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Current Approaches to Postoperative Pain Management

Edited by Peter Magnusson, Jo Ann LeQuang and Joseph V. Pergolizzi Jr.

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Pharmaceutical Science

Volume 14

Aims and Scope of the Series

Pharmaceutical science focuses on the design, synthesis, formulation, targeting, distribution, safety, and efficacy of active compounds as potential therapeutics. It is a large interdisciplinary discipline that aims to integrate the basic principles of physical and organic chemistry, biochemistry, biology, and engineering to discover, develop, and characterize active compounds and to optimize the formulation and delivery of drugs in the body for offering new and improved safe and efficacious therapies against human diseases. The research areas covered by the pharmaceutical sciences range from medicinal chemistry and pharmaceutical technology to pharmacology and toxicology, which represent the preliminary phases of drug development. Medicinal chemistry involves the design and synthesis of pharmaceuticals as well as the isolation of active agents from natural sources. Computer-aided strategies are increasingly involved in this drug discovery process. Pharmaceutics is a multidisciplinary science that examines the relationships between drug formulation, delivery, distribution, and clinical outcomes. Modern clinical approaches are increasingly relying on controlled release strategies and drug delivery and targeting systems, including nanotechnological platforms (nanomedicine). Pharmacology is the science of drug action in biological systems. Pharmacologists also make drugs as tools to explore aspects of cell and tissue functions. Toxicology is the study of the adverse effects of active agents on living organisms and the ecosystem, including the prevention and amelioration of such adverse effects. This book series includes volumes on Drug Discovery, Delivery, and Pharmacology. Their overall aim is to present the latest research in the whole path of drug discovery and development from different points of view of this multidisciplinary and dynamic field.

Meet the Series Editor

Prof. Rosario Pignatello is a Full Professor of Pharmaceutical Technology and Legislation at the University of Catania, Italy. He is the Director of the Department of Drug and Health Sciences. He has nearly 30 years of experience in the research and development of innovative formulations for the controlled release and targeting of bioactive molecules, through chemical approaches as well as nanotechnological carriers, aimed at treating different disorders. Prof. Pignatello has coauthored about 180 papers and edited a series of textbooks on biomaterials and their application in medicine. The main areas of his research are polymeric and lipid-based micro- and nanoparticles as modified drug delivery systems; vesicular nanocarriers (liposomes, micelles); lipophilic prodrugs and conjugates; synthesis and evaluation of new polymeric biomaterials for drug delivery and tissue regeneration. In particular, Prof. Pignatello works actively in the field of ocular drug delivery, leading the Research Centre for Ocular Nanotechnology, within the NANOMED Centre (Centre for Nanomedicine and Pharmaceutical Nanotechnology) at the University of Catania.

Meet the Volume Editors

Peter Magnusson is a university lecturer at Örebro University in Sweden and a senior consultant in cardiology in Falun, Sweden. He graduated from Lund Medical School and received his Ph.D. from Karolinska Institute, Sweden. His research primarily focuses on cardiology, specifically arrhythmias and cardiomyopathies, but he is also involved in various projects within academic medicine. He is passionate about teaching and supervision. He has been involved in several international projects and has published numerous academic papers on a wide range of topics.

Jo Ann LeQuang, MPH, began her medical writing career at Intermedics, a pacemaker company based in Texas. She was the International Director of Marketing Communications at the Cardiac Rhythm Management Division of St. Jude Medical, which has since been acquired by Abbott. She has contributed to the *Nuts & Bolts of Cardiac Pacing* series by the late Thomas Kenny, RN, and numerous educational and training books on pacing and paced ECG interpretation, including some CME activities. She embarked on a freelance medical writing career in 2003 and has been an author or medical editor contributor on over 100 peer-reviewed medical articles. She resides in Texas.

Dr. Pergolizzi, M. D., is an internationally renowned specialist in critical care, perioperative medicine, and pain management. He is the co-founder and currently serves as the Chairman of Native Cardio Inc. As an inventor, research scientist, and seasoned serial entrepreneur, he leverages his significant medical expertise, regulatory experience, and business skills to build a strong track record of success across various fields in the healthcare industry. Previously, Dr. Pergolizzi served as an adjunct assistant professor in the Department of Medicine at Johns Hopkins University School of Medicine. He has published over 400 peer-reviewed medical articles and book chapters on various topics, and he has been a distinguished invited speaker and presenter at numerous medical conferences and congresses worldwide.

Contents

Preface

Pain is a common symptomatic complaint after surgery. It can be described as an unpleasant emotional experience associated with tissue damage or linked to such damage, mental suffering or distress. Pain is a subjective experience influenced by biological, psychological, and social factors. Postoperative pain is a significant concern for both patients and healthcare providers due to its potential to prolong recovery and increase hospital stays and costs.

Pain in the immediate postoperative period is prevalent, can be moderate to severe, and is often inadequately treated. Left untreated, acute postoperative pain can persist and even transition into chronic pain. Heightened scrutiny on the use of opioid analgesics has resulted in limitations in their use, but this should not mean that acute postoperative pain goes untreated. A variety of novel analgesic products have come to market, which may be serviceable for many acute pain syndromes. Pain results from complex molecular alterations in the nervous system, including inflammation (elevated CRP, IL-6, and TNF-α), tissue repair processes (MMP-2 and MMP-9), oxidative stress (MDA), neuronal function (BDNF and NGF), and pain perception (substance P and GFAP). Social pain is the metaphorical equivalent of physical pain, triggered by thoughts, emotions, interpersonal problems, and unmet expectations. Identification of reliable social pain predictors will enable policymakers to promote health equity and minimize opioid abuse by developing necessary interventions.

This book covers many aspects of postoperative pain. It covers modern methods for managing postoperative pain based on the pathophysiology of pain, the role of inflammatory mediators, and the importance of early and effective pain control. The book aims to provide healthcare professionals with a detailed understanding of managing postoperative pain effectively and improving patient outcomes.

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Chapter 1

Perspective Chapter: Current Issues in Postoperative Pain Management

Negar Eftekhar and Babak Eslam

Abstract

Postoperative pain is a significant concern for both patients and healthcare providers due to its potential to hinder recovery, prolong hospital stays, and increase healthcare costs. This chapter explores the latest methods for managing postoperative pain, emphasizing the pathophysiology of pain, the role of inflammatory mediators, and the importance of early and effective pain control. The chapter also highlights different pain management strategies, such as basic analgesia, patient-controlled analgesia (PCA), and regional analgesia techniques like epidural catheters and nerve blocks. Additionally, the chapter covers the pharmacology of common analgesics, including NSAIDs, opioids, and local anesthetics, offering insights into their mechanisms, benefits, and risks. With this comprehensive approach, the chapter aims to provide healthcare professionals with a detailed understanding of how to manage postoperative pain effectively and improve patient outcomes.

Keywords: postoperative pain, pain pathophysiology, paracetamol, metamizole, NSAIDs, piritramide, pethidine, morphine, local anesthetic, PCA, epidural catheter

1. Introduction

Pain is a complex, unpleasant experience triggered by both physical injury and psychological reactions. In 2020, the International Association for the Study of Pain (IASP) redefined pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with actual or potential tissue damage" [1]. Pain transmission involves a sophisticated interaction between signals traveling from peripheral tissues to the central nervous system and back, influenced by various pathways that can either amplify or regulate the sensation. Pain is classified based on duration: acute pain typically lasts under 3 months, while pain persisting beyond that is categorized as chronic [2]. Postoperative pain is acute by nature, but without adequate management, it risks transitioning into chronic pain.

Why is managing postoperative pain so critical? Beyond alleviating discomfort, understanding its pathophysiology reveals that inflammatory pathways and mediators significantly impact recovery and surgical outcomes. Research in both behavioral and neurophysiological domains, often through preclinical incision models, indicates that surgical tissue damage leads to both peripheral and central sensitization, driving postoperative pain [3].

Effectively controlling pain requires a thorough grasp of its pathophysiology, transmission mechanisms, and the key mediators involved. Any disruption along this pathway can offer opportunities for pain management.

2. Pathophysiology of pain and pain conduction

Each nociceptor has a designated area, called the receptive field, where painful stimuli initiate the release of specific inflammatory mediators, resulting in an action potential. These mediators lower the activation threshold of pain receptors, heightening sensitivity through a receptor-mediated pre-depolarization process of the nociceptor membrane, also known as nociceptor sensitization. This leads to localized hyperalgesia, a characteristic of inflammation. The main pain mediators include prostaglandins, histamine, cytokines, kinins, and ions such as H^+ and K^+ [4].

Once nociceptors are stimulated, pain messages are transmitted to higher brain centers via the following pathways: [4].

1. Peripheral pain conduction: The action potential travels through the sensory neuron's dendrite (pseudounipolar neuron). It bypasses the perikaryon at the dendrite-axon junction (crus commune) and moves directly to the axon, entering the spinal cord's dorsal horn (cornu posterius medullae spinalis). There, in layers I–III of the gray matter, the signal connects to the second neuron.

2. Spinal cord connection: Aδ fibers synapse with neurons in layer I of the gray matter. Meanwhile, C fibers have a more complex route, connecting in layers II and III before reaching layer V via interneurons at the segmental level.

3. Central pain transmission and processing: Pain signals ascend through the anterolateral tract to supraspinal centers. These centers evoke reflexive physical responses (formatio reticularis), process the emotional aspects of pain (limbic system), and facilitate localization (somatosensory cortex). Higher brain centers can modulate pain perception through descending antinociceptive pathways.

In summary, tissue injury during surgery triggers the release of inflammatory mediators such as histamine, prostaglandins, and substance P, which stimulate peripheral nociceptors. The pain signals travel via the spinothalamic tract to the brain (thalamus), where they are perceived as pain (**Figure 1**).

Postoperative pain is common, especially in the initial days after surgery. While it generally subsides within 3 months, if it persists beyond this period, it is classified as chronic pain. It is crucial to recognize that pain perception varies among individuals, influenced by biological, psychological, and social factors.

2.1 Predisposing factors

Are there factors that predispose patients to postoperative pain? Absolutely [6]. Predictors of pain following surgery include preoperative pain, anxiety, young age, obesity, fear of surgery, and an exaggerated perception of the upcoming surgical procedure. The type of surgery (abdominal, orthopedic, thoracic) and its duration are also important predictors. Furthermore, the extent of tissue damage, the resulting

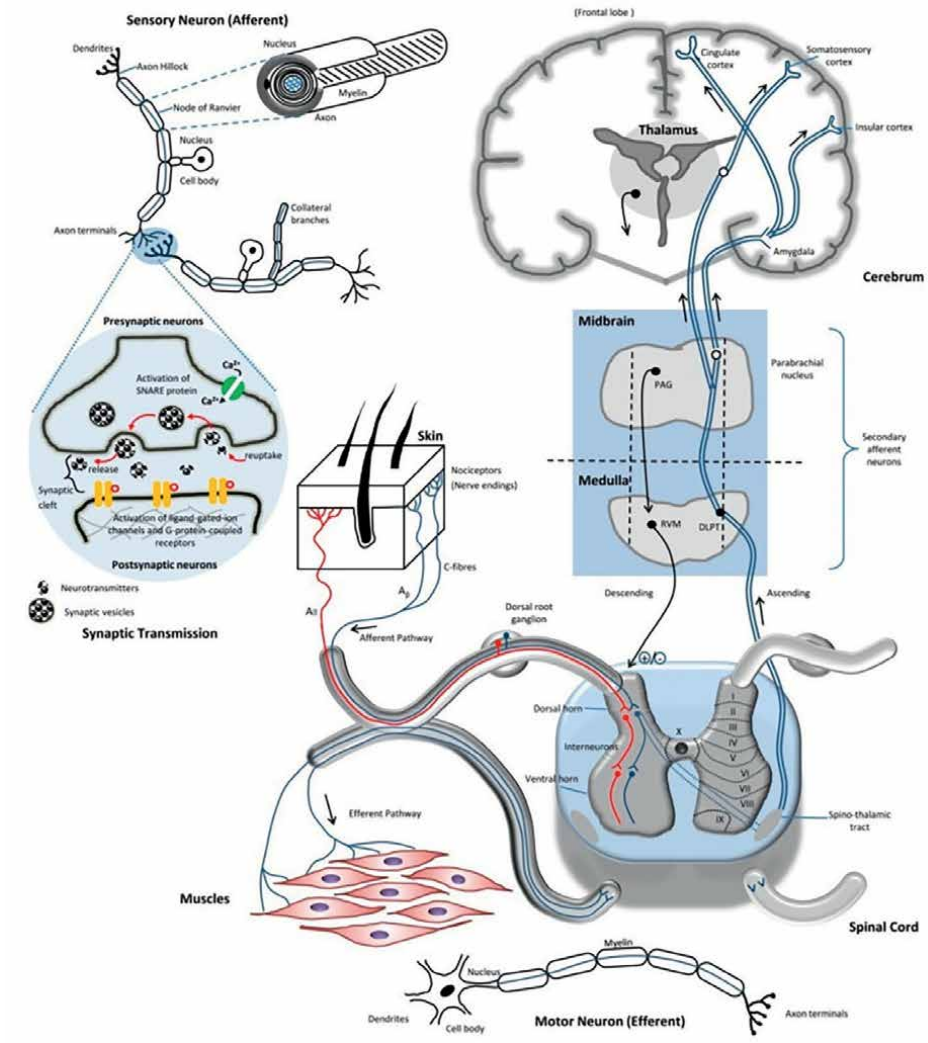

Figure 1.
The basic route of pain transmission upon noxious stimuli in ascending and descending order, and the illustration of synaptic transmission in the synaptic cleft [5].

inflammatory response, the patient's age, and psychological stress can determine the likelihood and intensity of postoperative pain and the need for analgesics.

The limited progress in acute postoperative pain treatment may be due to several factors, including inadequate pain assessment, the patient's increased awareness in reporting pain, the lack of specific postoperative pain management protocols, insufficient training for healthcare workers, underutilization of effective analgesic techniques (e.g., epidural analgesia, peripheral nerve catheters), and poor adherence to best practices.

2.2 Physiological responses to pain

Acute pain induces a variety of physiological responses that begin with tissue injury and nociceptor activation, triggering a local inflammatory response followed

by behavioral and physiological changes. The failure to adequately control pain can lead to sympathoneural and neuroendocrine activation, resulting in potentially harmful effects such as tachycardia, hypertension, hyperglycemia, immunosuppression, reduced regional blood flow, venous stasis, and platelet aggregation. These pathophysiological responses may contribute to increased morbidity in high-risk patients, such as those with multiple comorbidities or those undergoing major surgeries.

For these reasons, effective postoperative pain control is directly associated with reduced morbidity and mortality, particularly in high-risk patient populations.

Timely and effective pain control after surgery is crucial for facilitating recovery, improving patient satisfaction, reducing complications, and lowering healthcare costs.

2.3 The concept of nociception and what is analgesia

Nociception refers to the physiological process of pain perception. The receptors responsible for this process are called nociceptors, which are free nerve endings located in pain-sensitive tissues throughout the body. While nociception and pain are closely related, they are distinct concepts:

- *Nociception* involves the transmission of signals to the central nervous system (CNS) via specialized receptors (nociceptors) that provide information about potential or actual tissue damage.

- *Pain* is the subjective, unpleasant sensory and emotional experience resulting from actual or potential tissue damage.

Nociception can occur without the subjective experience of pain, but pain cannot occur without nociception (except in cases of neuropathic or psychogenic pain, where pain is generated independent of nociceptor activity).

2.4 Different types of pain

Depending on their location, nociceptors trigger various types of pain [7]:

1. *Somatic pain*: This pain is caused by damage to tissues like skin, muscles, bones, joints, and connective tissue. It is usually localized and confined to one area and can be subdivided into surface and deep somatic pain.

    - *Surface pain*: Occurs when nociceptors in the skin are activated. The location of the pain is clearly perceived in the damaged area.

    - *Deep pain*: Involves pain from deeper structures like muscles or bones, specifically the periosteum. Deep pain is harder to localize due to differences in fiber characteristics and projection areas.

2. *Visceral pain*: Nociceptors located in internal organs cause visceral pain, which may be triggered by stretching stimuli in smooth muscles, such as in renal or gallbladder colic. This pain originates from the internal organs and their supporting tissues, such as the intestines or bladder. Visceral pain is often dull, cramping, and difficult to pinpoint, though it becomes sharp and deep when solid organs (e.g., the liver or pancreas) are involved.

In postoperative care, pain often combines somatic and visceral components, each requiring tailored treatment.

2.5 Postoperative pain control

Many patients fear postoperative pain more than the surgery itself. Assessing pain intensity is a critical aspect of postoperative pain management. Given that pain is subjective and its sensory perception varies widely, treatment must be based on the individual's reported severity.

Pain scales are widely used to standardize and improve communication about pain intensity. The three most common scales used by healthcare providers are [8]:

1. *Numerical Rating Scales (NRS)*: Patients rate their pain on a scale of numbers.

2. *Visual Analog Scales (VAS)*: Patients select a picture that corresponds to their pain level.

3. *Categorical scales*: These scales use descriptive words, often paired with numbers, colors, or body location diagrams.

In pediatric patients, specialized scoring systems are used. Regardless of the chosen system, moderate pain must be appropriately managed.

2.6 Types of pain therapy

Pain management can be broadly divided into:

1. Basic analgesia: This involves systemic administration of non-opioids or opioids (via oral, rectal, intravenous, or subcutaneous routes).

2. Special analgesia: This includes advanced techniques like patient-controlled intravenous analgesia or regional analgesia using epidural or peripheral nerve catheters.

2.7 Basic analgesia

This approach is most effective for managing mild to moderate pain following surgical procedures. Standardized doses of non-opioid analgesics such as paracetamol, traditional non-steroidal anti-inflammatory drugs (NSAIDs), selective COX-2 inhibitors, or metamizole are typically sufficient. If necessary, opioids like tramadol or piritramide can be added to manage more severe pain.

The principles guiding basic analgesia include:

- *Regular assessment* of pain intensity using standardized scales.

- *Scheduled administration* of analgesics (non-opioids and tramadol if needed) at fixed intervals under a doctor's supervision.

Each healthcare facility is responsible for providing clear protocols for drug selection, dosage, and administration. These guidelines should be continuously updated, and relevant personnel should receive ongoing training.

2.8 Effectiveness of basic analgesia

Basic analgesia is particularly effective for managing mild to moderate pain after minor to moderately invasive surgeries. The following medications are commonly used, with intravenous administration preferred for immediate postoperative use:

3. Paracetamol

Paracetamol is an antipyretic and analgesic that lacks significant anti-inflammatory effects [9].

Mechanism of action: The exact mechanism is not fully understood, though its pain-relieving effects are thought to result from central nervous system activity. Paracetamol primarily inhibits COX-2 without the gastrointestinal side effects typical of NSAIDs.

Pharmacokinetics: Paracetamol is rapidly absorbed after oral administration, reaching peak concentration in 30–60 minutes with a high bioavailability (up to 90%). It is metabolized in the liver and excreted via urine.

Dosage: For adults, a single oral dose of 10–15 mg per kg body weight is typical. The maximum daily dose has been reduced from 6 to 4 g to prevent toxicity.

Side effects: Rare, but can include elevated liver enzymes, hematological changes, and hypersensitivity reactions.

Contraindications: Known hypersensitivity to paracetamol, severe liver insufficiency (Child-Pugh >9).

4. Nonsteroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are commonly prescribed for their pain-relieving, anti-inflammatory, and antipyretic properties [7]. Their primary mechanism involves inhibiting cyclooxygenase enzymes (COX), which are key players in inflammation.

Mechanism of action: NSAIDs inhibit COX-1 and COX-2, reducing prostaglandin and thromboxane production. This action not only reduces pain but also limits inflammation and fever. However, COX-2 inhibitors have been developed to target inflammation without affecting COX-1's protective functions.

Pharmacokinetics: Most NSAIDs are absorbed in the gastrointestinal tract and metabolized by the liver. Elimination occurs primarily through the kidneys.

Indications: NSAIDs are used to manage acute and chronic pain, inflammation, and fever. They are also used perioperatively to manage pain and prevent inflammation.

Side effects: NSAIDs can cause gastrointestinal issues (nausea, vomiting, bleeding), kidney damage, cardiovascular events, and hepatotoxicity. Combining NSAIDs with proton pump inhibitors can reduce the risk of gastric ulcers.

Contraindications:

- Hypersensitivity to NSAIDs
- Pregnancy (third trimester)
- Active ulcer disease
- Severe renal or hepatic impairment

5. Metamizole

Metamizole, a powerful non-opioid analgesic and antipyretic, belongs to the pyrazolone class of drugs. It is one of the strongest non-opioid painkillers available [10].

Mechanism of action: While the exact mechanism remains unclear, it is believed that metamizole inhibits cyclooxygenases (COX) both centrally and peripherally, leading to reduced prostaglandin synthesis. Central effects on neurons in the thalamus and hypothalamus may also influence pain processing and thermoregulation. Metamizole also has a spasmolytic effect, likely due to interactions with cannabinoid receptors and inhibition of calcium release in smooth muscle cells.

Pharmacokinetics: Metamizole is a prodrug, converted in the liver to its active metabolite methylaminoantipyrine (MAA). Its onset of action is within an hour when administered orally, with effects lasting for approximately 6 hours. The bioavailability of MAA is about 90%, and the plasma half-life ranges from 1.8 to 4.6 hours. Excretion occurs primarily through the kidneys, so dose adjustments are necessary in patients with renal insufficiency.

Indications: Metamizole is used to treat severe pain (e.g., after surgery or trauma, or in cases of tumor pain), high fever unresponsive to other treatments, and colic due to its spasmolytic effect. It is frequently used in intensive care units and emergency settings. The drug is approved for use in children older than 3 months.

Dosage: For adults, a typical dose is 500–1000 mg or 20–40 drops, depending on body weight. The maximum daily dose is 4 g orally and 5 g intravenously.

Side effects: Metamizole can cause rare but serious side effects, including agranulocytosis (bone marrow suppression) and severe drops in blood pressure, especially after rapid intravenous administration. Other side effects include skin reactions (e.g., Stevens-Johnson syndrome), nephrotoxicity, and hepatotoxicity. Gastrointestinal issues are less common compared to other non-opioids like ibuprofen or diclofenac.

Contraindications: Due to the risk of agranulocytosis, metamizole is contraindicated in patients with known bone marrow damage or blood disorders. Intravenous use requires close monitoring to avoid hypotension. Metamizole is not approved in some countries due to these safety concerns.

6. Tramadol

Tramadol is a weak opioid analgesic used to manage moderate to severe pain [11]. It acts as a partial agonist at μ-, δ-, and κ-opioid receptors, making it less potent than strong opioids but useful for postoperative pain.

Mechanism of action: Tramadol has approximately 10–17% of the potency of morphine. It also inhibits serotonin and norepinephrine reuptake, contributing to its pain-relieving effect by modulating descending pain pathways in the spinal cord. Additionally, tramadol has antitussive properties (cough suppression).

Pharmacokinetics: Tramadol is well absorbed, with oral bioavailability of about 70%. It reaches peak plasma levels within 1.5–2.4 hours after administration. In the liver, it is metabolized to O-desmethyltramadol, an active metabolite. Tramadol is primarily excreted by the kidneys, and its half-life is approximately 6 hours.

Indications: Tramadol is used for moderate to severe pain, particularly in orthopedic cases, trauma, and postoperative settings.

Dosage: The typical oral dose for non-retarded formulations is 50–100 mg every 4–6 hours, with a maximum daily dose depending on the patient's response and condition.

Side effects: Compared to strong opioids, tramadol causes fewer typical opioid side effects like constipation and respiratory depression. However, it commonly induces nausea, vomiting, dizziness, sedation, and headaches, especially when administered intravenously.

Contraindications: Tramadol should not be used in patients with hypersensitivity to the drug, those with acute alcohol or opioid intoxication, epilepsy, or a history of drug misuse.

7. Piritramide

Piritramide is an opioid analgesic commonly used postoperatively, with actions similar to morphine. It acts as an agonist at μ-opioid receptors, providing analgesic, sedative, and antitussive effects.

Pharmacokinetics: Piritramide can be administered intramuscularly or intravenously. IV administration produces effects within a few minutes, while IM injection takes about 15 minutes. The analgesic effect lasts around 6 hours. Piritramide is metabolized in the liver and primarily excreted in the stool, with a half-life of 4–10 hours.

Indications: It is used primarily for pain relief in the postoperative period. In patients with renal insufficiency, dosage adjustments are necessary.

Side effects: Compared to morphine, piritramide has a stronger sedative effect but similar respiratory depressant properties. It causes less nausea, vomiting, and constipation than morphine. Other side effects include hypotension after rapid IV injection, bronchospasm, constipation, and urinary retention. Naloxone can counteract its effects.

Contraindications: Piritramide is contraindicated in patients with acute hepatic porphyria, those on monoamine oxidase (MAO) inhibitors, patients with central respiratory depression, and individuals with severe obstructive lung diseases like exacerbated COPD.

8. Pethidine

Pethidine (also known as meperidine) is an opioid analgesic, acting as an agonist at μ, κ, and δ opioid receptors. It has a short duration of action and is commonly used for postoperative pain management and shivering.

Pharmacokinetics: Pethidine has a bioavailability of about 50% when taken orally, due to a pronounced first-pass effect in the liver. Its duration of action is typically 3–4 hours, with an elimination half-life of about 24 hours. Up to 25% of the drug is excreted unchanged by the kidneys. Pethidine is metabolized in the liver to norpethidine, an active metabolite that can accumulate in cases of renal insufficiency, leading to an increased risk of seizures.

Indications: Pethidine is used for postoperative pain management and is particularly effective in treating postoperative shivering.

Dosage: The standard dose for pethidine is 25–150 mg, depending on the route of administration (subcutaneous, intramuscular, or intravenous). Doses can be repeated every 2–3 hours if necessary. In patients with renal insufficiency, dosage adjustments are required.

