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Pain Management: A systematic review

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Abstract: *Pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. In general, pain is underestimated by healthcare providers. This underestimation might lead to poor management which negatively affects patients' outcomes, quality of life, and satisfaction. Therefore the purpose of this review was to understand what pain means, its physiology, types and what are the different therapies available to manage pain.*
Keyword: *pain, types of pain, pharmacological pain management, and non-pharmacological pain management*

I. Introduction

The search has been conducted through the use of various search engines such as CINAHL, PubMed, MEDLINE and Google Scholar. The criteria for the searching process included only articles that have been published from 2000 - 2016. However, some studies that have been published earlier were also considered under certain circumstances. All articles that have been reviewed were published in English. All relevant articles were included in this review. This review included the following sections:

1) Pain
2) Types of pain
3) Physiology of pain
4) Pain Management (Pharmacological and Non-pharmacological).

1. Pain:

Pain is still one of the most challenging prevalent problems. Worldwide, the prevalence of chronic pain reaches up to 30% [1]. In the United States, it was estimated that 126 million American adults reported some pain in the last three months [2]. In Canada, more than 47% reported that they experienced pain [3]. In Italy, pain was reported by more than 80% of patients [4].

The situation is approximately the same or even worse in the developing countries. For instance, 55% of chronic low back pain patients were classified to have neuropathic pain in Arabian Gulf region [5]. In Jordan the prevalence of pain experienced by cancer patients is estimated up to 73.3% [6]. Moreover, in another recent study conducted in Jordan, it was found that 72.0% of patients surveyed experienced moderate to severe postoperative pain at rest [7].

In the United States, it has been estimated that the cost of chronic pain may exceed $635 billion annually, which divided to direct medical expenditures and loss of work productivity [8]. Among Swedish patients, the socioeconomic cost burden of chronic pain was approximately €32 billion [9]. In Ireland, the cost of chronic pain was €5,665 per patient annually [10].

There are numerous difficulties in defining the concept of pain. This lack of definition is mainly because of the nature of the phenomenon. However, pain is defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage" [11]. In general, pain is underestimated by healthcare providers [11-13]. This underestimation might lead to poor management which negatively affects patients' outcomes, quality of life, and satisfaction [14].

2. Type of pain:

Pain is classified into two categories: acute and chronic, depending on its duration and time course [15]. Acute pain is defined as "pain which has a sudden onset with varied intensity lasting for less than six months" [16]. Chronic pain is defined as "pain that lasts for more than six months which may or may not have an underlying pathology to explain the patient's suffering" [16].

Moreover, there are other classifications of pain in regards to its location, etiology, duration, and neuro-physiological mechanisms [15]. Neuro-physiological mechanisms of pain are categorized as the following: nociceptive and non-nociceptive pain [17].

Nociceptive is a term that describes the normal physiological process relating to tissue damage [18]. Further, nociceptive pain can be divided into somatic and visceral pain [15]. Somatic pain is pain resulting from excitation and sensitization of nociceptors in tissues, such as bone, skin, joints, and muscles. It is intermittent or constant and it could be described as aching, stabbing, gnawing, or throbbing [15]. In contrast, visceral pain

involves organs such as heart, stomach, or liver. This pain is diffuse, for this reason it is referred to other location. However, visceral pain not always linked to visceral injury; for instance, stretching of the bladder can cause this pain [19].

Non-nociceptive pain can be subdivided into neuropathic and idiopathic pain [15]. Neuropathic, which relates to pain caused by damage to, or dysfunction of, the nervous system [20]. Neuropathic pain is usually described as sharp and burning pain [15]. In contrast, Idiopathic pain refers to the state of pain which is poorly understood such as myofascial pain syndrome and somatization pain disorder [15].

3. Physiology of pain

Nociception is the transfer of information from the site of tissue damage to the central nervous system [18]. However, nociceptive pain is caused by activation of chemoreceptors, mechanoreceptors, and thermoreceptors, depending on the cause of damage/ injury [21]. It alerts, thus, protects patients from damage or injury that might occur. Besides, it is considered as a constant reminder of the need to protect the affected area while healing is accomplished [20].

