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Review Article

Eliminating Opioid Dependency by Knowing the APTA (Anatomy, Pathophysiology, Treatment, and Assessment) of Pain

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Abstract

There are many causes for the current opioid epidemic in the United States. Government policies, law enforcement actions, and social support are helping to stem the rising tide of opioid use, dependency, and related deaths. However, due to the multifactorial nature of the crisis, one answer or solution is unlikely to resolve this dilemma. In the urgency to solve the opioid crisis and lessen its financial and social impact, an essential investigation might have been overlooked: what are the fundamental causes of opioid use, dependency, and addiction? Pain and the efforts to relieve pain (by physicians prescribing opioids and patients taking them) are the central cause sparking and stoking the opioid crisis. This paper summarizes the anatomy, pathophysiology, treatment, and assessment of pain. It is held that having an enhanced awareness of these four pillars of pain will lead to more efficacious treatment (with less adverse effects) and social support (with less stigma conjoined), thereby reducing opioid addiction, ending the opioid epidemic. The opioid-free protocol offers a practical and progressive alternative to traditional perisurgical pain management, which will result in fewer patients developing opioid use disorder and succumbing to opioid-related deaths.

Keywords: *Addiction; Hyperalgesia; Non-Opioid Pain Treatment; Opioid; Opioid Epidemic; Oxycodone*

Abbreviations

ACOEM: American College of Occupational and Environmental Medicine; APTA: Anatomy, Pathophysiology, Treatment, Assessment; ASC: Ambulatory Surgery Center; AI: Anterior Insula; CDC: Centers for Disease Control and Prevention; CFS: Cerebral Spinal Fluid; CNCP: Chronic Noncancer Pain; COX: Cyclooxygenase; COX-2: Cyclooxygenase-2; FDA: Food and Drug Administration; FPS: FACES Pain Scale; IASP: International Association for the Study of Pain; LEO: Law Enforcement Officer; MMA: Multimodal Anesthesia; MME: Morphine Milligram Equivalents; MTUS/ACOEM: Medical Treatment Utilization Schedule/American College of Occupational and Environmental Medicine; NRS: Numerical Rating Scale; NSAID: Nonsteroidal Anti-inflammatory Drug; ODG: Official Disability Guidelines; OFD: Opioid-Free Protocol; OUD: Opioid Use Disorder; PRN: As Needed; VAS: Visual Analog Scale

Preface

The word "pain" is used in various contexts. Most often, it is linked to emotions of grief, sorrow, and suffering. The word "pain" comes from "poena"—a Latin word—meaning a fine or penalty. In 1996, the American Pain Society introduced pain as "the fifth vital sign" [1]. According to the International Association for the Study of Pain (IASP), "pain is an unpleasant sensory and emotional experience arising from actual or potential tissue damage" [2]. Pain can be a mild, localized discomfort to agony, with physical and emotional components. The physical correlate of pain results from nerve irritation or stimulation, and can be confined to a specific area, as in an injury, or it can be diffuse, as in fibromyalgia [3]. The sensation or experience of pain is subjective; pain threshold varies among individuals as well as their reactions to pain.

Introduction

According to the Centers for Disease Control and Prevention (CDC): "The U.S. is experiencing an opioid epidemic as the rate of opioid overdoses has roughly tripled since 1999 and continues to climb. Opioid prescribing has quadrupled since 1999 and has risen in tandem

with the number of overdoses from the most frequently prescribed opioids [4]. Opioid use disorder (OUD) and overdose deaths most commonly involve oxycodone and hydrocodone [5]. Prescription opioid-related costs exceed $78.5 billion annually" [6,7]. To address this opioid epidemic, the CDC has implemented programs to expand prescription drug monitoring and naloxone and opioid use disorder treatment programs at state and federal levels [4]. The first step in opioid prescription and dependency reduction is to recognize the central cause for its use more thoroughly. Getting to know the fundamentals (the four pillars) of pain can help practitioners, policymakers, law enforcement officers (LEOs), and the general public plan how to reduce opioid treatment and dependency more effectively. The following review summarizes the four pillars of pain—the APTA (anatomy, pathophysiology, treatment, and assessment) of pain. According to Hah., *et al*. (2017):

