PAIN PERCEPTION AND MODULATION: PATHWAYS, PHYSIOLOGY AND THERAPEUTIC APPROACHES: A COMPREHENSIVE REVIEW

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ABSTRACT

Pain is a universal human experience that plays vital role in signaling illness, acting as a defense system. The complexity and multifaceted experience of pain is a crucial protective mechanism in our body that not only helps to counter act the adversity but also tells the site of injury. The involvement of sensory, emotional, and cognitive components alerts about the potential and site of tissue being damaged. This review on pain explores the aspects on types, feeling of pain, measurements and finally, the management approach to tackle the situation. In addition, methods for assessing pain-including self-report scales, behavioral observation emphasize the importance of accurate evaluation. Understanding the mechanisms and multifactorial nature of pain, healthcare providers can tailor an effective treatment of pain in clinical practice.

INTRODUCTION

When an injury or problem occurs in our body, body's natural phenomenon comes in front to appropriately addressing it, i.e., Pain which is a critical sensation to alert from these kinds of situation. This important information about tissue damage helps to tackle the problem until it gets worse. In response to pain, we tend to protect the damaged tissue from further use and seek appropriate medical attention.

HOW WE FEEL PAIN?

Nociceptors, also known as pain receptors, are the sensory receptors that detect signal from the tissue damaged or being damaged or indirect way of responding to chemicals released from the damaged tissue. They respond to nociceptive or noxious stimuli that lead to our perception of pain. These receptors vary in the specific stimuli that they respond to as well as how quickly they transmit information to the central nervous system. These nociceptors are not found in various tissues like articular cartilage, visceral pleura, lung parenchyma, pericardium, brain and cord tissue[1].

The noxious stimuli like extreme temperature, a pinch, blunt impact, epigastric stimulus, overuse of joints and many others elicit the sensation of pain. The activation of nociceptors occurs through these stimuli that leads to release of chemical substances, thereby activating nociception pathway.

TYPES OF PAIN:

Although there are many ways to distinguish type of pain because there is as such no category but generally these types of pain are used in terms2, they are:

- Acute pain
- Chronic pain
- Neuropathic pain
- Nociceptive pain
- Radicular pain

Acute pain: as the name describes, this type of pain is shorter in duration, lasting from minutes to few months. It may be due to soft-tissue injury or temporary illness. Generally, pain due during fever, any acute injury during any kind of work which does not last long enough. It might get evolved into chronic pain if not treated correctly[3].

Chronic pain: It is longer in duration because some injury takes long time to heal and can be permanent or intermittent. For example, headaches like migraine can be considered chronic pain when they continue over many months or years-even if the pain is not present[3].

Neuropathic pain: The damage to the nerves or other parts of the nervous system which leads to persistent, throbbing pain is neuropathic pain. It is often described as shooting, stabbing or burning pain. It can also affect sensitivity to touch and can make someone have difficulty feeling hot or cold sensations.

Nociceptive pain: It is a type of pain caused by damage to body tissue. People often describe it as sharp, achy or throbbing pain.

Radicular pain: it is a very specific type of pain, can occur when the spinal nerve gets compressed or inflamed. It radiates from the back and hip into the legs by way of spine and spine nerve root. People having radicular pain may experience tingling, numbness and muscle weakness[4].

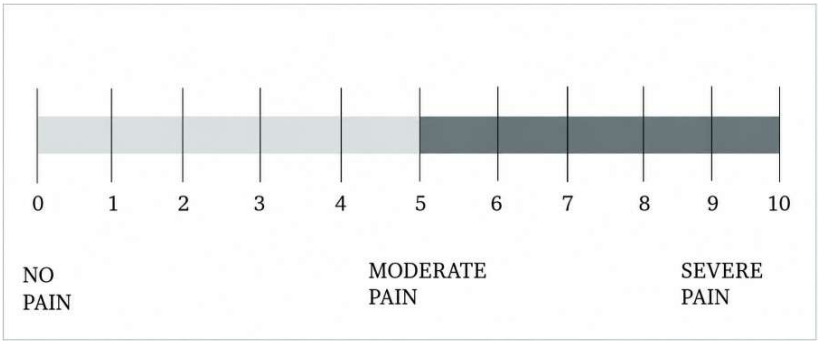
MEASUREMENT OF PAIN:

For measuring the pain, various pain scales are used which are the tools that healthcare providers use to help measure and for defining a person's pain in a better way. Pain scale results help guide the diagnostic process track the progression of a condition, a determine how effective a treatment is according to the pain scale[5,6].

