose, followed by 7.5 mg IV Q6H (maximum 4 days).

Acetaminophen

Acetaminophen is an antipyretic and an analgesic with both central and peripheral pain modulation activity. The mechanism of action of acetaminophen is unknown, but it may involve the inhibition of central prostaglandin synthesis and the activation of descending serotonergic pathways [19].

Acetaminophen is usually administered as an adjunct to opioids for major burns as it has a synergistic effect.

- The suggested starting dose is 1 g PO Q6H.

Ketamine

Ketamine is an NMDA (N-methyl- d-aspartate) receptor antagonist used as a dissociative anes-

thetic and adjunct pain medication [20]. Ketamine acts on the thalamic function and the limbic system as a potent noncompetitive NMDA receptor antagonist and inhibits central pathways associated with central and peripheral pain sensitization [21].

Ketamine has many potential advantages for the induction and maintenance of anesthesia in burn patients such as hemodynamic stability, preserving airway patency as well as hypoxic and hypercapnic responses, and decreasing airway resistance.

The suggested starting dose is:

- Intravenous infusion: 0.1 mg/kg/H. Preferred route.
- Oral: 30 mg Q6H. Low bioavailability.

Alfa Antagonist

Clonidine

Clonidine is an α-2 agonist used for its sedative, anxiolytic, and analgesic properties. It is useful as an adjunct as it enhances opioid analgesia, decreases opioid requirement, and prolongs local anesthetic action [22]. It can also be administered in the management of alcohol, opiate, and nicotine withdrawal.

- The suggested starting dose is 0.1 g PO Q12H.

Dexmedetomidine

Dexmedetomidine has specificity to the 2A subtype of the alpha-2 receptor, causing it to be a more effective sedative and analgesic than clonidine.

Dexmedetomidine has been used to provide sedation–analgesia for burned patients and to decrease opioid requirements [23]. Titration of dexmedetomidine may also allow weaning of benzodiazepine as patients get close to extubation. Dexmedetomidine has been shown to result in less delirium than benzodiazepines in several critical care studies [24]. However, it can cause hypotension at higher doses in the presence of hypovolemia, therefore, should not be given to hemodynamically unstable patients.

- The suggested starting intravenous infusion is 0.2 mcg/kg/h.

Gabapentinoids

Gabapentin

Gabapentin is a structural analog of GABA. Its mechanism of action is not fully defined, but it involves inhibition of the release of excitatory neurotransmitters and increases the release of inhibitory neurotransmitter GABA by binding to the alpha-2-delta-1 subunit of the voltage-gated calcium channel [25].

Gabapentin has been used to manage chronic neuropathic burn pain because it inhibits the central sensitization of pain and also relives postburn pruritus.

- The suggested starting dose is 100 mg PO Q8H.

Pregabalin

Like Gabapentin, Pregabalin binds to the alpha-2-delta-1 subunit of the presynaptic voltage-gated calcium channel in the dorsal horn of the spinal cord, with subsequent reduced release of the excitatory neurotransmitter glutamate. It has both analgesic and anxiolytic properties [4, 25].

- The suggested starting dose is 50–100 mg PO Q12H.

Cannabinoids

The *Cannabis sativa* plant contains over 100 bioactive lipid compounds, known as cannabinoids, which produce analgesia in animal models of acute and chronic pain. However, due to abuse potential and numerous additional side effects, such as dependence, tolerance, hypomotility, deficits in executive function, and memory consolidation, the use of cannabis for medicinal purposes has been restricted until recent times [26].

There are two types of cannabinoid (CB) receptors. The CB1 receptor which is found both in the periphery and central nervous system (CNS), and CB2 receptor which is typically expressed predominantly by cells of the immune system, including glial cells of the CNS [27].

The undesirable effects of cannabinoids are caused by the global activation of CNS CB1 receptors. Current research has focused on presumed site-specific modulation of endogenous ligand activity or effects at the non-psychotropic CB2 receptor.

Cannabinoids have been studied in the management of chronic and neuropathic pain in the nonburn population [15, 28].

Currently, the synthetic cannabinoids agents dronabinol [29] (synthetic delta-9-tetrahydrocannabinol), tetrahydrocannabinol, and cannabidiol (CBD) sprays are not FDA-approved for analgesia but are available in the United States.

Nabilone (Cesamet)

Nabilone is a synthetic CB1 and CB2 agonist. The mechanism of pain modulation by nabilone is complex and involves the peripheral afferent nerves, the dorsal root ganglia, and spinal dorsal horn as well as specific brain areas [30]. Nabilone is effective at decreasing pain and anxiety as well as improving sleep.

- The suggested starting dose is 0.5 mg PO Q12H.

Nitrous Oxide

Nitrous oxide is an inhalant anesthetic that has modest analgesic properties when delivered at subanesthetic doses [31]. Inhaled nitrous oxide and oxygen mixtures can be a very useful form of analgesia for short procedures, such as dressing changes as it has a rapid onset (within seconds) and short duration of action. Although it is generally well-tolerated, nitrous oxide can cause nausea and vomiting, precluding its use in some patients. Repeated or prolonged administration of nitrous oxide can interfere with vitamin B12 metabolism, causing serious hematological and neurological adverse effects and necessitating monitoring and vitamin B12 supplementation as required.

