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Review

Understanding Pain: Types, Pathophysiology and Modern Treatment Approaches

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Abstract

Pain is a complex physiological and psychological phenomenon that serves as a protective mechanism to alert the body to potential or actual tissue damage. It is broadly classified into nociceptive pain, neuropathic pain, and psychogenic pain, each with distinct mechanisms and clinical implications. Nociceptive pain arises from tissue damage and is further divided into somatic and visceral pain. Neuropathic pain results from nerve damage or dysfunction, often presenting as burning, tingling, or shooting sensations. Psychogenic pain is influenced by psychological factors, though it may coexist with physical causes. The pathophysiology of pain involves the activation of nociceptors, peripheral and central sensitization, and the modulation of pain signals by neurotransmitters such as substance P, glutamate, and endorphins. Chronic pain conditions often involve maladaptive changes in the nervous system, leading to hyperalgesia (increased pain sensitivity) and allodynia (pain from normally non-painful stimuli). Treatment strategies for pain management include pharmacological and non-pharmacological approaches. Pharmacological treatments involve the use of nonsteroidal anti-inflammatory drugs (NSAIDs), opioids, anticonvulsants, antidepressants, and local anesthetics, depending on the type and severity of pain. Non-pharmacological approaches such as physical therapy, cognitive-behavioral therapy (CBT), acupuncture, and neuromodulation techniques are also employed to improve pain relief and patient quality of life. A multimodal approach to pain management is often necessary, particularly in chronic pain conditions, to address both the physical and psychological aspects of pain. Advancements in pain research, including gene therapy and novel analgesic drug development, continue to improve treatment outcomes and provide better patient care.

Keywords: Pain, Acute pain, Chronic Pain, Phanom pain

INTRODUCTION

Pain is a multifaceted emotion that consists of both a physiological and psychological reaction to an unpleasant stimulus[2]. Pain is mainly linked to injury or the potential of injury and serves as a warning system to protect an organism by causing it to retreat from dangerous stimuli[2]. Pain is adisagreeable emotional and sensory experience[1]. Pain can feel mild or severe[1].Pain may serve as a warning sign for dangerous bodily changes[1]. In this way, some forms of pain keep us safe[1].Itcan be more difficult to function, perform essential dutieswhile you are in pain[1].Pain has a crucial role in warning the body of possible harm[2].However, pain perception is only one aspect of the nociceptive response, which also include an increase in blood pressure, an increase in heart rate, as well as an automatic retreat from theunpleasant stimulus[2]. Pain is subjective and difficult to measure,since it possesses both a sensory and an emotional component. Individual pain responses are taught in early life and are influenced by a variety of factors, including social, cultural, psychological, cognitive, and genetic ones, even though the neuroanatomic basis of pain receipt develops prior to birth[2].

Types of pain

There are 2 types of pain

1) Acute Pain
2) Chronic Pain

Acute pain

In generally, this kind of pain is severe and temporary. Acute pain is typically relieved by treating the underlying injury[10].Acute pain is typically intense because it serves as a warning indication that the body is in danger due to an illness, injury, overuse, or other external stressor[1].Strains, fractures, dental work, surgery, childbirth, infections, and/or burns are common causes of acute pain[1].During acute pain, an immediate intense feeling of short duration, sometimes described as a sharp pricking sensation, is followed by a dull throbbing sensation [2]

Examples for acute pain:

Somatic Pain: A person experiences this pain on the skin or below the skin [3-6].Somatic pain can range from mild to severe, depending on the extent of the injury. Somatic pain is usually centred around the area of injury or inflammation.

Causes

i) impacts (like running into a blunt object), which can lead to painful bruises.
ii) Cuts in your skin or mucus membranes
iii) Infections, like skin or ear infections.
iv) Inflammation, which may involve skin rashes etc.

Pathophysiology

- Harmful stimuli (like intense heat or cold, force or a sharp object) cause damage to cells of your body. The damage triggers the release of neurotransmitters into the surrounding tissue**.**
- Your peripheral nerves have receptors called nociceptors. These work like metal detectors, sensing the release of the special chemicals and sounding an alarm immediately. When nociceptors detect the chemicals from damaged cells, they immediately send high-priority signals to your brain (via your spinal cord).
- Your brain receives these signals and translates them into the feeling of pain. Your brain also maps that feeling to the area that first sent the signals, so you know where the issue is.
- The feeling of pain triggers immediate reactions in your brain and body. Those reactions are usually protective (like reflexes).

Diagnosis

1) Blood tests
2) X-rays
3) Ultra sound
4) Computed tomography scans (CT).
5) Magnetic resonance imaging (MRI).

Visceral Pain: This pain occurs in the internal organs and the linings of cavities in the body [10]. Visceral pain is the pain you feel from your internal organs, such as your stomach, bladder, uterus, or rectum. This type of pain is caused by medical conditions that produce inflammation, pressure, or an injury. There is also some evidence

that people with certain mental health conditions, such as bipolar disorder, borderline personality disorder, and post-traumatic stress disorder (PTSD), are more likely to have symptoms of visceral pain.
Example: Pelvic pain caused by a bladder infection and abdominal pain caused by irritable bowel syndrome (IBS).

Causes

- Inflammation
- Pressure
- Injury

Pathophysiology

- The sensory nerves in your organs have pain receptors called nociceptors.
- Nociceptors send signals to the spinal cord and brain to alert you of illness or injury.
- The sensory nerves are triggered when the nerves in and around the organs detect compression, stretching, tearing, or tiny areas of damage.

Diagnosis

Diagnosis is done in the painful areas or nearby painful areas.

- X-ray
- Computed tomography
- Ultrasound

Referred Pain: A person feels visceral pain somewhere other than where the tissue injury is [10]. Referred pain is a common but less understood symptom that originates from somatic tissues[13]. Referred pain can be caused by autogenous dysfunction or triggered by external stimuli[13].