Also, the nociception represents the process that starts with a painful stimulus or tissue injury, electrical nerve impulses transmission to the spinal cord then to the brain. The final step in this process is the full awareness of pain [20]. Actually, the nociception occurs in four phases: transduction, transmission, perception, and modulation [22].

When the tissue perceiving detrimental stimulus, a nerve impulse is generated in a process called transduction [18]. Transduction initiated when injured cells release nociceptor-sensitizing substances such as bradykinin, serotonin, histamine, prostaglandins, and substance P. The nociceptor-sensitizing substances generate a current, known as an action potential [22].

Throughout the transmission phase, the electrical signal information is transmitted along two types of peripheral nerve fibers (A and C) delta to the dorsal horn of the spinal cord [23]. For illustration, A-delta fibers are covered by a fatty myelin sheath that isolates the fibers, ensuring that the signals travel quickly. These nerves are responsible for the localized, sharp, stabbing pain that initially happens with injuries, alerting the person to the damage.

C-delta is unmyelinated fibers so the signals travel slower and create dull, aching pain that continues after an injury trying to foster rest and prevent further damage [20]. Awareness of pain characterizes perception. The somatosensory cortex helps to locate and interpret pain. Arousal, motivation and emotions are controlled by the reticular activating and limbic systems [20].

Finally, the human body modulates pain experiences of nociception [20]. Controlling structures located in the dorsal horn of the spinal cord modulate ascending nociceptive transmissions. Neurons located in the lower brain stem regulate this modulation. During the modulation process, nociceptive impulses transmit through dorsal horn projections in the spinal cord. The spinal cord then releases substances such as serotonin, endogenous opioids (e.g., endorphins, enkephalins), and norepinephrine. This process of modulation, ending in the release of these substances, helps in the decrease or "down-regulate" the pain response [22].

Neuropathic pain is chronic pain caused by injury or dysfunction in the nervous system [21]. In fact, it can occur in the peripheral or central nervous system [22, 24]. Also, it has absolutely no protective function [25]. The pathophysiology of neuropathic pain is complex and is not fully understood, but a number of mechanisms are believed to be involved [20].

The mechanism that may contribute to neuropathic pain in central nervous system is; central desensitization. This is develops when the part of nociception that should disappear when healing accomplished, continues and become permanent. The increased receptive field for peripheral nerve input may continue, interneurones might die, and there may be an excess in neurotransmitter release. Furthermore, the descending inhibitory mechanism that tries to modulate pain may also be affected in people with neuropathic pain. This means that endogenous opioid production or the pathways that decrease pain may be not effective [20, 25].

Further, Peripheral nerves may also be affected by some changes as a result of nerve damage. Increased excitability and spontaneous firing of neurons may occur after injury [25]. During the trails of repair and regeneration, propagation or enlarged nerve tissue forms a structure called a neuroma. Yet, neuromas can produce random signals along the nerve pathway [20].

4. Pain Management

Pain management is complex due to several causes, including the mechanisms of pain, classification, individualization, lack of commonly accepted guidelines, knowledge, psychological and social factors [26]. Pain management is well known since many decades. It has been improved a lot lately and is starting to involve plenty of diverse methods. Certainly, the management of pain is a multidisciplinary task, the control of pain can be pharmacological and non-pharmacological, or a combination of these two therapies.

4.1 Pharmacological Methods

Pain that affects patients' physical function or their quality of life should be recognized as a significant problem. Elderly, cancer, postoperative, and traumatic patients with functional impairment or diminished quality of life are ideal candidates for pharmacological therapy. However, the intervention decision either to be pharmacologic or non-pharmacologic is based on a cautious weighing of risks and benefits [27-29]. Pharmacotherapy are generally classified into two lines therapy which are first line or non opioid analgesics and second line or opioid analgesics [28].

