ISSN: 2476-5279; International Journal of Musculoskeletal Pain Prevention. 2026;11(3): 1434-1442

# Pain :Anatomy and Practical Tips

INFO

*Article Type*
Narrative Review

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How to cite this article

Motaqi M, Ghanjal A. Pain (Anatomy and Practical Tips): review article. Int J. Musculoskelet. Pain. Prev. 2026;11(4): 1434-1442

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ABSTRACT

**Aims:** This article presents information on the anatomy of pain, the concept of pain, and related topics.
**Method and Materials:** This article was conducted by reviewing scientific articles related to pain including the anatomy of pain, the concept of pain, types of pain, neural connections of pain, and other related topics.
**Findings:** Pain is an unpleasant sensation that usually occurs following physical or mental damage and is a topic discussed across various sciences, including medicine and psychology. Pain has been classified and defined in various ways, including intensity, type, cause, transmission pathways, and other side effects..
**Conclusion:** This review study addresses pain and related topics, including the nature of pain, pain receptors, pain pathways, the modulating effects of these pathways on pain reduction, and types of pain.

**Keywords**: Opioids, Pain Anxiety, Coping Strategies, Somatization Disorder, Chronic Pain

## Introduction

Pain is an unpleasant sensation that usually occurs after physical or psychological injury and can lead to disability and suffering for the affected individual [1]. The sensation of pain is a topic discussed across various sciences, including medicine and psychology, and is considered the most important sensory quality in humans [2]. From a medical perspective, pain alerts humans to harmful stimuli within the body and prompts them to seek medical care. Many physical and mental diseases cause pain, and the diagnosis of different diseases is largely related to a doctor's knowledge of pain and the information surrounding it. Pain has been classified and defined in terms of severity, type, causes, routes of transmission, and other side effects in various ways [3]. The pain system comprises primary afferents (sensory fibers) that interact with these sensory pathways and brain centers, which largely modulate projections to various brain areas, and the perception of pain intensity [4]. The purpose of this review is to provide information on the concept of pain, the anatomy and pathways of pain In the modulation phase, neural activity along transmission, and related topics.

**Pain and its meaning**:

Pain significantly affects the health and functioning of the affected individual [5]. According to the International Pain Society, pain is a feeling of discomfort and suffering, usually associated with tissue or emotional damage [6]. Today, pain is considered the fifth vital sign in patient care [7].

The steps required to perceive pain include four stages: Transduction, Transmission, Perception, and Modulation. The conduction process occurs at the peripheral endings of afferent nerves, where various types of energy (mechanical, thermal, chemical) are converted into electrical activity and action potentials (stimuli and damage resulting from them cause the release of compounds such as Prostaglandin, Bradykinin, Serotonin, Substance, and Histamine). In the transmission phase, the generated electrical activity is transmitted through the nervous system. In the perception stage, information from ascending pathways is processed in brain centers, and

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Article History
Received: Dec 21, 2025
Accepted: Mar 13, 2026
ePublished: June 30, 2026

pain is perceived[1]. The transmission pathway can cause pain to decrease or increase. The dorsal horn of the spinal cord is one of the major sites that plays a major role in modulation [1]. Cerebral and supraspinal mechanisms play an increasingly central role in the representation and modulation of the pain experience [8].

**Pain receptors**

Pain receptors (in the skin and other tissues) are free nerve endings. These receptors are present in the layers of the skin, some internal tissues of the body, the walls of arteries, joint surfaces, the sclera, and the meninges of the cranial cavity [9]. The number of these nerve endings in the body's deep tissues is very low; however, diffuse tissue damage can cause chronic, slow-onset pain in most of these areas [10]. Pain stimuli are classified into three groups: mechanical, thermal, and chemical. In general, thermal and mechanical stimuli produce fast or sharp pain, while slow or dull pain is produced by all three types of stimuli [11-12]. Some of the chemicals that cause pain include bradykinin, serotonin, histamine, potassium ions, acids, acetylcholine, and proteolytic enzymes. In addition, prostaglandins and substance P increase the sensitivity of free nerve endings, but do not directly stimulate them. Chemicals, in particular, play a role in causing slow pain caused by tissue damage [13]. Chemical, mechanical, and thermal stimuli can activate pain receptors, which are abundant in most parts of the body. The creation of pain in tissues is often due to the production of substances called prostaglandins, which increase the sensitivity of pain receptors. Aspirin and other non-narcotic pain relievers inhibit the production of prostaglandins and relieve pain. [12].