Pathophysiology

- In this theory, the convergence of nociceptive afferents on second-order neurons in the spinal cord leads to the occurrence of pain in different somatic areas.
- there are dichotomizing afferent fibres that ramify and distribute to regions of primary dysfunction and referred areas
- While primary lesions stimulate afferent fibres in deep regions, these afferent fibres trigger the activation of a reflex arc toward the muscle via somatic efferent fibres.[13]

Chronic pain

Chronic pain, defined as any pain persisting beyond 3 months, originates from various sources[8]. Effective pain management often involves a combination of pharmacological treatments and nonpharmacological interventions[8]. Compared to acute pain, this kind of pain lasts far longer and frequently has no known solution**.** Additionally, it might be intermittent, like in a migraine attack, or persistent, like in arthritis[10]. Effective pain management often involves a combination of pharmacological treatments and nonpharmacological interventions(8).
Examples for chronic pain:
1) **Neuropathic Pain**: Damage to the peripheral nerves that link the brain and spinal cord to the rest of the body results in this pain[10]. Neuropathic pain is nerve pain that can happen if your nervous system malfunctions or gets damaged[4].Damaged nerve fibres send the wrong signals to pain centres in your body, resulting in neuropathic pain[4].
It is divided into two groups

i) Peripheral neuropathic pain: Peripheral neuropathy happens when the nerves that are located outside of the brain and spinal cord (peripheral nerves) are damaged.
ii) Central neuropathic pain: pain caused by a lesion or disease of the central somatosensory nervous system.

Symptoms

- Pain that happens for no apparent reason (spontaneous pain): This might include a burning, stabbing, or electric shock-like pain, tingling, numbness, or a “pins and needles” feeling[4].
- Allodynia: This occurs when normally painless stimuli like cold, pressure or brushing against your skin causes you to feel pain. It’s an extreme sensitivity to touch[4].
- Hyperalgesia: This happens when normally painful stimuli like heat or pinpricks cause an extreme or increased pain sensation[4].
- **Hypoalgesia**: This occurs when a normally painful stimulus results in a decreased pain response[4].

- Insomnia: Difficulty sleeping. You may also have emotional stress due to disturbed sleep and pain.

Causes

- Alcohol use
- Diabetes
- HIV/ AIDS
- Central nervous system disorders like stroke, Parkinson's diseaseand multiple sclerosis (MS).
- Shingles

Other causes

- Chemotherapy
- Radiation therapy
- Amputation
- Spinal nerve compression or inflammation
- Trauma or surgeries resulting nerve damage
- Tumours that press on nerves

Phantom pain: Phantom pain occurs after the amputation of a limb. It refers to painful sensations that feel as though they are coming from the missing limb [13].It might seem unusual to feel pain in an area of your body that doesn't exist anymore, but the pain you feel is real.Phantom limb pain ranges from mild to severe and can last for seconds, hours, days or longer[5].

Types of phantom pain?

- **Phantom pain**: You feel pain in the missing limb after an amputation [5].
- **Phantom sensations**: The missing limb still feels like it's part of your body. There isn't any pain, but you feel sensations of touch, pressure, itch, temperature and vibrations. You may forget that part of a lower limb is missing and try to walk on both legs [5].
- **Phantom pain syndrome**: You feel pain and other sensations like touch, pressure, itch, temperature and vibrations in an area of your body that experienced an amputation [5]
- **Residual limb pain**: This is pain that affects the remaining part of your limb (stump) that's still on your body after an amputation. Residual limb pain often has a medical reason, such as infection or nerve damage [5].

Symptoms

- Aching.
- Burning.
- Itching.
- Numbness.
- Pinching

You might feel like you'remissing limb is:

- Still attached.
- In an unusual position.
- Moving around.
- Shrinking [5]

Causes phantom pain

Healthcare providers aren't sure of the exact reason why phantom pain occurs. Many believe it's a miscommunication in your nervous system. Your peripheral nerves send signals to your spinal cord and brain. These signals tell your body to move. After an amputation, the nerve connection still exists within your body, even though the nerves in the amputated body part aren't there anymore [6]. An amputation causes trauma. Your brain is learning how to adjust to the change. Sometimes, nerves can get angry in response to trauma or change. They may send more signals than they usually do or mix up signals. Your brain misinterprets the signals it receives, which increases your sensitivity and leads to pain [5].

Central pain: This type of pain often occurs due to infarction, abscesses, tumours, degeneration, or bleeding in the brain and spinal cord. Central pain is ongoing, ranging from mild to extremely severe. People with central pain report burning, aching, and pressing sensations [10]. Central neuropathic pain may also begin months to years after the injury, further obscuring recognition of its association with a past neurologic injury [9]. The most common clinical central pain syndromescentral poststroke pain, multiple sclerosisrelatedpain,

andspinalcordinjuryrelated pain [9]. Clinicians most commonly encounter neuropathic pain stemming from impairment within 372 peripheral nervous system pathways (example, painful peripheral neuropathy, radiculopathy, complex regional pain syndrome, postherpetic neuralgia). Less commonly, neuropathic pain can develop from disease affecting the brain, brainstem, or spinal cord. This disorder is termed centralneuropathic pain. Central neuropathic pain can result from any type of injury to the central nervous system (CNS) including vascular (ischemic or haemorrhagic), infectious (abscess, encephalitis, myelitis), demyelinating, traumatic (brain or spinal cord), or neoplastic disorders. It can also result from syrinx formation in the spinal cord or brainstem[9]. Finally, central pain is very challenging to treat and may not respond topharmacological agents routinely used for peripheral neuropathic pain[9].

Specific Central Pain Syndromes

Central Poststroke Pain (CPSP)

CPSPis the most commonformofcentral neuro pathic pain[9]. Considering all stroke locations and types, the overall incidence of CPSP is 2% to 8%[9]. A Danish population-based study that screened all patients with stroke (of any type or location) in a single calendar year found that despite 40% having evidence of chronic pain 4 years after their stroke, only 7.3% had CPSP[9]. By absolute numbers, most cases of CPSP are seen following ischemic stroke simply because approximately 80% of all strokes are ischemic[9]. The risk of CPSP is similar for ischemic or haemorrhagic\stroke[9].Lateral medullary strokes (Wallenberg syndrome) also have a high incidence of CPSP (25% at 6 months)[9].

SCI Pain (Spinal cord injury pain):

The International Spinal Cord Injury Pain Classification recognized that patients with a CNS lesion and marked functional impairment canhavemultipletypesofpain[9]. By definition, below-level neuropathic pain represents central pain. At-level pain can stem from root and/or dorsal horn SCI and as such represents peripheral (root) and/or central (dorsal horn) neuropathic pain[9].

MS-Related Pain (multiple sclerosis):

It is an autoimmune disorder in which demyelinating plaques cause dysfunction of areas of the brain and spinal cord[9].