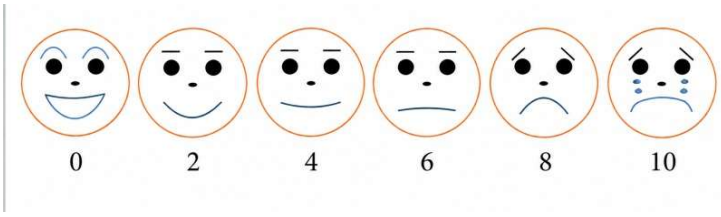
Types of pain scales: The different types of pain scales7 used to determine the severity of pain are:

- Numerical rating scale
- Wong baker faces pain scale
- Comfort scale

Numerical rating scale: It is designed to be used for children that are below 9 years old. It is one of the most commonly used pain scales in health care. Using the numerical scale, patient has the option to verbally rate pain from 0 to 10. The rate scale increases as the pain increases. Zero indicates the absence of pain while 10 represents the most intense pain possible[8].



Wong-Baker faces pain scale: It combines pictures and numbers for pain ratings. It can be used in children over the age of 3 and in adults. Six faces according to the pain depict different expressions, ranging from happy means no injury or hurt to extreme upset and crying means severe pain or injury. Each is assigned a numerical rating between 0 (smiling) and 10 (crying)[9,10].



Comfort scale:The pain scale that may be used by a healthcare provider when a person cannot describe or rate the pain. Some of the common population this scale might be used with include:

- →Children
- →Adults who are cognitively impaired
- →Adults whose cognition is temporarily impaired by medication or illness
- →People who are sedated in an ICU or operating room setting.

The comfort scale provides a pain rating between 9 and 45 based on nine different parameters with each rated from 1 to 5[11,12].Alertness

Alertness	1.→ Deeply asleep 2.→ Lightly asleep 3.→ Drowsiness 4.→ Fully awake 5.→ Hyper alertness	o→ o→ o→ o→ o→
Calmness	1.→ Fully calm 2.→ Slightly anxious 3.→ Anxious 4.→ Very anxious 5.→ Panicking	o→ o→ o→ o→ o→
Crying	1.→ Quiet breathing 2.→ Gasping 3.→ Moaning 4.→ Crying 5.→ Screaming	o→ o→ o→ o→ o→
Physical movement	1.→ No movement 2.→ Occasional movement 3.→ Frequent 4.→ Vigorous movement 5.→ Movement including torso and head vigorously	o→ o→ o→ o→ o→
Blood pressure	1.→ Below baseline 2.→ Consistently at baseline 3.→ More above baseline 4.→ Frequent elevations of BP Sustained elevations of BP	o→ o→ o→ o→

NOCICEPTION AND TYPES OF NOCICEPTORS:

It is a neural process in which encoding and processing of noxious stimuli in response to any injury occurs[13]. A signal is arrived from the site of injury through sensory receptors called nociceptors[14] in the peripheral nervous system to the central nervous system. Nociceptors are activated by potentially noxious stimuli, as such nociception is the physiological process by which body tissues are protected from damage[15]. It is important for the 'fight and flight response' of the body and protects us from harm in our surrounding environment.

TYPES OF NOCICEPTORS: They can be distinguished15 into three classes based on their type of activity:

- → **Based on mechanical stimuli,** nociceptors can be divided into two main classes, mechanically sensitive afferents (MSA) and mechanically insensitive afferents (MIA), the latter have very high mechanical thresholds or are unresponsive to mechanical stimuli.
- →**Based on conduction velocity of their axons or fibres diameter,** Nociceptors can also be classified into two types:

1.→ Myelinated afferents (type Aδ)

2. Unmyelinated afferents (type C)

Type Aδ medium diameter myelinated afferents that mediate acute, well localized, sharp pricking type pain, known as group III afferent. They have average fibre diameter 2-5mm and conductive velocity 5-30 m/s. Aδ can be further sub-classified into two types:

1.→Type I Aδ are MSA that respond with a slowly adapting discharge to strong punctuate pressure. They also respond to heat and chemical stimuli and have relatively high heat thresholds.

2.→Type II Aδ have lower heat threshold than type I units but have very high mechanical thresholds (MIA). The activity of this afferent mediated the "first" acute pain response to noxious heat. They have been reported in the knee joint, viscera and cornea.