> Approximately 51 million Americans undergo inpatient surgery annually. Acute postoperative pain occurs in 80% of patients, with 86% of these patients experiencing moderate to severe pain". Given the approximately 234 million surgeries performed worldwide each year, acute postoperative pain is a significant public health problem. Opioids are the primary prescription drug for pain during recovery. Over 80% of patients receive opioids after low-risk electives surgery, and more than 80% of these prescriptions involve oxycodone or hydrocodone. [8]

Discussion

Anatomy and types of pain

The subjective experience of pain has two components: 1) a localized sensation in a particular body part and 2) an undesirable sensation, resulting in actions to alleviate the sensation [9]. Pain typically occurs when tissues are damaged, affecting the pain receptors in the tissue. There are specific pain receptors present in most body tissues that respond to damaging or potentially damaging stimuli. Specific nerves transmit the messages initiated by noxious stimuli to the central nervous system. Pain receptors are present in superficial layers of skin, periosteum, arterial walls, joint surfaces, falx cerebri and tentorium. The pain receptors are stimulated by mechanical, thermal, and chemical stimuli [10].

There are two general classifications of pain: fast pain and slow pain. Fast pain is experienced within 0.1 seconds, commonly in superficial tissues, uncommonly in deeper tissues. Fast pain is described as sharp, acute, electric, or pricking pain. Fast (sharp) pain causes a person to react immediately to remove the stimulus causing the pain. The fast pain pathway is actuated by mechanical or thermal stimuli and carried by specialized nerve fibers at a speed of 6–30 m/sec. Slow pain is experienced as burning, aching, throbbing, gnawing, nauseating, or chronic pain. It can occur in the skin and deep tissues. Mechanical and thermal stimuli can activate the slow pain pathway, but more so by chemical stimuli. Slow pain involves distinct nerve fibers at speeds of 0.5–2 m/sec. Certain intrinsic substances are involved in causing pain (i.e. bradykinin, serotonin, histamine, potassium ions, acids, acetylcholine, and proteolytic enzymes) [11].

According to Yam., *et al.* (2018), there are four principal processes involved in the pathway of pain: transduction, transmission, modulation, and perception. Transduction refers to the processes by which a tissue-damaging stimulus activates nerve endings. Transmission refers to the relay function by which the message is carried from the site of tissue injury to the brain regions underlying perception. Modulation is a recently discovered neural process that acts specifically to reduce activity in the transmission system. Perception is the subjective awareness produced by sensory signals; it involves the integration of many sensory messages into a coherent and meaningful whole. Perception is a complex function of several processes, including attention, expectation, and interpretation [12].

The structure of the pain-producing and pain-sensing nervous system is complex, and a thorough description of the numerous fibers, connections, and impulses peripherally or centrally is beyond the scope of this summary.

Pathophysiology and pathways of pain

Abdulkhaleq., *et al.* (2018) reported that the chemical mediators of inflammation, such as histamine, bradykinin, acids, and serotonin, are typically released by damaged cells. Chemical mediators stimulate receptors, which influences a protein-enzyme cascade and up-regulates ion channels and sodium-specific nociceptive channels [13]. This cascade-event results in increased sensitivity to the chemical mediators, which produces pain.

Hypersensitivity, following an injury, allows the damaged tissues to heal by "telling" the brain to avoid further injury to the area. When hypersensitivity becomes prolonged, peripheral sensitization develops with increased sensitivity to the chemical modulators or a decreased threshold to the stimulus. Peripheral sensitization can impact treatment and the patient's experience of pain [11-13].