Side effects: Common side effects include respiratory depression, euphoria, sedation (stronger than morphine), nausea, vomiting, urinary retention, and

constipation. Norpethidine, the active metabolite, can provoke seizures, particularly in patients with renal impairment. Pethidine has an atropine-like effect, causing mydriasis (pupil dilation).

Reversal: Naloxone can reverse the effects of pethidine.

9. Morphine

Morphine, the prototype opioid, has historically been one of the most widely used analgesics [12]. While its use has diminished in some regions, it remains a key medication for managing severe postoperative pain, particularly in developing countries.

Mechanism of action: Morphine acts as an agonist at μ-opioid receptors in the CNS, preventing pain transmission and reducing the perception of pain.

Pharmacokinetics: Intravenous morphine typically takes 15 minutes to reach maximum effect. To avoid overdose, subsequent doses should be administered only after waiting for the full effect to manifest.

Side effects: Morphine can cause respiratory depression, constipation, hallucinations, hypotension, and suppression of the cough reflex (similar to codeine).

Contraindications: Caution is necessary in patients with liver or kidney failure, as morphine can accumulate due to reduced excretion. It is also contraindicated in patients with asthma (due to histamine release), ileus, and in certain cases of ureteric or biliary colic.

Reversal: Naloxone can reverse the effects of morphine.

10. Special analgesia

Basic analgesia may not suffice for managing severe pain after major surgeries due to limitations in drug dosages, side effects, and the nature of the pain. Therefore, more advanced techniques such as *patient-controlled analgesia (PCA) and regional analgesia with catheter techniques* are implemented. These methods provide more effective pain relief in postoperative settings.

11. Patient-controlled analgesia (PCA)

Patient-controlled analgesia (PCA) is a method that allows patients to self-administer analgesics parenterally (intravenously or spinally) using electronically controlled pump systems. By pressing a button, the patient receives a pre-programmed dose of pain medication [13]. This system is usually connected via a Y-piece to a peripheral or central venous line. To prevent overdoses, a safety mechanism restricts the frequency of doses. Vital parameters must be monitored regularly to ensure patient safety.

Patients can administer a *bolus* of analgesics by pressing a button. The dosage is pre-set by the attending physician, and a *blocking interval* is programmed to prevent multiple doses in quick succession. This system is widely used postoperatively and in chronic pain management or palliative care. PCA has been the standard method of pain management in the postoperative phase since the 1980s.

Contraindications for PCA:

- Inability to operate the PCA independently (e.g., in cases of dementia or confusion).
- Medication or drug addiction.
- Intolerance to the analgesics used.
- Severe renal or liver failure.
- Alcohol abuse.
- Malnutrition.

12. Epidural analgesia

Epidural analgesia involves administering local anesthetics and/or opioids into the epidural space through a catheter [14]. This method is particularly beneficial for managing postoperative pain in major abdominal and thoracic surgeries.

An epidural catheter is often placed before anesthesia begins. By administering small doses of anesthetics or opioids before the surgical stimulus, the pain pathways from the spinal cord to higher brain centers are blocked, significantly reducing postoperative pain and stabilizing cardiovascular responses.

Benefits:

- Studies show that *epidural analgesia*, which blocks the spinal sympathetic chain, improves surgical outcomes and reduces complications such as postoperative ileus.
- Proper pain relief facilitates *early mobilization*, reducing the risks of deep vein thrombosis, pulmonary embolism, and atelectasis.

Drugs used:

- *Local Anesthetics*: Commonly used drugs include Ropivacaine and Bupivacaine.
- *Opioids*: Sufentanil is a frequently used opioid in epidural analgesia.

For postoperative analgesia, lower drug doses are administered compared to epidural anesthesia. Each treatment center should have specific protocols, and all personnel should be regularly trained to ensure safety and efficacy.

Complications:

- Spinal cord injury.
- Spinal epidural hematoma.
- Hypotension.

- Urinary retention.
- Pruritus (itching).
- Late-onset respiratory depression (due to neuraxial opioids).
- Central nervous system toxicity (excessive doses of local anesthetics).
- Infection (e.g., meningitis).

Contraindications:

- Patient refusal.
- Sepsis.
- Coagulopathy.
- Uncorrected hypovolemia.
- Elevated intracranial pressure (ICP).
- Local infection at the injection site [7, 11, 12].

12.1 Local anesthetics

Local anesthetics are agents that reversibly inhibit the excitability of sensory nerve fibers [15]. They are categorized into **amide** and **ester** groups based on their molecular structure.

12.2 Mechanism of action

Local anesthetics block *voltage-gated sodium channels* in the neuronal membrane, preventing sodium influx, which is essential for depolarization and action potential propagation. This action halts the transmission of pain signals. For the anesthetic to work, it must first enter the axon in its unprotonated (lipophilic) form and then bind to the intracellular portion of the sodium channel in its protonated (charged) form.

Local anesthetics can also affect *potassium channels* and other ion channels, including those in the myocardium, which is why drugs like *lidocaine* are used as antiarrhythmics.

Side effects:

Local anesthetics can cause *serious complications* if administered improperly. Although rare, allergic reactions can lead to *anaphylactic shock*.

Local anesthetics can cause *arrhythmias* in the heart, so proper administration and injection techniques are critical.

In the CNS, symptoms such as *paresthesia* (especially around the mouth), restlessness, nausea, and seizures can occur if local anesthetics enter the systemic circulation. This can be avoided by adhering to dosage limits and careful administration techniques.

12.3 Nerve block

A *nerve block* involves the temporary or permanent disruption of signal transmission along a peripheral nerve, providing effective pain relief [16].

Temporary nerve block:

This method involves injecting local anesthetics near a target nerve, temporarily blocking its sensory and, sometimes, motor functions. In cases where extended relief is needed, *catheter systems* can be used for continuous administration of local anesthetics over days or weeks.

Permanent nerve block:

In cases of intractable pain, a nerve can be permanently disabled either surgically (through severing or *high-frequency ablation*) or by injecting toxic substances like *ethanol, glycerin*, or *phenol* into or near the nerve.

Nerve blocks are particularly effective in postoperative settings, especially for procedures like joint prosthesis placement. Continuous peripheral nerve blocks allow for *early physical therapy*, reducing recovery time and complications like *deep vein thrombosis* or *atelectasis*.

Side effects:

- Nerve damage.
- Neurotoxicity and systemic toxicity.
- Infection at the catheter insertion site.

To minimize these risks, strict adherence to sterility and continuous *neurological monitoring* is required.

In conclusion, pain has always been one of the most challenging and unpleasant human experiences. The advances in medical science, especially in the field of pain management, represent significant achievements. Postoperative pain is one of the most common forms of pain patients experience, and in this chapter, we have discussed the most common and up-to-date methods for managing postoperative pain, with a focus on pharmacological principles. The choice of analgesic method depends on various factors, including the patient's condition, the type of surgery, and post-surgical circumstances. Thus, understanding each patient's unique history and surgical situation is key to developing an effective pain management plan.

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Chapter 2

Perspective Chapter: Cardiothoracic Postoperative Pain Therapy

Dragana Lončar Stojiljković

Abstract

Pain, as a symptom, is the most common symptomatic complaint and the main reason why people seek medical care after cardiothoracic surgery. The definition of pain was given by the International Association for the Study of Pain (IASP) in 1979 as: "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage, mental suffering or distress". This definition has been extended with notification that pain is a subjective experience influenced by biological, psychological, and social factors. It is accepted by individuals with all changes in social and psychological well-being. A person's report of an experience as pain should be accepted as such and respected.

Keywords: physiology of the pain, opioids, cardiosurgical pain, thoracal pain, pain therapy

1. Introduction

Nociception process: thermal, mechanical, or chemical stimuli of noxious intensity come into contact with a tissue [1].

Phases of pain transmission:

1. Transduction
2. Transmission
3. Modulation
4. Central Perception

In the pathophysiology of the pain, inflammatory mediators such as globulin, protein kinases, arachidonic acid, histamine, nerve growth factor (NGF), substance P (SP), and calcitonin gene-related peptide (CGRP) are very important [2].

These mediators stimulate transducer channels, initiate receptor potentials (transduction) which evoke action potentials (AP) in sensory nerve fibers. AP are

carried as afferent signals *via* sensory nerve fibers to the dorsal root ganglia and dorsal horn of the spinal cord (transmission). The signal is transmitted up the spinal cord to the brain stem and thalamus, where significant processing (modulation) may occur [1, 3]. The signal continues to the somatosensory cortex (central perception). The biopsychosocial interpretation of the painful experience also involves amygdala (emotional and affective response to pain and pain modulation), hypothalamus (neuroendocrine corticotropin response), periaqueductal gray matter (pain modulation), basal ganglia (cognitive, affective, and discriminative localization of sensory input), and cerebral cortex: (ultimate site of pain perception, potential for conscious activation of descending pathways for pain modulation) [1, 3].

1.1 Modulation of pain

Modulation of pain signals is a process in which endogenous opioid peptides (endorphins, dynorphins, and enkephalins) modulate the transmission of the pain in the "descending" ("inhibitory") pathways in the spinal cord, dorsal root ganglia, midbrain periaqueductal gray (PAG) matter [4].

1.2 Mechanisms of action of endogenous opioid peptides

Endogenous opioids activate mu, kappa, and delta opioid receptors (rp) by decreasing presynaptic Ca^{2+} influx, releasing glutamate and SP, and increasing potassium (K^{+}) conductance in dorsal horn neurons. The other modulators of pain include too: norepinephrine (NE), glycine, and GABA (**Figure 1**).

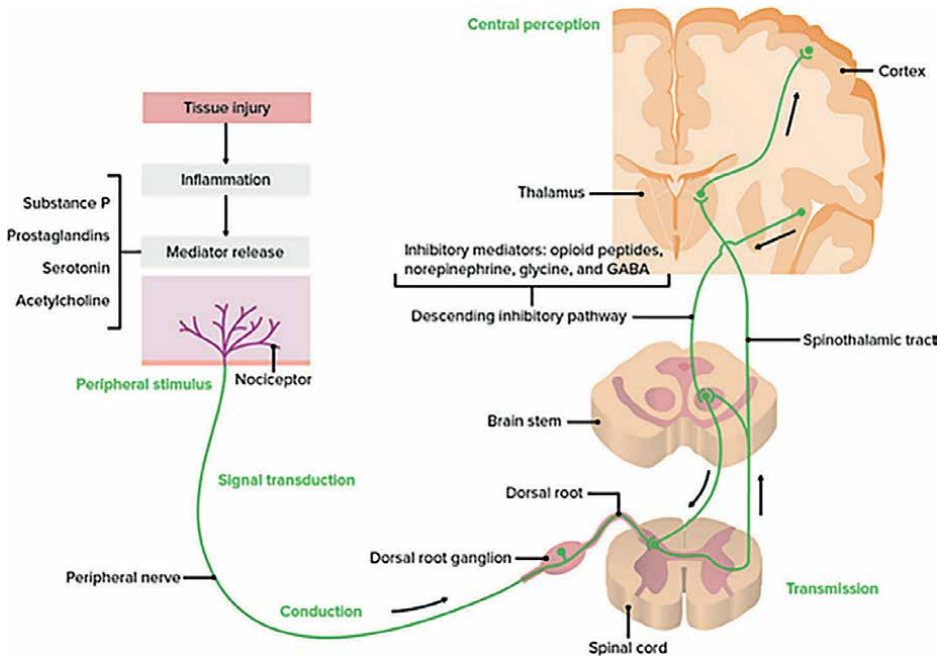

Figure 1.
Diagram showing the pathway of pain transduction, transmission, modulation, and central perception. Image by: Website Lecturio https://www.lecturio.com

1.3 Types of afferent nerve fibers

Types of afferent nerve fibers are A, B, and C fibers. Their characteristics are previously described.

1.4 Ascending and descending pain pathways

1.4.1 Ascending pathway of pain

Rp and nociceptors are situated in the periphery and are activated by heat, intense cold, mechanical distortion, changes in pH, and chemical irritants such as ADP, bradykinin, serotonin, and histamine. Afferent nerve conduction is first-order neurons which are located in the dorsal horn and dorsal root ganglia of the spinal gray matter (or trigeminal ganglia).

After synapsing in the spinal cord, first-order neurons project to second-order neurons. A second-order neuron crosses the midline at the anterior white commissure. Glutamate, SP, and CGR are the main neurotransmitters released by primary afferent second-order neurons [3, 5].

The neurons ascend to the thalamus through the contralateral spinothalamic tract, carrying pain and temperature sensations. The thalamus then sends the signal to the somatosensory cerebral cortex. Other thalamic neurons project the areas of the cortex associated with emotional responses, such as the cingulate gyrus and insular cortex. Pain modulation involves the release of inhibitory mediators and hormones from the hypothalamus and cortex, which make pain suppression more effective. These substances include opioids, peptides, norepinephrine, glycine, and GABA [4].

1.5 Visceral pain

Visceral pain is received from the somatic structures. Characteristics of the visceral pain: poorly localized, unpleasant, associated with nausea and autonomic symptoms (**Figure 2**) [3, 6–8].

1.6 Postoperative pain patophysiology

Postoperative pain treatment is very important because it is a major factor aggravating the general condition of the patient. Pain systemic sequels (activation of stress hormones) stimulate the sympathetic nervous system, cause disorders of the respiratory and cardiovascular systems, impair general and muscular mobility and physical fitness of the patient, and develop chronic pain if it lasts over 3 months. Severe pain is also burdensome for the patient's psyche [9–12].

The pain experienced by the patient is influenced by the location of the surgery (thoracotomy in thoracal surgery vs. sternotomy or lateral thoracotomy in cardiac surgery), its extent, the degree of tissue traumatization (open vs. mini sternotomy), the direction of the skin incision, the preoperative anxiety level, and the analgesic techniques used in the perioperative period (regional block and local analgesia) [4, 13].

The most intense pain following cardiac surgery occurs within the first 24 hours and then decreases in the following days. This is considered a "self-limiting" phenomenon [2, 4, 12, 14]. After open thoracic surgery and in women, elderly patients, and

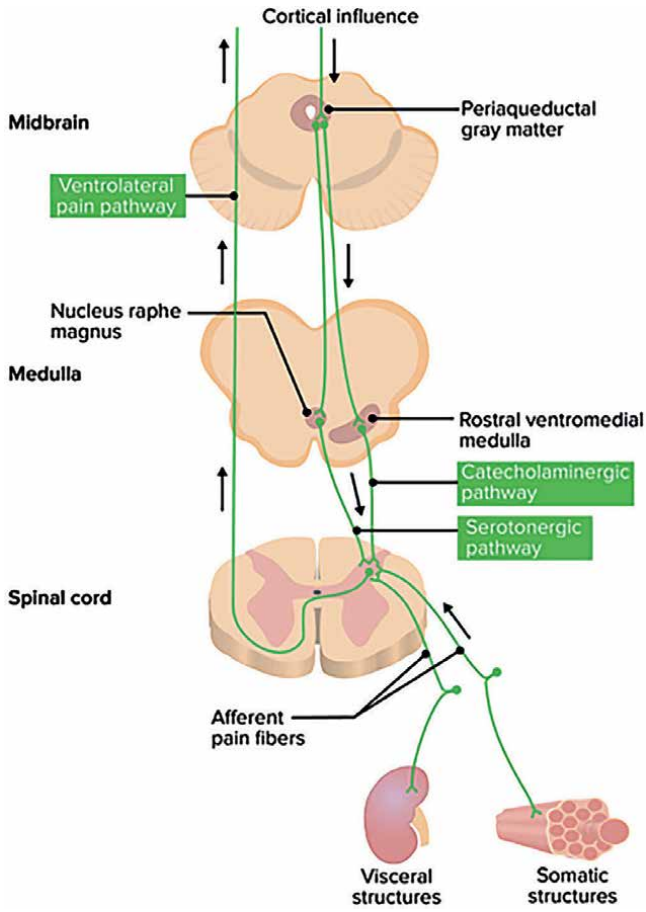

Figure 2.
Illustration of the convergence-projection theory of visceral pain. Image by Website Lecturio https://www.lecturio.com

those who undergo extracorporeal circulation during cardiac surgery, there is a higher intensity of pain and a greater number of painful areas [2, 4, 14]. Extracorporeal circulation is linked to the development of systemic inflammatory response syndrome and potential dysfunction of vital organs [2, 4, 14].

A heart valve surgery and coronary artery bypass grafting (CABG) are the most commonly performed procedures in cardiac surgery worldwide [15]. In order to reduce postoperative pain intensity, minimally invasive operative techniques like minimally invasive direct CABG or the totally endoscopic CABG should be used more often. Minimally invasive surgery reduces surgical trauma, decreases postoperative bleeding, reduces the incidence of sternal wound infections, and shortens the recovery period after surgery [16].

Minimally invasive techniques in heart valve surgery are for atrioventricular and aortic valve surgery, atrial septal defect, and radiofrequency ablation with closure of the left atrial appendage [11]. In the last decade, percutaneous access techniques, transcatheter aortic (TAVI) or mitral valve implantation, have become more popular and are considered an alternative to surgical treatment for patients who are not suitable or willing or are at high risk for open-heart surgery [11].

1.6.1 Pathophysiology of thoracic pain

Postoperative pain in thoracic surgery is both nociceptive and neuropathic and comes from somatic and visceral afferents [17, 18]. Neuropathic pain occurs in more than 29% of thoracotomy patients and can reach 35% after thoracoscopy [17, 18]. Kahloul et al. found that 79.6% of patients experienced chronic pain after chest trauma [19]. The percentage of pain varies according to the procedure, physical and mental health, preoperative pain, the tissue trauma's severity, and the analgesia's timing. The severity of acute pain is associated with the incidence of chronic pain after thoracic surgery; efficient pain management is of the utmost importance [18, 19].

Somatic nociception is carried by all intercostal nerves and their branches. Nociception is produced by direct lesion, through a skin incision, rib spreading, or fracture, stretching of the wall muscles (latissimus dorsi, intercostal, trapezius, and serratus anterior muscles), pleura effraction, and chest drain insertion. Release of the inflammatory mediators is caused by tissue injury. It leads to a direct activation of the nociceptors and reduces the pain threshold. Visceral nociception is carried by the phrenic and nerve vagus and is caused by lesions of the visceral pleura, pericardium, or bronchi. Peri and intraoperative position manipulations of the patient participate in the process of peripheral and central sensitization, in particular *via* the dorsal nerve of the scapula, long thoracic, and thoracodorsal nerve. Neuropathic pain is due to nerve injury related to care [19, 20].

In intensive care, there are multiple catheters, tubes, mechanical ventilation, and forced immobilization on the bed at rest or during procedures. There are also medical complications that may occur during the ICU stay, such as surgical complications, pneumothorax, phlebitis, and myocardial infarction [21].

Somatic pain, superficial or deep, arising from skin, muscle, and bone. This superficial, sharp, well-localized pain had been stimulated by dermal nerve endings. In contrast, deep pain, from muscles, is dull and poorly localized [21–23].

Common cardiac surgery incisions involve cervical, thoracic, and lumbar dermatomes. Pain is located within the wound and drain sites. Over time, it may become more generalized to trunk and limb, particularly following internal mammary artery (IMA) conduits. Routine cardiac surgery produces a combination of somatic, visceral, and neuropathic pain, which in 50% leads to chronic pain (**Table 1**) [19, 21–23].

1.7 Pain assessment

All patients should be informed about the procedure in the preoperative period. To effectively treat pain postoperatively, the examination of the patient should be applied with professional expertise, ethics, and a psychological approach: measuring, documenting and diagnosing pain in detail. If the patient is not communicative or has difficulty communicating due to the use of a respirator, sedation, dementia, or delirium, one should monitor agitation, reactions in bed, attitude toward relatives and visitors, as well as changes in behavior toward healthcare workers. The family should be contacted for additional anamnestic information [24].

An adequate examination achieves the prerequisites for satisfactory analgesia with the minimization of side effects. In acute postoperative pain, recovery is accelerated, and the frequency of the development of postoperative chronic pain is reduced.

System disadvantages
Cardiovascular Chronotropy Inotropy Blood pressure Cardiac work O_2 demand with – supply – ischemia, dysrhythmias
Respiratory Respiratory rate and tidal volume – Work of breathing Atelectasis Impaired cough, retention of secretions Infection risk
CNS exhaustion, disorientation, agitation Satisfaction
Peripheral incidence chronic pain in nervous system
GI Nausea, vomiting, anorexia
Other Hypercoagulability DVT and graft stenosis Poor wound healing Impaired glucose tolerance Altered immunological function! Risk of infection Electrolyte imbalance! Risk of arrhythmias Length of stay
Psychological Anxiety Depression Stress

Table 1.
Effects of pain following cardiothoracic surgery.

By definition, pain is an internal, subjective experience that cannot be directly observed by others, nor it can be measured using biological markers or bioassays. It is a multidimensional experience that incorporates coordinated sensory and affective components [24]. We receive information from the patient who is suffering from pain, that is, autoanamnestically. Assessment of the intensity of postoperative pain should be based on standardized and documented assessment scales. Pain intensity measurement scales can be unidimensional and multidimensional, with a wider range of information [15, 25, 26].

Unidimensional tests are used to assess the intensity of acute or chronic pain. Three scales are most commonly used [25, 26]:

- Verbal Intensity Scale (VRS)
- Numeric rating scale (NRS)
- Visual analog scale (VAS).

Postoperative pain management is crucial, as inadequately controlled pain delays rehabilitation, prolongs the duration of treatment, and worsens the patient's quality of life [15].

1.7.1 Visual analog scale (vas)

One of the most commonly used scales for pain is the visual analog scale (VAS), which is represented by a line that includes the range from the point where there is no pain to the point with the worst possible pain. It is a straight line with extreme categories marked like a numerical scale (NRS) with 0 – "no pain at all" and 10 – "worst possible pain." The distance determines the intensity of all pain, and presents a measure of pain intensity. The length of the line may or may not be marked [24].

Studies show minimal differences between scales. However, it is considered that the VAS scale best correlates with the relationship between behavior and pain level [21].

The verbal descriptor scale (VDS) has five intensity descriptors: no, mild, moderate, severe, and extreme pain [27]. Difficulties are present in assessing pain in nonverbal patients (e.g., those who are intubated or have dementia). In these cases, visual aids can be used, such as using five fingers to indicate the five levels of pain, or using a fixed iPad with cartoons in different colors to represent each type of pain [28].

For patients unable to communicate (either intubated or nonintubated), the Observational Behavioral Scales (OBS) can be used. Patients with delirium or deeply sedated patients, which is very often after cardio surgery, are one of the top risk of self-assessment failure in ICU [21]. In such patients, scoring systems based on changes in the face – Facial Action Coding System (FACS) or behavioral changes, as well as the Behavioral Pain Scale (BPS) and critical care pain observation tool (CPOT), can be used [28, 29]. To these scales can be added physiologic indicators [mean arterial pressure, heart rate, respiratory rate, and transcutaneous oxygen saturation (SpO_2)] [29].

To enhance the electrophysiological measurement of stress response related to pain or other stressful factors (e.g., anxiety and fear), new devices which are based on the measurement of surrogate markers of the adrenergic response: increase of the pupillary diameter, a decrease of heart rate variability (HRV) related to a decrease of parasympathetic tone, or other parameters, for exp. the increase of electric skin conductance due to increased sudation can be used [27, 29].

1.8 Acute postoperative pain therapy

Postoperative acute pain therapy is a continuation of perioperative analgesia. The main goal of acute postoperative pain therapy is to reduce it as effectively as possible or eliminate it with as few side effects as possible and as cheaply as possible. In postoperative pain therapy, should be paid attention to the patient's preoperative health condition (respiratory, cardiac diseases, allergies, previous diseases, and therapy), the type of operation, the expected severity of postoperative pain, the risk-benefit ratio of the applied techniques, and the patient's wishes based on his previous experiences related to pain therapy [24].

Opioids are the most used remedies and have had the best analgesic effect since the beginning of time. On the other hand, their practical use has quite the opposite effect due to side effects, prolonged recovery, and significant abuse. The multimodal (balanced) analgesia concept has been used for over 20 years [30, 31]. It is Kehlet's concept of saving opioids, which implies the use of multimodal analgesia. The concept, part of ERAS (enhanced recovery after surgery), was introduced as a protocol for a faster postoperative waking up and received the name multimodal analgesia. Coordination is achieved by the combined use of opioid and non-opioid analgesics, as well as regional techniques. **Figure 3** provides a potential outline of components of a multimodal approach to pain management for the cardiac surgery, encounter on the

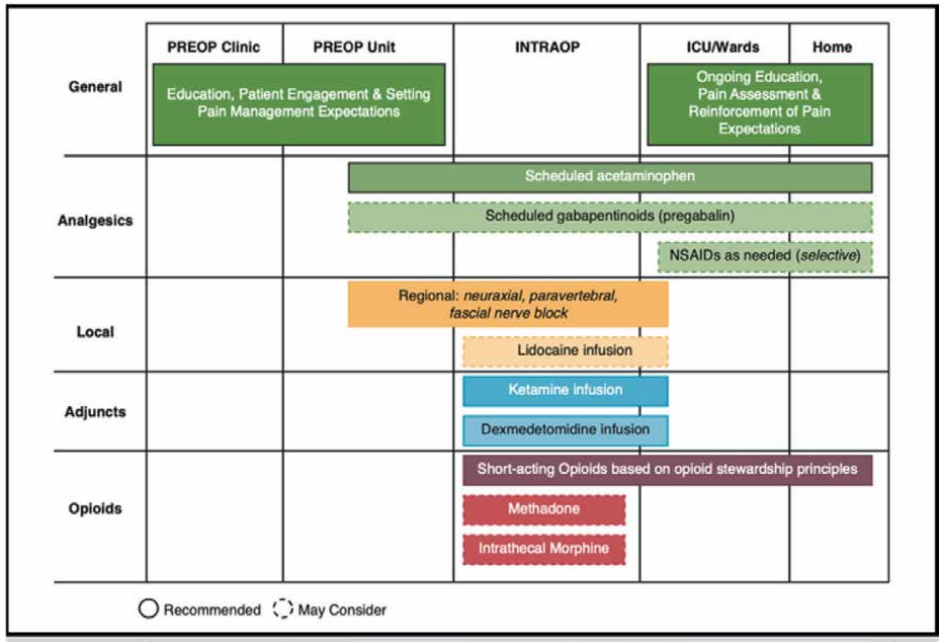

Figure 3.
Recommendation for pain management and opioid in cardiac surgery. Source from Ref. Grant et al. [32].

adoption of fast-track cardiac surgery [32], which provides shorter stay in the intensive care unit, shorter mechanical ventilation, and mortality [32].