Type C unmyelinated afferent fibres that convey poorly localized dull, burning, so called "second" or slow pain are known as group IV. Average fibre diameter is below 2mm and conductive velocity is 2 m/s or less. This is due to the light or non-myelination of the axon fibre.

As a result, pain comes in two phases. The first phase is mediated by fast conducting Aδ fibers and the second are due to C fibers (polymodal).

Type Aδ release glutamate and Type C releases substance P as their primary neurotransmitter respectively[2]

- →Based on stimuli, they respond to:

Thermal: they respond to extreme hot or cold temperatures.

Mechanical: They respond to intense stretch or strain, like when you pull a hamstring or strain your Achilles tendon beyond their ability[14].

Chemical: They respond to chemicals released from tissue damage, for example prostaglandins and substance P or from external chemicals (topical capsaicin)

Silent: They must be first activated by tissue inflammation before responding to a mechanical, thermal or chemical stimulus.

Polymodal: They are number of receptors (multi) that functions as one and respond to all stimuli[16].

NOCICEPTIVE PATHWAYS:

It includes afferent and efferent pathways starting from activation of nociceptors from any stimuli, then sending the information, sensing the information by the CNS and then reacting to the information.

The nociceptive afferent pathway is the phase in which the information is sent by the neurons to brain and the brain senses the pain. It involves three neurons:

- →Primary sensory neurons or first order neurons are the neurons in the peripheral nervous system, which conduct painful sensations from the periphery to the dorsal root of the spinal cord[17].
- →Secondary sensory neurons, also known as second order neurons in the spinal cord or brainstem, which transmit the painful sensation to the thalamus through spinothalamic tract which ascends cranially.
- →Tertiary sensory neurons or third order neurons which transmit the painful sensation from the thalamus to the primary somatosensory areas of the cerebral cortex.

The efferent nerve fibers in the in peripheral nervous system are:

Preganglionic motor neurons are neurons that connect the CNS to ganglia and are cholinergic (acetylcholine as neurotransmitter).

Postganglionic motor neurons are neurons from the ganglion to the effector organ or tissue. They use norepinephrine and acetylcholine as neurotransmitter.

Both the motor neurons carry the impulses of motor - movement signals out from the spine to peripheral effector organs.

BASIC PHYSIOLOGY OF PAIN:

When an injury occurs (such as accidentally cutting your finger with a knife), the stimulated nociceptors activate the A fibers, causing a person to experience sharp, prickling pain. This is the first phase of pain (fast pain), because it is not especially intense but comes right after the painful stimulus.

During the second phase of pain, the C fibers are activated, causing a person to experience an intense, burning pain that persists even after stimulus has stopped. The fact that burning pain is carried by the C fibers explains why upon touching a hot stove, there is a short delay before feeling the burn.

Despite from the receptors, there are also several chemicals produced by the body that excite pain receptors include bradykinin, serotonin and histamine.

Role of prostaglandins in pain: Prostaglandins are unsaturated fatty acids that are released when an inflammation occurs and can heighten the pain sensation by sensitizing the nerve endings. They are one of the more potent mediators that cause increased blood flow, chemotaxis and subsequent dysfunction of tissues. They are a body's response to noxious agents and as long as noxious agents persist; PGs will continue to be produced.

PROCESS OF PAIN PHYSIOLOGY:

There are four mechanisms involved in the physiology of pain. They are:

Transduction: On getting stimulus, pain receptors in peripheral tissues are activated. Transduction refers to the process by which external stimuli are converted to electrical signals for the transmission of signals.

Transmission: Signals from mechanical, chemical, thermal and mechano-thermal nociceptors transmitted to the dorsal horn of spinal cord predominantly by Aδ fibers, while polymodal nociceptors transmit their signals into dorsal horn of C fibers.

Aδ fibers (myelinated) send sharp, localized and distinct sensations due to low threshold, hence are responsible for transmitting of first pain felt while C fibers (unmyelinated) relay impulses that are poorly localized, burning and persistent pain. They are often responsible for secondary pain.

Perception: The perception of pain is experiencing the pain and is aware of pain- somatosensory cortex identifies the location and intensity of pain. Person unfolds a complex reaction- physiological and behavioral responses is perceived. The experience of pain known to have two distinct neural pathways.