**Types of Pain**

Pain is classified into different types based on its severity, type, cause, routes of transmission, and other side effects. Some of them are briefly mentioned below [3].

The cause of pain can be physiological or psychological. Accordingly, pain is generally divided into two large parts: pain that is caused by direct stimulation of specific receptors (nociceptors) (physical or chemical), and pain that is not caused by stimulation of these receptors. There is also a third type of pain caused by neuroplasticity (the adaptation or change of nerve cells in response to a stimulus) [14].

**Acute Pain**

Acute pain usually occurs after a sudden injury, such as trauma, acute illness, or inflammation, and accounts for about 33% of visits to the doctor. Acute pain is usually associated with illness or injury and can be distressing to the patient. Acute pain can be short-lived, such as an insect bite, or last for weeks, such as a burn. When a person experiences acute pain, they know exactly where the pain is coming from. Acute pain is sometimes called "severe pain," which can include the long-term course of a disease. Men tend to tolerate acute pain better than women do [15].

**Chronic Pain**

Chronic pain is pain that lasts between three and six months and can be continuous or intermittent. Chronic pain can be divided into three distinct but interacting pathways (anatomically and phenomenologically): the lateral pathway (the nociceptive pathway), the medial pathway (the pain pathway), and the descending pathway of pain inhibition. A person may have a lot of pain without suffering, or a lot of suffering without a lot of pain[15]. The prevalence of chronic pain increases with age, with the prevalence reaching at least 20% in people over the age of 55. Chronic pain often causes depression. It usually heals very slowly, like burns, and may even lead to death [16]. Another characteristic of chronic pain is that its cause is not completely clear (in some cases). Chronic pain is often disabling and makes life difficult for the person. Patients with chronic pain have a longer experience of pain, and their pain may have frequent relapses [17-18].

**Superficial and deep pain**

If the pain is in the superficial layers of the skin, it is called superficial pain, such as a needle-like or stinging pain. Superficial pain is felt clearly after the contact of the pain agent (such as the tip of a needle with the hand) and disappears immediately when the stimulus stops.

This pain is also called "primary pain".If the

stimulation is more intense, usually after half a second to a second, the person feels a vague, burning pain. This pain disappears slowly when the stimulation stops and is called "secondary pain".If the pain is in the muscles, bones, connective tissue, and joints, it is called "deep pain".Muscle cramps and headaches are types of pain that may be accompanied by deep burning[4-5,19].

**Rapid or sharp pain**

Rapid pain is felt within about 0.1 seconds of the application of the noxious stimulus. Rapid pain is also known as sharp, stabbing, acute, or electrical pain. This type of pain is felt when a needle is inserted into the skin, or the skin is cut with a knife, or when it is burned suddenly, or when the skin is exposed to an electric shock. Rapid pain is not felt in deeper tissues of the body [3,5,20].

**Slow or dull pain**

Slow pain is felt a second or so after the noxious stimulus is applied and increases gradually over a few seconds or even minutes. Slow pain also has various names, such as slow-burning, dull, throbbing, nagging, and chronic pain. This type of pain is usually associated with tissue damage and can cause long-term and unbearable suffering. Slow pain occurs in both the skin and other tissues or organs deep within the body [3,5,21].

**Visceral pain**

Viscers are naturally sensitive to touch, pressure, heat, and even cutting. Except for the mesentery, which has a few Pacinian corpuscles and a small number of thermal receptors, the other parts lack specialized receptors. In cases where the viscera are displaced from their physiological and normal state (such as dilation of the internal cavities, pressure due to a tumor in the viscera, or lack of oxygen), pain is felt because pain receptors are present in the viscera but are more scattered than in the skin. Visceral pain is poorly localized and often radiates to surrounding areas or is referred to other regions. Pain receptors are present in the sebaceous glands, cavities, capsules, and arterial walls. Visceral pain is accompanied by nausea and excitatory reactions of the autonomic nervous system. In many cases, there is no obvious underlying pathological cause of the pain. Accordingly, chronic visceral pain is debilitating, reduces the quality of life of sufferers, and has large concomitant socioeconomic costs [3,21-22].