4.1.1 Non opioid drugs

Generally, a recommended practice by clinicians is usually to start with non opioid analgesics such as Acetaminophen, Non Steroidal Anti-Inflammatory Drugs (NSAIDs), and gradually advance to more potent analgesics till the pain is relieved [28]. Acetaminophen is useful as a primary analgesic or in combination with other drugs for treating mild to moderate pain [28]. Acetaminophen has analgesic and antipyretic effects similar to NSAIDs, it works by inhibiting the synthesis of neurotransmitter prostaglandins in central nervous system (CNS), and this is why it has no specific anti-inflammatory effect [30].

Acetaminophen safe dose should not exceed four gram per day to reduce the risk of asymptomatic elevations of aminotransferase levels, thus, hepatotoxicity [29, 30]. Moreover, the very low cost and apparent risks of acetaminophen therapy suggest a highly favorable risk-benefit ratio that might justify the repetitive use of Acetaminophen. However, it was reported that the use of acetaminophen and an NSAID as a combination was superior to use acetaminophen alone [31].

Aspirin and other related compounds constitute a category of drugs known as (NSAIDs) [32]. The NSAIDs are useful analgesics for managing mild to moderate pain, particularly of somatic origin such as bone, muscle, and skin. These medication are frequently used if there are no contraindication because of gastrointestinal, renal, or cardiovascular disease [29].

Traditional NSAIDs have three major effects: analgesics, anti-inflammatory and antipyretic, because of their effect as inhibitors of prostanoid synthesis via blockade of both cyclo-oxygenases (COX-1 and COX-2) [32]. Although it is known that NSAIDs are less potent than opioids for the treatment of pain, several NSAIDs drugs provide a documented percentage of 30–50% of Morphine-sparing effect and improve analgesia when co-administered with patient control analgesia (PCA) morphine [31]. It is well known that the use of these drugs is associated with gastrointestinal, cardiac, renal and other adverse effects [31]. In order to reduce the incidence of severe gastrointestinal adverse effects associated with long-term use of traditional NSAIDs, selective COX-2 inhibitors were developed [33]. In the meantime, the use of these drugs remains under scrutiny, especially for those who are at cardiovascular risk [31].

However, American Heart Association recommended acetaminophen, nonacetylated salicylates and even opioids instead of NSAIDs and particularly COX-2 agents in patients with coronary artery disease [30]. Further, in some situations, NSAIDs can cause acute renal failure due to the inhibition of the biosynthesis of prostaglandins involved in the maintenance of renal blood flow [31].

4.1.2 Opioid drugs

Opioid analgesics are commonly used as the first-line treatment of moderate to severe pain either in acute, chronic, cancer related or at the end of life [34]. However, opioids are very effective analgesics in the short term, but the evidence showed some limitations of efficacy in long-term [35]. As a consequence, patients on opioids therapy should have regular check up for both; drug efficacy, patients' tolerability [35]; the need to increase the dose to achieve the needed effect of analgesia.

Despite the controversy about the use of opioids in the treatment of non-cancer pain, opioids drugs reported effective response in the treatment of selected patients with persistent non-cancer pain [34]. In contrast, the long term use of opioids in the treatment of persistent pain may be associated with few serious potential risks compared with long term use of NSAIDs, [34]. Opioids have their specific potential risks such as respiratory depression, sedation, impaired cognition and psychomotor function, constipation, nausea and vomiting, and urinary retention [34, 36] Generally, the available opioids are either μ-opioid receptor agonists or drugs with direct affinity for μ-opioid receptors which appear to be responsible for pain relief [30]. In this review we discussed the main available opioids, which are currently used in clinical practice such as Morphine, Meperidine, Fentanyl and Tramadol.