In the first pathway, the pain signal comes from any part of the body and activates the anterior cingulate cortex of brain, which is associated with the perception of pain.

People react differently to this stimulation because of the feeling is determined by the activation of the second pathway involving the medial prefrontal cortex and nucleus accumbens which are associated with motivation and emotion. Further there are non-psychological factors that contribute to pain perception such as personality, cognitions, beliefs, socio-cultural variables, learning and emotional reactivity[18].

Modulation: Within the central nervous system, there are three types of opioid receptors which regulate the neurotransmission of pain signals the receptors are mu(μ), delta(δ)and kappa (κ) opioid receptors[19].

What are opioid receptors? They are G-protein coupled receptors with opioid as ligands and their activation leads to reduction in neurotransmitter release, thereby, reducing cell excitability. They are distributed widely in the brain in the spinal cord, on peripheral neurons and digestive tract.

Exogenous opioids such as morphine, provide excellent analgesia by acting on these receptors. Likewise, our body contains endogenous opioids which can modulate pain physiologically. There are three types of endogenous opioids:

- →**B-endorphins** - they predominantly bind to mu opioid receptors.
- →**Dynorphins** - they predominantly bind to kappa receptors.
- →**Enkephalins** - which predominantly bind to delta receptors.

MANAGEMENT METHODS FOR ALGIA:

Pain management refers to techniques to reduce and control the amount of pain a person experiences over the long term. There are many ways to manage pain and not all of them include taking medication.

PHYSICAL TECHNIQUES: It includes physical therapy, hot and cold therapy, massage and acupuncture[20].

Hot and cold therapy: it is a common and safe therapy to reduce pain. Heat can help relax the muscles and dilate the blood vessels. It can also promote healing after an injury. Cold therapy reduces blood flow and reduces inflammation that causes pain. It involves applying an ice pack wrapped in a towel to the skin.

Massage: It is a type of soft tissue manipulation. People may benefit from this technique when used with other pain management treatments such as physical therapy and pain medication. The benefits include- relaxation, increased flexibility, reduced inflammation, improved posture, improved circulation.

Acupuncture: it involves a practitioner applying thin needles to the skin at precise points in the body. This includes short-term relief from pain in the lower back, neck, knee and osteoarthritis.

MIND-BODY TECHNIQUES: Methods that combine psychology and the body can help many people manage chronic pain.

Cognitive behavior therapy (CBT): It is a short-term therapy that can help people find new ways to behave by changing their thought patterns. Psychological treatments aim to reduce the negative impact that pain can have on person's mental health.

Yoga: It is a mind and body practice. Various styles of yoga combine physical postures, breathing techniques and meditation or relaxation. It aims to relax, strengthen, an keep the body flexible through stretching, with specific poses focusing on particular body areas. It is a safe and accessible pain management techniques that people can try at home, using online videos or in a class with an instructor.

DRUG THERAPY: it includes the analgesics that are used as a medication for pain relief.An analgesic drug, pain reliever or painkiller is any member of the group of drugs that selectively relieves pain by acting in CNS or on peripheral pain mechanism, without significantly altering consciousness. They are conceptually distinct from anesthetics which temporarily reduce or eliminate sensation (loss of function)[21].

TYPES OF ANALGESICS- Analgesics can be broadly classified into two categories:

- →Non-narcotic analgesics
- →Narcotic analgesics

1. Non-narcotic or non-opioid analgesics are over the counter (OTC) and prescription medications used to alleviate pain. They have become increasing emphasized in a variety of clinical settings as a preferred, safe, and effective first-line therapy alternative to opioid medications for mild to moderate pain[22].

Analgesia: Prostaglandins induce hyperalgesia by affecting the transducing property of free nerve endings so that stimuli that normally do not elicit pain are able to do so. NSAIDs do not affect the tenderness induced by direct application of PGs, but block the pain sensitizing mechanism induced by bradykinin, TNFs, interleukins and other algesic substances primarily by inhibiting COX-2. This constitutes the peripheral component of analgesic action of NSAIDs. They are therefore more efficient against inflammation associated pain. Lately, the central component of analgesic action of NSAIDs has also been shown to involve inhibition of PG synthesis in the spinal dorsal horn neurons as well as in brain.

Some of the most commonly used agents include:

●→**Acetaminophen (paracetamol):** It is categorized under NSAIDs which has a central analgesic effect hat is mediated through activation of descending serotonergic pathways. Its primary site of action is inhibition of prostaglandin synthesis by interfering in the cycle (COX inhibitor)[23].