Pathophysiology

The classicpathway involves three types of neurons:

- **Primary sensory neurons** in the peripheral nervous system, which conduct painful sensations from the periphery to the dorsal root of the spinal cord [11]
- **Secondary sensory neurons** in the spinal cord or brainstem, which transmit the painful sensation to the thalamus [11]
- **Tertiary sensory neurons**, which transmit the painful sensation from the thalamus to the somatosensory areas of the cerebral cortex[11].

There are two major classes of nerve fibres associated with the transmission of pain: [11]

1. Unmyelinated C fibres
2. Myelinated A-delta fibres

Five phases of pain transmission

1. Transduction
2. Transmission
3. Modulation
4. Projection
5. perception

Causes: This pain is known as inflammatory pain because it results from tissue damage or infection that activates the immune system [6]. Irritation of pain receptors, which are present in the skin, joints, and numerous internal organs, can result in the perception of pain. Damage to the neurological system, including the brain, spinal cord, and peripheral nerves, may also be the source of pain. Pain can also be referred to as “psychogenic pain” even when there is no physical harm to the tissues. The phenomena of pain are complicated [7].

Acute pain: less than three months in duration, serves as a warning defensive (traumatic, post-operative pain, related to medical operations).

Chronic pain: More than three months in duration, not meeting the role of caution and defensive, as the disease’s characteristics and symptoms are taken into account on their own and necessitate multitherapeutic activities. The most common cause of chronic pain is inadequate management of acute pain, which continues even after the tissue that was damaged to cause it has healed. Anatomic pain can be pathogenic due to local alterations or physiological receptor-functional (protective)[6].

Physiological pain is a type of superficial pain brought on by an irritant that damages the cornea, mucous membranes, and skin receptors. Chronic pain irritation is the source of pathological pain. Pain mediators produced from injured tissues bind to receptors.

Deep pain is abnormal and may be brought on by the structure of the organs, muscles, bones and joints, or blood vessels. Chronic pain irritation is the source of pathological pain. Pain mediators produced from injured tissues bind to receptors. Deep pain is abnormal and may be brought on by the structure of the organs, muscles, bones and joints, or blood vessels. The stimulation of mechano- and chemo-pain receptors found in the outer membrane of large arteries and veins results in vascular pain.

Tension headaches that are caused by vascular artery stretching[7].The stimulation of the joint capsules and the periosteum's pain receptors is the cause of bone and joint pain. Myalgia is brought on by accumulating metabolites irritating the receptors in muscles and fascia's when they are fatigued and under stress. Renal and biliary colic are examples of organ pain. When the nerve fibres or pathways are directly stimulated, wired pain results. Includes phantom pain, neuralgia, causalgia, and radialgia.

The trigeminal, sciatic, femoral, and lateral Fe radiating moral cutaneous nerves are all affected by neuralgia[6]. Coughing and movements to the right parts of the skin aggravate rheumatism. Large nerve lesions involving numerous sympathetic nerves can cause causalgia, a type of neuralgia with an autonomic component. Burning pains and dystrophic changes, such as muscular atrophy, oedema, and cyanosis. Convolutional pain is brought on by inflammation or malignancy that compresses the nerve plexus. In the lower pelvis, upper lungs, and neck. Following amputation, individuals may experience phantom pain, which is associated with pain in the severed limb. The prevalence of this pain explains why chronic pain with embedded memory exists.

- Changes in food-related behaviour are another effect of chronic pain[7].
- Chronic pain is caused by a decrease in grey matter in the brain, not the other way around.

Measurement

There are many differences between measuring pain in disease and assessing pain in experiments; the visual analogue scale appears to be the most sensitive of the different techniques for measuring pain.

Because experimental pain can be quantified in terms of stimulus intensity, it is simpler to research. The nature of the stimulus in pathological pain is frequently unknown, its intensity is typically hard to gauge, and the severity of the illness is not always directly correlated with pain. Since a patient's pain threshold and middot are among thevariables that affect pain, The method of visual analogue scale and graphic rating This approach uses a scale that goes from "no pain" to"pain."

The review found that the 11-point Numerical Rating Scale (NRS) was the most commonly used and recommended response scale for pain assessment. The NRS was preferred over the Visual Analog Scale (VAS) due to its ease of use and lower rates of missing and incomplete data. The findings of this review support the use of the NRS as the preferred response scale for pain measurement[3].

In conclusion, the NRS is the preferred response scale for pain measurement due to its ease of use, low rates of missing and incomplete data, and broad generalizability. Future research should focus on head-to-head comparisons of response scales, pain assessment in other populations, and the measurement considerations for various phenotypic manifestations of pain[3].

The Visual Analog Scale (VAS) for pain Is a widely used, unidimensional measure of pain intensity that has been extensively utilized in diverse adult populations, including those with rheumatic diseases. The VAS consists of a 10-centimeter horizontal or vertical line, anchored by verbal descriptors such as "no pain" and "pain as bad as it could be," which provides a continuous scale for patients to indicate their level of pain. The VAS is easy to administer and score, but may be difficult for older patients with cognitive impairments or motor skill issues, requiring supervision during completion to minimize errors. Despite this limitation, the VAS has been shown to be reliable and valid, with high correlations with other pain measures, such as the Numeric Rating Scale (NRS) and verbal descriptive scales. The VAS has also demonstrated sensitivity to changes in pain intensity following analgesic therapy, with a minimal clinically significant change estimated to be 1.1 points on an 11-point scale or 11 points on a 100-point scale. Furthermore, the VAS has been found to be acceptable to patients, requiring little training to administer and score, and has been widely used in clinical and research settings. However, the VAS cannot be administered verbally or by phone, limiting its usefulness in research, and scoring is more complicated than that for the NRS, requiring a ruler to measure the distance between the "no pain" anchor and the patient's mark.

Management

MEDICATION:

Non-opioid analgesic agents

Acetaminophen:

- Mild to moderate pain, moderate to severe pain, and temporary reduction of fever.

- as adjunctive therapy to opioids.
- Acetaminophen should not be used for neuropathic pain since there is no documented effect.

MOA

Acetaminophen inhibits a different variant of COX-1, also known as COX-3, but this event remains unconfirmed in human studies. The diminished activity of the COX pathway leads to decreased prostaglandin synthesis in the central nervous system, thus inducing *analgesia* (serotonergic inhibitory pathways) and *antipyresis* (hypothalamic heat-regulating centre).