1.8.1 Opioids

Opioids, due to the best analgesic effects, represent the gold standard in the treatment of severe pain.

1.8.2 Opiod receptors

Opioids achieve their action through opioid receptors – protein transmembrane structures located at the presynaptic endings of various neurons – adrenergic, peptidergic, and cholinergic. The clinically most important opioid receptors are mi, kappa, and delta. Although they all have effect on acute pain, κ-receptor stimulation has been found to contribute to chronic pain [24].

Opioids act by binding to μ (mi), κ (kapa), and δ (delta) receptors. μ-Receptors are present in brain and thalamus cells. By stimulating these receptors, the effects of analgesia, sedation and euphoria, respiratory depression, constipation, and addiction are achieved [24]. κ-Receptors are found in the limbic system, diencephalon, brain, and spinal cord cells. Stimulation of these receptors leads to mild analgesia, sedation, miosis, dysphoria, and addiction. Opioid δ-receptors are primarily represented in brain and spinal cells and digestive tract cells. They cause analgesia and mild respiratory depression. Administration of opioids can be peroral, intramuscular, intravenous (bolus or continuous infusion), intraspinal, buccal, or rectal. They are prepared in the appropriate forms for the specified benefits. There is no limited dose. The dose can be increased until pain relief is achieved, with monitoring and prevention of side effects.

Dosing can be as needed or, which is preferable for acute pain in postoperative therapy, on a regular basis (round the clock), PCA (patient-controlled analgesia), or continuous *IV* infusion.

Opioids act on the neuroendocrine system by releasing antidiuretic hormones, prolactin, and somatotropin. Opioid analgesics block the release of gonadotropin and corticotropin-releasing factors from the hypothalamus.

1.8.3 Analgesia in cardiothoracal operations

The opioid-based anesthetic technique originated in the late 1960s. Morphine, in high intravenous (IV) doses, was demonstrated to be remarkably hemodynamically stable and stress stabilizing in patients undergoing open-heart surgery [33, 34]. Synthetic opioids, such as fentanyl, sufentanil, and remifentanil, have replaced morphine these days.

Opioids decrease cardiac output and stroke volume (especially when applied with benzodiazepines) and cause bradycardia, histamine release, heart electrical disturbance, and cardiac arrhythmia [35, 36]. The most common cardiac side effect of opioids is the prolongation of the QT interval, which can lead to *torsades de pointes* (TdP). As analogs of the fentanyl, sufentanyl, remifentanil, alfentanil and carfentanil are being used as sedatives before surgeries and as analgesics and have the same side effects as fentanyl [35]. Fentanyl and remifentanil do not change QTc interval, Cafiero et al. [35, 36] suggested that remifentanil may be the best solution for cardiosurgical pain therapy.

Main problems with opioids are: ORADEs are opioid-related adverse drug events from mild pruritus/dermatitis, nausea, vomiting, urinary retention, constipation, sweating, and pruritus to acute respiratory failure requiring mechanical ventilation choice of opioid treatment in patients at risk of dysrhythmias. It is in connection with dose: high-dose (fentanyl >20 mg/kg, sufentanil >2 mg/kg, remifentanil >1.7 mg, and morphine >2 mg/kg) versus low-dose opioids in cardiac surgery, and it was associated with shorter postoperative intubation time. There is no connection between the risk of myocardial infarction, stroke, or reintubation between the two regimens [31, 32, 37].

POU is generally defined as previously opioid-naıve patients continuing to use opioids 90 to 180 days after surgery (incidence rates of new POU between 5% and 15%). Due to that opioid stewardship is defined as "the judicious use of opioids to treat post cardio surgical pain and optimize postoperative patient outcomes" [38].

1.8.3.1 Remifentanil

Remifentanil is more potent than fentanyl. Its effect is dose-dependent. Its effect after IV administration occurs extremely quickly. The elimination of the drug is after 5–10 minutes because plasma esterases destroy it. The effect wears off after 5–10 minutes. It is used perioperative for long operations and for postoperative pain control [39].

1.8.4 Patient-controlled analgesia, PCA

This method is a standard technique in the clinical therapy of postoperative pain in Western Europe and the United States. PCA pumps allow the patient to self-administer a predetermined dose of analgesics. This maintains the achieved level of analgesia, and the patient self-administers a dose of analgesic when the effect of the

previously given dose decreases. The computerized system records the amount of analgesic given in a period of 1–24 h and the number of attempts to self-administer analgesics in a period of 1 h. This information helps to optimize a given drug based on analgesic needs and a specific analgesic administration schedule. PCA models include variables determined by the physician: initial loading dose, requested bolus dose, basal continuous infusion, and lockout interval. The lockout interval is the time interval after the bolus is delivered during which the device will not respond (deliver the drug) to the patient's request, thus keeping the patient safe from accidental overdose. The maximum application interval is 4 hours. The on-demand dose is large enough to provide analgesia but also small enough to minimize the side effects of the opioid analgesic administered – most often morphine or fentanyl [24].

Opioids retain an important role in both acute, intraoperative, and chronic postoperative pain management. To diminish effects, providers are increasingly favoring short-acting agents to provide significant pain relief quickly and with easy titratability. Fentanyl and remifentanil have been implicated for their potential to induce acute tolerance and hyperalgesia (short- and ultra-short-acting forms), contributing to a scenario in which subsequent opioid dosing is rapidly escalated to achieve similar pain control [35, 36, 39]. Other opioids in use are tramadol, oxycodone, hydrocodone, morphine, tapentadol, hydromorphone, methadone, and buprenorphine.

1.9 Multimodal analgesia

Multimodal analgesia (MMA) is aimed at enhancing analgesia after cardiac and thoracal surgery and reducing the use of opioids, lower pain scores on the numeric rating scale on postoperative days 0–3 [40], higher number of extubations in the operating room, and reduction in total intubation times [41], and the likelihood of associated harmful side effects. MMA emphasizes the concurrent use of several mechanistically different agents to provide additive, if not synergistic, analgesic effects [42].

MMA results in a conscious patient, a reduction in postoperative nausea and vomiting (PONV), less frequent occurrence of rhythm disturbances and bradycardia, and the absence of pain is achieved by the combined use of spinal or continuous block anesthesia and a small dose of opioids and NSAIDs and APAPl, which significantly reduces the need for analgesic doses of opioids [24, 42]. In the treatment of postoperative pain, within the concept of MMA, combinations of opioids are used with alpha2-adrenergic agonists (clonidine, dexmedetomidine, which, however, cause hypotension and bradycardia), APAP, gabapentinoids (gabapentin and pregabalin), ketamine, dexamethasone (except pain reduction and reduction of postoperative nausea and vomiting) and serotonin and noradrenaline uptake blocker (duloxetine) which is shown in **Table 2** [24, 42].

1.9.1 Acetaminophen (APAP and PARACETAMOL)

Paracetamol (called acetaminophen in the United States) is a first-line analgesic for mild to moderate pain and an antipyretic. It is well tolerated and widely used, with a few interactions with other drugs; the analgesic effect is caused by significant central inhibition of prostaglandin synthesis and minimal peripheral prostaglandin synthesis. It is available in all forms and can be administered orally, rectally, and IV. Due to its hepatotoxicity, daily dose is limited to 4 g, divided into four doses, and the maximum single dose to 1 g. In patients with mild liver damage, the maximum daily dose is 2 g divided into four daily doses. Its half-life is 2–3 h. If used for more than 10 days, the daily dose should not

Medication	Mechanism	Dosing	Side effects/limitations to use
Acetaminophen	COX inhibition • Central COX inhibition and other -Separate mechanism for NSAIDs and can have a synergistic effect. Generally well tolerated when taken within recommended dose	650–1000 mg PO/ IV every 6–8 h; Maximum 3–4 g/d; duration of 7–14 d	Liver toxicity Caution with hepatic impairment
Gabapentin	Voltage-gated calcium channe modulator	00–600 mg once, 100–300 mg every 8 h; duration 5–7 d 50–150 mg every 8 h; duration 7–14 d	Sedation and respiratory depression, renal excretion, age-based dose adjustment; questionable efficacy
Pregabalin	Voltage-gated calcium channel modulator	Pregabalin 50–150 mg (preoperative);	Altered vision, renal excretion, age-based dose adjustment
Ketamine	N-methyl-D-aspartate antagonist	0.1–1.0 mg/kg bolus; 0.1–0.2 mg/ kg/h	Tachycardia and questionable efficacy with bolus, hallucinations
Dexmedetomidine	Alpha-2 agonist	0.5–1.5 mg/kg/h	Hypotension, bradycardia
NSAID ibuprofen, naproxen, and meloxicam	Cyclo-oxygenase inhibitor Decrease peripheral production of inflammatory signaling molecules -Particularly effective during the acute phase of injury, although can be beneficial for chronic musculoskeletal pain. Chronic daily use caries increased risk of renal and cardiovascular complications.	Ketorolac: 15–30 mg IV every 6–8 h, Ibuprofen: 400–800 PO mg every 6–8 h	Platelet dysfunction, gastrointestinal irritation, renal dysfunction; FDA "black- box warning" for CABG
Lidocaine	Voltage-gated sodium channel inhibitor		Optimal dosage uncertain, local anesthetic toxicity

Per os PO, intravenous IV; nonsteroidal anti-inflammatory drug NSAID; Food and Drug Administration FDA; coronary artery bypass grafting CABG; thoracic epidural analgesia TEA, acetaminophen APAP; serotonin SNRI, and norepinephrine reuptake inhibitor; tricyclic antidepressant TCA. The decision to use a given agent or agents requires consideration of anticipated efficacy.

Table 2.
Summarizes the typical dosing for key non-opioid medications and specific considerations for cardiac surgery patients.

exceed 2.5 g. As an adjunct to opioids after cardiac surgery, we were given during the first 24-h reduced incisional pain [18, 19, 21–23]. In our hospital, the standard analgesic regimen for postoperative analgesia is a combination of morphine and APAP IV every 6 hours for all patients unless contraindicated (advanced age, renal failure, and hypovolemia) as a standard procedure. The next day, opioids doze diminish, and APAP stays the same until transfer to the postoperative unit.

APAP and nonsteroidal anti-inflammatory drugs (NSAIDs) have opioid-sparing properties, especially when administered concomitantly, and should be administered

regularly to all patients in the postoperative period [40]. A selective NSAID can be considered because it decreases postoperative pain and opioid requirements after major surgery [43]. It is very important to point out that it does not alter platelet function, which is impaired in the perioperative period after extracorporeal circulation and the use of anticoagulants for thromboprophylaxis [44].

The gabapentinoids are effective too, and commonly used in cardiac surgery patients [40, 45]. Anwar et al. [46] reported that patients receiving pre-gabalin 150 mg, preoperatively, followed by 300 mg for 14 days post-surgery had significant reductions in surgical site pain, morphine consumption, and persistent pain at both 3 and 6 months. An MMA protocol at our institution does not include preemptive pregabalin due to a higher risk of adverse drug reactions (e.g., dizziness and visual disturbance) with no clinically significant benefit [40]. Lower doses of pregabalin are only prescribed for 4 days post-surgery in patients who need extra pain therapy.

Topical lidocaine patches can be used for chest tube and sternotomy sites [40, 47]. However, after robotic cardiac valve surgery, thoracotomy, and sternotomy, 5% lidocaine transdermal patches with PCA were ineffective at reducing acute or persistent pain [40].

When intraoperative fentanyl was substituted with a combination of methadone, ketamine, dexmedetomidine, and ketorolac at 6-h post-surgery at 6-h post-surgery and decreased opioid consumption was observed on postoperative day 1 w [15].

1.9.2 Corticosteroids

Corticosteroids are used as adjuvants, that is, aids to reduce the use of opioid analgesics. The most commonly used corticosteroid is dexamethasone because it reduces postoperative nausea and vomiting, reduces inflammation by suppressing the migration of polymorphonuclear leukocytes, and reduces capillary permeability. The onset of the effect is from a few minutes to a few hours, depending on the application method. The elimination half-life is 1.5–3.5 h. They are metabolized in the liver and excreted through the kidneys. Glucocorticoids affect the synthesis of prostaglandins and have a mild analgesic effect. The dose of dexamethasone is 4–16 mg IV.

2. Regional analgesia

Regional analgesia, such as neuraxial analgesia, encompasses techniques such as epidural anesthesia, nerve blocks (percutaneous intercostal nerve block (ICNB), serratus anterior plane block, pectoral nerve blocks, and paravertebral blocks), and surgical local infiltration. The effectiveness of regional analgesia depends on the operator's skills, surgical techniques, and the patient's underlying medical conditions [48].

2.1 Neuraxial analgesia

2.1.1 Regional nerve block

Regional nerve block, the targeted injection of local anesthetics to block pain sensation to nerves that correspond to the site of surgical incision. Regional nerve block has a significant role in MMA [32].

Thoracic epidural analgesia (TEA) is more often used than spinal analgesia. Benefits are reduced peri-postoperative opioid consumption, improved pain control, earlier extubation, and possibly reduced cardiopulmonary complications [49–51]. However, concerns are present due to potentially devastating neuraxial hematoma, particularly in the setting of systemic heparinization, as well as the potential for sympathectomy-mediated hypotension, which represent barriers to the widespread adoption of neuraxial techniques [32, 50]. In mediastinoscopy, epidural placement should be considered, especially if there is a probability of conversion to open thoracotomy [52, 53]. Median sternotomy or thoracotomy should block the perforating branches of the intercostal nerves from the thoracic spine nerves (T1-T11) [30].

Ipsilateral somatic and sympathetic coverage of the hemithorax provides the paravertebral block (PVB). PVBs are achieved by blocking the spinal nerves directly. Intercostal and epidural spread can be expected [30].

For surgical incisions and drain sites, it is easy to perform nerve blocks. However, their duration is limited due to unreliable anesthetic spread and the anesthetic's pharmacological characteristics. The placement of a catheter could potentially overcome this limitation, but it is. Not appropriate for long-acting analgesia [52, 53].

Regional nerve block alternatives have emerged, including paravertebral and fascial plane blocks, addressing concerns associated with neuraxial instrumentation. Paravertebral techniques have similar efficacy as thoracic epidural analgesia with fewer side effects [32, 48]. Ultrasound-guided nerve blocks, erector spinae, pectoralis, serratus anterior, and parasternal nerve blocks have been described. Various studies have suggested decreased pain scores and less opioid requirements with few side effects. Additional investigation is needed to establish the optimal block timing and dosing and to formally assess the safety profile associated with regional use, especially given the concomitant use of systemic anticoagulation in cardiac surgery, as well as to determine which technique is better for a particular surgical approach (i.e., sternotomy vs. thoracotomy vs. minimally invasive surgery) [32, 54, 55].

The surgeon's direct vision increased the succession rate of the ICNB performed before the thoracotomy closure, decreasing complications related to the ICNB. Blocking under direct visualization is easy to perform, and it improves analgesic effects, pulmonary functions, and CNS depression [48].

Epidurals have been used for VATS surgery. However, the lesser surgical trauma and less intense postoperative pain compared to thoracotomy, the potential for significant side effects associated with thoracic epidural catheterization and the availability of effective, simpler regional analgesia blocks make the use of epidural analgesia questionable in this context [52, 53].

Epidural placement may be considered when there is a high probability of conversion to open thoracotomy [52, 53].

All regional techniques can be done as a "single shot" or continuously by catheter placement with ultrasound.

3. Chronic pain

Thoracic surgery is associated with a high incidence of chronic postsurgical pain (CPSP or PPP), defined by the International Association for the Study of Pain as pain that develops or increases in intensity after a surgical procedure and persists beyond 3 months after surgery [3].

A pain develops after a surgical procedure or increases in intensity after the surgical procedure. The pain is of at least 3–6 months duration and significantly affects the quality of life. The pain is a continuation of acute postsurgery pain or develops after an asymptomatic period and is localized to the surgical field, projected to the innervation territory of a nerve situated in the surgical field, or referred to a dermatome, and other causes of pain should be excluded. Risk factors include young age, female gender, preexisting pain, anxiety, a catastrophizing mindset, higher body mass index, and a history of osteoarthritis [43, 44, 48, 49, 56]. Patients' psychological comorbidities also play a key role in the approach to preventing postoperative persistent pain (PPP) after cardiac surgery. Patients may have preexisting psychological risk factors for the development of chronic pain, including anxiety, depression, post-traumatic stress disorder, and pain catastrophizing [15, 43, 44]. Early involvement of a pain psychologist or integrative pain team may offer valuable insights to both identify and address these psychological risk factors outside of the cardiothoracic anesthesiologist and surgeon's area of expertise [43, 44].

Multidisciplinary approach to cardiothoracal pain therapy may provide the ideal strategy in preventing postoperative pain (PPP) in the cardiac surgery patients. A multi-disciplinary, perioperative pain team may optimally treat complex pain through specialization, communication, and education among providers and patients [27].

A differential diagnosis of PPP after cardiac surgery can be from myocardial ischemia, mediastinitis, and sternal instability. Pain may be present at the site of the sternotomy or in the legs due to vein-graft harvesting [11].

4. Conclusion

The incidence of chronic pain after cardiothoracic surgery is associated with the severity and duration of the acute pain. The assessment of postoperative pain in cardiosurgical patients has been more clearly standardized in the last two decades, based on the elaboration of different clinical pain assessment tools adapted to the patients' condition in different cultures and postoperative care units, and included in studies. Opioids are still the basis of pain therapy, but their use has been significantly reduced to decrease the unwanted side effects. It is suggested that fentanyl and remifentanil should be used (peri- and postoperatively) due to the best hemodynamic and antiarrhythmic effects. Protocolized MMA and used to improve standardized pain therapy. Analgesic protocols within the recommendations vary from hospital to hospital and can be changed according to patients' needs and status (worsening of the general condition).

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Chapter 3

Perspective Chapter: Analgesic Use of Esketamine

Ferdi Gülaştı

Abstract

Esketamine is ketamine's left enantiomer. It is alternatively referred to as (S)-(+)-ketamine or (S)-ketamine. Experiments investigating the analgesic properties of esketamine were commenced upon its discovery. Esketamine, which has begun to be used as a different analgesic option due to the undesirable effects of opioids, can be used in perioperative pain control and in subanesthetic doses for chronic pain. Esketamine's analgesic properties are commonly accepted to be 2–4 times as potent as racemic ketamine. Though esketamine's psychomimetic effects appear to be related to inhibition of the N-methyl-D-aspartate (NMDA) receptor, its use is not free of risk, with undesirable mental effects. Nevertheless, it is likely to produce less cholinergic inhibition. Following the discovery of ketamine in 1962, efforts were made in the 1990s to find a therapeutic use for esketamine in the treatment of depression. In 2019, the Food and Drug Administration (FDA) approved the use of esketamine for treatment-resistant depression. Interest in esketamine's uses as an analgesic drug has increased alongside its FDA approval for new indications.

Keywords: esketamine, analgesic, NMDA receptor, perioperative pain, neuropathic pain

1. Introduction

A mixture of equal parts of ketamine's two enantiomers is referred to as racemic ketamine. (S)-ketamine, like (R)-ketamine, binds to NMDA receptors, albeit with a lesser affinity. Ketamine also interacts with mu, kappa, and, to a lesser degree, delta-opioid receptors (Ki = 42.1, 28.1, and 272 mM, respectively). Esketamine's affinity for mu and kappa opioid receptors is between two and four times that of (R)-ketamine [1].

In addition to NMDA receptors, esketamine also affects cholinergic receptors, opioid receptors, potassium/sodium hyperpolarization-activated cyclic nucleotide-gated channel 1 (HCN1) receptors, 8-monoamines, and sodium and Ca^{2+} channels, modifying the working of a multitude of systems and nerve networks [2, 3]. Esketamine and its isomers have varying affinities for phencyclidine (PCP) binding sites within NMDA receptor channels. Binding affinity to this region has been shown to determine the strength of analgesia [4–6]. Analgesic and anesthetic effects of esketamine, or

PCP binding region affinity, have been shown to be four times that of arketamine and two times that of racemic ketamine [3, 7].

(S)-ketamine, like (R)-ketamine, is metabolized by cytochrome P450 enzymes into norketamine, dehydronorketamine (DHNK), hydroxy-ketamine (HK), and hydroxynorketamine-like (HNK) [2]. (S)-ketamine is demethylated into (S)-norketamine by CYP3A4 or CYP2B6. (S)-norketamine is further metabolized into (S)-DHNK or HNK molecules. Hydroxylation of (S)-norketamine by CYP2A6 results in the HNK metabolite (2S,6S)-HNK, found in plasma after initiation of ketamine infusions [8]. CYP2A6 may also directly hydroxylate (S)-ketamine to form (2S,6S)-HK and later metabolize it into (2S,6S)-HNK. Esketamine's capacity to provide analgesia at lower doses than arketamine may result in its dissociative and psychomimetic side effects being less pronounced [9–11]. Due to this, purified S(+)- or esketamine acquired approval for clinical use in Germany, followed by the Netherlands, Austria, and Scandinavian countries. It was approved by the FDA in 2019 for use in treatment-resistant depression [12]. When ketamine is used for the treatment of pain in patients who are awake, it may result in extremely disturbing psychopathological experiences. Psychopathological effects of esketamine are defined as "dissociative analgesic/anesthetic" acute effects that are dose-dependent. Lower and subanesthetic doses of esketamine are associated with analgesic, antidepressant, and "detached" consciousness. Increasing doses are associated with sedation and loss of consciousness. Low doses of esketamine have been found to produce relatively light and temporary side effects. Conversely, some research has supported the opposing view that psychomimetic effects are more pronounced in esketamine compared to arketamine. Mathisen and colleagues found that, despite lower doses administered of esketamine than arketamine (0.45 mg/kg and 1.8 mg/kg, respectively), patients assigned to the esketamine group experienced more psychomimetic side effects [13]. Vollenweider and colleagues carried out a study on healthy volunteers that found that esketamine administration was associated with psychosis-like reactions (ego death, illusions and hallucinations, thought disorders, paranoid thoughts), while arketamine did not produce such effects and was found to be more relaxing [14].

Due to its properties of sympathetic stimulation and reuptake inhibition of circulatory catecholamines, ketamine increases heart rate (HR) and blood pressure (BP). Esketamine and arketamine in respectively similar doses produce similar sympathetic effects [15–17]. Esketamine, in contrast to arketamine, has been shown to produce positive myocardial inotropic effects. Uncontrolled increases in sympathetic activity can be counteracted by the administration of propofol and/or GABA agonists.

Esketamine, like racemic ketamine, can be administered for treatment-resistant status epilepticus [18]. Esketamine has also been shown to have neuroprotective effects following acute brain damage [18].

2. Analgesic uses of esketamine

Esketamine is used as a powerful analgesic in acute and chronic pain. It is a powerful analgesic that can be chosen to avoid addiction and other side effects of opioids. Due to its rapid onset of action, it is a good option for postoperative acute pain and for chronic pain of the neuropathic type that cannot be controlled due to its anti-inflammatory and powerful effect.

3. Esketamine for perioperative pain control in cesarean sections

Administration of i.v. boluses of (S)-ketamine result in 19.7% lower required doses of spinal ropivacaine, as well as decreasing incidence of hypotension and related symptoms. Despite this, i.v. (S)-ketamine boluses alongside 12 mg of spinal ropivacaine should be used with caution in patients at high risk of hypotension or with a history of extreme anger [19]. Li-Li Xu and colleagues utilized a subanesthetic dose prior to the first incision in women undergoing cesarean sections (CS) under epidural anesthesia. This study found little analgesic effect of esketamine, and researchers expressed concern due to the high rate of sedative and mental side effects. Despite esketamine readily crossing the placenta, significant neonatal depression was not observed [20].

Esketamine can be used with high (>0.3 mg/kg) and low (≤0.3 mg/kg) dosing regimens. Esketamine administration decreases morphine requirements and improves recovery. Both high- and low-dosing regimens of esketamine reduce postoperative pain and the incidence of postpartum depression. Nevertheless, taking into account potential side effects caused by esketamine, low-dose esketamine regimens may be more appropriate for patients undergoing CS [21]. Adjuvant use of (S)-ketamine reduces postoperative pain and the development of PPD [22]. Postpartum depression (PPD) is a common psychological condition in women during the perinatal phase. PPD occurs with a frequency ranging from 10% to 20%. It tends to be higher in middle- and low-income countries [23]. PPD has been observed to occur at a range of time points after birth, from as early as 6 weeks postpartum to as late as 36 months postpartum [24, 25]. PPD is characterized by feelings of sadness, persistent low mood, anorexia, loss of interest in previously enjoyable activities, psychomotor retardation, and sleep disturbances. Suicidal thoughts are also an increased risk for severe PPD [26]. The effectiveness of pharmaceutical treatments for PPD, despite their frequent use, is limited by the delayed onset of action and poor treatment efficacy [27, 28].