**Emotional pain**

The cause of emotional pain, as the name suggests, is emotional and related to feelings. Sometimes, unfortunate events occur that make a person feel bad, such as the loss of loved ones. If the intensity of these feelings is high, it leads to pain and illness in affected people. Although the term "emotional pain" is a term to indicate "painful feelings", it sometimes turns into physical pain with external manifestations. Neurobiological research documents the neural processes that distinguish affective from sensory pain dimensions, link emotion and pain, and generate central nervous system pain sensitization. Psychological research demonstrates that greater pain is related to emotional stress and limited emotional awareness, expression, and processing. Social research highlights the potential importance of emotional communication, empathy, attachment, and rejection [3, 23].

**Pain receptors and the mechanism of pain**

There are various and specialized nerve receptors throughout the body. They are diverse in shape, function, and stimulus type, but pain receptors are not specialized or macroscopic; they are free nerve endings called nociceptors. Pain points are actually the location of pain receptors, which are more numerous than pressure receptors. In different parts of the body surface, there are an average of 200 pain receptors and about 20 pressure receptors per square centimeter. Nociceptors are generally divided into two groups: somatic and visceral [24].

Somatic nociceptors are divided into two groups:

1- Superficial nociceptors, which are distributed on the surface of the skin.

2- Deep nociceptors, which are found in muscles, fascia, joints, and connective tissues.

Nociceptors are distributed in the skin, deep tissues, and viscera, and their distribution varies in different parts of the body. For example, the number of these receptors is lower in the fingertips and higher in the

cornea.

Visceral receptors are distributed throughout the body's viscera and have a variety of mechanisms for stimulation. In hollow viscera such as the colon and stomach, pain receptors are stimulated by distension, whereas in solid viscera, they are stimulated by pressure. Nociceptors generally respond only to stimuli that cause or threaten to cause tissue damage. Therefore, stimuli that do not cause tissue damage do not activate nociceptors. The speed of impulse conduction in the slower nociceptors is 0.5-30 meters per second, whereas in the faster receptors it is 30-120 meters per second [24].

Nociceptor stimuli are divided into three categories:

1- Chemical stimuli: By causing cell damage, chemicals inside the cells are pushed out of the cells and stimulate pain receptors.

These substances include prostaglandins (e.g., PGE1, PGE2, PGD2), histamine, bradykinin, serotonin, leukotrienes, thromboxane, and substance P.

2- Thermal stimuli (heat and cold).

3- Mechanical stimuli (pressure and impact)[24].

Nociceptor sensory neurons protect organisms from danger by eliciting pain and driving avoidance. Pain also accompanies many types of inflammation and injury. It is increasingly clear that active crosstalk occurs between nociceptor neurons and the immune system to regulate pain, host defense, and inflammatory diseases. Immune cells at peripheral nerve terminals and within the spinal cord release mediators that modulate mechanical and thermal sensitivity. In turn, nociceptor neurons release neuropeptides and neurotransmitters from their nerve terminals, thereby regulating responses of vascular, innate, and adaptive immune cells. Therefore, the dialog between nociceptor neurons and the immune system is a fundamental aspect of inflammation, both acute and chronic. A better understanding of these interactions could yield approaches to treating chronic pain and inflammatory diseases [24].

## Pain afferent nerve fibers

Nerve messages resulting from stimulation of nociceptors are transmitted by specific nerve fibers of the Aδ and C types to the spinal cord. Nerve fibers involved in the transmission of pain impulses or pain relief are: Large fibers (A) and Small fibers (C).

A fibers have different types, only two of which play a role in the transmission of pain impulses or pain relief:

ABeta fibers (Aβ). These fibers have thick myelin and are the largest and longest nerve fibers, which have the fastest transmission of nerve messages due to the presence of Ranvier nodes and myelin. These fibers transmit touch, vibration, and pressure sensations and play a role in the mechanism of action of TENS (transcutaneous electrical nerve stimulation). Therefore, these fibers do not play a role in the transmission of pain impulses, but they play a role in pain relief. The speed of nerve impulse transmission in these fibers is 30-70 meters per second.

A Delta (Aδ) fibers are myelinated, but less myelinated than Aβ fibers. They are also smaller, shorter, and have slower conduction speeds (12-30 meters per second) than Aβ fibers. These fibers transmit pain and heat signals and contain 25% of nociceptors. Stimulation of Aδ fibers causes localized, sharp, prickly pain and is used in acupuncture.