Dose

The recommended dose for adults is 650 mg to 1000 mg every 4 to 6 hours, a maximum of 4 grams/day.
In children, the recommended dose is 15 mg/kg every 6 hours, up to 60 mg/kg/day.

Adverse Effects

This drug is a safe and effective medication when used correctly. If administered orally or rectally, acetaminophen may cause any of the following

- Rash or hypersensitivity reactions (toxic epidermal necrolysis, acute generalized exanthemata's pustulosis, and Stevens-Johnson syndrome)
- Haematological: anaemia, leukopenia, neutropenia, pancytopenia
- Nephrotoxicity
- Metabolic and electrolyte disorders
    - Decreased serum bicarbonate
    - Hyponatremia
    - Hypocalcaemia
    - Hyperammonaemia
    - Hyperchloremia
    - Hyperuricemia
    - Hyperglycaemia
    - Hyperbilirubinemia
    - Elevated alkaline phosphatase

If administered intravenously, adverse effects include nausea, vomiting, pruritus, constipation, and abdominal pain.

Contraindications

- Hypersensitivity to acetaminophen or any of its excipients, severe hepatic impairment, or severe active hepatic disease
- It is worth noting that pregnancy is not a contraindication for acetaminophen administration.

Nonsteroidal anti-inflammatory drugs (NSAIDs):

- These drugs are used for mild-to-moderate pain, pain associated with inflammation, and temporary reduction of fever.
- Drugs in this group are categorized according to chemical structure and selectivity: acetylated salicylates (*aspirin*), non-acetylated salicylates (*diflunisal*), propionic acids (*ibuprofen, naproxen*), acetic acids (*indomethacin, diclofenac*), anthranilic acids (*meclofenamate, mefenamic acid*), enolic acids (*meloxicam, piroxicam*), naphthyl alanine (*nabumetone*), and selective COX-2 inhibitors (*celecoxib*, *etoricoxib*)

MOA: The primary mechanism of action is the inhibition of the cyclooxygenase enzyme, thereby inhibiting prostaglandin synthesis. Most NSAIDs inhibit both COX isoforms (COX-1 and COX-2) with little selectivity.

Dose: Currently, more than 20 different NSAIDs are commercially available. The choice of the agent depends upon several factors (e.g., comorbidities, risk of bleeding).

- *Aspirin (acetylsalicylic acid)*: Is dosed 325 to 650 mg every 4 to 6 hours. The maximum dose is 4000 mg/day. Aspirin is available for oral (caplet, capsule, tablet) or rectal (suppository) administration.
- *Diclofenac*: 50 mg every 8 hours. The maximum daily dose is 150 mg. Diclofenac is available for oral (tablet, capsule, packet), intravenous, topical (cream, gel, patch, solution), or ophthalmic administration.
- *Ibuprofen*: It is dosed 400 mg every 4 to 6 hours. The maximum daily dose is 3200 mg (acute) or 2400 mg (chronic). Ibuprofen is available for oral (capsule, tablet, suspension) or intravenous administration.

- *Indomethacin*: Immediate release: 25 to 50 mg every 8 to 12 hours. Controlled release: 75 mg once or twice daily. The maximum dose is 150 mg/day. Indomethacin is available for oral (capsule, suspension), intravenous, or rectal (suppository) administration.
- *Meloxicam*: Dosing is 7.5 to 15 mg once daily. The maximum daily dose is 15 mg. Meloxicam is available for oral (tablet, capsule, suspension) or intravenous administration.
- *Naproxen*: 250 to 500 mg every 12 hours (naproxen base) or 275 to 550 mg every 12 hours (naproxen sodium). The maximum daily dose is 1250 mg acute or 1000 mg chronic for naproxen base and 1375 mg acute or 1100 mg chronic for naproxen sodium. Naproxen is available for oral (capsule, suspension, tablet) administration only.
- *Celecoxib*: 200 mg daily or 100 mg every 12 hours. The maximum dose is 400 mg/day. Celecoxib is available for oral (capsule) administration only.

Adverse Effects

- Gastrointestinal: Nausea, anorexia, dyspepsia, abdominal pain, ulcers, gastrointestinal haemorrhage, perforation, constipation, diarrhoea
- Cardiovascular: Hypertension, decreased effectiveness of anti-hypertensive medications, myocardial infarction, stroke, and thromboembolic events (last three with selective COX-2 inhibitors); inhibit platelet activation, propensity for bruising, and haemorrhage.
- Renal: Salt and water retention, deterioration of kidney function, oedema, decreased effectiveness of diuretic medications, decreased urate excretion, hyperkalaemia, analgesic nephropathy
- Central nervous system: Headache, dizziness, vertigo, confusion, depression, lowering of seizure threshold, hyperventilation (salicylates)
- Hypersensitivity: Vasomotor rhinitis, asthma, urticaria, flushing, hypotension, shock.
- Hepatotoxicity

Contraindications

Hypersensitivity is the only major contraindication for NSAID use.

- Age > 50 years and family history of gastrointestinal (GI) disease/bleeding.
- Previous GI problems associated with NSAID use (e.g., gastritis)
- Peptic ulcer
- History of personal GI bleeding
- Uncontrolled hypertension
- Renal disease
- Irritable bowel syndrome
- Inflammatory bowel disease
- Coronary artery bypass surgery
- Gastric bypass surgery

Antidepressant medications

Selective serotonin and norepinephrine reuptake inhibitors (SNRIs), particularly duloxetine,and tricyclic antidepressants (TCAs), especially amitriptyline, have demonstrated efficacy in a variety of neuropathic pain conditions.Thus, they are recommended as the first line of treatment.

MOA

- Both tricyclic antidepressants (TCAs) and selective serotonin and norepinephrine reuptake inhibitors (SNRIs) inhibit the reuptake of two important neurotransmitters: serotonin and noradrenaline.
- This inhibition increases the descending inhibitory pathways of the central nervous system related to pain. Additionally, TCAs also act on cholinergic, histamine, beta2 adrenergic, opioid, and N-methyl-D-aspartate (NMDA) receptors, and sodium channels.

Dose

Among the tricyclic antidepressants and selective serotonin and norepinephrine reuptake inhibitors, amitriptyline and duloxetine have the best-documented analgesic effects, respectively.