Abbadie (2005) noted that neuropathic pain can be caused by compression, transection, infiltration, ischemia, or metabolic injury to specific nerves, and is identified as peripheral or central [14]. Noxious stimuli, such as injury or damage, are transformed into electrical impulses by nociceptors located in the tissues. The intensity, quality, and location of the pain are transmitted to specific areas of the brain. Pain signals an "alarm" leading to protective responses. However, neuropathic pain does not signal imminent danger [15]. Neuropathic pain is a delayed and persistent response to injury or damage that is no longer acute but exists as pain.

Injury, disease, or drugs can damage sensory nerves leading to protracted excitability—termed "wind-up"—resulting in the perception of pain being higher than what a patient should experience typically [16]. Nerves of the peripheral and central nervous systems continue to transmit pain signals well after the original injury occurred. Thus, damage to the peripheral or central nervous system can result in chronic pain, such as seen in diabetes mellitus or alcohol toxicity. The pain threshold varies among individuals as well as their reaction to pain [17].

Medical treatment of pain

Acetaminophen

Acetaminophen, also known as paracetamol, is a nonsteroidal anti-inflammatory drug (NSAID) with potent antipyretic and analgesic actions but with insufficient anti-inflammatory activity [18-20].

NSAIDs and COX-2 inhibitors

NSAIDs provide a prompt analgesic effect, within minutes to hours; however, the anti-inflammatory effect may take 1–2 weeks or longer. This anti-inflammatory effect can indirectly relieve some pain by reducing tissue swelling. The relatively recent discovery that cyclooxygenase (COX) has two isoforms, COX-1 and COX-2, has advanced NSAID pharmacology [18-20].

Gabapentin and pregabalin

Gabapentinoids (gabapentin and pregabalin) have gained popularity as part of a multimodal approach to postsurgical pain management. Introduced in the mid-1990s, gabapentin, a synthetic analog of g-aminobutyric acid, was initially approved as an anticonvulsant. Although specific perioperative doses remain unclear, higher doses of gabapentin (1200 mg), as well as pregabalin (300 mg), are significantly more effective than lower doses. Also, the continuation of gabapentin or pregabalin postoperatively has been reported to be more effective than a single preoperative dose [21-23].

Opioids

Opioids are used to treat moderate to severe pain that does not respond to nonopioids alone, by modifying sensory and affective aspects of pain [24]. Opioids are often combined with nonopioids, permitting lower doses of the opioid (e.g., dose-sparing effect). Nearly

all types of pain respond to opioids; however, nociceptive pain is generally more responsive to opioids than neuropathic pain. Neuropathic pain might require higher doses of opioids. Opioids play a significant role in the treatment of acute pain (i.e., trauma and postoperative pain), cancer pain, and some types of chronic noncancer pain [25,26]. Responsiveness to opioids varies significantly among individuals; therefore, a patient who has failed to respond to an adequate trial of one type of opioid might benefit from another type [27]. Long-acting and sustained-release opioids are useful for patients with continuous pain. Long-acting and sustained-release opioids lessen the severity of end-of-dose pain and help the patient to sleep through the night. Most opioids can be given around the clock for continuous pain or as needed (PRN) [24-27].

Side effects of some classes of opioids include sedation, mental clouding or confusion, respiratory depression, nausea, vomiting, constipation, pruritus (itching), and urinary retention. Except for constipation, these side effects tend to subside over time [28]. Most opioids should be used with caution in patients with impaired ventilation, bronchial asthma, liver failure, or increased intracranial pressure.

Multimodal analgesia (MMA)

In a meta-analysis of 52 randomized trials, including 4893 adults, acetaminophen, NSAIDs, or selective cyclooxygenase-2 (COX-2) inhibitors significantly reduced 24-hour morphine consumption after surgery. Similarly, a systematic review found that coadministration of paracetamol, NSAIDs, and COX-2 inhibitors with opioids decreases 24-hour postoperative morphine consumption, however, without a clear benefit of one category versus another in terms of adverse effects [29-32]. Although many medical associations highly endorse MMA, it remains underutilized.