C fibers: These fibers are the thinnest and shortest nerve fibers that have the slowest nerve signal transmission speed (0.2-5 m/s) due to the lack of myelin and nodes of Ranvier. These fibers contain 75% of nociceptors and, like Aδ fibers, transmit pain signals. Stimulation of C fibers causes a sensation of pain that is poorly localized, continuous, dull, and burning [25-26].

The role of the spinal cord in the transmission and modulation of pain impulses:

Most pain information begins at simple, naked nerve endings called nociceptors that form a functional pain unit with nearby tissue capillaries and mast cells. Tissue injury causes these nerve terminals to depolarize, an event that is propagated along the entire afferent fiber, thereby producing sensory impulses that reach the spinal cord. This firing of primary afferent fibers at the site of tissue injury causes axonal release of vesicles containing neuropeptides such as substance P,

which acts in an autocrine and paracrine manner to sensitize the nociceptor and increase its rate of firing. Cellular damage and inflammation increase the concentrations of other chemical mediators, such as histamine, bradykinin, and prostaglandins, in the area surrounding functional pain units. These additional mediators act synergistically to augment the transmission of nociceptive impulses along sensory afferent fibers. Primary fibers travel from the periphery to the dorsal horn, where they synapse on secondary neurons and interneurons. When activated, interneurons exert inhibitory influences on the propagation of further pain signals. Efferent supraspinal influences, in turn, determine the activity of interneurons by releasing a variety of neurotransmitter substances, thus resulting in a high degree of modulation of nociception within the dorsal horn. Events occurring in the periphery and the dorsal horn can cause a dissociation between pain perception and the presence or severity of actual tissue injury. These phenomena involve many chemical mediators and receptor systems, and can increase pain experience qualitatively, quantitatively, temporally, and spatially. The complexity and plasticity of the nociceptive system can make clinical management of pain difficult [27-29].

Aδ and C fibers enter the dorsal horn of the gray matter of the spinal cord through the dorsal root and terminate there. These fibers travel in the opposite direction after synapsing with the next neuron. The synapse is the site of action of drugs and neurotransmitters (nerve mediators). Opioids, by releasing inhibitory transmitters in the synapse, inhibit further transmission of nerve signals to higher centers. The synapse is actually the site of modulation of nerve messages. In 1965, the Gate-control theory was proposed by two scientists, Melzack and Wall, as follows: In the dorsal horn of the spinal cord, there is a region called the Substantia gelatinosa, where the Gate-Control system, with the activity of the T cell (Transmission cell), is located. Stimulation of C and Aδ fibers causes pain messages to enter the Substantia gelatinosa in the spinal cord. These messages, by exerting an excitatory effect on the valve, can cause it to open, thereby transmitting the nerve signal to higher centers and the brain. The greater the intensity of the painful stimulation, the more the valve opens. In other words, by stimulating C fibers, the transmission of pain to higher centers is facilitated. On the contrary, some factors exert an inhibitory effect on the valve, causing it to close:

1- Factors that pull the valve towards itself from the outside:

Stimulation of Aβ fibers by vibration, touch, and electricity exerts an inhibitory effect on the valve by secreting enkephalins (endogenous opiates) in the dorsal horn, resulting in its closure. Clinically, massaging the painful area, physiotherapy with vibration, electrical stimulation of the painful area (TENS), and acupuncture stimulation of Aβ fibers cause the valve to close, thereby reducing the transmission of pain signals to higher centers and reducing pain. Injection of narcotics into the cerebrospinal fluid (CSF) by penetrating the nerve synapses in the dorsal horn causes the valve to close and relieve pain. Since Aβ fibers are destroyed in herpes zoster, acupuncture does not improve pain relief [27-29].

2- Factors that direct the valve from the inside to the outside:

Pain messages from the environment enter the spinal cord and then the brain, and the brain, in response, sends inhibitory signals back to the spinal cord. Inhibitory messages act through chemicals and adrenergic neurotransmitters, gamma-aminobutyric acid (GABA), serotonin (5-HT), and beta-endorphins, and can activate descending inhibitory systems on the valve, causing the valve to close. Therefore, the entry of pain impulses from the environment into the brain is reduced, and as a result, the patient's pain sensation is diminished. In and around the pituitary gland, there is an endogenous opioid called beta-endorphin, which is released by electrical stimulation of that area and causes the valve to close and relieve pain [27,29, 30].