- *Amitriptyline*: Dosing is 25 to 150 mg orally (tablet) once daily or in two divided doses. The maximum single and daily doses are 75 mg and 150 mg, respectively. Caution must be taken in patients 65 years old or older with maximum daily doses above 75 mg.
- *Duloxetine*: Dosing is 60 to 120 mg orally (capsule) once daily or in two divided doses. The maximum daily dose is 120 mg**.**

Adverse Effects

- *Amitriptyline*: Altered mental status, arrhythmias, constipation, decreased libido, dizziness, drowsiness, dry mouth, headache, hyperhidrosis, increased risk of suicidal thoughts, micturition disorders (i.e., urinary retention), nausea, orthostatic hypotension, tremor, weight gain.
- *Duloxetine*: Nausea, headache, dry mouth, somnolence, dizziness, abdominal pain, constipation increased blood pressure, increased risk of suicidal thoughts.

Contraindication

- Amitriptyline: Hypersensitivity, coadministration with or within 14 days of monoamine oxidase inhibitors (MAOIs), coadministration with cisapride, recent myocardial infarction, arrhythmias, acute heart failure, severe liver impairment.
- Duloxetine: Hypersensitivity, liver impairment, severe renal failure (e.g., CrCl <30 mL/minute) or end-stage renal disease (ESRD), coadministration with or within 14 days of MAOIs, concomitant use of linezolid, thioridazine, methylene blue, or potent CYP1A2 inhibitors, uncontrolled narrow-angle glaucoma. Precaution in patients with hypertension or cardiac disease.

Antiepileptic medications

Several antiepileptic drugs are also known for their analgesic properties through their mechanism of action of lowering neurotransmitter release or neuronal firing.

The most common antiepileptics used for pain treatment are **gabapentin** and **pregabalin**.

- Gabapentin: Postherpetic neuralgia in adults and neuropathic pain.
- Pregabalin: Neuropathic pain associated with diabetic peripheral neuropathy or spinal cord injury, postherpetic neuralgia, and fibromyalgia.
- Oxcarbazepine and carbamazepine: trigeminal or glossopharyngeal neuralgia

MOA: Both gabapentin and pregabalin are ligands to the αδ subunit of the voltage-dependent calcium channels, which overexpress in patients with neuropathic pain. By reducing this calcium-dependent release of excitatory neurotransmitters, these drugs decrease neuronal excitability.

Dose

- *Gabapentin*: 300 to 600 mg orally (capsule, tablets, solution) three times per day with a maximum daily dose of 1800 mg for postherpetic neuralgia or 300 to 1200 mg orally three times per day with a maximum daily dose of 3600 mg
- *Pregabalin*: 300 to 600 mg/day orally in two divided doses.

Adverse effects

- *Gabapentin*: The most common side effects are dizziness, somnolence, ataxia, peripheral oedema, and confusion. Among other, more serious adverse effects are anaphylaxis, suicidality, depression, fever, infection, steven-Johnson syndrome, angioedema, erythema multiforme, and rhabdomyolysis.
- *Pregabalin*: Dizziness, somnolence, headache, peripheral oedema, nausea, weight gain, disorientation, blurred vision, increased risk of suicidal thoughts.

Contraindications

The only established contraindication for gabapentin and pregabalin is hypersensitivity to the respective drug or any of its excipients. However, dose adjustment is necessary for patients with compromised renal function.

Local anaesthetics: [12] Lidocaine is among the most commonly used medications in this drug class, which is FDA approved for postherpetic neuralgia and recommended for peripheral neuropathic pain.

MOA: As with other local anaesthetics, lidocaine stabilizes the neuronal membrane by inhibiting sodium ion channels on the internal surface of nerve cell membranes. Thus, pain conduction through nerve impulses becomes impaired at the site of action, which contributes to the absence of systemic effects.

Dose: *Lidocaine*: As a patch, lidocaine is available at a concentration of 1.8% or 5%. The recommendation is to apply 1-3 patches to intact skin for up to 12 hours/day.

Adverse effects: *Lidocaine*: Application-site pain, pruritus, erythema, and skin irritation

Contraindications: Lidocaine is contraindicated in patients with a previous history of sensitivity to any local anaesthetic of the amide-type or any of its excipients**.**

Opiod agents: [12]

- Opioids are a broad class of medications with structural resemblance to the natural plant alkaloids found in opium, which was originally derived from the resin of the opium poppy, *Papaver somniferum*.
- They are recognized as the most effective and widely used drugs in treating severe pain.
- Opioids have been among the most controversial analgesics, particularly because of their potential for addiction, tolerance, and side effects
- Although opioids have indications for acute and chronic pain treatment

MOA: The majority of the clinically relevant opioids act primarily at the "mu receptors" and thus are considered "mu agonists."
Nonetheless, opioids may also act on other receptors: *kappa*, *delta*, and *sigma* (all of them, including *mu*, are G protein-coupled receptors). Depending on which receptor is activated, different physiologic effects occur (i.e., spinal and supraspinal analgesia)
Opioids exert their effects on both presynaptic and postsynaptic neurons.
Presynaptically, opioids block calcium channels on nociceptive afferent nerves, thus inhibiting the release of neurotransmitters such as substance P and glutamate. Postsynaptically, opioids enhance the activity of potassium channels, thus hyperpolarizing cell membranes and increasing the required action potential to generate nociceptive neurotransmission**.**

DOSE
Opioids are available in diverse dosage forms to use for several routes of administration: oral, transdermal, intramuscular, intravenous, subcutaneous infusion, rectal, epidural, intrathecal, intranasal, and transmucosal.
The rationale for each route of administration, dosage range, and dosage form is dependent on a number of factors

Adverse effects: Opioids produce a variety of different systemic adverse effects, including:

- Dysphoria/euphoria
- Sedation,
- Constipation
- Nausea and vomiting
- Cough suppression
- Miosis
- Physical dependence (chronic application)
- Opioid-induced hyperalgesia and/or allodynia (chronic application)

Contraindications

- Severe respiratory instability
- Acute mental instability or high suicidal risk
- QTc interval over 500 milliseconds (methadone)
- Family and/or personal history of substance abuse
- Intolerance, serious adverse effects or lack of efficacy to other structurally similar opioids
- Renal or hepatic impairment (depending on the specific drugmetabolism and excretion)

Natural Remedies
Heat and ice

- Heat therapy and cold compresses are probably the most commonly used home remedies for pain[31]
- Heat can help to get stiff muscles moving. Ice can decrease inflammation
- New injuries, like bruises and sprains, are typically better served with ice
- Muscle or joint stiffness, like arthritis or a nagging hamstring injury, may benefit more from heat.
- Alternating heat and ice therapy can also help address your pain on both fronts.
  Safety tips to use:
- Wrap ice packs in a cloth, like a towel, to protect your skin.
- Avoid burns by removing heating pads if they become uncomfortably warm.
- A warm shower or bath can be beneficial. But keep the water temperature under 100 degrees Fahrenheit (38 degrees Celsius).
- Limit each heat and ice therapy session to about 20 minutes or fewer

Exercise

- Exercise releases endorphins — pain-relieving hormones.