Intrathecal analgesia

Intrathecal analgesia involves the administration of analgesic drugs directly into the cerebral spinal fluid (CSF) in the intrathecal space [33]. According to Dougherty and Lister (2001), analgesic drugs given via this route are approximately ten times as potent as those given into the epidural space, so required doses and volumes are potentially much smaller [34].

Currently, three medications (morphine, ziconotide, and baclofen) have been approved by the U.S. Food and Drug Administration (FDA) for use via an intrathecal route. Morphine is considered to be the "gold standard" intrathecal opioid agonist [35]. Baclofen is used to treat muscle spasms, spasticity, and neuropathic pain. Bottros and Cristo (2014) reported that while these three medications (morphine, ziconotide, and baclofen) are the only FDA-approved drugs to be used intrathecally, in practice, other medications, such as clonidine, bupivacaine hydromorphone, fentanyl, and sufentanil are also used [35].

Epidural analgesia

Epidural analgesia (the administration of opioids and or local anesthetics into the epidural space) can be used to manage pain. Schwartz (2006) noted that pediatric, adult, and older adult populations can benefit from epidural analgesics on a short-term (hours to days) or long-term (weeks to months) basis. A perioperative epidural—via a catheter that is inserted into the epidural space—can be used to manage postoperative pain, procedural pain, chronic pain, or trauma pain [36]. In addition to the control of pain, epidural anesthesia results in the loss of sensation and motor function [37].

Epidural analgesia provides better pain management than systemic opioids, maintains gastrointestinal function, reduces the risk of postoperative myocardial infarction, and decreases the risk of postoperative mortality. Epidural analgesia might also decrease the severity of persistent pain syndrome (such as phantom limb pain or post-thoracotomy pain) [38].

Adverse reactions to opioids administered epidurally include pruritus, nausea, vomiting, urinary retention, decreased level of consciousness, and respiratory depression [37,38].

Nerve block

Brachial plexus blocks, for upper extremity surgery, contribute to lower postoperative pain scores and perioperative opioid consumption. Lower extremity blocks can also significantly decrease pain scores and perioperative opioid consumption in a variety of procedures [39-41].

Physical rehabilitative methods and prehab

Physical rehabilitative methods of pain management are appropriate for many types of pain and are essential in patients with chronic noncancer pain (CNCP). In addition to relieving pain, such methods can reduce fear and anxiety, improve physical function, and alter physiological responses to pain. Treatments used in physical rehabilitation include stretching, exercise and reconditioning (to improve strength, endurance, and flexibility), gait and posture training, and attention to ergonomics and body mechanics [42]. Other non-invasive physical treatments for pain include thermotherapy (application of heat), cryotherapy (application of cold), counter-irritation, and electroanalgesia (e.g., transcutaneous electrical stimulation). In some cases, patients choose to pursue non-allopathic (alternative treatments), such as acupuncture or therapeutic massage.

"Prehabilitation" refers to physical therapy rehabilitation before having shoulder, knee, total knee, or total hip arthroplasty. According to Wynter-Blyth and Moorthy (2017), prehabilitation consists of stretching and flexibility exercises and strength training. Also, electrical modalities, such as neuromuscular electrical stimulation, are used to hypertrophy the muscles around the injured joint, by as much as 30% before surgery. Prehabilitation is recognized as an integral part of extremity surgery per MTUS/ACOEM guidelines and the ODG [43].

Opioid-Free Perioperative Acute Pain Management in Non-Spinal Orthopedic Procedures

The opioid-free protocol (OFP) is similar to MMA but without the opioids pre, peri, andat any stage (pre, peri, or postoperatively). Patient exposure to opioids at any stage (pre, peri, or postoperatively) sets the stage for OUD in previously opioid-exposed or initially opioid-exposed patients. This OFP was co-designed by Drs. John V. Flores, Neil Ghodadra, Grant Williams, and Chris Brown, CRNA, of the United States, and has been used to treat perioperative pain successfully without opioids since 2016, eliminating patient exposure to opioids and decreasing the incidence of OUD in this patient population.