**Pain Transmission Pathways**

Pain involves a complex interplay between messages sent from the environment to the central nervous system and vice versa.

Specific pathways play a critical role in transmitting these messages and modulating or exacerbating their downstream effects.

**A: Ascending pain pathways**

After entering the dorsal horn of the spinal cord, Aδ and C fibers synapse and continue their path in the opposite direction. Aδ fibers ascend through the spinothalamic pathway to the thalamus, and pain is felt in the thalamus. Then, after synapsing, they travel to the brain's sensory cortex, where pain is perceived (the truth determines the pain's intensity and origin). The degree of pain perception depends on the intensity of stimulation, anxiety, the extent of tissue damage, and the patient's/injured person's confusion and distraction. C fibers ascend through the spino-reticular pathway to the reticular formation, and after synapsing there, continue their path to the thalamus. Like Aδ fibers, these fibers continue their path to the sensory cortex of the brain after re-synapsing in the thalamus.

Although all pain receptors are free nerve terminals, these terminals use two separate pathways to transmit pain signals to the central nervous system. These two pathways correspond primarily to two types of pain: the fast pain pathway and the slow pain pathway [28-29, 31].

In peripheral pain fibers (fast and slow fibers), fast pain signals are generated by mechanical or thermal stimuli. These signals are transmitted to the spinal cord by small type Aδ fibers (conduction velocities of 6 to 30 m/s) in the peripheral nerves. In contrast, slow pain is mainly generated by chemical stimuli and sometimes by sustained mechanical or thermal stimuli. Slow pain is transmitted to the spinal cord by type C fibers (conduction velocities of 0.5 to 2 m/s). Because of this dual system for innervation of pain, a sudden painful stimulus often produces a dual pain sensation. The fast, sharp pain that reaches the brain via the Aδ fiber pathway is replaced after a second or so by a slow pain that is transmitted via the C fiber pathway. Sharp pain quickly alerts a person to a noxious stimulus, so it plays an important role in triggering an immediate response to avoid it. However, slow pain tends to increase over time. This sensation eventually becomes unbearable pain, forcing the person to eliminate its cause. After entering the spinal cord (via the dorsal roots of the spinal cord), the pain fibers terminate on relay neurons in the dorsal horn. Here, too, there are two systems for processing pain signals on their way to the brain. The dual pain pathways in the spinal cord and brainstem are the neospinothalamic pathway(for fast pain transmission) and the paleospinothalamic pathway (for slow pain transmission). After entering the spinal cord, pain signals travel along these two pathways to reach the brain [28-29,31].

**B: Descending pain pathway**

Pain is a multifaceted process that encompasses unpleasant sensory and emotional experiences. The essence of the pain process is aversion, or perceived negative emotion. Central sensitization plays a significant role in initiating and perpetuating chronic pain. Melzack proposed the concept of the "pain matrix", in which brain regions associated with pain form an interconnected network, rather than being controlled by a singular brain region. Furthermore, there is a reciprocal relationship between ascending and descending pathways that play a role in pain modulation[32]. Upon receipt in the dorsal horn of the spinal cord, nociceptive (pain-signaling) information from the viscera, skin, and other organs is subject to extensive processing by a diversity of mechanisms, certain of which enhance, and certain of which inhibit, its transfer to higher centers [33]. The path of pain-carrying afferent fibers leads to the brain's sensory cortex. The brain reacts to receiving pain messages through descending inhibitory systems, causing the pain valve to close, resulting in a decrease in pain and peripheral reactions through: sympathetic stimulation (with increased heart rate and blood pressure, dilation of the pupils, rigidity of skeletal muscles, tachypnea, sweating and pallor.) and parasympathetic (nausea, vomiting, weakness, lethargy, decreased consciousness, decreased heart rate, decreased blood pressure, pallor) and behavioral reactions. The gray matter surrounding the aqueduct of Sylvius (PAG)

contains enkephalins and beta-endorphins, which are relieved by electrical stimulation of the pain. Stimulation of the Raphe Magnus nucleus, which is located in the brainstem, can lead to the inhibition of pain impulses at the site of the pain valve. Morphine injection into the PAG can also relieve pain by activating a descending pathway (causing inhibition of primary afferent transmission in the dorsal horn of the spinal cord). This activation is mediated by neurons connecting the PAG and the Raphe Magnus. Descending serotonergic fibers from the Raphe Magnus then enter the dorsal horn of the spinal cord and inhibit pain by closing the valve [27,32-37].