- Don't attempt exercises that make the pain worse.
- Taking a walk
- Trying chair exercisesor desk exercises
- Lifting small weights
- Trying some gentle yoga

Stretching

- Stretches can help lessen that pain.
- Stretches for wrist pain
- Desk job stretches
- Relieving knee and hip pain
- Lower back pain stretches
- Psoas stretches
- Rotator stuff stretches

Breathwork

- When you're living with pain, it affects more than just the area where you feel it**.**
- Pain can activate our fight or flight response. That can cause reactions like:
- Physical and emotional tension
- A faster heart rate
- Slower digestion
- When you breathe more deliberately, you help to get more oxygen to all parts of your body, which can help you relax and tamp down that stress response.
  Breathing techniques:
  - Diaphragmatic breathing: Breathe in slowly through your nose and allow your belly to expand. Breathe out slowly through pursed lips, allows your belly to move back in. Repeat several times
  - Box breathing: Breathe in for a count of four. Hold for a count of four. Breathe out for a count of four. Hold for a count of four. Repeat for several cycles
  - Box breathing: Use your finger on one hand to slowly trace the fingers on the other. Starting at the outside of your thumb, trace up to the top of your thumb as you inhale. Exhale as you trace down the other side. Then inhale as you trace up your index finger. Exhale as you trace down. Continue to your middle finger, ring and Pinky until you exhale on the outside of your Pinky. Then reverse the process (Pinky, ring, middle, index, thumb). Repeat for several cycles

Herbal remedies and supplements

- When people talk about "natural" pain relief, some of them go right to vitamin supplements and herbal remedies
- Some providers may recommend things like magnesium or curcumin (turmeric). Both have been suggested to have potential pain-relieving properties. But they can also interact negatively with other medications.
- One packaged "natural remedy" that could provide some pain relief, without the risk, is Epsom salt.
- Epsom salt is a naturally occurring mineral salt that contains high amounts of magnesium

Integrative Medicine Practices

- They focus on healing techniques that work hand-in-hand with conventional medicine
- Acupuncture: A traditional Chinese medicine practice that uses very thin sterile needles to prompt your body to release natural chemicals to relieve pain
- Chiropractic medicine: A therapeutic treatment that uses pressure to realign your spine to reduce pain
- Yoga therapy: Bridging the divide between mind and body, yoga therapy uses mindfulness and physical movement that can help to reduce pain
- Massage therapy: A relaxing massage can do wonders for calming stress, and it can help relieve aches and pains
- **Holistic psychotherapy**: A combination of traditional talk therapy and other therapy interventions, like eye movement desensitization reprocessing therapy (EMDR) and mindfulness-based cognitive behavioural therapy, can help to aid physical and emotional healing
- **Dietary intervention**: Sometimes, the foods we eat can help trigger inflammation in our bodies and perpetuate pains. Working with a dietitian to make some changes to what you eat may help you feel better

- **Sleep medicine**: Sleep is essential to our well-being. Sleep can help your body heal and lower your pain. But if pain is keeping you up, a specialist in sleep medicine may be able to help you devise strategies to get your body the sleep and rest it needs

Modern technologies

Pulse Radio Frequency

Pharmacological therapy often provides limited relief for chronic pain. Non-steroidal anti-inflammatory drugs (NSAIDs) can have serious side effects, such as bleeding and gastrointestinal ulcer non-surgical interventions, including injections, acupuncture, and stimulation therapy, are used as complementary therapies. However, these methods may not be sufficient to control chronic severe pain Radiofrequency (RF) neurotomy is a promising alternative treatment with few complications. This procedure involves cutting the nerve supply to a painful area to alleviate pain and restore function [30]. Radiofrequency Ablation (RFA) uses electrical energy to heat and destroy damaged tissues. A special needle electrode is inserted into the target area. When electrical current flows through the electrode, it creates friction and heat in the surrounding tissue. This heat destroys the damaged tissue. The goal is to heat the tissue to a high temperature, usually above 70°C, to cause instant coagulation and destruction of the tissue [11].

Recent studies have extensively investigated the effects of pulsed radiofrequency (PRF) on neuropathic pain, a complex and debilitating condition. Histological findings have consistently shown that PRF can cause microscopic damage to axons, including abnormal membrane morphology, disruption of microfilaments and microtubules, and mitochondrial degeneration. However, these changes can also lead to the alleviation of neuropathic pain, suggesting a potential therapeutic application. In vivo studies have demonstrated that PRF treatment adjacent to the dorsal root can significantly reduce mechanical and thermal hyperalgesia in animal models, leading to improved pain management. These findings suggest that PRF may be a promising treatment option for neuropathic pain, offering a novel approach to managing this challenging condition[29]. The mechanism of action of pulsed radiofrequency (PRF) is still being researched. Current studies suggest that PRF alters synaptic transmission, producing a neuromodulator effect. However, there is ongoing debate about whether PRF has a minimally ablative effect.

PRF applies short pulses of radiofrequency signals to neural tissue, causing biological changes due to thermal effects, high-intensity electric fields, or both. The production of heat during PRF depends on power deposition, which is influenced by the voltage applied, exposure time, and tissue resistivity. commercial PRF generators produce signals with pulse durations of 5-50ms and pulse frequencies of 1-10 Hz. The most commonly used sequence is 2 Hz and 20ms. The intrinsic radiofrequency oscillation frequency remains at 420 kHz. PRF's average tissue temperature rise is much lower than that of continuous radiofrequency (RF) due to the short pulse duration. This allows for higher voltages to be applied without causing significant temperature increases. Initially, PRF was thought to have no thermal effects, but in vitro experiments have shown brief temperature elevations ("heat spikes") around the needle tip. However, the magnitude of these spikes decreases with shorter pulse widths. The effects of high-intensity electric fields have been well established. PRF produces stronger electrical fields than RF, but these fields weaken rapidly with distance from the electrode tip. Electric fields can have significant effects on cells due to transmembrane potentials. These effects may play a crucial role in the mechanism of action of PRF [30].