Medical assessment of pain

The experience of pain is subjective and varies among individuals. A multitude of responses by individuals characterizes the subjective experience of reported pain. Evidence suggests that the measure of disease activity or tissue damage are poor predictors of pain [4]. Zhang., *et al.* (2010) reported that the majority of individuals who show radiographic evidence of osteoarthritis report no pain [44].

Rating scales provide a simple means for patients to rate subjective pain intensity. Typical scales use numeric (e.g., 0–10), word (verbal), or visual (image) descriptors to quantify their level of pain [45].

As reported by Bergstrom, *et al*. (1998): in the numeric rating scale (NRS), patients rate their pain on a 0-to-10 scale or a 0-to-5 scale, with 0 representing "no pain at all" and 5 or 10 representing "the worst pain they have ever experienced". Pain intensity levels are measured at the initial patient encounter, following treatment, and periodically thereafter, depending on the clinical situation [46].

The visual analog scale (VAS) consists of a 10-cm line with anchors at both ends. One end is marked "no pain" and the other end is marked "pain as bad as it could be" or "the worst imaginable pain". The patient marks a point on the line to indicate his or her pain intensity. The clinician then measures the line with a ruler and assigns a score [47].

Categorical scales provide a simple means for patients to rate pain intensity, using verbal or visual descriptors of the pain [48]. Melzack and Torgerson (1971) introduced a scale with five verbal descriptors (e.g., mild, discomforting, distressing, horrible, and excruciating) [48].

The FACES Pain Scale (FPS) for Adults and Children and the Wong-Baker Faces Rating Scale (for children) are visual descriptor scales. The FPS is composed of eight images of faces with various expressions (e.g., smiling, frowning, and grimacing). The patient selects the face that is consistent with his or her level of pain. The FPS is the most widely used scale in a hospital setting [49].

Anaesthesiologists use a specialized rating tool to evaluate a patient's sickness or physical state before selecting appropriate anaesthesia, which spans the typical healthy patient to moribund patient—to a declared brain-dead, organ-donor patient [50,51].

Conclusion

The United States is in the throes of an opioid epidemic. Opioid use disorder involves oxycodone, hydrocodone, and morphine equivalents primarily, and often results in overdose deaths. The economic cost of prescription opioid-related overdose, abuse, and dependence is extreme. Opioids are used traditionally to treat surgical patients. More than 80% of patients receive opioids after low-risk elective surgery. However, it is not just post-surgical pain setting the stage for opioid addiction—many body ailments cause pain, fomenting a reliance on opioids and morphine equivalents to diminish such pain temporarily.

The coadministration of paracetamol, NSAIDs, and COX-2 inhibitors without opioids eliminates the need for 24-hour postoperative morphine consumption as is the standard of care. Multimodal anesthesia is highly recommended, yet, it remains underutilized, and if used, will fail as the patient is exposed to opiates pre- or post-operatively, rendering multimodal anesthesia an expensive and unnecessary protocol. Also, physical rehabilitative methods with specific pain management protocols are appropriate for many types of pain. The individual differences and the personal experiences of pain for patients with comparable pathology or disease severity are variable.

Pain and the need to reduce or eliminate pain is the core cause of opioid dependency and the opioid epidemic. Gaining an enhanced foundation in the APTA of pain—the anatomy, pathophysiology, treatment, and assessment of pain—can help practitioners, policymakers, law enforcement officers, and the general public choose how to reduce opioid treatment and dependency more strategically, and have greater compassion for those suffering from opioid addiction. The OFP offers a practical and progressive alternative to traditional perisurgical pain management, which will result in fewer patients developing OUD and succumbing to opioid-related deaths.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest. The first author acknowledges proprietary interests in several surgical centers that specialize in opioid-free perioperative pain management in Los Angeles, California, USA.

Supplementary Note

The research supporting the opioid-free protocol (OFP) for perioperative acute pain management in non-spinal orthopedic procedures will be presented in an upcoming issue of *EC Orthopaedics*, published by E-Cronicon Open Access.

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