Esketamine may effectively reduce the risk of PPD in women undergoing elective cesarean section. Additionally, esketamine has been shown to result in lower pain scores during movement and reduce the need for opioid consumption after cesarean section.

Use of i.m. boluses or continuous i.v. infusions of esketamine in CS patients increases morphine's analgesic effects even after ketamine's effects have subsided. Obstetric patients can use esketamine after undergoing CS safely, with no effects on breastfeeding [29]. Minimally dosed esketamine (0.015 mg/kg/hour for 48 hours) is as effective for decreasing opioid use and hyperalgesia as conventional low-dose esketamine (0.25 mg/kg initial bolus followed by 0.125 mg/kg/hour). Delirium risk is dose-dependent, with lower doses producing lower rates of delirium [30].

4. Use of esketamine for perioperative pain in thoracic surgery

Multiple studies have demonstrated the benefits of esketamine for perioperative pain control in patients undergoing thoracoscopic lung surgeries [31–33]. Subanesthetic doses of esketamine (0.25 mg/kg/hour) in a continuous intravenous infusion have been shown to produce significant reductions in postoperative opioid use [32]. In patients undergoing video-assisted thoracic surgery with spontaneous ventilation, esketamine can be used for opioid free anesthesia (OFA), providing a

similar standard of postoperative pain control as comparable anesthetic techniques using opioids. Furthermore, esketamine is superior in terms of preservation of circulatory and respiratory stability compared to opioids [33]. Esketamine can also be administered in combination with hydromorphone for postoperative pain control in thoracoscopic surgeries. This approach can produce a significant decrease in medium to severe postoperative pain [34].

5. Use of esketamine for postoperative pain control in spinal surgery

Following lumbar spinal fusion surgeries, oxycodone supplemented with esketamine in a 1:0.75 ratio has been shown to be effective for postoperative pain management. This approach reduces cumulative oxycodone consumption without producing additional side effects [35]. Esketamine is recommended for use in conjunction with dexmedetomidine as a component of multimodal analgesia. Esketamine-dexmedetomidine combinations improve subjective sleep quality and analgesia without an increase in adverse effect incidence [36]. Nevertheless, psychiatric side effects and dizziness have been reported in postoperative patients [37].

6. Use of epidural esketamine

Esketamine and opioids can be used intravenously or in an epidural infusion for postoperative pain management. Epidural administration of esketamine reduces chronic postoperative pain and side effect incidence [38, 39]. For epidural use, administration in conjunction with morphine is recommended [39].

Lou S. and colleagues reported an ED90 value of approximately 1 mg/mL for esketamine administered with 0.075% ropivacaine. Epidural esketamine may cause slight dizziness in a dose-dependent manner. Esketamine has not been approved as a sole adjuvant agent for labor anesthesia [40].

7. Use of esketamine in neuropathic pain

Neuropathic pain is defined as "pain caused by a lesion or disease of the somatosensory nervous system." Sufficient remission of neuropathic pain is only achieved in a very small number of patients. General analgesic agents such as non-steroidal anti-inflammatory drugs (NSAIDs) do not produce a pronounced reduction in neuropathic pain. Opioid use in chronic pain frequently leads to tolerance and dependence, and the search for de-opioidization therapies is ongoing. Esketamine is one of a select few non-opioid potent analgesics [41]. Glutamate is an excitatory amino acid that has been shown to have an effect on neuropathic pain. N-methyl-D-aspartate (NMDA) receptors, a subtype of glutamate receptors, have a role in the perception of pain, and due to their nociceptive modulatory properties, NMDA receptor antagonists have been used in neuropathic pain [42]. Esketamine has a higher affinity for NMDA receptors compared to other NMDA antagonists, with a lower required dose and presumed lower incidence of psychomimetic side effects being an initial factor for investigation of the molecule. Esketamine's utility in chronic pain, particularly treatment-resistant neuropathic pain, is limited by its relatively short half-life. This property necessitates repeated doses or a continuous infusion, resulting in low patient

compliance [43]. Delirium and hallucinations are unwanted side effects associated with esketamine use [44]. Development of an esketamine/nanoparticle-hydrogel system aimed at reducing side effects and increasing clinical utility is ongoing.

8. Use of esketamine in cancer pain

Every year, more than 18 million cancer diagnoses are made worldwide, and the incidence is constantly increasing. It continues to be one of the leading causes of morbidity and mortality in the world. Cancer-related pain is one of the most frequently reported symptoms, which leads to increased anxiety, depression, irritability, and even cognitive impairment [45]. As a result, this can reduce the patient's quality of life and even life expectancy. The World Health Organization defines cancer pain as one of the world's medical emergencies [46]. Depressive disorders are common in cancer patients, as is chronic pain. Data on the use of esketamine in depression are very widespread [47, 48].

Cancer causes pain through different mechanisms, apart from the disease itself, through the damage that treatment processes, such as chemotherapy, give to the body. Chemotherapy can lead to peripheral neuropathy that continues even weeks or years after treatment [49]. Chronic pain may occur due to inflammation after cancer surgery and fibrosis that may be caused in the tissues affected by radiotherapy. Although cancer pain is tried to be controlled with multimodal analgesia methods, both addiction and tolerance to opioids may develop. Esketamine prevents allodynia by reducing central sensitization by inhibiting NMDA receptors on the neuropathic component, with its ability to regulate glutamate release in cancer pain. Intrathecal esketamine has been proven in resistant neuropathic or cancer pain. However, in the study conducted by Vranken et al., they revealed neuropathological damage in autopsies after 3 weeks of 50 mg/day intrathecal administration [50]. For this reason, it seems appropriate to use it only in patients with unbearable pain and no life expectancy.

9. Use of esketamine in rebound pain

Rebound pain after regional anesthesia can be defined as transient acute postoperative pain that occurs after the resolution of sensory blockade, and the severity of rebound pain is clinically important in terms of its effect on recovery and daily life activities. Rebound pain occurs especially after surgery and after the cessation of high-dose opioid use as more severe pain. Systemic analgesia, together with nerve block or the addition of adjuvants to the block, is recommended due to their synergistic effects [51, 52]. Especially in patients who have regional block for acute postoperative pain control, rebound pain after the block effect has worn off is still an important problem [53]. There are studies on the reduction of rebound pain with esketamine. In many studies conducted in recent years, esketamine has been shown to reduce opioid use and prevent rebound pain [53–55]. As a result, esketamine has been found to be quite useful both in preventing the occurrence and in the treatment of such hyperalgesic conditions [49, 52].

10. Use of esketamine in chronic postoperative pain

Chronic postoperative pain is a common complication that significantly affects patients' quality of life and is closely associated with mortality. This creates a

significant economic and healthcare burden. The median incidence of chronic pain 6–12 months after surgery is 20–30%, with a slight decrease over time. The incidence varies depending on the type of surgery [56]. Numerous pharmacological studies have been conducted to prevent the development of chronic postoperative pain. However, in a 2021 meta-analysis that included these studies, the effect of the drugs was generally small, and the clinical significance was uncertain. This is largely due to methodological deficiencies and differences in the studies [57]. In recent years, studies have shown that esketamine reduces the incidence of chronic postoperative pain, especially after breast cancer surgery [58, 59]. In addition, repeated, relatively subanesthetic doses of esketamine are often required for several days to affect the symptoms of chronic pain. However, there are still insufficient studies, and the data are still inconsistent, but esketamine seems promising for chronic postoperative pain. In addition, it should be kept in mind that long-term IV esketamine infusions are hepatotoxic.

11. Conclusions

Esketamine is an agent used in pain control as part of multimodal analgesia, with its analgesic effect mechanism different from other analgesics. Esketamine is more usable with lower doses and fewer side effects than arketamine. In addition to its known and more reliable use intraoperatively, its use in postoperative acute pain and chronic pain has begun to increase in subanesthetic doses. It appears to be an effective agent for pain control in thoracic and lumbar surgeries, pain control in cesarean section patients, as well as postpartum depression. In the chronic pain group, it appears to be quite effective in neuropathic pain and rebound pain. However, even at subanesthetic doses, its analgesic properties are satisfactory, but its psychomimetic side effects are an important reason to avoid its use. Therefore, ideal dose research for esketamine that maintains its analgesic effect but does not have or disturb the psychomimetic effect should continue.

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Chapter 4

NeuraPan Flex®: Molecular Mechanisms in Postoperative Neuropathic Pain Relief

Apurba Ganguly and Anondeep Ganguly

Abstract

Neuropathic pain (NP) results from complex molecular alterations in the nervous system, including inflammation (elevated CRP, IL-6, and TNF-α), tissue repair processes (MMP-2 and MMP-9), oxidative stress (MDA), neuronal function (BDNF and NGF), and pain perception (substance P and GFAP). NP may arise from conditions such as diabetes, shingles, spinal cord injuries, multiple sclerosis, or postoperative complications and is often characterized by burning, tingling, or stabbing sensations. This chapter examines the efficacy of *NeuraPan Flex*® (NPF), a topical bioactive lipophilic formulation, as an alternative to standard management (SM) in postoperative pain scenarios. A 16-week double-blind randomized controlled trial involving 72 patients treated with NPF versus 63 controls receiving SM was conducted. NPF includes bioactive ingredients such as *Syzygium aromaticum* (eugenol), *Lavandula angustifolia* (linalool), *Eucalyptus globulus* (eucalyptol), *Zingiber officinale* (gingerol), and others. Clinical efficacy was evaluated using the Neuropathic Pain Scale (NPS), radiological imaging, and serum biomarker analysis, with biomarkers assessed pre- and posttreatment. NPF demonstrated high diagnostic performance with area under the curve between 0.981 and 0.901 ($p < 0.0001$), showing significant improvements in clinical outcomes and biomarker modulation compared to SM ($p < 0.0001$). NPF shows strong potential for improving NP management and modulating key biomarkers, supporting its integration into clinical practice. Further trials are needed for broader application.

Keywords: neuropathic pain, *NeuraPan Flex*®, molecular mechanisms, neuroinflammation, phytoextracts, neurological disorders

1. Introduction

Neuropathic pain (NP) poses a significant and complex challenge, affecting approximately 7–10% of the global population. This type of pain results from injury or dysfunction within the nervous system and is notoriously difficult to manage due to its multifaceted nature [1]. Unlike nociceptive pain, which is directly linked to tissue damage, NP is characterized by an intricate interplay of

molecular changes across various biological pathways, including inflammation, oxidative stress, neuronal dysfunction, and abnormal pain processing [1, 2]. Key biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), matrix metalloproteinases (MMP-2 and MMP-9), malondialdehyde (MDA), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), substance P, and glial fibrillary acidic protein (GFAP) are often dysregulated in NP [3–8].

The etiology of NP spans a range of conditions, including diabetes, herpes zoster infection (shingles), cancer, nerve injury, and postoperative complications [9, 10]. Its complexity depends on various molecular pathways, such as inflammatory responses, oxidative stress, and neuroimmune interactions.

Current standard management (SM) of NP mainly involves pharmacological agents like anticonvulsants, antidepressants, and opioids [9, 10]. However, these treatments often fall short, providing inadequate relief and posing risks of significant side effects and dependency [11]. This gap has spurred interest in alternative therapies that target the underlying molecular mechanisms of NP.

One promising approach is the use of bioactive compounds derived from natural sources. *NeuraPan Flex*® (NPF) is a novel topical formulation designed to address NP's molecular complexities through a bioactive lipophilic composition. It incorporates a blend of botanical extracts, including *Syzygium aromaticum* (eugenol) [12], *Lavandula angustifolia* (linalool) [13], *Eucalyptus globulus* (eucalyptol) [14], *Zingiber officinale* (gingerol) [15], *Mentha piperita* (menthol) [16], *Gaultheria procumbens* (methyl salicylate) [17], *Pinus sylvestris* (α-pinene, β-pinene) [18], *Celastrus paniculatus* (celastrol) [19], *Aloe barbadensis* (acemannan) [20], *Cocos nucifera* (lauric acid, capric acid) [21], and *Triticum vulgare* (tocopherol) [22]. These ingredients were selected based on their efficacy in targeting multiple NP-related biomarkers and receptors, including TRPV1, NMDA, GABA-A, 5-HT, TRPA1, TRPM8, substance P, COX, NF-κB, CB2, TNF-α, PPAR-γ, PPAR-α, CGRP, and cytokines like IL-1β, IL-6, and TNF-α. The formulation also impacts oxidative stress biomarkers and neurotrophic factors, enhancing antioxidant defense and neuroprotection [23–26].

This chapter presents a study evaluating the clinical efficacy of NPF compared to standard management (SM) in postoperative pain scenarios through a 16-week double-blind randomized controlled trial. The trial assessed changes in the Neuropathic Pain Scale (NPS), radiological imaging, and serum biomarkers pre- and posttreatment. The findings indicate significant improvements in clinical outcomes and biomarker modulation in the NPF group, suggesting its potential as a more targeted and safer alternative for NP management. Further research and larger clinical trials are needed to validate these results and explore NPF's broader applicability in NP management.

2. Materials and methods

2.1 Study design

This study was a 16-week double-blind randomized controlled trial conducted to evaluate the efficacy of NPF in managing neuropathic pain (NP) compared to standard management (SM). OPTM Research Review Board approved the study at OPTM Health Care Pvt. Ltd. and NanoPhyto Care Pvt. Ltd. Informed consent was obtained from all participants before enrollment.

2.2 Participants

The study enrolled 153 patients with clinically diagnosed neuropathic pain from OPTM Health Care Pvt. Ltd. and NanoPhyto Care Pvt. Ltd. between April 2023 and June 2024. Rigorous inclusion and exclusion criteria were applied to ensure a homogenous participant group and to enhance the validity and reliability of the study results.

a. *Inclusion criteria*:

- Adults aged 18–75 years with a confirmed clinical diagnosis of neuropathic pain lasting at least 6 months.
- Patients reporting moderate to severe pain intensity, defined as an NPS score of ≥4 at baseline.
- Individuals with stable medical conditions, not undergoing significant changes to their existing pain management regimen during the study period.
- Participants who provided informed consent demonstrated willingness and ability to adhere to all study protocols and procedures.

b. *Exclusion criteria*:

- Patients with pain conditions not primarily neuropathic, such as fibromyalgia or pain related to malignancy.
- Individuals receiving other experimental pain treatments or investigational drugs within 30 days before study enrollment.
- Patients with significant psychiatric or cognitive disorders that might affect accurate pain assessment or adherence to study protocols.
- Pregnant or breastfeeding women, or those planning to conceive during the study.
- Participants with known hypersensitivity or contraindications to any component of the NPF formulation.

These criteria were meticulously enforced to ensure the selection of a representative and suitable sample, strengthening the study outcomes' robustness.

Participants were randomly assigned to either the NPF group (n = 72) or the SM group (n = 63) using a computer-generated randomization schedule. Stratification based on baseline neuropathic pain severity was employed to ensure comparable groups at the outset of the trial.

2.3 Intervention

The intervention group received NPF, a topical bioactive lipophilic formulation containing the following botanical extracts: *Syzygium aromaticum* (eugenol: 80–90%); *Lavandula angustifolia* (linalool: 20–45%; linalyl acetate: 25–45%); *Eucalyptus globulus*

(eucalyptol: 70–85%); *Zingiber officinale* (gingerol: 15–30%); *Mentha piperita* (menthol: 35–50%); *Gaultheria procumbens* (methyl salicylate: 90–98%); *Pinus sylvestris* (α-pinene: 30–50%; β-pinene: 15–25%); *Celastrus paniculatus* (celastrol: 0.05–0.2%); *Aloe barbadensis* (acemannan: 15–30%); *Capsicum annuum* (Capsaicin: 0.1–1.5%); *Cocos nucifera* (Lauric Acid: 45–55%; Capric Acid: 5–10%); and *Triticum vulgare* (Tocopherol: 0.5–1.5%).

NPF was applied twice daily to the affected area for 16 weeks. The control group received SM for neuropathic pain, which included anticonvulsants, antidepressants, and topical analgesics.

2.4 Clinical assessments

The primary clinical outcome was the change in the NPS score from baseline to week 16. Secondary outcomes included radiological imaging assessments and patient-reported outcomes on pain severity, sleep quality, and daily function.

2.5 Biomarker analysis

Fasting blood samples were collected at baseline and after 16 weeks of treatment. Serum levels of biomarkers associated with inflammation (CRP, IL-6, and TNF-α), tissue repair (MMP-2 and MMP-9), oxidative stress (MDA), neuronal function (BDNF and NGF), and pain perception (substance P and GFAP) were measured using enzyme-linked immunosorbent assays (ELISA) following the manufacturer's instructions, as detailed in **Table 1.** All samples were processed and analyzed in a blinded manner at Galaxy Medical Centre, an ISO 9001:2015 certified laboratory in Kolkata, India.

The normal levels and deviations of biomarkers in individuals with neuropathic pain are shown in Table 2.

2.6 Neuropathic pain scale (NPS)

In this study, NPS [27] was employed to quantitatively assess the multidimensional aspects of neuropathic pain experienced by participants. NPS is a validated tool

Biomarkers	Human assay kit	Manufacturer	Place
CPP	CRP ELISA Kit	Nirmal Bioscience Pvt. Ltd.	Haryana 134,113
Il-6	IL-6 ELISA Kit	RayBiotech Life, Inc.,	New Delhi 110,008
TNF-α	TNF-α ELISA Kit	Elite Biotech	New Delhi 110,044
MMP-2	MMP-2 ELISA Kit	Biobasic India	Bangalore 560,095
MMP-9	MMP-9 ELISA Kit	Biobasic India	Bangalore 560,095
MDA	Colorimetric Assay Kit	Labcare Diagnostics	New Delhi 110,005
BDNF	BDNF, ELISA Kit	Krishgen Biosystems	Bangalore 560,095
NGF	NGF, ELISA Kit	Krishgen Biosystems	Bangalore 560,095
Substance P	Substance P, ELISA Kit	Krishgen Biosystems	Bangalore 560,095
GFAP	GFAP, ELISA Kit	Meril Diagnostics	Gujarat 396,191

Table 1.
Details of human assay kits used in the study, including manufacturer names and locations.

Biomarker	Normal range (Men)	Normal range (Women)	Neuropathic pain range
CRP	<1 mg/L	<1 mg/L	Elevated, often >3 mg/L
Il-6	<2 pg./mL	<2 pg./mL	Elevated, typically 2–15 pg./mL
TNF-α	1–5 pg./mL	1–5 pg./mL	Elevated, 5–30 pg./mL
MMP-2	400–600 ng/mL	400–600 ng/mL	Elevated, often >600 ng/mL
MMP-9	20–80 ng/mL	20–80 ng/mL	Elevated, typically 80–300 ng/mL
MDA	1–3 μmol/L	1–3 μmol/L	Elevated, often >3 μmol/L
BDNF	10–50 ng/mL	10–50 ng/mL	Lowered, usually <20 ng/mL
NGF	10–50 pg./mL	10–50 pg./mL	Elevated, often >50 pg./mL
Substance P	<20 pg./mL	<20 pg./mL	Elevated, typically >20 pg./mL
GFAP	100–300 pg./mL	100–300 pg./mL	Elevated, often >300 pg./mL

Table 2.
The ranges represent typical levels and deviations observed in individuals suffering from neuropathic pain.

designed to capture neuropathic pain's intensity and quality by evaluating parameters such as sharpness, burning sensation, coldness, and sensitivity to light touch.

Participants were asked to rate their pain on a scale of 0–10 for each item, with 0 indicating the absence of pain and 10 representing the most severe pain imaginable. The scores from each item were then analyzed to provide a comprehensive profile of the neuropathic pain experienced, facilitating the evaluation of treatment efficacy and the understanding of pain mechanisms in the context of the study.

This method allowed for a detailed and nuanced assessment of pain characteristics, contributing to the robustness of the study's findings.

2.7 Receiver operating characteristic curve analysis

Receiver operating characteristic (ROC) curve analysis was conducted to determine the diagnostic performance of each biomarker. Sensitivity and specificity were assessed, and the area under the curve (AUC) values were computed, accompanied by 95% confidence intervals. These intervals were established using the bootstrap method as per established protocols [28] and in line with previous publications. This analysis provided insights into the predictive power of biomarkers for NP [29, 30].

2.8 Meta-analysis and heterogeneity tests

A meta-analysis was conducted to aggregate data from multiple studies, enhancing reliability. Heterogeneity across studies was assessed using Cochran's Q-test and the I-squared index to determine consistency. Effect-size indices quantified the results within the meta-analysis [29, 30].

2.9 Radar chart analysis

Radar charts were used to visualize standardized mean differences and percentage changes in biomarkers between NPF and MS groups, focusing on the severity of neuropathic pain.

2.10 Standardized mean deviation and 95% confidence interval of biomarkers

In this study, standardized mean differences (SMD) and 95% confidence intervals (CI) were calculated to quantify the differences in biomarker levels between the NPF group (n = 72) and the SM group (n = 63). SMD assessed effect sizes, reflecting intergroup differences relative to within-group variability.

Mean differences (MDs) and their 95% CIs were computed for each biomarker to evaluate the precision of these estimates. Statistical significance was determined using p-values for both MD and SMD, highlighting biomarkers with significant group differences. The detailed results, including SMDs, CIs, and p-values for each biomarker, are presented in the "Results" section.

2.11 Correlation coefficient analysis

To elucidate the intricate relationships among key molecular biomarkers governing inflammation, oxidative stress, neuronal dysfunction, and abnormal pain processing, a comprehensive Pearson correlation coefficient analysis was evaluated. The analysis was conducted for both the NPF and MS groups, assessing the strength and direction of associations between biomarkers, including CRP, IL-6, TNF-α, MMP-2, MMP-9, MDA, BDNF, NGF, substance P, and GFAP. Pearson's correlation coefficients (r-values) were computed for each biomarker pair, accompanied by p-values to assess statistical significance. A two-tailed test with a significance level of $p < 0.05$ was used to identify meaningful correlations. The strength of correlation was classified as strong ($r > 0.7$), moderate (r between 0.3 and 0.7), or weak ($r < 0.3$). Statistical analyzes were conducted using appropriate software, ensuring the robustness and reproducibility of results [30].

2.12 Statistical analysis

Descriptive statistics, including means, standard deviations, and ranges, were calculated for both demographic and biomarker data. Comparisons of serum biomarker levels between NPF patients and MS subjects were performed using independent t-tests or Mann-Whitney U tests for nonnormally distributed data. ROC curves were constructed to evaluate the diagnostic performance of each biomarker, with AUC values calculated to determine a predictive value for neuropathic pain. Risk ratios and 95% confidence intervals were computed to assess associations between biomarker levels and biological neuropathic risk factors. Data were analyzed using IBM SPSS software version 20 [31], with statistical significance set at $p < 0.05$. Data accuracy and completeness were verified before analysis.

2.13 Ethical considerations

The study was approved by the OPTM Health Care Pvt. Ltd. Review Board. Informed consent was obtained from all participants before their inclusion in the study.

3. Results

3.1 Patient enrolment and baseline characteristics

The study involved 135 participants: 72 (53.33%) in the NPF group and 63 (46.67%) in the SM group. Both groups were similar in age, weight, height, BMI,

and symptom duration, with the NPF group having a slightly higher proportion of females (68.31 vs. 65.51%). Pain intensity was reported by 76.39% of the NPF group and 80.95% of the SM group. Common pain features included sharpness, hot/burning sensation, and deep pain. The NPF group exhibited higher smoking and alcohol use, while the SM group had more tea and coffee consumption. Occupational status varied, with more self-employed individuals in the NPF group and more full-time employees in the SM group. Ethnic distribution, dietary habits, and marital status were comparable across groups (see **Table 3**).

Characteristic	NPF group	MS group
No of subjects (%)	72 (53.33)	63 (46.67)
Female (%)	49 (68.31%)	41 (65.51%)
Mean age (SD) in years	59.1 (3.2)	58.8 (3.1)
Mean weight (SD) in kg	71.12 (5.78)	70.77 (6.21)
Mean height (SD) in meter	1.52 (0.79)	1.54 (0.84)
Mean BMI (SD) in kg/m^2	30.78 (6.88)	31.04 (7.27)
Mean symptom duration in years (SD)	5.25 (1.85)	5.35 (1.65)
Indian ethnic group (%)		
Bengali	19 (26.39)	18 (28.57)
Gujrati	7 (9.72)	5 (7.94)
Marwaree	6 (8.33)	6 (9.52)
Marathi	9 (12.5)	7 (11.11)
Tamil	8 (11.11)	8 (12.7)
Punjabi	7 (9.72)	7 (11.11)
Shindhi	8 (11.11)	5 (7.94)
North East India	8 (11.11)	7 (11.11)
Dietary habits (%)		
Vegetarian	49 (67.60)	39 (62.58)
Nonvegetarian	23 (32.40)	24 (37.42)
Other habits (%)		
Smoking	13 (1032)	7 (6.48)
Drinking alcohol	11 (8.73)	9 (8.33)
Drinking tea and coffee	15 (11.91)	16 (14.81)
Chewing tobacco	6 (4.76)	6 (5.56)
No other habits	9 (7.14)	13 (12.04)
Neuropathic Pain scale (number) (%)		
Intensity of pain:	55 (76.39)	51 (80.95)
Sharpness	45 (62.5)	40 (63.49)
Hot/burning sensation	30 (41.67)	28 (44.44)
Cold sensation	15 (20.83)	18 (28.57)
Dullness	10 (13.89)	11 (17.46)

Characteristic	NPF group	MS group
Itching:	12 (16.67)	8 (12.7)
Tingling/prickling	21 (29.17)	10 (15.87)
Sensitivity to light touch:	11 (15.28)	9 (14.29)
Surface pain:	7 (9.72)	8 (12.7)
Deep pain:	30 (41.67)	22 (34.92)
Occupational Hazards (%)		
Employed fulltime	9 (12.5)	12 (19.05)
Employed part-time	8 (11.11)	9 (14.29)
Housewife/Homemaker	11 (15.28)	17 (26.98)
Retired	19 (26.39)	15 (23.81)
Self-employed	25 (34.72)	10 (15.87)
Marital status (%)		
Single	9 (12.5)	7 (11.11)
Married	39 (54.17)	38 (60.32)
Separated	9 (12.5)	7 (11.11)
Divorced	7 (9.72)	6 (9.52)
Widowed	8 (11.11)	5 (7.94)

Table 3.
Demographic data and baseline characteristics of the study subjects.