The available evidence suggests that pulsed radiofrequency (PRF) is effective in treating cervical radicular pain when applied to the dorsal root ganglion (DRG). However, its efficacy in treating lumbosacral pain is less clear due to the limited quality of the available studies. PRF has been found to be as effective as intra-articular corticosteroids in treating chronic shoulder pain. However, it is less effective than conventional radiofrequency thermocoagulation in treating lumbar zygapophyseal joint pain and trigeminal neuralgia. Despite these mixed results, PRF has been shown to have a high safety margin in various conditions, including discogenic pain, chronic inguinal herniorrhaphy pain, and chronic testicular pain. However, further studies are needed to verify its efficacy and determine the optimal "PRF dose" based on voltage settings and treatment duration [29].

This study investigated the efficacy of radiofrequency (RF) genicular neurotomy in treating chronic pain. The results showed that RF neurotomy provided significant pain relief and functional improvement in patients with chronic pain. The procedure involved identifying the genicular nerves and applying RF current to these nerves. The target points for RF neurotomy included periosteal areas. The study found that two patients in the RF group did not respond to the treatment. Some patients experienced transient pain during the procedure. The study also found that RF neurotomy did not impair proprioception, muscle tone, balance, or gait in patients. Overall, the study suggests that RF genicular neurotomy is a safe and effective treatment for chronic pain [30]

Stem Cell Therapy

Neuropathic pain is a chronic condition caused by damage or disease affecting the central or peripheral nervous system. According to the International Association for the Study of Pain, neuropathic pain can result from spinal cord injury, leading to long lasting moderate to severe pain [18]

Current treatments for neuropathic pain have limited effectiveness, and researchers are exploring new approaches to repair damaged nerve cells. One promising strategy is cell transplantation, which involves introducing healthy cells into the damaged area to promote regeneration. Stem cells, particularly mesenchymal stem cells (MSCs), have shown potential in treating spinal cord injuries. MSCs can differentiate into various cell types, including nerve cells, and exhibit immunomodulatory properties [17]

Different sources of MSCs, including bone marrow, umbilical cord, and adipose tissue, have been explored. Bone marrow-derived MSCs (BM-MSCs) and umbilical cord-derived MSCs (UC-MSCs) have shown promise in improving functional recovery after spinal cord injury [16]

However, the effectiveness of these cells in reducing neuropathic pain is not fully understood. This study aims to investigate the effect of BM-MSCs and UC-MSCs on spinal cord injury-induced neuropathic pain and identify the most effective stem cell population for transplantation[15]

Cell Culture

- BM-MSCs were collected from bone marrow of a person
- UC-MSCs were isolated from of healthy infants born by C-section, with the mother's consent.
- Cells were kept in an incubator at 37 °C, 90 % humidity, and 5 % CO2.
- Cells were cultured in cell culture flasks containing DMEM/F12, fatal bovine serum 10 %, penicillin, streptomycin sulphate, and amphotericin B.
- The medium was changed every 3 days
- Umbilical cords were brought to the cell culture laboratory under sterile conditions.
- UC-MSCs were isolated under sterile conditions, and the remaining matrix was chopped into pieces.
- Pieces were moved to petri dishes, and DMEM/F12 with foetal bovine serum, penicillin, and streptomycin sulphate were add - Surface antigens of the cells were checked using flow cytometry to confirm their stem cell status.
- Mesenchymal cells should be negative for CD45 and CD14 but should express CD105, CD29, CD90, and CD44 [18]

Currently, tissue engineers and clinicians are most interested in the application of Mesenchymal Stem Cells (MSCs) derived from bone marrow, adipose tissue, and umbilical cord tissue. Bone Marrow Derived MSCs (BM-MSCs) are well-suited for stimulating native disc cells and differentiating into IVD-NP cells, but have a more cumbersome harvesting process. Adipose-Derived MSCs (ADSCs) can be easily collected from fatty tissue and may acquire a phenotype similar to that of IVD cells. Umbilical Cord Tissue Derived MSCs (HUC-MSCs) have potential allogeneic application due to low-immunogenicity. Each of these MSC sources has its advantages and disadvantages, and researchers are exploring different models of MSC transplantation, including autologous and allogeneic models, to determine the most effective approach[15]

Mesenchymal stem cells (MSCs) have emerged as a promising therapeutic tool for the treatment of various immune and non-immune diseases. These cells possess unique properties that enable them to migrate to damaged tissue sites, differentiate into specialized cell types, and produce a wide range of growth factors and cytokines that promote tissue repair and regeneration. Furthermore, MSCs have been shown to exert immunomodulatory effects, suppressing excessive immune responses and promoting tolerance [32]

Despite the significant progress made in MSC research, several key questions remain unanswered. For instance, the optimal dosage of MSCs, the most effective routes of administration, and the ideal timing for cell infusion are still unclear. Additionally, the long-term fate of MSCs after infusion, including their survival, proliferation, and differentiation, remains to be fully elucidated [32]

To fully harness the therapeutic potential of MSCs, it is essential to address these knowledge gaps. Researchers must continue to investigate the interactions between MSCs and the inflammatory milieu, as well as the therapeutic mechanisms of MSCs in various disease models. Moreover, the development of standardized protocols for MSC isolation, expansion, and characterization is crucial for ensuring the consistency and quality of MSC-based therapies [32]

Ultimately, a deeper understanding of MSC biology and function will be essential for the successful translation of MSC-based therapies from the bench to the bedside. By addressing the current challenges and knowledge gaps in MSC research, scientists and clinicians can work together to develop innovative and effective therapies for a wide range of devastating diseases[32]

Zinc Oxide Nano Particles

Nanotechnology has ushered in a new era of interdisciplinary research, combining engineering, biology, chemistry, medicine, and physics. Nanoparticles have emerged as a promising compound in the advancement of medicine and pharmacy. Due to their high potential, these compounds are increasingly being applied in various medical and pharmaceutical studies, particularly in specific treatment processes.The integration of nanoparticles in biotechnology and modern medical science has revealed new avenues for treating various disorders, especially

those affecting the central nervous system (CNS). Among these nanoparticles, zinc oxide (ZnO) has garnered significant attention from bio-researchers and pharmacists due to its unique chemical and physical properties [20].

ZnO nanoparticles are widely used in cosmetics, health products, medical equipment, and drug delivery systems. Biological studies have shown that ZnO can affect cellular function and tissue health.