## Pain control system (analgesia system or painkiller)

Multiple distinct supraspinally organized descending inhibitory systems have been identified that can powerfully modulate spinal nociceptive transmission. Each person's reaction to pain is different. This is due to the brain's ability to modulate pain signals by activating the pain control system [33]. The mechanism of action of this system is as follows: In the gray matter around the Sylvian aqueduct in the midbrain and upper pons, there are large cell bodies of enkephalinergic neurons. The axons of these neurons descend to the brain and terminate in the raphe magnus nucleus, located in the midline of the lower pons and the upper medulla. In this nucleus are the cell bodies of serotonergic neurons. The axons of these neurons reach the spinal cord and synapse on the axon terminal of the first-order neuron type C. By acting as synaptic inhibitors, they prevent the release of the first-order neuron neurotransmitter, an 11-amino-acid neuropeptide called substance P. The lack of secretion of the neurotransmitter p prevents the transmission of messages from the first-order neuron to the second-order neuron (this synapse occurs in the dorsal horn of the gray matter of the spinal cord) and effectively blocks the pain pathway. It is thought that local neurons also secrete enkephalin, and that enkephalin, by inhibiting the presynaptic first-order neurons (types Aδ and C), prevents their synapses with the second-order neurons and blocks the pain pathway. It is also possible that enkephalin blocks the calcium channels of the axon terminal and prevents the entry of calcium ions into the axon terminal, thus preventing the release of the neurotransmitter p. There are drugs, such as morphine, that cause severe analgesia [33]. These drugs are called opiates. Opiates act on receptors in several brain regions, including those that control pain. Engagement of descending inhibition by the opioid analgesic (morphine) fulfills an important role in its pain-relieving properties. At the same time, induction of analgesia by the adrenergic agonist ( clonidine) reflects actions at alpha(2)-adrenoceptors (alpha(2)-ARs) in the dorsal horn normally recruited by descending pathways. However, opioids and adrenergic agents exploit but a tiny fraction of the vast panoply of mechanisms now known to be involved in the induction and/or expression of descending controls[33].

Conclusion: Pain is a common symptom of many diseases and a common reason for visiting doctors; it is also one of the body's protective mechanisms against stimuli and damage. In principle, pain results from stimulation of pain receptor cells (Nociceptors) in the peripheral nervous system (non-central, lateral) or from damage to the central nervous system. The steps necessary for the perception of pain are: conduction (Transduction), transmission (Transmission), perception (Perception), and modulation (Modulation). Pain receptors are located in the skin and other tissues in the form of free nerve endings. Pain stimuli are classified into three groups: mechanical, thermal, and chemical. Thermal and mechanical stimuli produce sharp or fast pain, while all three types of stimuli produce slow pain. In addition to the purely sensory aspect, pain has an emotional and affective component that depends on each person's psychological structure. Types of pain include acute, chronic, superficial, deep, fast, slow, visceral, and emotional. Pain receptors are free nerve endings called nociceptors. Nociceptors are divided into two general groups: somatic and visceral. Pain involves a complex interaction between messages sent from the environment to the central nervous

system and vice versa. Specific nerve fibers transmit the nerve messages resulting from the stimulation of nociceptors to the spinal cord. The spinal cord plays an important role in transmitting and modulating pain impulses. The pathways for transmitting pain messages include ascending (from the spinal cord to the brain) and descending (from the brain to the spinal cord and organs). These pathways play an important role in modulating and reducing pain.

**Acknowledgments**
The authors hereby express their deepest gratitude and appreciation to all those who helped us with their guidance in preparing this article.

**Author Contributions**
All authors actively participated in preparing research sources and writing the text at all stages. All authors approved the study.

**Conflict of interest**
The authors declare no conflict of interest for this study.

**Ethical Permission**
This study is a review study. All ethical principles have been observed in this study.

**Funding**
None.

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