3.2 Neuropathic pain scale analysis

The meta-analysis showed significant effects for all NPS descriptors. Specifically, the effect sizes were as follows: intensity of pain (SMD = −3.01, $p < 0.001$), sharpness (SMD = −3.45, $p < 0.001$), hot/burning sensation (SMD = −2.99, $p < 0.001$), cold sensation (SMD = −2.52, $p < 0.001$), dullness (SMD = −3.27, $p < 0.001$), itching (SMD = −2.65, $p < 0.001$), tingling/prickling (SMD = −2.42, $p < 0.001$), sensitivity to light touch (SMD = −2.49, $p < 0.001$), surface pain (SMD = −1.92, $p < 0.001$), and deep pain (SMD = −1.95, $p < 0.001$). The overall effect size was −2.21, with moderate heterogeneity ($Q = 28.54$, $I^2 = 68.46\%$). A random-effects model confirmed significant effect sizes (SMD = −2.65, $p < 0.001$) (see **Figure 1**).

3.3 Biomarker analysis

Figure 2 and **Table 4** display receiver operating characteristic (ROC) curve analyzes for biomarkers associated with neuropathic pain. Substance P showed the highest AUC of 0.977, followed by MDA (AUC = 0.972), GFAP (AUC = 0.962), and MMP-2 (AUC = 0.954). Sensitivity for these markers ranged from 97.22% for substance P to 95.83% for MDA, GFAP, and MMP-2, with corresponding specificities ranging from 82.54 to 71.43%.

CRP demonstrated a significant AUC of 0.965, with 93.06% sensitivity and 80.95% specificity, indicating its potential as a biomarker for pain processing abnormalities. IL-10 (AUC = 0.937), TNF-α (AUC = 0.913), and other biomarkers

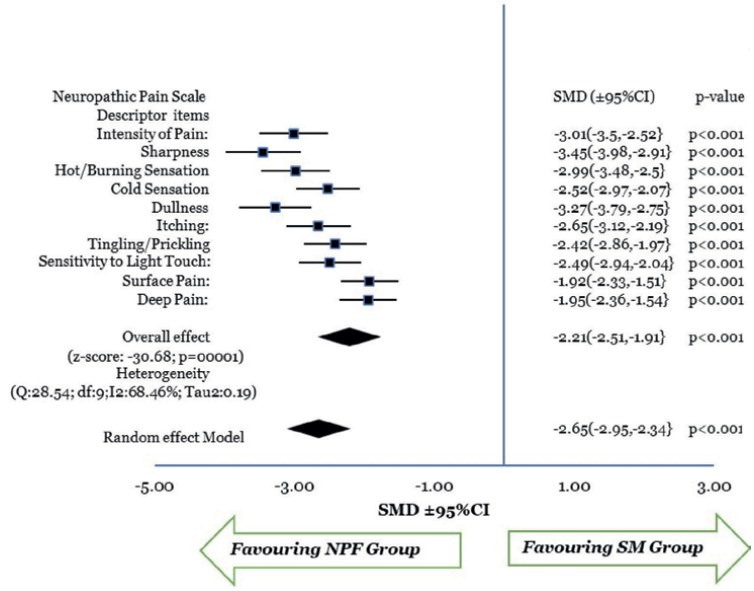

Figure 1.
Standardize mean difference of the items of neuropathic pain scale: NPS group versus SM group at 16 weeks.

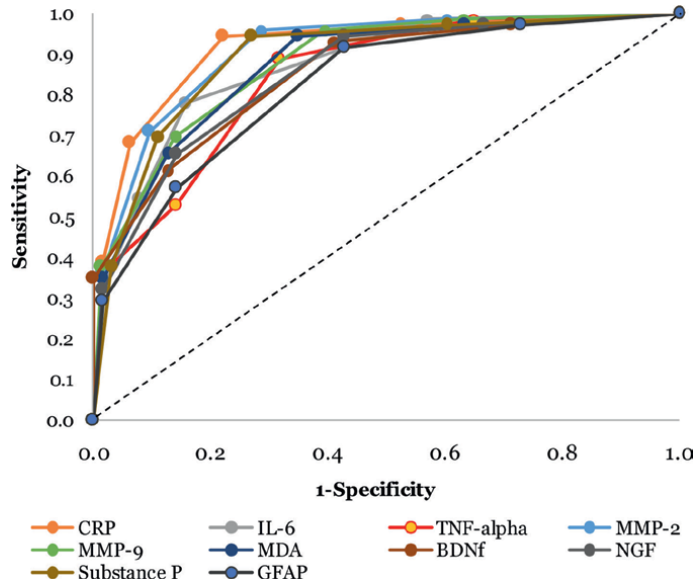

Figure 2.
ROC curves for biomarkers of biological risk factors of neuropathic pain: Experimental group (n = 72) versus control group (n = 63).

also demonstrated clinical relevance based on cutoff values (e.g., CRP: 1.5 mg/L, IL-10: 1.9 pg./mL, TNF-α:10.6 pg./ml, MMP-2:450 ng/ml, MMP-9:81 ng/ml, MDA:3.1 μmol/, BDNF:55 ng/ml, NGF:199 pg./ml, substance P:232 pg./ml, and GFAP:<10 ng/ml).

Biomarkers	AUC (95%CI)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Accuracy (%)	Cutoff value
CRP	0.965 (0.94,0.99)	93.06	80.95	96	71.76	80.74	1.5 mg/L
IL-10	0.937 (0.9,0.97)	77.78	84.13	88.64	63.74	71.85	1.9 pg./ml
TNF-alpha	0.913 (0.87,0.95)	88.89	69.84	96.3	57.41	65.19	6 pg./ml
MMP-2	0.954 (0.93,0.98)	95.83	71.43	89.47	73.08	80	450 ng/mL
MMP-9	0.949 (0.92,0.98)	95.83	63.65	87.72	71.29	78.52	81 ng/ml
MDA	0.972 (0.95,0.99)	95.83	84.13	96	71.76	80.74	3.1 μmol/L
BDNF	0.922 (0.88,0.96)	93.06	58.73	84.62	66.27	73.33	55 ng/ml
NGF	0.923 (0.89,0.96)	94.44	57.14	83.93	68.35	74.81	199 pg./ml
Substance P	0.977 (0.96,1)	97.22	82.54	96.43	77.22	85.19	232 pg./ml
GFAP	0.962 (0.94,0.99)	95.83	68.25	95.65	68.54	77.78	<10 ng/m

Table 4.
Analysis of important parameters receiver operating characteristic curves of biomarkers for the biological risk factors of neuropathy pain: NPF group versus SM group at 16 weeks.

3.4 Meta-analysis of biomarker reductions

The meta-analysis identified significant reductions in key biomarkers associated with neuropathic pain. Inflammatory markers such as CRP (RR = 0.19, 95% CI: 0.10–0.29) and IL-10 (RR = 0.21, 95% CI: 0.11–0.32) were reduced significantly ($p < 0.0001$). Similarly, reductions were seen for TNF-α (RR = 0.26, 95% CI: 0.15–0.37, $p < 0.0001$), MMP-2 (RR = 0.32, 95% CI: 0.19–0.45), and oxidative stress marker MDA (RR = 0.14, 95% CI: 0.07–0.21).

Neurotrophic markers, such as BDNF (RR = 0.15, 95% CI: 0.08–0.22), NGF (RR = 0.13, 95% CI: 0.07–0.20), and pain-related markers such as substance P (RR = 0.11, 95% CI: 0.05–0.16), were also significantly modulated ($p < 0.0001$). The overall effect size was significant, and no heterogeneity was detected (see **Figure 3**).

3.5 Radar chart comparison of NPF and SM groups

1. **Figure 4** illustrates that NPF demonstrated superior efficacy over SM in alleviating pain across various metrics.

   Intensity of pain: NPF achieved a 73.97% reduction compared to 13.52% with SM (60.45% more effective). Sharpness: NPF saw a 69.82% reduction versus 16.35% for SM (53.47% more effective). Hot/burning sensation: NPF led to a 70.70% decrease compared to 14.68% with SM (56.02% more effective). Cold sensation: NPF resulted in a 73.85% reduction versus 4.81% for SM (69.04% more effective).

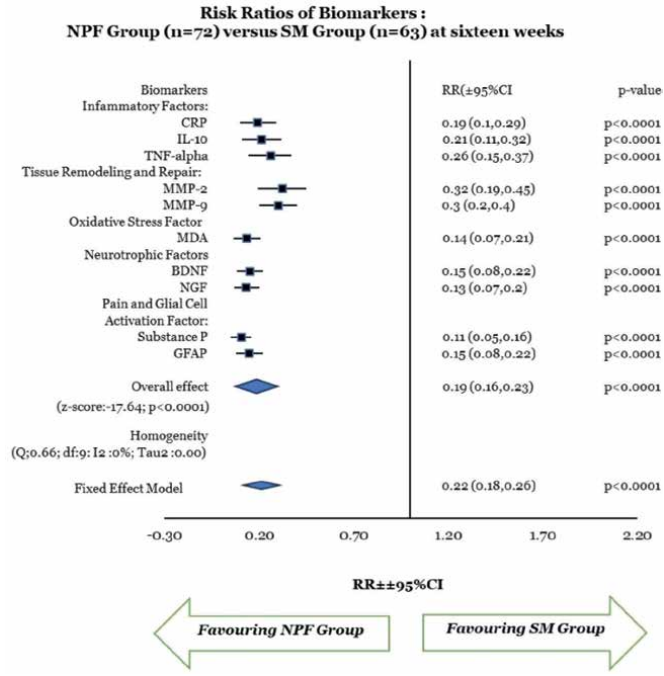

Figure 3.
Risk ratio of biomarkers: NPF group versus SM group at 16 weeks.

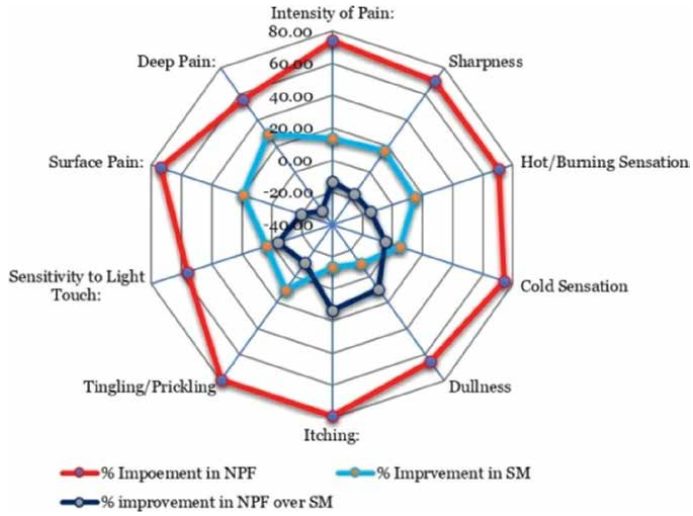

Figure 4.
Percentage of improvement of standardized mean of descriptors of NPS: NPF group, SM group, and NPF group over SM group at 16 weeks.

Dullness: NPF achieved a 65.22% reduction compared to −9.66% with SM (74.88% more effective). Itching: NPF showed a 79.04% improvement versus −13.35% with SM (92.39% more effective). Tingling/prickling: NPF resulted in a 79.25% decrease compared to 10.39% with SM (68.86% more effective).

Sensitivity to light touch: NPF saw a 56.21% reduction versus 3.49% for SM (52.72% more effective). Surface pain: NPF achieved a 73.80% reduction compared to 19.21% with SM (54.59% more effective). Deep pain: NPF resulted in a 55.77% decrease versus 29.13% for SM (26.64% more effective).

2. **Figure 5** illustrates substantial biomarker improvements in the NPF group relative to the SM group after 16 weeks. Notably, there were significant increases in several biomarkers, indicating enhanced therapeutic effects of NPF.

   CRP levels increased by 107.41%, reflecting a marked reduction in inflammation. IL-10 showed a 112.02% increase, suggesting improved anti-inflammatory responses. TNF-α levels rose by 105.29%, indicating reduced pro-inflammatory activity. MMP-2 increased by 103.00%, highlighting enhanced tissue remodeling. MMP-9 saw a dramatic 329.55% rise, suggesting significant modulation of matrix degradation processes. MDA levels increased by 215.97%, demonstrating improved oxidative stress management. BDNF levels surged by 985.00%, reflecting substantial neuroprotective effects. NGF levels rose by 1278.13%, indicating significant neurogenic benefits. Substance P increased by 1037.50%, pointing to enhanced modulation of pain pathways. GFAP levels rose by 451.25%, suggesting improved glial cell activation and response.

3.6 Comparative analysis of biomarker differences

A comparative analysis of MD, SMD, and their respective 95% CIs between the NPF and SM groups at 16 weeks demonstrated significant variations across key biomarkers. Notably, the NPF group exhibited markedly lower levels of CRP, IL-6, TNF-α, MMP-2, and MDA compared to the SM group. For instance, MD for CRP was 9.83 (95% CI: 7.97 to 11.69, $p < 0.0001$) with an SMD of 1.91 (95% CI: 1.50 to 2.32, $p < 0.0001$), indicating a substantial reduction in the NPF group.

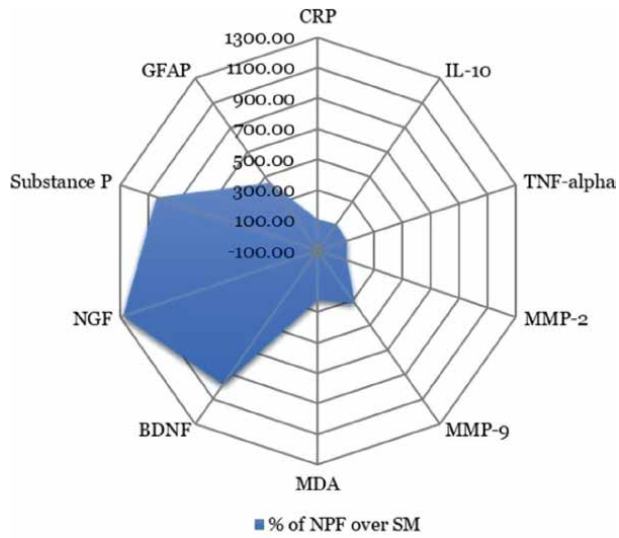

Figure 5.
Percentage of biomarkers of healthy cohorts of NPF group over SM group at 16 weeks.

Similar trends were observed for TNF-α, where MD was 19.45 (95% CI: 15.38 to 23.52, $p < 0.0001$) and SMD was 1.72 (95% CI: 1.33 to 2.12, $p < 0.0001$). In contrast, biomarkers like BDNF and NGF were significantly higher in the NPF group, with negative MDs and SMDs, highlighting their inverse relationship with the inflammatory markers.

These findings underscore the effectiveness of the NPF regimen in modulating key biomarkers associated with neuropathic pain, demonstrating significant improvements in inflammatory and neurotrophic factors when compared to the SM group (see **Table 5**).

3.7 Correlation coefficient

The Pearson correlation analysis revealed significant associations between key biomarkers in both the NPF and SM groups after 16 weeks. In the NPF group, strong positive correlations were observed between CRP and IL-6 ($r = 0.782$, $p < 0.001$),

Biomarker	NPF group (n = 72)		SM group (n = 63)		MD (95% CI)	p-value (MD)	SMD (95% CI)	p-value (SMD)
	Mean	SD	Mean	SD				
CRP	5.89	0.9	15.72	7.47	9.83 (7.97, 11.69)	<0.0001	1.91 (1.5, 2.32)	<0.0001
IL-6	4.91	1.2	8.27	5.73	3.36 (1.92, 4.8)	<0.0001	0.84 (0.49, 1.19)	<0.0001
TNF-alpha	8.88	2.7	28.33	16.3	19.45 (15.38, 23.52)	<0.0001	1.72 (1.33, 2.12)	<0.0001
MMP-2	101.45	12.45	275.5	64.28	174.05 (157.92, 190.18)	<0.0001	3.88 (3.31, 4.46)	<0.0001
MMP-9	148.41	23.65	221.4	117.08	72.99 (43.57, 102.41)	<0.0001	0.89 (0.54, 1.25)	<0.0001
MDA	2.41	1.01	7.32	2.92	4.91 (4.15, 5.67)	0.0042	2.31 (1.87, 2.75)	0.0002
BDNF	21.28	2.4	15.21	4.76	−6.07 (−7.37, −4.77)	0.339	−1.64 (−2.03, −1.25)	0.0004
NGF	36.45	6.7	15.24	9.78	−21.21 (−24.08, −18.34)	0.1423	−2.56 (−3.02, −2.11)	0.0006
Sub. P	14.45	7.2	22.32	10.98	7.87 (4.69, 11.05)	0.1278	0.86 (0.51, 1.21)	0.0025
GFAP	9.87	2.9	15.04	9.15	5.17 (2.81, 7.53)	0.4808	0.78 (0.43, 1.13)	0.0013

Table 5.
Comparative study of mean difference, standardized mean difference, and their 95% CI and p-values between NPF group and SM group at 16 weeks.

CRP and TNF-α ($r = 0.762$, $p < 0.001$), and CRP and MMP-9 ($r = 0.722$, $p < 0.001$). Negative correlations were noted between CRP and BDNF ($r = -0.533$, $p < 0.001$) and CRP and NGF ($r = -0.437$, $p < 0.001$).

Similarly, in the SM group, significant correlations were found, particularly between IL-6 and TNF-α ($r = 0.994$, $p < 0.0001$) and IL-6 and MMP-9 ($r = 0.992$, $p < 0.0001$). The SM group also exhibited strong negative correlations between CRP and BDNF ($r = -0.378$, $p < 0.0001$) and between IL-6 and BDNF ($r = -0.367$, $p < 0.0001$).

Additionally, markers like MDA, which were significantly correlated with MMP-9 ($r = 0.764$, $p < 0.001$) and IL-6 ($r = 0.811$, $p < 0.001$) in the NPF group, showed weaker associations in the SM group ($r = 0.235$, $p = 0.0074$ and $r = 0.258$, $p = 0.0034$, respectively).

These findings highlight the differential biomarker interactions in the two treatment groups and underscore the importance of these biomarkers in the context of neuropathic pain (see **Table 6).**

Biomarker pair	**NPF group (n = 72)**		**SM group (n = 63)**	
	Pearson's r	**p-value**	**Pearson's r**	**p-value**
CRP and IL-6	0.782	<0.001	0.683	<0.0001
CRP and TNF-alpha	0.762	<0.001	0.681	<0.0001
CRP and MMP-2	0.758	<0.001	0.488	<0.0001
CRP and MMP-9	0.722	<0.001	0.782	<0.0001
CRP and MDA	0.719	<0.001	0.246	0.0051
CRP and BDNF	−0.533	<0.001	−0.378	<0.0001
CRP and NGF	−0.437	<0.001	0.698	<0.0001
CRP and Sub. P	0.761	<0.001	−0.43	<0.0001
CRP and GFAP	0.489	<0.001	0.542	<0.0001
IL-6 and TNF-alpha	0.876	<0.001	0.994	<0.0001
IL-6 and MMP-2	0.748	<0.001	0.496	<0.0001
IL-6 and MMP-9	0.802	<0.001	0.992	<0.0001
IL-6 and MDA	0.811	<0.001	0.258	0.0034
IL-6 and BDNF	−0.646	<0.001	−0.367	<0.0001
IL-6 and NGF	−0.447	<0.001	0.982	<0.0001
IL-6 and Sub. P	0.733	<0.001	−0.433	<0.0001
IL-6 and GFAP	0.513	<0.001	0.545	<0.0001
TNF-alpha and MMP-2	0.706	<0.001	0.48	<0.0001
TNF-alpha and MMP-9	0.742	<0.001	0.544	<0.0001
TNF-alpha and MDA	0.753	<0.001	0.258	0.0033
TNF-alpha and BDNF	−0.618	<0.001	−0.36	<0.0001
TNF-alpha and NGF	−0.486	<0.001	0.612	<0.0001
TNF-alpha and Sub. P	0.699	<0.001	−0.431	<0.0001
TNF-alpha and GFAP	0.518	<0.001	0.942	<0.0001

Biomarker pair	NPF group (n = 72)		SM group (n = 63)	
	Pearson's r	p-value	Pearson's r	p-value
MMP-2 and MMP-9	0.761	<0.001	0.479	<0.0001
MMP-2 and MDA	0.69	<0.001	0.165	0.0704
MMP-2 and BDNF	−0.523	<0.001	−0.027	0.826
MMP-2 and NGF	−0.415	<0.001	0.487	<0.0001
MMP-2 and Sub. P	0.657	<0.001	0.077	0.467
MMP-2 and GFAP	0.466	<0.001	0.32	<0.0001
MMP-9 and MDA	0.764	<0.001	0.235	0.0074
MMP-9 and BDNF	−0.621	<0.001	−0.387	<0.0001
MMP-9 and NGF	−0.458	<0.001	0.555	<0.0001
MMP-9 and Sub. P	0.711	<0.001	−0.426	<0.0001
MMP-9 and GFAP	0.487	<0.001	0.944	<0.0001
MDA and BDNF	−0.566	<0.001	0.111	0.3007
MDA and NGF	−0.408	<0.001	0.234	0.0077
MDA and Sub. P	0.692	<0.001	0.148	0.102
MDA and GFAP	0.445	<0.001	0.07	0.5104
BDNF and NGF	0.294	0.019	−0.353	<0.0001
BDNF and Sub. P	−0.567	<0.001	0.169	0.062
BDNF and GFAP	−0.583	<0.001	−0.245	0.0052
NGF and Sub. P	0.364	0.001	−0.437	<0.0001
NGF and GFAP	0.361	0.001	0.741	<0.0001
Sub. P and GFAP	0.436	<0.001	−0.453	<0.0001

Table 6.
The Pearson correlation coefficients and p-values for each pair of biomarkers of NPF group (n = 72) and SM group (n = 63) at 16 weeks.

3.8 Bioactive compounds and biomarker modulation in NPF formulation

The analysis of bioactive compounds and their associated biomarker modulation reveals a comprehensive approach to managing neuropathic and muscular pain through the NPF formulation. The key bioactive ingredients, including clove oil, lavender oil, eucalyptus oil, ginger oil, and others, were assessed for their impact on various biomarkers such as CRP, IL-6, TNF-α, MMP-9, MMP-2, MDA, BDNF, NGF, substance P, and GFAP.

Each bioactive compound targets specific biomarkers through distinct receptors and mechanisms. For instance, eugenol in clove oil modulates inflammatory markers like CRP, IL-6, and TNF-α by inhibiting the TLR4 and NF-kB pathways. Similarly, linalool in lavender oil exhibits antioxidant activity, reducing oxidative stress and promoting neurogenesis by interacting with TrkB receptors.

The modulation of these biomarkers by various bioactive compounds demonstrates the potential efficacy of the NPF formulation in addressing the multifaceted nature of neuropathic and muscular pain. This table encapsulates the interplay between these compounds and biomarkers, providing insight into their therapeutic roles (see **Table 7**).