Morphine

Morphine deemed as the drug of choice for treatment of moderate to severe cancer pain [37]. It can provide clear reductions in pain intensity, therefore, it is one of the most commonly prescribed opioids in critical care units [37]. Morphine act as μ-receptor pure agonist, it is hydrophilic, which contribute to its slow onset and long duration of action [38]. Morphine is primarily effective for the treatment of nociceptive pain. On the other

hand, it was found that Morphine could be effective for the treatment of neuropathic pain particularly when combined with antidepressants and the gabapentinoids [38]. Mainly, Morphine is metabolized in the liver and eliminated by the kidneys. For this reason, Morphine should be prescribed cautiously for patients with renal failure [37, 39]

Meperidine

Meperidine is less potent opioid than Morphine and is considered as the weakest of the opioids [40]. Most often, it is administered in frequent doses because of its short duration of action. Meperidine has a several disadvantages particularly when compared with other opioids [40]. Its analgesic effects are not pronounced [41]. Further, Meperidine has numerous potential drug interactions, which includes the possibility of serotonergic crisis, and metabolite toxicity that may induce central nervous system dysfunctions which includes seizure [41, 42].

Fentanyl

Fentanyl is a fast acting lipophilic opioid, and it is available in several forms such as parenteral, transmucosal, and transdermal formulations [36]. However, intravenous fentanyl is 70 to 100 times more potent than IV morphine [36]. Fentanyl therapy can lead to serious side effects such as hypotension, respiratory depression, hypoxemia, or sedation [43].

Tramadol

Tramadol is a centrally acting as μ -opioid receptor agonist [30]. It acts as a weak nor-epinephrine and serotonin reuptake inhibitor. Although the mechanism of action of tramadol is not fully understood, it is known that tramadol have dual activity: an opioid like mechanism and non-opioid like mechanism [44, 45]. It is actually indicated for the management of moderate to severe pain [44].

Tramadol therapy is associated with seizures, thus, this medication is contraindicated for those patients. In addition, patients who are on the following medications: a) tricyclic or selective serotonin reuptake inhibitors (SSRI), b) antidepressant, c) a monoamine oxidase inhibitor, and d) an antipsychotic drugs should not take Tramadol; because of increasing risk of seizures [32]. Tramadol dose should not exceed 400 mg daily. Moreover, dose reduction is recommended, particularly, in older adult patients and for those with renal impairment or cirrhosis [30].

4.2 Non-pharmacological Methods

Non-pharmacologic treatments are important adjuncts to treatment modality for patients with pain [46]. Non-pharmacological methods may be used independently with mild pain. In addition, it can be used along with pharmacological therapy as a complementary option for moderate to severe pain [47, 48]. Non-pharmacological treatments are defined as: therapies that do not require taking medication or any other active substances, but make pain more tolerable and give patient a sense of control over the situation [49].

In the scope of non-pharmacological pain management, the systematic research still very little and the evidences are contradictory [50]. However, non-pharmacological treatments are divided into multiple categories: a) cognitive behavioral, b) emotional support, c) physical technique, d) creating a comfortable environment, and e) helping with activities of daily living [51, 52].

Cognitive-behavioral: focuses on the interactions between the brain, body, mind and behaviors. This is done with the intention to use the mind to affect physical functioning such as: thinking about something else, hypnosis, imagery, relaxation, distraction, breathing techniques and preparatory information [51, 53].

Emotional support: concentrates on sensitive, caring and understanding approaches. These approaches facilitate communication of anxiety or fears and provide assistance in the management of difficulties [53].

Physical technique: usually focuses on the systems and structures of the body, including the joints, bones, soft tissues, circulatory and lymphatic systems. These techniques include positioning, massage, and thermal regulation, heat/cold application, and rubbing over the painful area [53].

Creating a comfortable environment: focuses on ameliorate the intensity/amount of stress and making comfortable environment as much as possible. Examples include:: minimizing noise, providing the patient's with his favorite belongings and maintaining a pleasant room temperature [51].

Helping with activities of daily living: focuses on assistant needed to perform these activities; bathing eating, and walking [51].

II. Conclusion

Pain an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage. In general, pain is underestimated by healthcare providers. This underestimation might lead to poor management which negatively affects patients' outcomes, quality of life, and

satisfaction. This review focused on different pain management techniques that are used in the clinical settings; including pharmacological and non-pharmacological.

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