●→**Anticonvulsants** including **gabapentin** and **pregabalin** work by changing the way the nerves send message to the brain because of their high affinity for voltage-gated calcium channels. It blocks the tonic phase of nociception induced by formalin and exerts a potent inhibitory effect in neuropathic pain models.

●→**Antidepressants** including **amitriptyline** and **duloxetine** act by blocking the reuptake of both serotonin andnorepinephrine neurotransmitters, thereby, lowering the pain signals to the brain.

●→**Aspirin (acetyl salicylic acid):** Aspirin causes several different effects in the body, mainly the reduction of inflammation, analgesia, the prevention of clotting and reduction of fever. It acts as an acetylatingagent where an acetyl group is covalently attached on the active site of COX-enzyme. Its ability to suppress the production of prostaglandins and thromboxane is due to irreversible inactivation of COX-enzyme.

●→**Other NSAIDs (ibuprofen, diclofenac, naproxen** is class of NSAIDs, the non-selective inhibition of enzyme called as cyclooxygenase (COX), which is required for the synthesis of prostaglandins viaarachidonic acid pathway, while COX-2 inhibitors (such as celecoxib, rofecoxib etc.) selectively bind to COX-2 enzyme which is responsible for the prostaglandins production after injury[24].

●→Topical agents or painkillers are sprayed or rubbed in or applied onto the skin over painful muscles or joints like Lidocaine numbs the area where you have used it and works by stopping nerves from sending pain signals to the brain, thereby, producing temporary loss of function and Capsaicin, the main ingredient of hot chili peppers is one of the most effective topical pain relievers. When applied, it causes a warm tingling or burning sensation by depletion of substance P.

2.●→Narcotic analgesics or opioid narcotics are those substances or medications that act on opioid receptors produce morphine-like effects usually for pain relief. Opioids are a class of drugs naturally found in the opium poppy plant (Papaver Somniferum). Generally, for mild headache or muscle pain, OTC drugs are enough, but if the pain is severe doctor might recommend something strong, a prescription opioid.

How do opioids work?

Opioids produce effects on neurons by acting on receptors located on neuronal cell membranes. There are three major types of opioids receptors(mu, delta and kappa) as mentioned above responsible for antagonizing pain perception where drug binds. Opioid receptors are distributed throughout the central nervous system and within peripheral tissue of neural and non-neural origin.

Within the CNS, activation of mu receptors in the midbrain is thought to be a major mechanism of opioid induced analgesics. Mu receptor agonists act by indirectly stimulating descending inhibitory pathways which act on periaqueductal grey with the effect of an activation of descending inhibitory neurons and increase the stimulation of 5-HT and enkephalin- containing neurons which connect directly with substantia gelatinosa of the dorsal horn. This results in reduction of nociceptive transmission from the periphery to the thalamus

CLASSIFICATION OF OPIOIDS:

1.●→**Opioids are classified according to their mode of synthesis into alkaloids- natural, semi-synthetic and synthetic.**

Though morphine is the most widely known extract of Papaver Somniferum, four naturally occurring alkaloids can be isolated from it: morphine, codeine, papaverine and thebaine. Of these alkaloids, morphine, codeine and papaverine have found a place in clinical practice (morphine and codeine as analgesic agents while papaverine, a compound devoid of any pain killing properties and as a smooth muscle relaxant.

Simple chemical manipulations of these basic opiate alkaloids began to yield a range of semi-synthetic opioids useful in clinical medicine (such as diamorphine, dihydrocodeine, buprenorphine, naloxone, etc.).

A third category of synthetic opioids were also designed and categorized into four chemical groupings: the morphinan derivatives (levorphanol, butorphanol), the diphenylheptane derivatives (methadone, propoxyphene), the benzomorphan derivatives (pentazocine, phenazocine) and the phenylpiperidine derivatives (pethidine, fentanyl, sufentanil)

2.●→Opioids can also be classified according to their effect at opioid receptors (synthetic process)

In this manner opioids can be considered as agonists, partial agonists and antagonists. Agonists interact with a receptor to produce a maximal response (morphine). Conversely antagonists bind to receptors but produce no functional

response, but at the same time preventing an agonist from binding that receptor (naloxone). Partial agonists bin to receptors but only elicit a partial functional response no matter the amount of drug administered (buprenorphine).