Ingredient	Bioactive compounds	Target biomarkers	Receptors/Mechanisms
Clove oil	Eugenol	CRP, IL-6, TNF-alpha	TLR4, NF-kB pathway, COX-2 inhibition
		MMP-9, MMP-2	MMP inhibition, ECM remodeling
		MDA	Antioxidant activity, lipid peroxidation reduction
		BDNF, NGF	TrkB receptors, neuroprotective pathways
		Substance P	NK1 receptor modulation
		GFAP	Glial cell activation pathways
Lavender oil	Linalool, linalyl acetate	CRP, IL-6, TNF-alpha	TLR2, NF-kB pathway, COX-2 inhibition
		MMP-9, MMP-2	MMP inhibition, tissue repair
		MDA	Antioxidant activity, oxidative stress reduction
		BDNF, NGF	TrkB receptors, neurogenesis
		Substance P	NK1 receptor modulation
		GFAP	Glial cell response modulation
Eucalyptus oil	Eucalyptol (1,8-cineole)	CRP, IL-6, TNF-alpha	TLR4, NF-kB pathway, COX-2 inhibition
		MMP-9, MMP-2	MMP modulation, ECM remodeling
		MDA	Antioxidant effects, lipid peroxidation reduction
		BDNF, NGF	TrkB receptors, neuroprotective effects
		Substance P	NK1 receptor modulation
		GFAP	Glial cell activity modulation
Ginger oil	Gingerol	CRP, IL-6, TNF-alpha	TLR4, NF-kB pathway, COX-2 inhibition
		MMP-9, MMP-2	MMP inhibition, tissue repair
		MDA	Antioxidant activity, oxidative stress reduction
		BDNF, NGF	TrkB receptors, neurogenesis
		Substance P	NK1 receptor modulation
		GFAP	Glial cell activation pathways
Peppermint oil	Menthol, menthone	CRP, IL-6, TNF-α	TLR4, NF-kB pathway, COX-2 inhibition
		MMP-9, MMP-2	MMP modulation, ECM remodeling
		MDA	Antioxidant effects, lipid peroxidation reduction
		BDNF, NGF	TrkB receptors, neuroprotective pathways
		Substance P	NK1 receptor modulation
		GFAP	Glial cell response modulation

Ingredient	Bioactive compounds	Target biomarkers	Receptors/Mechanisms
Wintergreen oil	Methyl salicylate	CRP, IL-6, TNF-α	TLR4, NF-kB pathway, COX-2 inhibition
		MMP-9, MMP-2	MMP inhibition, tissue repair
		MDA	Antioxidant effects, lipid peroxidation reduction
		BDNF, NGF	TrkB receptors, neuroprotective effects
		Substance P	NK1 receptor modulation
		GFAP	Glial cell activation pathways
Pine oil	α-pinene, β-pinene	CRP, IL-6, TNF-α	TLR4, NF-kB pathway, COX-2 inhibition
		MMP-9, MMP-2	MMP modulation, ECM remodeling
		MDA	Antioxidant activity, oxidative stress reduction
		BDNF, NGF	TrkB receptors, neuroprotective pathways
		Substance P	NK1 receptor modulation
		GFAP	Glial cell response modulation
Malkangni oil	Celastrol, celastrine	CRP, IL-6, TNF-α	TLR4, NF-kB pathway, COX-2 inhibition
		MMP-9, MMP-2	MMP modulation, tissue repair
		MDA	Antioxidant effects, oxidative stress reduction
		BDNF, NGF	TrkB receptors, neurogenesis
		Substance P	NK1 receptor modulation
		GFAP	Glial cell activation pathways
Aloe vera extract	Aloectin, acemannan	CRP, IL-6, TNF-α	TLR4, NF-kB pathway, COX-2 inhibition
		MMP-9, MMP-2	MMP modulation, ECM remodeling
		MDA	Antioxidant effects, lipid peroxidation reduction
		BDNF, NGF	TrkB receptors, neuroprotective effects
		Substance P	NK1 receptor modulation
		GFAP	Glial cell response modulation
Coconut oil	Lauric acid, capric acid	CRP, IL-6, TNF-α	TLR4, NF-kB pathway, COX-2 inhibition
		MMP-9, MMP-2	MMP modulation, ECM remodeling
		MDA	Antioxidant effects, lipid peroxidation reduction
		BDNF, NGF	TrkB receptors, neuroprotective effects
		Substance P	NK1 receptor modulation
		GFAP	Glial cell response modulation
Wheat germ oil	Tocopherols, squalene	CRP, IL-6, TNF-α	TLR4, NF-kB pathway, COX-2 inhibition
		MMP-9, MMP-2	MMP modulation, ECM remodeling
		MDA	Antioxidant activity, oxidative stress reduction
		BDNF, NGF	TrkB receptors, neuroprotective effects
		Substance P	NK1 receptor modulation
		GFAP	Glial cell response modulation

Table 7.
Bioactive compounds and biomarker modulation.

Table 8 elaborates on the roles of various bioactive compounds in targeting specific biological risk factors through their synergistic effects on the biomarkers involved in neuropathic pain.

Biomarker	Description	Bioactive compounds of lipophilic botanical extracts
1. Inflammatory and immune response factor:		
CRP	A marker of systemic inflammation	Eugenol, linalool, eucalyptol, gingerol, menthol, methyl salicylate, alpha-pinene, celastrol, aloectin, lauric acid, vitamin E
IL-6	A cytokine involved in inflammation	Eugenol, linalool, eucalyptol, gingerol, menthol, methyl salicylate, alpha-pinene, celastrol, aloectin, lauric acid, vitamin E
TNF-α	A pro-inflammatory cytokine	Eugenol, linalool, eucalyptol, gingerol, menthol, methyl salicylate, alpha-pinene, celastrol, aloectin, lauric acid, vitamin E
2. Tissue repair and remodeling factor:		
MMP-2	Involved in ECM remodeling	Eugenol, linalool, eucalyptol, gingerol, menthol, methyl salicylate, alpha-pinene, celastrol, aloectin, lauric acid, vitamin E
MMP-9	Involved in ECM remodeling	Eugenol, linalool, eucalyptol, gingerol, menthol, methyl salicylate, alpha-pinene, celastrol, aloectin, lauric acid, vitamin E
3. Oxidative damage and cellular stress factors:		
MDA	A marker of lipid peroxidation	Eugenol, linalool, eucalyptol, gingerol, menthol, methyl salicylate, alpha-pinene, celastrol, aloectin, lauric acid, vitamin E
4. Neurotrophic factors:		
BDNF	Supports neuron survival and growth	Eugenol, linalool, eucalyptol, gingerol, menthol, methyl salicylate, alpha-pinene, celastrol, aloectin, lauric acid, vitamin E
NGF	Essential for nerve cell survival and growth	Eugenol, linalool, eucalyptol, gingerol, menthol, methyl salicylate, alpha-pinene, celastrol, aloectin, lauric acid, vitamin E
5. Pain perception and glial cell activation factors:		
Substance P	A neuropeptide involved in pain perception and inflammation	Eugenol, linalool, eucalyptol, gingerol, menthol, methyl salicylate, alpha-pinene, celastrol, aloectin, lauric acid, vitamin E
GFAP	An indicator of glial cell activation	Eugenol, linalool, eucalyptol, gingerol, menthol, methyl salicylate, alpha-pinene, celastrol, aloectin, lauric acid, vitamin E

Eugenol: (clove - Syzygium aromaticum), linalool: (lavender - Lavandula angustifolia), eucalyptol: (eucalyptus - Eucalyptus globulus), gingerol: (ginger - Zingiber officinale), menthol: (peppermint - Mentha piperita), methyl salicylate: (wintergreen - Gaultheria procumbens), α-pinene: (pine - Pinus species), celastrol: (malkangni - Celastrus paniculatus), aloectin: (aloe vera - Aloe barbadensis), lauric acid: (coconut - Cocos nucifera), vitamin E: (wheat germ - Triticum vulgare).

Table 8.
Summary of biomarkers of lipophilic botanical extracts synergistically affecting the biological risk factors of neurological pain.

3.9 Safety and cost evaluation

The safety, tolerability, and comparative cost of using topical NPF-lipophilic phytocomplexes were evaluated. There were no problems with NPF oil and no significant safety problems requiring the suspension of the product or altering compliance to the supplementation plan were observed. The use of other medicines, including physiotherapy, and painkillers, was completely suspended for the subjects in the NPF group compared to subjects in the control group (SM) ($p < 0.05$).

The average management cost was evaluated for the subjects using NPF oil. This cost was defined as an average of 100% (for the 16 weeks of management) including treatment, diagnostic, and loss of working days, and these were reduced to 94% with a range of 78–98 ($p < 0.05$) compared to using the best standard management for neuropathic pain.

4. Discussion

The investigation of the topical formulation NPF underscores its comprehensive approach to managing postoperative neuropathic and muscular pain through a precisely formulated synergy of essential oils and botanical extracts, each selected for its potent bioactive properties. These components target key pain-related biomarkers, central to modulating inflammatory and neurogenic pathways. The efficacy of NPF is demonstrated by its ability to influence biomarkers closely linked to neuropathic and muscular pain, including C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), matrix metalloproteinases (MMP-2 and MMP-9), malondialdehyde (MDA), brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), substance P, and glial fibrillary acidic protein (GFAP), thus providing targeted pain relief in the postoperative context.

4.1 Neuropathic pain scale analysis

A meta-analysis of NPF's effects on the NPS demonstrates significant improvements across all pain descriptors. The results show SMDs that indicate notable reductions in pain intensity (−3.01), sharpness (−3.45), and hot/burning sensations (SMDs ranging from −2.42 to −2.99). All findings showed strong statistical significance (p-values <0.001), with the overall effect size recorded at −2.21. The random effects model further confirmed a significant reduction in pain with an effect size of −2.65 ($p < 0.001$), despite some heterogeneity ($Q = 28.54$, $I^2 = 68.46\%$) (see **Figure 1**).

4.2 Overview of bioactive compounds and their molecular targets

NPF harnesses diverse bioactive compounds from essential oils and botanical extracts, each targeting molecular biomarkers related to inflammation, oxidative stress, tissue repair, and neuroprotection. The formulation's multitargeted approach modulates critical biomarkers like CRP, IL-6, TNF-alpha, MMP-2, MMP-9, and MDA, playing a pivotal role in reducing inflammation and oxidative damage, while promoting neuronal health via modulation of BDNF, NGF, and substance P. These targets are crucial in both the onset and progression of neuropathic and muscular pain.

4.3 Anti-inflammatory effects and cytokine modulation

Bioactive compounds such as eugenol from clove oil, linalool from lavender oil, and eucalyptol from eucalyptus oil demonstrate significant anti-inflammatory properties. These compounds inhibit key pro-inflammatory cytokines, including CRP, IL-6, and TNF-α, by modulating the NF-kB and TLR4 signaling pathways. This reduction in systemic inflammation is particularly critical in mitigating chronic pain conditions [32].

4.4 Matrix metalloproteinases (MMPs) inhibition and tissue repair

Key components like gingerol from ginger oil and methyl salicylate from wintergreen oil inhibit MMP-2 and MMP-9, enzymes critical in the degradation of the extracellular matrix. By inhibiting these MMPs, NPF promotes tissue repair and prevents excessive tissue breakdown, a common issue in chronic inflammation and musculoskeletal disorders [33].

4.5 Antioxidant activity and oxidative stress reduction

Bioactive compounds in pine oil (α-pinene, β-pinene) and coconut oil (lauric acid and capric acid) contribute significant antioxidant properties. These compounds reduce oxidative stress by neutralizing free radicals, as reflected by the decrease in MDA levels, a marker for oxidative damage. This antioxidant activity is crucial for mitigating the oxidative damage linked to chronic pain conditions [34].

4.6 Neuroprotective pathways and pain modulation

The neuroprotective effects of NPF are mediated by compounds like eugenol from clove oil and linalool from lavender oil, which target neurotrophic factors BDNF and NGF. These factors are essential for maintaining neuronal health and modulating pain pathways. Moreover, bioactive compounds like menthol from peppermint oil and celastrol from malkangni oil modulate substance P, further enhancing pain relief and neuroprotection [35].

4.7 Glial cell modulation and neurological impact

Glial fibrillary acidic protein (GFAP), a marker for glial cell activation, is influenced by components like aloe vera extract (aloectin and acemannan) and wheat germ oil (vitamin E). Modulation of GFAP is significant for chronic pain management, as glial cell activation is associated with persistent pain states [36].

Recent research underscores the critical involvement of inflammatory biomarkers such as CRP, IL-6, and TNF-α in NP. Elevated levels of these biomarkers in NP patients reflect their significant roles in neuroinflammation and central sensitization. Notably, studies by Tuttle et al. [37] and Ramer et al. [38] highlight IL-6 as a pivotal player in both peripheral and central mechanisms of NP. Inhibition of IL-6 has been shown to reduce pain symptoms in animal models, positioning it as a potential therapeutic target. Similarly, TNF-α is known to amplify inflammatory responses in chronic pain conditions such as diabetic neuropathy and chemotherapy-induced peripheral neuropathy, further solidifying its role in exacerbating NP.

In the context of oxidative stress, MDA has been closely linked to neuronal damage and the chronicity of NP. Uceyler et al. [39] identified this connection, reinforcing the understanding that oxidative stress contributes to the persistence of neuropathic conditions. Neurotrophic factors, particularly BDNF, are equally important in regulating pain responses. Obata and Noguchi [40] demonstrated that BDNF plays a crucial role in chronic pain and neuronal plasticity, making it an attractive target for novel therapies aimed at mitigating pain-related neuroplastic changes.

Glial cell activation is another key contributor to the progression of acute pain to chronic NP. Ji et al. [41] conceptualized NP as a "gliopathy," wherein microglia and astrocytes, once activated, release pro-inflammatory cytokines like TNF-α and IL-1β, sustaining the pain state through central sensitization. This cellular activation amplifies neuroinflammatory responses, driving the chronicity of NP.

Moreover, the neuropeptide substance P (SP) has been shown to play a significant role in amplifying pain signaling pathways, particularly through its interaction with neurokinin 1 (NK1) receptors. Xu et al. [42] detailed how SP facilitates synaptic transmission, contributing to neuroplastic changes such as sprouting and dendritic spine alterations, which are critical for the persistence of NP. The maladaptive responses driven by SP underscore its importance in pain modulation, particularly after nerve or tissue injury.

Overall, the interplay among inflammatory biomarkers, oxidative stress, neurotrophic factors, and glial activation offers a comprehensive view of the molecular mechanisms underlying NP. This multifaceted understanding provides a foundation for developing innovative therapeutic strategies that target these molecular pathways, potentially improving pain management outcomes.

Table 4 and **Figure 2** detail the ROC curve analysis, showing high diagnostic sensitivity for biomarkers such as substance P and MDA. **Figure 3** highlights significant reductions in inflammatory and oxidative stress markers, while **Figure 4** demonstrates superior pain alleviation with NPF compared to standard management. **Table 5** and **Table 6** provide detailed insights into biomarker differences and correlations, underscoring the formulation's impact on inflammatory and neurotrophic factors.

4.8 Broader implications and clinical relevance

The comprehensive bioactive profile of NPF suggests its potential utility beyond pain management. By modulating neurotransmitters and supporting neuroprotective pathways, the formulation may also benefit cognitive function and mood stabilization, addressing broader aspects of patient well-being. Botanical extracts such as *Syzygium aromaticum* (clove), *Lavandula angustifolia* (lavender), *Eucalyptus globulus* (eucalyptus), and *Zingiber officinale* (ginger) contribute to its anti-inflammatory, analgesic, and antioxidant properties, enhancing overall efficacy.

4.9 Study limitations and future directions

While the findings are promising, this study has some limitations, notably the duration of the trial and the patient population sample size. Future studies should focus on larger, more diverse populations, with longer follow-up periods to fully validate the efficacy and long-term benefits of NPF.

5. Conclusion

NPF presents a promising and innovative therapeutic strategy for the management of neuropathic pain, addressing both symptomatic relief and the underlying pathophysiological mechanisms. Through the targeted modulation of critical biomarkers—including nociceptive receptors, pro-inflammatory cytokines, oxidative stress indicators, and neurotrophic factors—NPF emerges as a potential adjunct or alternative to conventional pain management therapies, with particular relevance for addressing postoperative complications. Preliminary findings are optimistic, but additional clinical trials and research must validate its efficacy and define its place within standard pain management protocols. Its potential to improve the quality of life, especially for patients suffering from postoperative pain, warrants further exploration.

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Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper. Ganguly Apurba and Ganguly Anondeep are affiliated with Nano Phyto Care Pvt. Ltd., which produces *NeuraPan Flex*®. This affiliation did not influence the design, data collection, analysis, or interpretation of the study outcomes.

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Chapter 5

Social Pain and Opioid Misuse: A Synergistic Epidemic (Syndemic)

Brandon M. Brooks, Bradley M. Brooks, Malachi I. Brown, Valentina Clinton, Francisco J. Cordero and Michelle L. Butterworth

Abstract

Social pain is the metaphorical equivalent of physical pain triggered by thought, emotion, interpersonal problems, and expectations. The consensus on the role of social pain in understanding and managing opioid misuse is yet to be reached, although social pain is generally recognized as a potentiator of physical pain. The purpose of this systematic review was to evaluate the use of social pain indicators in opioid risk assessment tools. Opioid risk assessment tools are commonly used for patients with chronic pain but also should be considered for acute pain, particularly in patients undergoing surgery who have established pain management concerns. Integrating social pain into opioid assessment tools is a necessary step towards comprehensive pain management. Further identification of reliable social pain predictors will enable policy makers to promote health equity and minimize opioid abuse by developing necessary interventions.

Keywords: emotional distress, social pain, substance use disorder, surgery, opioid misuse, opioid risk tool, rejection

1. Introduction

The North American opioid epidemic, characterized by misuse and overdose deaths linked partly or directly to opioids in the last three decades, has had substantial medical, economic and social implications. From the early 1990s to 2020, over 500,000 drug overdose deaths were directly linked to medical prescriptions and illicit opioids [1, 2]. In 2019, an estimated 125,000 Americans overdosed on opioids [3]. Notably, most patients prescribed opioids report that they follow their prescriptions faithfully, yet the incidences of non-fatal overdoses are even more common than overdoses that result in death [3]. According to WHO in 2023, the opioid crisis has become more pronounced in recent years due to increased availability of prescription opioids used in chronic pain management and increased accessibility of highly potent illicit opiates [3]. Opioid tolerance requires patients to consume stronger opioids to achieve the same level of analgesia and opioid euphoria; as such, prescription opioid misuse can turn to potent and illicit opioid abuse (i.e., Fentanyl). Fentanyl is a

potent-synthetic opioid that is approximately 100 times more potent than morphine as an analgesic; Fentanyl and other potent opioids carry a higher risk for opioid overdose and death, especially if misused or abused.

Chronic pain (CP) patients are at an increased risk for opioid abuse and misuse [4]. Numerous factors determine the level of vulnerability for or resilience against such behavior among the patients [5]. Notably, there exists social risk factors which can complicate treatment outcomes [6]. In response to high incidences of misuse and abuse of opioid prescriptions, several recommendations and guidelines for pain management using opioid drugs have been established [3, 5]. These recommendations cover treatment initiation, continued use, risk assessment, dosage, monitoring and discontinuation [7–11]. Additionally, such guidelines stipulate the protocol for assessing patients' risk factors and strategies for managing such risk [3]. The administration of urine drug screen (UDS) is recommended to follow-up on medication compliance [12, 13]. Furthermore, these tests facilitate verification of self-reported prescription compliance, thus allowing appropriate adjusts of the treatment plan to be accordingly, and, ultimately, the results obtained from UDS are used to determine continuation of treatment [13].

The opioid crisis is notably more pronounced in rural areas plagued by income inequality and that are underserved medically [14]. According to Kariisa et al., inadequate accessibility to healthcare accounts for the disparity in death rates between some communities [14]. Case and Deaton posit that opioid deaths are associated with socioeconomic attributes including poverty, income levels, employment status and social capital [15]. As such, more deaths are reported among the poor, socially isolated, unemployed, uninsured, and the medically underserved [15]. An underlying common factor linking the various aforementioned social determinants of health is social pain. Social pain is the metaphorical equivalent of physical pain triggered by thought, emotion, and interpersonal problems [16]. The rise of social pain has functioned as fuel to the fire of opioid misuse, forming a synergistic epidemic (also called a syndemic).

Owing to the complexity of social pain, which can potentiate physical pain, and the accompanying challenges of accounting and adjusting for various relevant factors, a multidisciplinary approach was called for in the development of opioid risk assessment tools [17–24]. These tools would enable the prompt identification of those at risk of opioid aberrancy. The development of these tools was one among many strategies created by healthcare stakeholders to combat the opioid crisis. One notable campaign is the Overdose Data to Action (OD2A) aimed at surveillance and prevention efforts including improving prescription drug monitoring programs and improving access to care for those at risk for opioid overdose [1]. However, social pain is not explicitly coded within the risk assessment tools designed to identify individuals at risk for opioid use disorder (OUD) [23, 25–29]. As such, the role of social pain and the integration of social pain indicators into opioid risk assessment tools remains inadequately researched [23, 25–29].

Understanding and incorporating social pain indicators could potentially enhance the predictive accuracy and clinical utility of these tools; social pain in many cases can serve as an unrealized confounder and patient risk factor that goes unaddressed. The concept for social pain and its indicators should guide the personalization of pain management strategies while addressing the root causes of opioid misuse, thus improving patient care and outcomes [9, 30–32]. It is the intent of this review to realize collaboration at local, national, and global levels to develop and retain the capacity of health providers to identify data needs, collect, and synthesize useful

data, and use that data for health decision-making in pain management with opioids. Thus, this systematic review sought to describe and examine the social pain indicators used in existing opioid risk assessment tools.

2. Methods

This systematic review was conducted based on the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [33]. This study also adhered to the methodological guidelines set out by the JBI (Joanna Briggs Institute) for systematic extraction, synthesis, and presentation of results in systematic reviews.

2.1 Searches

A comprehensive search was conducted across two electronic databases (Medline via PubMed and Google Scholar) in April 2024. The utilized search strategy was designed to retrieve literature relevant to a prespecified inclusion and exclusion criteria. Notably, the strategy included citation searching and reference list checking. To guarantee repeatability and reproducibility, the search strategy utilized Medical Subject Headings (MeSH) and keywords including opioid/adverse effects, drug overdose, opiate overdose, prescription drug misuse, aberrant drug behavior, chronic pain, social distress/social pain, and emotional distress. The titles and abstracts of identified articles were screened for eligibility and relevance using the predefined criteria. Titles of the articles were imported into a reference management software (Zotero, Version 6.0.36; Digital Scholar) to identify and remove duplicates.

2.2 Data extraction (selection and coding)

The articles to be included had to meet the following requirements: (1) case-control studies, cross-sectional studies, and qualitative research, (2) in English, (3) published up to April 2024, and (4) evaluated opioid risk assessment tools. The included studies also reported on opioid risk assessment tools with any social pain indicator. More importantly, the studies had to report on validated assessment tools. Exclusion criteria were studies not published in English, studies lacking clearly defined metrics for the utility of assessment tools, as well as editorials, conference summaries, opinion articles, and clinical case series. To ensure a rigorous selection process, the screening of the titles and abstracts of the studies identified in the preliminary search was conducted based on objective relevance to the research question and the scope of the study. After excluding duplicates, the selected full texts were assessed against the inclusion and exclusion criteria (**Figure 1**).

Data extraction was performed using a standardized data extraction form. The extracted data included the authors' names, year of publication, study design, population characteristics, opioid assessment tool(s), social pain descriptive terms, and results (impact of social pain coding). The studies included are listed in **Tables A1** and **A2** (see Appendix).

2.3 Quality assessment

The risk of bias for all full texts was assessed by the Newcastle-Ottawa Scale (NOS) and objective score was assigned based on methodological quality (**Table A2**). The

quality assessment parameters analyzed include selection, comparability of groups, and outcome assessment. The risk of bias was indicated as low, high, or unclear according to the performance in each item of the assessment tool.

3. Results

The initial database search yielded a total of 212 articles. After removing duplicates, 198 unique records remained (**Figure 1**). The extracted data from the 39 included studies are described in **Tables A1** and **A2**.

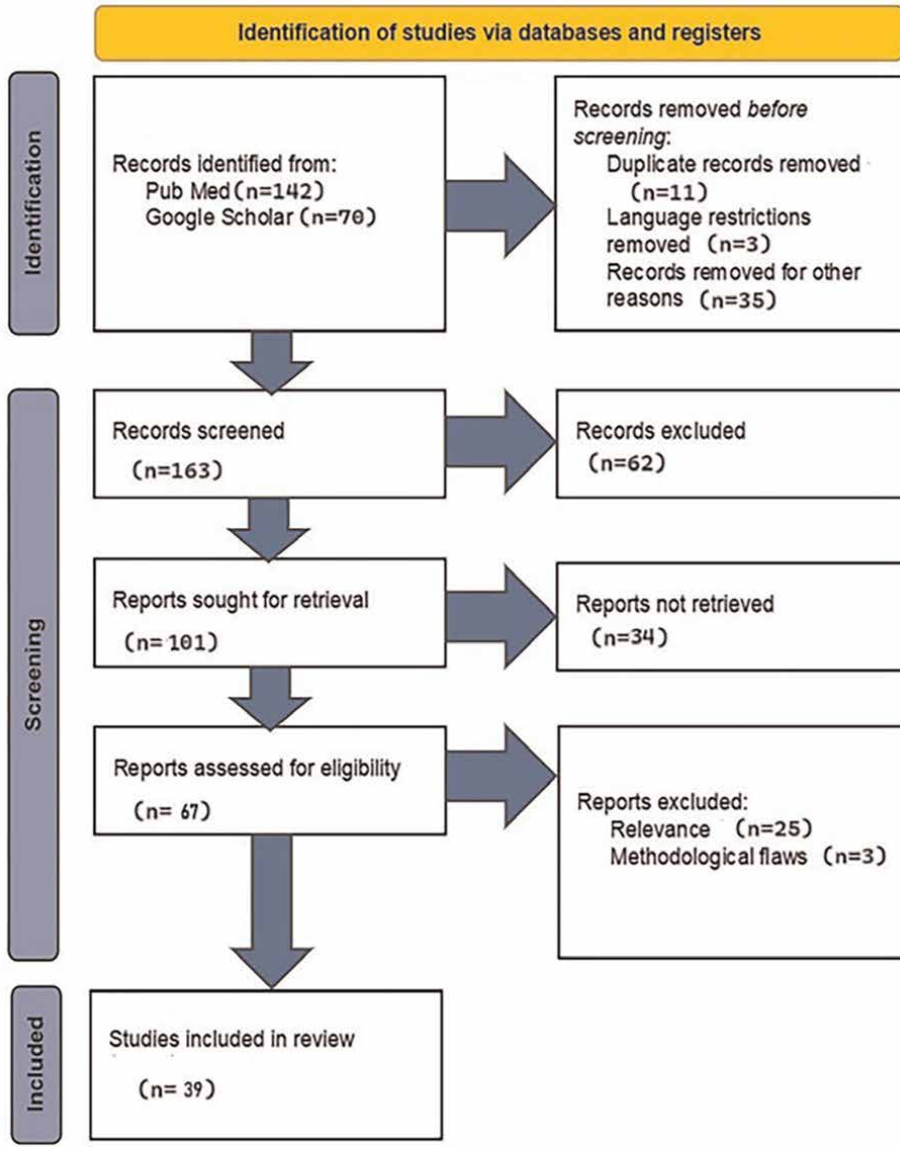

Figure 1.
PRISMA flow diagram.