- The suggested starting dose is mixures of 50% N_2O.

Benzodiazepines

Benzodiazepines act by amplifying GABA in the central nervous system, and by reducing catecholamines in the peripheral nervous system.

Although not considered analgesic, benzodiazepines can be effective in alleviating pain symptoms in combination with other analgesics, most likely due to their sedative and anxiolytic effects. Benzodiazepines, with a short-to-moderate duration of action, such as midazolam and lorazepam, are preferred to longer-acting drugs [32].

Benzodiazepines administered along with ketamine can reduce dysphoria. When administered as an adjunct to opioids, benzodiazepines have been shown to decrease both background pain and pain in those patients with high levels of procedural pain [12].

The suggested starting dose is:

- Lorazepam: 1 mg PO.
- Midazolam: 1 mg IV.

Lidocaine

Lidocaine acts on the voltage-gated sodium channels by blocking the inflow of sodium, causing inhibition in the propagation of the action potentials in neurons [33].

Lidocaine can be used as a local, topical, or systemic anesthetic. However, topical use has been associated with toxicity due to rapid systemic absorption. The efficacy of Lidocaine as an intravenous infusion for the treatment of central and peripheral sensitization as well as neuropathic pain is still being investigated [34].

- The suggested starting intravenous infusion is 1 mg/kg/h.

Antidepressants

Posttraumatic stress disorder and depression has been reported to occur in up to 30% of patients with severe burn injury, often developing in the setting of inadequate treatment of anxiety and pain [35].

Tricyclic antidepressants and serotonin-norepinephrine reuptake inhibitors, appear to enhance opiate-induced analgesia, especially in

patients with neuropathic pain. In addition, antidepressants can help to manage the depression, anxiety, and insomnia that frequently accompany severe burn injury [15].

Due to the potential risk of toxicity, it is essential to monitor the patient for signs of serotoninergic syndrome and cardiac arrhythmias.

The suggested starting dose is:

- Amitriptyline: 20 mg PO at night.
- Duloxetine: 30 mg PO once a day.

Magnesium

Magnesium is a weak non-selective NMDA receptor antagonist that is involved in neuromodulation of central and peripheral excitability and sensitization. Also, it enhances and promotes mu receptor upregulation, which is very useful in opioid tolerance and opioid induce hyperalgesic states.

- The suggested starting intravenous infusion is 20 mcg/kg/h. Maximum 2 g/h for a maximum of 24 h.

4.2 Regional Anesthesia

- Regional anesthesia has an important role in the intraoperative management of burn patients because it provides anesthesia in the operating room, can offer postoperative pain control, and facilitates rehabilitation. Regional anesthesia should be considered both for burn wound pain and donor site pain [10].
- There are several forms of regional anesthesia, starting from simple techniques such as tumescent local anesthesia injected into a donor site before harvesting [36], subcutaneous catheter infusions [37], or more complex techniques such as peripheral nerve, or central neuraxial blocks [38].
- Central neuraxial techniques (spinal, epidural) have been used with good effect. There are no reports suggesting that epidural abscesses are more common in burn patients, but studies have suggested that intravascular catheters are more likely to become infected if placed in or near burned tissue [39].
- The lateral femoral cutaneous nerve block is an excellent target for blocks because it is exclusively a sensory nerve and innervates the lateral thigh, which is frequently chosen for split-thickness skin grafts. A fascia iliaca block can also be performed if there is a need to cover the anterior and medial thigh [37, 38, 40].

4.3 Non-pharmacological

Factors such as depression or anxiety strongly affect the perception of pain in burn patients. Although pharmacological agents targeted to control pain are important, non- pharmacological therapies are essential adjuncts for optimal pain control [15].

It is beyond the scope of this chapter to review the indication and evidence of non-pharmacological interventions. Table 3 lists the most common non-pharmacological interventions.

5 Summary

- The management of burn pain is exceedingly complex as it is affected by patient factors, burn characteristics, and mechanisms of injury.
- Burn pain will vary in the same individual throughout the different phases of recovery.

Table 3 Non-pharmacological interventions

Acupuncture
Aromatherapy
Biofeedback
Cognitive-behavioral therapy
Cooling
Extracorporeal shock wave therapy
Hypnosis
Interactive gaming console
Massage
Mindfulness
Music
Laser therapy
Noncontact low-frequency ultrasound
Transcranial direct current stimulation
Transcutaneous electrical nerve stimulation
Virtual reality/augmented reality
Whole-body vibration

Therefore, analgesic regimens should be continuously evaluated and adjusted accordingly.
- An adequate pain control has severe short- and long-term consequences in the patient journey to recovery.
- Despite the side effects and potential for dependence and misuse, opioids are the cornerstone of pharmacologic pain control.
- Management of burn pain requires a multimodal approach strategy, including pharmacological and non-pharmacological modalities.
- Chronic and neuropathic pain are common sequelae in burn patients. Cannabinoids had shown promissing results in recent studies, but further investigation is required.

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