DRUGS:

I. **Morphine:** This natural opioid analgesic act on the CNS. Its analgesic action is due to the action on opioid receptors. Its analgesia, euphoria and dependence are due to its action on mu-receptors. It reduces the pain threshold, thereby reducing the perception of pain. This action is assisted by the feeling of well-being. Its action on kappa receptors causes spinal analgesia. It directly acts on the cough centre and suppress cough. It is slowly absorbed through orally, during sub cutaneous and iv injection, it is absorbed rapidly. It is widely distributed throughout body. 50% of its seen as bound and rest is seen unbound with plasma protein it crosses the placental barrier. It is metabolized in liver by glucuronide conjugation. Morphine 6-glucuronide is one of the active metabolites and it is excreted via urine and through bile.

II. **Codeine:** Codeine or methylmorphine is morphine derivative with less analgesic and sedative effects than morphine. It has an exceptionally low affinity for mu receptors and the analgesic effect of codeine is caused by its conversion into morphine by cytochrome P450 enzyme. Hence, it may be useful for management in moderate pain or for antidiarrhea.

III. **Naloxone:** A semisynthetic opioid receptor antagonist used to reverse the effects of opioid drug overdose, naloxone is a pure antagonist, with no intrinsic agonist activity. Following subcutaneous or intramuscular injection,reversal begins within 2 to 5 minutes, as compared with 30 seconds to 2 minutes following intravenous administration.

IV. **Oxycodone:** Oxycodone is a semisynthetic opioid agonist. Oxycodone is indicated for the management of postoperative pain or other severe pain treatment when opioid analgesics are needed. It has high oral bioavailability. Its half-life is approximately 2-4 h and it is primarily excreted by the kidney25. Maximum plasma concentrations increase in renal failure and can cause toxicity. Its principal metabolites are nor-oxycodone and oxymorphone. Oxymorphone has some analgesic activity but is present in low plasma concentrations, and the parent compound is the main analgesic (Heiskanen and Kalso 1997). Its analgesic effect is about the same as morphine but its higher oral bioavailability means that its oral potency is approximately 1.5-2 times that of oral morphine.

V. **Buprenorphine:** It is a semisynthetic opioid structurally similar to morphine, yet reported to be at least 25 times more potent26. The strong receptor affinity prevents binding of other opioids, such as fentanyl, interfering with the effect of these other opioids and thus preventing their analgesic or antagonistic benefits. Several buprenorphine formulations are being used to treat chronic pain or substance abuse.

VI. **Methadone:** it is a synthetic μ-opioid receptor agonist. It is a racemic mixture of two enantiomers, out of which R-form is more potent having high affinity for mu receptor while S-methadone is the NMDA (N-methyl-D-aspartate) antagonist. The inherent NMDA antagonistic effects make it potentially useful in neuropathic and opioid resistant pain states. It is a basic and lipophilic drug with an excellent oral bioavailability[27].

VII. **Fentanyl:** it is a strong synthetic phenylpiperidine opioid agonist interacting primarily with mu receptor and available in parenteral, transdermal and trans-buccal preparation. It is 80 times more potent than morphine[28].

VIII. **Levorphanol:** it is a synthetic morphine analogue which is used to treat moderate to severe pain. It is potent as hydromorphone but long lasting. It is mu, delta and kappa agonist as well as NMDA antagonist. Therefore, it makes levorphanol like methadone useful for types of pain that other analgesics may not be as effective agonist such as neuropathic pain[29].

IX. **Tramadol:** it is a strong pain medication used to treat moderate to severe pain that is not being relieved by other medications. Tramadol is a synthetic opioid and it acts on brain and spine to reduce the amount of pain you feel. When taken orally, the onset of action usually begins within an hour for immediate release formulation. Common side effects including nausea, constipation, itchiness[30].

CONCLUSION

Pain is more than just a physical sensation that serves to protect the body, but prolonged or poorly managed nociception significantly reduce the quality of life. Understanding the etiology behind pain is necessary for both healthcare providers and patients for proper diagnosis and treatment with some preventive measures, because this is the only way to manage pain and if any, mistake will be taken during these procedures can cost the life and if not then, it simply affects the quality of life. Accurate measurements through reliable tools are important. As our knowledge of pain continue to evolve, a comprehensive and empathetic approach

remains vital for improving outcomes and supporting those affected by pain in both clinical and everyday settings.

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