3.1 Systematic review study characteristics

In the 39 studies, the three tools mostly reported are Pain Medication Questionnaire (PMQ), Current Opioid Misuse Measure (COMM), and Screener and Opioid Assessment for Patients with Pain (SOAPP-R). The other reviewed tools included: Prescription Opioid Misuse Index, the Opioid Risk Tool (ORT), Self-Reported Misuse, Abuse, and Diversion (SR-MAD), Generalized Anxiety Disorder Scale (GAD-7), National Institutes of Health's Patient-Reported Outcomes Measurement Information System (PROMIS), Center for Epidemiological Studies-Depression Scale (CES-D), GenORs, DIRE, screening tool for addiction risk (STAR), Opioid Compliance Checklist (OCC), Prescription Drug Use Questionnaire (PDUQ), Pain Assessment and Documentation Tool (PADT), ICD-10 and DSM-IV-TR definitions. The following terms were the most used to evaluate social pain: history of drug abuse, employment status, legal problems, depression, history of emotional or physical abuse, family history of substance abuse, mood disorders, and anxiety.

According to Adams et al. variables including sex, age, litigation status, and pain duration have no observable influence on risk of opioids misuse [34]. On the contrary, Bright et al. reports that from 180 genetic markers tested based on previous citations, ten unique single-nucleotide polymorphisms (SNPs) in females and nine unique SNPs in males were identified which had predictive utility for opioid addiction [22]. As such, Bright et al. suggest that their logistic regression analyses reveal a relationship between sex and risk of opioids abuse [22]. Consequently, programs for managing opioid use disorder through personalization of pain interventions based on addiction risk have been initiated [66–68]. Nevertheless, available risk assessment algorithms based on genetic markers predicting opioid use disorder (OUD) are still being investigated for clinical implementation [69, 70]. These SNPs are based on the differing opioid metabolism and drug reward pathways specific to each sex [22]. Notably, the development of a sex-based genetic opioid misuse risk score gives credence to a prior assertion by Jamison et al., displaying that women tend to score higher on metrics relating to psychological distress, while the male patients score higher in legal and behavioral problems [21]. Regardless, the observation by Jamison et al. underscores the problems presented by social pain in the management of chronic pain [21]. Buelow et al. reports that incidences of physical distress and impairment are pronounced among patients who scored higher on the PMQ, or at higher risk for medication misuse [37]. Furthermore, patients that are on either extreme of the L-PMQ or H-PMQ scores differed significantly in the variables including history of alcohol abuse and history of rehab for drugs [37]. Both these variables represent the incorporation of social pain in assessments for pain medication abuse.

According to Butler et al., the COMM offers a reliable measure of potential risks of pain medication administration [38]. The tool demonstrates its utility in availing vital information to a pain management specialist during a follow-up evaluation [38]. Particularly, the COMM tool allows for the assessment of opioid misuse risk profile of social pain coded as mood disorders, thus guiding clinical practice of pain management [38]. Importantly, Butler et al. reports that the SOAPP-R may be a better screening tool than other measures, thus allowing opioids administrators to confidently determine the level of monitoring appropriate for each patient enrolled in long-term opioid therapy [39]. However, based on the self-report attribute of SOAPP-R scores, practitioners need to contextualize the results obtained using historical data and guidance provided by specialties including psychiatrists [39]. Notably, the combination of the COMM and SOAPP-R have demonstrated better performance for the prediction of future problems associated with the use of prescription opioids for pain.

According to Butler et al., COMM investigates the changes in patient status through the course of pain intervention thus allowing for observations including alcohol or drug use and emotional problems [40]. The latter is observed through reports of anger, suicidal concerns, and emerging family or marital problems [40]. Furthermore, the routine administration of the tool allows for assessment of changes in patient quality of life through the treatment period [40].

Coloma-Carmona and Luis Carballo investigated measurement invariance of the POMI between male and female patients [43]. However, when adjusting the parameters for sex, none of the six items of the scale revealed any opioid misuse discrepancies in males and females [43]. As such, the POMI demonstrates utility for daily clinical practice as it allows for the monitoring of opioid use without discriminating between male and female patients [43]. Feingold et al. investigated the relationship between socio-demographic data, including sex, employment status, eligibility for disability allowance, marital status and number of children to predict the opioid misuse [45]. Of note, another proxy for social pain, co-occurring depression was also considered [45]. Holliday et al. reports that the implementation of requirements for addiction management by national health authorities might improve both the management of pain and opioid dependency [48]. In agreement, Jamison et al. determined that accounting for comorbid affective disorder may alleviate substance abuse behaviors, particularly in patients self-managing psychiatric symptoms [53]. Jamison et al. further reported that patients with mood disorders are at increased risk for substance abuse [53]. Thus, patients should be screened for mood swings, anxiety, and depression symptoms prior to surgery and after surgery if patients are consuming excess quantities of opioids. This patient population may be at risk to consume greater than average postoperative opioids. Varney et al. acknowledged the intricacies of patients' opioid use behavior while admitting the utility of SOAPP-R and COMM self-assessment tools to assess both potential and current aberrant opioid behavior [63]. Nevertheless, the application of recommendations by Gestalt, SOAPP-R, and COMM present a more comprehensive basis for pain management using opioids than any single instrument. High PMQ scores are associated with significant physical impairment and psychosocial distress [49]. Another study underscored the need to promptly identify social pain predictors as a pre-treatment step in the management of pain [60]. Notably, a study reported that marijuana use might incorrectly categorize users into the high-risk category, yet the underlying problem is a mood disorder; such patients may be excluded from opioid pain treatments [64]. Akbik et al. reiterated that men are at higher risk of prescription misuse than women [35]. Surprisingly, geriatric patients in a community dwelling had low risk for prescription misuse [59]. Friedman et al. reported that patients with previous SUD were more likely to be addicted to prescription medication [46]. So, what can be done? Opioid stewardship programs (OSPs) can address social pain and ultimately provide a holistic, efficient, and comprehensive means of guiding safe opioid prescribing within a health system; these programs can provide additional support to clinicians including guidelines, non-opioid alternatives, and screening recommendations [71]. Further, the ORT is a risk mitigation strategy that should be used with UDS and physical exams to improve the detection of opioid misuse and abuse. Ducharme and Moore state that opioid risk assessment tools cannot be used independently of other mitigation strategies [72].

3.2 Discussion

The following terms were the most used to evaluate social pain: alcohol intake, history of drug abuse, employment status, legal problems, depression, history of

emotional or physical abuse, family history of substance abuse, mood disorders, and anxiety. The findings suggest that including social pain indicators into opioid risk assessment tools enhanced the predictive accuracy for identifying individuals at high risk for opioid misuse and overdose [22, 34]. The integration of social pain indicators into opioid risk assessment tools may improve their predictive accuracy. Social pain provides additional context that traditional assessments are prone to overlook, thus allowing for a more nuanced understanding of the individual's risk profile, leading to more precise and effective interventions. The evidence suggests that addressing social pain can mitigate some of the psychological triggers that contribute to opioid misuse, thereby reducing the likelihood of overdose and other adverse outcomes [16, 18–20, 73]. As such, considering social pain provides an opportunity to address the risk of opioid use disorders among chronic pain patients.

Neuroscientific studies have shown that social pain activates similar brain regions as physical pain, underscoring its profound impact on individuals' mental health and behavior [17, 18, 20, 74]. The distress caused by social pain can lead individuals to seek relief through various means, including substance use, thus contributing to the risk and severity of OUD [20, 73, 75]. The concept of social pain—emotional distress stemming from experiences of social rejection, isolation, or loss—has been overlooked for its potential impact on opioid misuse behaviors [18, 20, 42]. Individuals experiencing social pain may turn to opioids for relief, as these substances can temporarily alleviate emotional and social distress [39–42, 64, 76, 77]. Studies have suggested that social affiliation has an impact on health, thus with better integration comes similar health outcomes [22, 37, 38].

Individuals in socially stressful environments may have higher rates of opioid misuse due to the compounded stress and lack of social support [78]. As such, social distress for many patients experiencing problems within their social environment is one of the main predictors of opioid misuse [76, 79]. Notably, there are several comorbidities that further complicate the matter including anxiety disorders, and mood disorders. Coincidentally, most of patients with any social pain are usually diagnosed with substance use disorder [76, 77, 80, 81]. Importantly, individuals with social pain tend to self-medicate, especially if they are undiagnosed or untreated; this can lead to an increased risk for the development of alcoholism or other kinds of substance abuse [81].

It is worth noting that social pain is a common occurrence within societies and usually necessary for effective social functioning and developmental growth [73, 75]. However, the challenge is encountered in identifying the acceptable levels of such pain [18, 20]. Furthermore, determining the tolerance levels and the accompanying adjustments vary greatly among patients [43]. Typically, patients may be promptly diagnosed with social pain if the determinants are easily observable or extreme as in the case of childhood abuse [82]. Notably, maladaptive management in the early stages of the disorder may result in persistent maladaptive behavior which increases the risk of SUD [4, 82]. Alarmingly, the number of chronic pain patients is on the rise, thus the incidences of SUD could similarly increase, consequently presenting a worsening problem for society. As such, close monitoring of opioid prescriptions is essential [83].

The criteria used to distinguish between clinical and other forms of social pain include the intensity and level of behavioral and psychosomatic distress experienced and reported or observed. Patients that reported to have significant social pain tend to overestimate their physical pain, akin to pain catastrophizing [47, 48]. Fortunately,

there is evidence supporting the modification of such cognitive biases through therapy interventions such as attention bias modification training. Concerningly, there exist triggers that can initiate unwanted events among chronic pain patients with social pain. Exposure to such triggers could lead the patient to misuse their prescriptions either consciously or otherwise [57, 58, 84]. In the latter case, a vicious cycle is initiated in which further exposure to trigger reinforces prescription misuse behavior [57, 58, 84].

3.3 Lessons from COVID-19 lockdowns in the United States

It is crucial to acknowledge that the coronavirus disease 2019 (COVID-19) pandemic not only revealed weak points in American healthcare's infrastructure and emergency preparedness, but also initiated and exacerbated physical and mental conditions with the nationwide lockdown. In particular, it worsened the United States's current opioid epidemic and contributed "fourth wave" or next iteration of this public health crisis [85, 86]. Along with the stay-at-home order, there came an interruption on what was deemed non-essential services, such as chronic pain management and mental health services [85, 86]. Despite prescribing modification efforts and new pharmacological policies, the US continues to have the world's largest number of opioid-related deaths prior, during, and after the COVID-19 pandemic [85, 86]. According to the National Center for Health Statistics at the CDC in the United States, in 2020, there were approximately 70,000 opioid overdoses (94,000 total drug overdoses) that lead to death and an approximate 15% increase in 2021 where there were approximately 81,000 opioid overdoses (108,000 total drug overdoses) that resulted in death [85, 86].

The disruption of normal societal functions and alterations in the American healthcare system brought about psychosocial impacts such as anxiety, depression, stress, and seclusion [85, 86]. Individuals with an established chronic disease or SUD (or similar), felt these impacts exponentially due to prior traumatic and negative experiences. With the loss of medical and social support and an increase in physical and social pain, there was an inclination to revert to prior drug-participating behavior and seek alternative treatment methods [85, 86]. With delayed or non-existent doctor visits available and little to no follow up, monitoring, or support, the likelihood of these patients obtaining their medications through other routes increased, bringing into question the reliability and potency of said replacement medications [85, 86]. In order to contribute to the resolution of the opioid crisis, there needs to be a greater global understanding of the human need not just for access to health care but also social support and mental well-being. Understanding social pain indicators can be part of the solution.

3.4 Limitations

This study included a wide range of study designs allowing for a detailed evaluation of the clinical implications of incorporating social pain assessment in opioid risk tools. However, the varied study methodologies and measures of social pain may limit the generalizability of the findings. Furthermore, it needs to be acknowledged that the concept of social pain within risk tools has its share of problems. To begin with, the concept of social pain may be easily understandable, but the term itself lacks a

universally accepted definition, hindering its clinical application. Nevertheless, there is sufficient evidence that links underlying social pain to higher incidences of current opioid abuse and increased risk for future abuse. As such, this review sets a milestone in the effort to develop social pain into a sound conceptual basis. Additionally, the opioid crisis, although wide-reaching, remains primarily a North American crisis (specifically the United States and Canada). Consequently, this chapter is largely focused on perspectives and cultural attitudes that are likely more applicable to North America; as such, we believe this to a limitation in terms of perspective.

3.5 Future directions and clinical and policy implications

There is the need to develop and standardize methods for assessing social pain within the context of chronic pain management and postoperative pain. While the findings herein highlight the need for social pain evaluation in opioid risk assessments, there is a need for more longitudinal studies to establish causal relationships and long-term outcomes. Future research should focus on developing standardized social pain metrics that are generalizable. Policymakers should prioritize funding for studies exploring the integration of social pain into clinical practice and its broader public health implications.

Healthcare providers should incorporate social pain metrics into routine opioid risk assessments to enhance predictive accuracy and inform targeted interventions. As such, clinicians need to be trained, starting at the medical school and post-graduate training levels to promptly recognize and address social pain. Additionally, there is need for policies that promote interdisciplinary approaches, involving mental health professionals, social workers, and addiction specialists in the assessment and pain management process.

4. Conclusions

Social pain and opioid misuse have formed a synergistic epidemic (or syndemic) in the United States. Integrating social pain into opioid assessment tools is a necessary step towards comprehensive and personalized pain management. By acknowledging and addressing the multifaceted nature of pain, healthcare providers can improve patient outcomes, reduce the risk of opioid misuse, and enhance the overall quality of life for individuals experiencing pain. The revision and improvement of existing assessment tools, training for healthcare providers, and the implementation of routine social pain assessments are essential strategies for achieving this integration. Future research and policy support will be essential to respond to this urgent public health crisis.

Conflict of interest

The authors declare no conflict of interest.

Appendices

Study	Opioid assessment tool(s)	Social pain coding (descriptive terms used)	Impact of social pain coding (e.g., risk stratification, prescribing decisions)
Adams et al. [34]	Pain Medication Questionnaire (PMQ)	Depression, Abusers of alcohol, Marital status,	Results showed that the H-PMQ group contained significantly more patients who were married (67.7%) or separated/divorced (17.7%), as compared to the L-PMQ group (54.5% and 10.6%, respectively)
Akbik et al. [35]	Screener and Opioid Assessment for Patients with Pain (SOAPP)	history of substance abuse, legal problems, mood swings.	The factor analyses appeared to demonstrate five factors that make up the predominant constructs of the SOAPP. Past studies have supported similar constructs in predicting substance abuse, with particular emphasis on family history of substance abuse and a personal history of aberrant behavior problems
Banta-Green et al. [36]	PDUQ	substance abuse	A reduced set of PDUQ items resulted in a three-factor solution that was deemed a good fit statistically as well as clinically. The first factor identified was labeled Addictive Behaviors and included items such as buying opioids on the street, using for other symptoms and having a history of alcohol abuse.
Bright et al. [22]	GenORs	sex	Logistic regression analyses stratified by sex identified ten unique SNPs in females and nine unique SNPs in males that were significantly associated with OUD.
Buelow et al. [37]	revised Pain Medication Questionnaire (PMQ)	history of drug abuse	A moderate correlation of the PMQ to a measure of physical impairment and distress.
Butler et al. [38]	Current Opioid Misuse Measure (COMM)	stress	The COMM seems to be a reliable and valid screening tool to help detect current aberrant drug-related behavior among chronic pain patients.

Study	Opioid assessment tool(s)	Social pain coding (descriptive terms used)	Impact of social pain coding (e.g., risk stratification, prescribing decisions)
Butler et al. [39]	Screener and Opioid Assessment for Patients with Pain—Revised (SOAPP-R)	Tension at home, social and family factors	The SOAPP-R is found to be a reliable and valid screening tool for risk of aberrant drug-related behavior among chronic pain patients.
Butler et al. [40]	Current Opioid Misuse Measure	emotional problems/ psychiatric issues. Emerging family or marital problems, etc.	The COMM was found to have promise as a brief, self-report measure of current aberrant drug-related behavior
Cheatle, [41]	ICD-10 and DSM-IV-TR definitions	anxiety or depression	Revisions are needed to improve sensitivity and specificity in making a diagnosis of OUD in patients prescribed COT.
Clark et al. [42]	Opioid Risk Tool (ORT)	Insurance, employment, and marital status	The only risk variable associated with aberrant behavior was personal history of prescription drug misuse.
Coloma-Carmona and Luis Carballo, [43]	Prescription Opioid Misuse Index (POMI) in a larger sample of	problems other than pain	POMI is a valid and clinically feasible screening instrument for detecting CNCP patients who misuse opioid medications.
Compton et al. [44]	Prescription Drug Use Questionnaire (PDUQ)	marital status, employment status, usual pain visual analog scale, mood visual analog scale, OWESTRY index, and baseline PDUQ score	Significant correlations were found between the opioid-specific use criterion and the following items: 5 (has tried nonmedication treatments), 8 (receiving pain medications from more than one clinic), 9 (thinking they might be addicted to pain medications), 17 (ever lost pain medications), 18 (needing to go to emergency room for pain medications), and 30 (history of alcohol or drug abuse treatment).
Dunn et al. [4]	Survey	Drug abuse	Nearly one in five patients who have experienced chronic pain for three months or more and are receiving a prescription opioid for pain management report having experienced at least one nonfatal opioid-related overdose during their lifetime.

Study	Opioid assessment tool(s)	Social pain coding (descriptive terms used)	Impact of social pain coding (e.g., risk stratification, prescribing decisions)
Feingold et al. [45]	Generalized anxiety disorder scale (GAD-7) and the Current Opioid Misuse Measure (COMM).	Anxiety	After controlling for sociodemographic variables, patients with anxiety were significantly more prone to screen positive for opioid misuse.
Friedman et al. [46]	screening tool for addiction risk (STAR)	History of emotional or physical abuse, family history of substance abuse, mood disorders, and unemployment.	Psychosocial factors associated with dependence disorders were not different in the two groups of pain patients.
Gilam et al. [47]	National Institutes of Health's Patient-Reported Outcomes Measurement Information System (PROMIS).	anxiety, anger, and/or depression	Most significant predictors of prescribed opioid misuse severity were as follows: anxiety, anger
Holliday et al. [48]	CNMP practice guidelines	Alcohol abuse	Patients frequently present with comorbidities spanning pain and addiction.
Holmes et al. [49]	Pain Medication Questionnaire (PMQ), BDI and the SF-36/MCS	psychosocial distress	One-way ANOVAs were significant for both instruments ($P \leq 0.01$), indicating lower levels of psychosocial distress and depressive symptomatology among those patients in the L-PMQ group.
Ives et al. [50]	Center for Epidemiological Studies-Depression Scale (CES-D)	history of alcohol or cocaine abuse and alcohol or drug related convictions	Race, income, education, depression score, disability score, pain score, and literacy were not associated with misuse. No relationship between pain scores and misuse emerged.
Jamison et al. [51]	SOAPP v.1	Anxiety, Depression	The results showed that although high-risk patients for opioid misuse reported significantly higher levels of disability, and depressed mood at baseline ($P < 0.05$), only pain intensity ratings were found to differentiate groups over time ($P < 0.01$).
Jamison et al. [21]	SOAPP-R, PDUQ, and POTQ	psychological distress, legal and behavioral problems.	Risk factors associated with prescription opioid misuse may differ between men and women.
Jamison et al. [52]	OCC	Active litigation and disability or worker's compensation payments.	No significant differences were found between patients who were followed and those who were not with respect to age, gender, race, or pain site

Study	Opioid assessment tool(s)	Social pain coding (descriptive terms used)	Impact of social pain coding (e.g., risk stratification, prescribing decisions)
			(all Ps > .05). No differences were found between positive and negative DMI groups on age, gender, race, disability status, employment status, anxiety or depression (HADS), pain site, pain duration, pain intensity, and whether or not they were taking short-acting opioids.
Jamison et al. [53]	SOAPP-R	Affective disorders.	There is a strong suggestion that individuals with a mood disorder who self-medicate for negative affect are at increased risk for substance abuse.
Jamison et al. [53]	OCC	illicit substance abuse	The OCC might serve as a useful tool for providers who need to document their patients' continued compliance and appropriate use of opioids for pain.
Jones et al. [24]	SOAPP-R), the Pain Medication Questionnaire, the Opioid Risk Tool, & a clinical interview	Behavioral issues, emotional issues	The results suggest that a clinical interview by an experienced psychologist offers the highest level of risk assessment sensitivity.
Just et al. [54]	COMM	Depression	Co-prevalence of depression is a significant issue and should always be screened for in patients with chronic pain
Knisely et al. [55]	Prescription Opioid Misuse Index (POMI)	upset, problems other than pain, alcohol and illicit drug abuse/dependence, and psychiatric histories	Reported use of medications for psychiatric problems was 70% and 63% by the use and misuse groups, respectively, and mean number of psychiatric problem days in the previous month was 5.9 and 10.5 for the use and misuse group, respectively. Significant group differences were found for family history of drug use (use 45%, misuse 72%, $p < .04$) but not for alcohol use (use 70%, misuse 88%) or psychiatric disorders (use 55%, misuse 61%).
Krebs et al. [56]	guideline-recommended opioid-monitoring processes	documented active alcohol or drug abuse, trauma or arrest	Substance abuse was significantly correlated with

Study	Opioid assessment tool(s)	Social pain coding (descriptive terms used)	Impact of social pain coding (e.g., risk stratification, prescribing decisions)
		related to intoxication, or any +UDS for an illicit drug.	serious aberrant behaviors ($r = 0.47$, $P < 0.001$) but not with minor aberrant behaviors ($r = 0.13$, $P = 0.086$).
McCaffrey et al. [57]	Current Opioid Misuse Measure (COMM)	Anger towards others	Although efforts were made during development of the COMM item pool to craft items that were not obviously measuring aberrant opioid-related behaviors (e.g., abuse), patients (especially patients who are familiar with the COMM or have researched the COMM) may be aware of the instrument's purpose.
Meltzer et al. [58]	Current Opioid Misuse Measure (COMM)	Employment, education, marital status (partnered, divorced, single), health insurance; (2) lifetime post-traumatic stress disorder (PTSD) diagnosis from the CIDI v. 2.1 PTSD module [21]; (3) current Major Depression from the Patient Health Questionnaire (PHQ) for Depression	Participants with PDD were more likely to experience current depression, to smoke, or to have past-year other drug disorder.
Moore et al. [26]	Screener and Opioid Assessment for Patients with Pain (SOAPP), (DIRE), and/or the Opioid Risk Tool (ORT)	Family history of substance use, mood swings, legal problems	The clinical interview and the SOAPP were most effective at predicting risk at baseline.
Park et al. [59]	brief PMQ scale	Anxiety	Failed to meet cutoff at times, I take pain medication when I feel anxious and sad, or when I need help sleeping.
Passik and Kirsh [60]	Pain Assessment and Documentation Tool (PADT)	situational stressors, family dysfunction	the PADT appeared to be a useful tool for clinicians to guide the evaluation of several important outcomes during opioid therapy and provide a simple means of documenting patient care.
Passik and Kirsh [60]	SOAPP, DIRE, and ORT	Social distress/problems	Many tools are intended to characterize the degree of medication misuse or the aberrant behavior that characterizes the patient's opioid use

Study	Opioid assessment tool(s)	Social pain coding (descriptive terms used)	Impact of social pain coding (e.g., risk stratification, prescribing decisions)
Pergolizzi et al. [61]	Literature	Mental health disorders	Compromised mental health may be a risk factor for opioid misuse in chronic opioid patients, and it must be periodically re-evaluated in that anxiety, depression, and other mental comorbidities may occur in chronic pain patients over time, possibly secondary to chronic pain syndromes
Rogers et al. [62]	Current Opioid Misuse Measure (COMM).	psychiatric problems, drug use	Examination of all items suggests that these items generally fall into the concept cluster categories (e.g., emotional problems/ psychiatric issues and aberrant drug behavior) determined in the initial measurement development manuscript.
Varney et al. [63]	SOAPP-R, COMM, and provider gestalt	social functioning, and family history.	A combination of gestalt and self-assessment scores can be used to identify at-risk patients who otherwise miss the cutoff scores for SOAPP-R and COMM.
Wasan et al. [64]	SOAPP, COMM, POTQ, and urine screens	psychosocial stressors	Psychiatric factors, such as a history of mood disorder, psychologic problems, and psychosocial stressors, may place patients at risk for misuse of prescription opioids.
Wu et al. [65]	Addiction Behaviors Checklist (ABC)	Alcohol or illicit substance abuse	The psychometric findings support the ABC as a viable assessment tool that can increase a provider's confidence in determinations of appropriate vs. inappropriate opioid use.

Note: COMM: Current Opioid Misuse Measure; SOAPP-R: Screener and Opioid Assessment for Patients with Pain; PMQ: the Pain Medication Questionnaire; ORT: the Opioid Risk Tool; OCC: Opioid Compliance Checklist; ABC: Addiction Behaviors Checklist; PADT: Pain Assessment and Documentation Tool; GenORS: Genetics Opioid Risk Score; CNMP: Chronic Nonmalignant Pain.

Table A1.
Included studies.

Study	Selection	Comparability	Outcome	Total
Adams et al. [34]	4	2	3	9
Bright et al. [22]	3	2	4	9
Buelow et al. [37]	4	1	3	8
Butler et al. [38]	3	2	4	9
Butler et al. [39]	4	2	3	9
Butler et al. [40]	3	1	4	8
Cheatle [41]	4	2	3	9
Clark et al. [42]	3	2	4	9
Coloma-Carmona and Luis Carballo [43]	4	1	3	8
Dunn et al. [4]	4	2	3	9
Feingold et al. [45]	4	2	3	9
Gilam et al. [47]	3	2	4	9
Holliday et al. [48]	4	1	3	8
Ives et al. [50]	3	2	4	9
Jamison et al. [21]	4	2	3	9
Jamison et al. [51]	3	1	4	8
Jamison et al. [52]	4	2	3	9
Jamison et al. [53]	3	2	4	9
Jones et al. [24]	4	1	3	8
Just et al. [54]	3	2	4	9
Krebs et al. [56]	4	2	3	9
McCaffrey et al. [57]	4	2	3	9
Meltzer et al. [58]	3	2	4	9
Moore et al. [26]	4	1	3	8
Passik and Kirsh [60]	3	2	4	9
Pergolizzi et al. [61]	4	2	3	9
Rogers et al. [62]	3	1	4	8
Varney et al. [63]	4	2	3	9
Wu et al. [65]	3	2	4	9
Knisely et al. [55]	4	1	3	8
Holmes et al. [49]	3	2	4	9
Friedman et al. [46]	4	2	3	9
Jamison et al. [53]	4	2	3	9
Compton et al. [44]	3	2	4	9
Passik and Kirsh [60]	4	1	3	8
Wasan et al. [64]	3	2	4	9
Akbik et al. [35]	4	2	3	9
Banta-Green et al. [36]	3	1	4	8

Study	Selection	Comparability	Outcome	Total
Park et al. [59]	4	2	3	9

Table A2.
Results of quality appraisal on studies using NOS for non-randomized studies.

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Chapter 6

Novel Nonopioid Analgesics for Postoperative Pain

Joseph V. Pergolizzi Jr., Jo Ann LeQuang and Peter Magnusson

Abstract

Pain in the immediate postoperative period is prevalent, can be moderate to severe, and is often inadequately treated. Left untreated, acute postoperative pain can persist and even transition into chronic pain. Heightened scrutiny on the use of opioid analgesics has resulted in limitations in their use, but this should not mean that acute postoperative pain goes untreated. A variety of novel analgesic products have come to market which may be serviceable for many acute pain syndromes. These include transient receptor potential (TRP)-1 antagonists, several types of sodium channel blockers, and a "next-generating opioid" with a dual mechanism of action: cebranopadol. Other drugs in development include a next-generation cyclooxygenase inhibitor (AAT-06) and an experimental drug chemically similar to paracetamol (NTM-006). Nanomedicine can be applied to existing analgesics such as nonsteroidal anti-inflammatory drugs (NSAIDs) to enhance analgesic efficacy. Older drugs, such as ketorolac, can be repurposed for easier and more efficient delivery during the postoperative period (NTM-001). Sublingual ketamine has been utilized in the postoperative setting despite a lack of consensus guidelines on dosing or indications. While ketamine is an older drug, the sublingual formulation is novel and has been used for both analgesia and psychological conditions, such as depression. These agents represent innovative developments and exploration of new pain pathways and delivery mechanisms. More research is needed to develop an even more robust armamentarium against acute postoperative pain.

Keywords: analgetics, non-opioids, pain management, pharmacology, postoperative pain

1. Introduction

Acute postoperative pain is a prevalent and expected condition. Without adequate analgesia, early ambulation, rehabilitation, and recovery may be delayed or adversely impacted. The intensity of acute postsurgical pain correlates with the risk of developing persistent postsurgical pain, a condition that can be challenging to treat effectively because of it often involves a neuropathic component [1]. The role of prompt, effective postsurgical analgesia for managing acute pain plays an important role in the full recovery of the surgical patient [2]. Opioids are effective analgesic agents but are often discouraged in this context because of issues related to opioid-associated side effects, poor tolerability, dependence, and the risk of opioid use disorder [3].

Further, acute postoperative pain control can be particularly complex when the surgical patient already has an active substance use disorder, is on opioid replacement therapy, or may be at high risk of developing substance use disorder [4]. In some parts of the world, opioids may not be available for acute postoperative pain management or may be severely restricted or unavailable altogether [5–7].

Pain following surgical intervention may be affected by patient factors, comorbidities, duration, and type of surgery. For example, approximately half of lung cancer patients undergoing thoracotomy experience persistent postsurgical pain [8]. Pain is usually most severe immediately after surgery and lessens over the ensuing days as tissues and incisions heal. However, like other forms of pain, acute postsurgical pain is multifactorial and exists within a biopsychosocial environment: the patient's expectations, support network, psychological state, attitudes about health and the benefits of this particular surgery, and anxiety may all impact postsurgical pain intensity levels. In some patients, acute postsurgical pain persists; the standard cutoff to define persistent postsurgical pain is 3 months, but this is an arbitrary boundary [9].

Despite numerous and important medical advancements in the past decades, postoperative pain control has improved substantially [10]. The old mainstays of acute postoperative pain care were nonsteroidal anti-inflammatory drugs (NSAIDs) and opioids, with multimodal approaches sometimes used by developing regimens that included adjuvant agents such as gabapentinoids or antidepressants [11]. The focus on opioids as analgesia is scientifically driven because these medications directly target the receptors directly involved in pain processing [12]. The initial challenging tasks in the development of novel postoperative analgesic drugs are followed by rigorous, time-consuming, and expensive regulatory hurdles and then recognition by insurers and payers once the drug has been cleared to market.

Yet great breakthroughs in analgesia and even pain science remain elusive; the "gold standard" blockbuster pain agent has yet to materialize. Nevertheless, worldwide research into safer and more effective pain control is ongoing, bringing innovations in nonopioid analgesics to market [13]. New strategies for drug development include targeting ion channels and specific enzymes and G-protein-coupled receptors (GPCRs).

The future of pain medicine will likely involve improved and highly targeted drug delivery, multimodal approaches to pain management, and personalized medicine whereby the agent is matched to the specific pain type and the needs of the patient.

2. TRPV1 antagonists

Transient receptor potential (TRP) ion channels are sensors for a wide variety of environmental stimuli involved in pain perception and temperature systems; they are expressed in all tissues. TRPV1 is a calcium-permeable channel and has been associated with pain signal processing as well as epilepsy [14]. The 27 different types of TRP channels play a role in a variety of conditions, including acute postsurgical pain and inflammation, but are also involved in chronic pain, hypothermia, and certain cancers [15]. They are signaling molecules with multiple functions in cellular physiology and sensory perception [16]. The 27 TRP ion channels are grouped into 6 categories, of which TRPV (vanilloid) is one of the largest and contains 6 sub-channels.

The TRPV channels are the primary receptors for vanilloids, which are found in a variety of organic substances, including capsaicin [15]. TRPV1 is a non-selective cation channel. The greatest expression of TRPV1 occurs on the small-diameter unmyelinated C-fibers and medium-diameter myelinated A fibers, both of which

help mediate painful stimuli. In a murine study, the deletion of TRPV1 reduces their response to pain when capsaicin is applied. Phosphorylation can limit the range of temperatures to which TRPV1 channels will open. Pro-inflammatory cytokines will reduce the temperature at which TRPV1 will respond, which may increase pain. Thus, the pro-inflammatory mediators that are released with surgical incision may lower TRPV1 thresholds and contribute to pain [15].

Capsaicin is a natural TRVP1 agonist; initial application of this substance inflicts pain and is often accompanied by local analgesia, but repeated administrations of capsaicin stimulate TRPV1 channels and downregulate them so that TRVP1 down-regulation will eventually reduce pain [17]. TRVP1 blockade is known to reduce neuropathic pain, but the mechanism of this analgesia is not known [18].

TRVP1 has anti-inflammatory effects and activation of this channel reduces the release of pro-inflammatory mediators, such as TNF-a. TRVP1 is activated by heat, so fever may cause anti-inflammatory effects from TRVP1 while hypothermia may inactivate the TRVP1 channels [19].

Endogenous TRPV1 agonists are known as endovanillioids and are expressed mainly in the primary sensor neurons in certain parts of the brain [20]. There are two distinct mechanisms for TRPV1 blockade. The first involves the repeated activation of TRPV1 by an agonist until desensitization occurs; the other involves an antagonist drug targeting the TRPV1 receptor [21]. TRVP1 antagonists could be developed as competitive antagonists, binding to the agonist binding site and in that way blocking the TRPV1 channel so that it remained in a closed and non-conducting state, or non-competitive. A noncompetitive antagonist could be considered a pore blocker because it could either block the pore or it could interact with allosteric sites in such a way that the channel could not open.

A number of TRPV1 antagonists have been developed and more are in the pipeline [22]. Some of these novel small-molecule agents have been tested in clinical trials, but potentially serious side effects, including hyperthermia, have caused some of the studies to be terminated [23]. At present, it is not clear whether such adverse events are inherent in TRPV1 antagonism, which is an unavoidable part of such an agent, or whether drug molecules can be developed that retain the analgesic benefit of these agents while avoiding their adverse effects [24]. The newest development in TRPV1 blockade is the formulation of a dual-acting agent that combines a fatty acid amide hydrolase (FAAH) inhibitor and a TRPV1 antagonist. Such a combination product inhibits FAAH and TRPV1 *in vitro* and has been tested in mice, resulting in the drug having analgesic effects without the side effect of hyperthermia [25].

3. Sodium channel blockers

Voltage-gated sodium channels (abbreviated either as VGSC or NaV channels) exist in numerous isoforms, such as NaV 1.8 and NaV 1.9, the functionality of which is still being elucidated. They are transmembrane channel proteins selective to positive sodium ions. Upon cell depolarization, the membranes open to allow an inflow of positive sodium ions into the cell; a process called fast inactivation inactivates the channel, which then closes upon hyperpolarization of the membrane. This rapid influx of sodium contributes to the generation and propagation of the action potential necessary for the transmission of numerous somatosensory signals, including but not limited to pain perception [26]. Thus, sodium channels have three main states: resting (closed), open, and inactive. When an agent interacts with a sodium channel, it tends

to prefer one of those three states and, in that way, alters how sodium is conducted. Neurotoxins from other taxa have been used to help study and develop drugs that affect sodium channels, of which certain spider venoms play a major role. Spider knottins (toxins) are some of the most versatile venom peptides in sodium channel drug development [27].

At least three of these isoforms, NaV 1.7, 1.8, and 1.9, are involved in pain modulation, making these ion channels an important focus for drug research. The development of sodium channel blockers has remained challenging because of their inability to target drug delivery; lidocaine, for example, is an effective sodium channel blocker but cannot be reliably delivered to specific channels. Innovations in nanomedicine may solve this problem in the future [28]. Sodium channel antagonists are approved for cardiovascular indications and makeup Class I anti-arrhythmic agents. In addition, anticonvulsant drugs including phenytoin and oxcarbazepine are sodium channel blockers.

Sodium channel blockade of NaV1.8 appears most beneficial when rapid and short-term pain control is needed, such as to manage postoperative pain. The safety and tolerability of these drugs are favorable [29].

4. Suzetrigine (VX-548)

The NaV1.8 sodium channels are particularly interesting as potential drug targets because they are prominent in neurons that sense pain but are not expressed much in other types of neurons [30]. A new agent under the working name VX-548, subsequently suzetrigine, is an oral agent that selectively inhibits NaV1.8 to confer analgesic benefits [31]. As a small molecule, it is a nonopioid analgesic being evaluated in treatment of acute pain. Its role in chronic painful conditions has not been established but is being evaluated for the indication of painful diabetic peripheral neuropathy and radiculopathy. As a novel nonopioid analgesic, it was granted priority regulatory review in the United States.

Sodium channel inhibitors have been used as local anesthetics, anti-arrhythmic agents, and antiepileptic drugs. Like suzetrigine, these agents possess "use-dependent inhibition," meaning that repeated channel activation can enhance inhibition [32]. This "reverse use dependence" has been observed in other sodium channel inhibitors and can be relieved with short repeated depolarizations as demonstrated *in vitro* [32].

Two phase II studies conducted in abdominoplasty and bunionectomy patients (n = 303 and 274, respectively) reported that suzetrigine was an effective analgesic for acute postoperative pain when administered as an oral loading dose of 100 mg and then followed by doses of 50 mg every 12 hours. Pain relief in these two studies was superior to a placebo and comparable to that of a fixed-dose hydrocodone plus acetaminophen analgesic. At lower doses of suzetrigine, results were similar to those of the placebo in both trials. The most frequently reported side effects of suzetrigine in both studies were headache and constipation [33]. When patients with diabetic neuropathy received higher doses of suzetrigine for 12 weeks, there were reports of reduced creatinine clearance, giving rise to safety concerns for that population [31].

5. Cebranopadol

One of the first innovative new analgesics in years, cebranopadol offers dual agonist action at the opioid receptors and at the nociception/orphanin FQ peptide (NOP)

receptors. As such, cebranopadol is a first-in-class and centrally acting analgesic [34]. In animal models of acute and chronic pain conditions, cebranopadol has provided both antinociceptive and antihyperalgesic effects and was more effective in treating neuropathic than nociceptive pain [34, 35]. In terms of pain control, cebranopadol appears in preclinical studies to be at least equivalent to morphine and may have less abuse liability [35].

In human clinical trials, cebranopadol 400 μg or 600 μg provided more effective analgesia than morphine for acute pain control following bunionectomy [36].

The concept behind cebranopadol has been nicknamed that of "mixed ligands," and it may be the platform for other innovative analgesics. Conventional opioids, such as morphine, act on the mu-opioid receptors (MOR). However, the activity of the delta and kappa opioid receptors (DOR and KOR, respectively) have been shown to be associated with analgesic effects but with less potential for abuse or respiratory depression [37, 38]. Further studies led to the identification of nociception opioid peptide receptor (NOP). NOP is encoded in humans by the opioid-like-1 (ORL-1) gene, a G-protein-coupled receptor that is similar to an opioid receptor but lacks the ability to bind opioid ligands [39]. The endogenous NOP ligand, a peptide, was then identified in the central nervous system of humans and named the nociception/orphanin FQ or NOP ligand. Of particular interest is the fact that the MOR and the NOP enjoyed a synergistic interaction that potentiated pain relief but not side effects [40].

Cebranopadol is a spiroindole derivative with a unique mechanism of action, acting as a full agonist at MOR and DOR and a partial agonist at KOR and NOP [41]. It has been aptly described as a bifunctional agonist at the NOP and opioid receptors [42].

Intravenous cebranopadol offers a relatively long duration of action compared to morphine and fentanyl but with a slower onset of action [43]. Currently, there is also an oral formulation of immediate-release cebranopadol for clinical testing. Early testing suggests it has a late Tmax (4–6 hours), a half-life of approximately 24 hours, and slow but nearly complete absorption [41].

Cebranopadol was shown to be noninferior when compared to morphine in a double-blind, parallel-group multidose trial in 126 cancer patients treated for moderate to severe pain. Cebranopadol was administered at doses ranging from 200 to 1000 μg [44]. In a follow-up study, cebranopadol was safe, effective, and well-tolerated for 26 weeks in this population [45].

In a study of a rat model of cocaine addiction, cebranopadol was tested as a potential treatment for cocaine dependence at single and multiple doses. In this preclinical study, the suggested dose to balance the effectiveness against safety was 50 μg/kg, but further study is needed [46]. It is believed that cebranopadol's affinity for NOP blunts the rewarding properties of cocaine and possibly other drugs of abuse [47]. Indeed, it is the agonism at the NOP receptors that is believed to reduce the potential for abuse of cebranopadol when used for analgesic purposes [48, 49]. Preclinical studies have suggested that cebranopadol may attenuate heroin self-administration in rats [50].

6. AAT-076

AAT-076 originated at RaQualia Pharma in China as RQ-00317076 and is a so-called "next-generation" cyclooxygenase (COX)-2 inhibitor which is in phase I studies for neuropathic pain indications and phase 2 for acute painful conditions; it has a chemical structure distinct from other coxibs. In a dental pain study, the onset of action and duration of pain relief were superior to ibuprofen [51].

The distinction between AAT-076 and other conventional coxibs is that AAT-076 works at both the central and peripheral nervous systems, while previous-generation coxibs work at the peripheral level only.

7. HTX-011 (ZYNRELEF)

Nanomedicine uses advanced nanotechnology and bioengineering methods to develop microparticles and nanoparticles that facilitate drug delivery, improve drug effectiveness, and/or reduce toxicity. Nanotechnology is in its infancy and now relies on "passive targeting," whereby the nanodrugs do not target a specific organ [52]. Passive targeting makes these drugs more systemic rather than controlled at the target. Active targeting can be accomplished when a nanoparticle loaded with the agent is functionalized with a ligand in such a way that it binds to the anchoring molecules on the surface of the target cells [53]. Active targeting by a nanodrug poses challenges in drug development and only one such agent has been cleared to market by the FDA (Ontak, denileukin diftitox for oncology) [53]. Nanotechnology may offer another advantage with opioids in particular in that nanodrugs resist drug tampering [53].

The ability to encapsulate an NSAID analgesic into a nanocarrier could result in less NSAID toxicity without sacrificing analgesic efficacy [52]. In many cases, nanodrugs rely on previously approved molecules nanoformulated for improved PK and/or PD. These improvements may encompass increased serum half-life (better PK), greater bioavailability (better PK), and controlled release formulations. When a drug can be conjugated to a polymer polyethylene glycol (PEG), the drug becomes more hydrophilic and has less uptake by the organs of the reticuloendothelial system [54].

In general, nanomedicine focuses more attention on incurable or life-threatening conditions with high rates of mortality, such as cancer or infectious diseases. Pain medicine may benefit from nanomedicine, but in addition to the technological hurdles, there is a higher threshold for regulatory approval for pain medications than for lethal disease treatments. This may explain why so few nano-NSAIDs are in development, much less approved [53].

8. NTM-001

Ketorolac is an older and potent NSAID analgesic that was reformulated into an alcohol-free pre-bagged analgesic for continuous intravenous (IV) infusion over 24 hours following surgery. A study found that NTM-001 offered similar pharmacokinetic properties, bioavailability, and safety in both young, healthy volunteer subjects as well as geriatric subjects. The geriatric subjects had normal renal function or mild to moderately impaired renal function. This suggests that NTM-001 is a safe, effective nonopioid analgesic to be used for acute pain management. The continuous IV infusion eliminated the peaks and troughs sometimes observed with bolus dosing [55, 56].

The primary advantage of NTM-001 is that it prepackages an effective postoperative analgesic and offers a delivery system that minimizes injection site pain and provides for a continuous infusion that provides more reliable pain control than periodic bolus dosing. As a pain reliever, ketorolac is not an agent for broad universal use as its long-term use and/or high doses are associated with side effects [57]. Clinically supervised intravenous ketorolac used for acute postoperative pain is considered safe and effective [58, 59]. Ketorolac had been previously limited by the fact that it was not

readily available for immediate intravenous use in a hospital setting or when prepared for continuous or bolus intravenous infusion; further, this reformulation has been designed to minimize injection site reactions.

It is important in this context to note that drug innovation can be in terms of molecular design, but it may also occur through improvement in the drug delivery system or packaging.

9. NTM-006

NTM-006 was an experimental drug formerly known as JNJ-10450232, a novel nonopioid analgesic drug that is chemically similar to acetaminophen (paracetamol) but offers long-acting pain control. Available as an oral product, it has been shown to be effective in pain control following third-molar extraction [60]. In a study of acute pain, NTM-006 conferred pain relief similar to 1000 mg acetaminophen in the first 6 hours after dosing and superior analgesia seven to 24 hours after a single dose. The onset of action was slower with NTM-006 compared to acetaminophen (45 minutes to first perceptible pain relief for NTM-006 versus 28 minutes for acetaminophen) [60]. In the dental pain study, significantly more NTM-006 patients did not require rescue medication in the first 24 hours after dosing compared to those taking 1000 mg acetaminophen [60].

Structurally similar to acetaminophen (paracetamol), NTM-006 has similar antinociceptive and antipyretic effects in preclinical studies and does not cause hepatotoxicity even at supratherapeutic doses [60, 61]. Sometimes called a non-nonsteroidal drug, metabolism in preclinical studies shows that the major route of excretion was in the urine and consisted of 88.6% or 73.7% of the dose in rats and dogs, respectively. Glucuronidation is the major metabolic pathway in humans [62].

10. Sublingual ketamine

Ketamine is an *N*-methyl-D-aspartate receptor (NMDAR) blocker that has analgesic efficacy but is rarely used for pain indications apart from acute postoperative pain managed in the hospital setting [63]. Technically, ketamine is an older drug—over half a century old—but it has enjoyed numerous renaissances over the decades for its role in anesthesia, psychiatry, and pain management. Although its activity as an NMDAR antagonist is well recognized, it also appears to interact with other receptor systems, including the opioid, GABA, cholinergic, dopaminergic, sodium channel, and other systems [64, 65]. Despite a lack of consensus guidelines on dosage and indications for ketamine in treating painful symptoms, the drug is widely used as an analgesic, albeit at subanesthetic dose ranges. This dose range is not strictly defined, but it is thought to be approximately 0.5–0.6 mg/kg intravenously over the course of 0.5–1 hour [63].

Ketamine is available in intravenous, intramuscular, subcutaneous, oral, rectal, topical, intranasal, sublingual, epidural, and caudal formulations. The drug may be abused by recreational users who inhale, smoke, or inject it [66].

Ketamine consists of a cyclohexanone ring with a chiral center made up of R(−) and S(+) optical stereoisomers. The S(+) variant, also known as esketamine, has a greater affinity for the NMDAR receptor and preclinical evaluations suggest that R(−) is more effective as an antidepressive agent. In most parts of the world, the racemic mixture is on the market, but certain European countries have released

esketamine to the market as well [63]. As a lipophilic compound, ketamine crosses the blood-brain barrier and has a rapid onset of action [63]. Side effects can be severe with hallucinations, derealization, depersonalization, panic attacks, nausea, vomiting, and hypertension most frequently among them, but such side effects resolve upon cessation of the drug [63].

As a lipophilic agent, ketamine can cross the blood-brain barrier, allowing it to provide rapid-onset relief of acute pain [63]. Ketamine has been evaluated for relief of acute postoperative pain, and both used alone or in combination with an opioid analgesic in patient-controlled analgesia systems [67–69].

Sublingual ketamine is a new formulation, and it has been used in the treatment of depression and other psychological conditions but has only been recently studied in the treatment of chronic noncancer pain [70]. In a retrospective review of 29 patients treated with sublingual ketamine lozenges for pain control, 59% of those taking sublingual ketamine reduced their consumption of opioids, gabapentinoids, and benzodiazepines and 39% used no other analgesic agents besides the ketamine lozenges. About a quarter of patients (24%) experienced side effects, but only 7% discontinued the use of the sublingual ketamine because of them. Adverse events of hepatotoxicity, renal dysfunction, or cystitis were not reported. In this study, patients took 25–600 mg of ketamine in divided doses over the course of treatment that ranged from 2 to 89 months [70].

In a pharmacokinetic study of sublingual ketamine 10 mg IV by a 30-minute constant rate infusion compared to a 25 mg sublingual wafter in two treatment periods, the absolute bioavailability of sublingual ketamine was 29% and the median (minimum to maximum) time of peak plasma concentration was 0.75 hours (0.25–1.0 hours) following sublingual dosing. Tolerability in this pharmacokinetic study of eight healthy volunteers was good [71].

In a randomized, double-blind, crossover-design study, 23 inpatients were given placebo or a 50 mg ketamine oral lozenge or a 50 mg ketamine sublingual lozenge for the management of breakthrough pain. The time to first effect was 13.1 minutes for the oral lozenge compared to 6.6 minutes for the sublingual formulation ($p = 0.069$). Likewise, the time to meaningful pain relief was 29.4 minutes for the oral versus 10.8 minutes for the sublingual products ($p = 0.02$). Over time, pain scores were similar and both active agent groups had similar high satisfaction scores, but adverse events occurred more frequently with the sublingual ketamine product ($p = 0.02$) [72]. While this study is relevant for its evaluation of acute pain and rapid onset of action of analgesia, it was not evaluated in postoperative pain specifically.

The innovation in this product is based on the sublingual formulation based on wafer technology. iX Biopharma has developed Wafermine, a racemic ketamine sublingual product. The product is based on a proprietary product made up of matrix-forming agents that are freeze-dried with the goal of rapid dissolution of all components in the sublingual mucosal membrane. The goal of the sublingual formulation is to decrease the amount of active agent swallowed by the patient and to maximize the agent that enters the system *via* the sublingual mucosa. There, the wafer dissolves, and the drug is absorbed through the thin epithelium, entering the circulatory system by way of the jugular vein. This allows most of the active agent to completely circumvent the gastrointestinal system and to avoid the first-pass hepatic effect, where many bioactive substances are degraded [73].

Outside of the perioperative setting, the use of sublingual ketamine for pain management appears limited [63]. Consensus guidelines published by the American Society of Regional Anesthesia and Pain Medicine, the American Academy of Pain

Medicine, and the American Society of Anesthesiologists support the use of ketamine to manage acute pain in a variety of clinical settings, including perioperatively and states that contraindications for the use of peri- and postoperative ketamine for acute pain control are similar to those for chronic pain [74]. These guidelines did not include sublingual ketamine.

11. Conclusions

Pain is one of the oldest medical complaints and remains a frequent reason for consultation with a clinician, yet despite energetic efforts, finding the breakthrough "new" pain reliever that is both safe and effective with little or no issues of tolerance, tolerability, or abuse potential remains elusive. Numerous important drug targets have been identified, such as voltage-gated sodium channels, TRPV1 channels, and novel delivery systems utilizing nanotechnology are actively being explored. Older agents are being repurposed in ways that minimize their shortfalls while accentuating their analgesic effects. More research is needed to find and develop a safe, effective analgesic for use following surgery since postsurgical pain is prevalent and can be severe. The proper management of acute postsurgical pain can prevent its transition into persistent postsurgical pain, which can be very challenging to treat.

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Pain after surgery is a common complaint. This unpleasant feeling due to tissue damage, mental suffering, and distress must be handled adequately. Postoperative pain is a significant concern for patients, relatives and healthcare providers. It may prolong recovery, increase hospital stays and increase the economic burden. Furthermore, postoperative pain can persist and turn into chronic pain. Identification of reliable pain predictors will enable optimal pain management. Pain management involves methods for managing postoperative pain based on the pathophysiology of pain, the role of inflammatory mediators, and the importance of early and effective pain control. The book aims to provide healthcare professionals with a detailed understanding of how to manage postoperative pain effectively and improve patient outcomes.

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