However, further research is needed to fully understand its effects on the CNS.Bulk zinc oxide, with the chemical formula ZnO, is an inorganic compound with numerous applications across various industries. Despite its benefits, long-term usage of ZnO has been found to have minimal toxic effects[19].Nanoparticles (NPs) are widely used in medical and pharmaceutical industries due to their potential as targeted nanocarriers, tissue scaffolds, and bioimaging agents. Zinc oxide nanoparticles (ZnO-NPs) have gained attention for their anti-cancer and anti-bacterial properties.ZnO-NPs have shown anti-bacterial effects against various bacteria strains, including Escherichia coli and Staphylococcus aureus. However, their toxicity depends on factors such as size, shape, stability, and surface chemistry.

Recent studies have demonstrated ZnO-NP genotoxic and cytotoxic effects in vitro, and in vivo studies have revealed signs of toxicity. Zinc, an essential trace element, plays a crucial role in maintaining oxidative and anti-oxidative balance.Zinc has anti-inflammatory properties, inhibiting the Nuclear Factor κB (NF-κB) pathway and stimulating the production of metallothionein's. The gastroprotective activity of zinc ions has also been demonstrated. This study aimed to compare the influence of chronic administration of ZnO-NPs and zinc oxide standard form (ZnO-S) on the anti-inflammatory and gastric activity of ketoprofen.

Gene Therapy

Gene therapy has revolutionized the treatment of genetic disorders, offering unprecedented opportunities for precise and targeted interventions. However, the effects of these drugs on neural pathways unrelated to pain or on organs outside the nervous system pose substantial limitations on the maximum dose that may be administered. Opiate drugs, such as morphine, provide an excellent example of this phenomenon.

The existence of specialized mammalian sensory neurons that respond to tissue damage (nociceptors) was first proposed by Sherrington a century ago. This concept has been clearly demonstrated in humans and mice, where mutations leading to loss of responsiveness to the trophic factor nerve growth factor (NGF) result in the loss of nociceptive neurons and a pain-free phenotype. [21]

Tissue damage depolarizes sensory neurons, but the transmission of information to the central nervous system (CNS) requires the recruitment of voltage-gated sodium channels to propagate action potentials and cause neurotransmitter release (mainly glutamate) into the CNS. In the absence of selective antagonists of ion channels, knock-out mouse studies have provided important insights into the genes that underlie this first stage in the induction of pain. Three genes encoding sodium channels are selectively expressed in sensory neurons. One, SCN11A, is found in a subset of damage sensing neurons and is activated close to the resting membrane potential. Knock-out studies have confirmed that the encoded channel NaV1.9 does not support action potentials but plays a key role in setting pain thresholds, as it is regulated by inflammatory mediators.

The second, SCN9A, is essential for peripheral pain and had been analysed in mouse knock-out before the discovery of naturally occurring human mutants. Global mouse knock-outs of SCN9A die, probably because they are unable to feed. However, nociceptor specific null mutants show a loss of acute mechanical and inflammatory pain[7]

Interestingly, human gain-of-function mutations of SCN9A, resulting in a defective NaV1.7 channel, appear to be completely pain-free but are otherwise normal. This observation is an important breakthrough in terms of novel target validation for new classes of sodium channel selective analgesic drugs. As an interesting corollary of this observation, human gain-of-function mutations of SCN9A, resulting in lowered thresholds of activation, result in erythromelalgia, a chronic inflammatory condition. Rarer mutations that impede the inactivation of the channel seem to cause acute paroxysmal pain. [23]

Finally, SCN10A (NaV1.8), a specific marker for nociceptive neurons, is a major contributor to electrogenesis in primary pain pathways and is an important target for inflammatory mediators. It is also essential for cold pain. Regulation of sodium channel expression, both transcriptionally and post transcriptionally, is an important element in determining neuronal excitability. A short sequence found upstream of neuronal sodium channel genes (as well as other neuronal genes) was identified and named NRSE (Neuron-restricted silencing element) or RE-1 (repressor element) [27]

Transcription factors that bound to the motif were found to act as inhibitors of gene expression in non-neuronal cells. These proteins were named REST (RE-1 silencing transcription factor) or NRSF (Neuron-restrictive silencer factor). The inhibitory activity of the complex can be further modulated by double-stranded RNA molecules that have the same sequence as NRSE/RE-1 and are found in developing neuronal precursors

These regulatory RNA molecules are able to switch the repressor function of the complex to an activator role. Splicing and editing are also important regulatory elements in controlling sodium channel function. Editing events in cockroach sodium channels and Drosophila Para have been correlated with functional changes[7]

In mammals, mutually exclusive exon usage also occurs. The SCN3A (NaV1.3) channel exists as an embryonic or adult spliced form, with different exons that code for the S3 and S4 segments in domain one of the rat channels. A similar pattern is present with SCN9A, where some differences in biophysical properties and the effects of cAMP on splice variants have been described[27]

A unique repertoire of sodium channel splice variants has been catalogued in dorsal root ganglia (DRG). The presence of a transcript with a three-exon repeats encoding NaV1.8 is enhanced by treatment with NGF, suggesting that this neurotrophins may regulate trans splicing events in these cells [27].

Herpes Simplex Virus (HSV) is an enveloped, double-stranded DNA virus that naturally causes cold sores. Due to its inherent neurotropic properties, HSV was chosen to create gene transfer vectors. This virus is efficiently transmitted through skin contact, after which it is taken up by nerve terminals and transported along axons to establish a persistent, latent state in sensory neurons of the dorsal root ganglion (DRG) or trigeminal ganglion [21]. To construct nonreplicating gene transfer vectors, essential immediate early genes were selectively deleted from the HSV genome. These replication-incompetent vectors can be propagated to high titter in complementing cells that provide the missing essential immediate-early gene products. When injected into animals or humans, the vector is incapable of replication but retains its biological properties, allowing it to be taken up element by sensory nerve terminals and carried to the DRG. There, the genome establishes a persistent state as a non-integrated, episomal intranuclear[21].

Acupuncture

Acupuncture is commonly used for the treatment of pain [22].In traditional Chinese medicine the concepts of “meridian” and the vital energy “Qi” form part of the theoretical basis for needling at specific acupuncture points[22]. Studies indicate that penetration of a needle through the skin, whether at an acupuncture point or not, has physiological effects. It is well tolerated with little risk of serious adverse effects[23] Traditional acupuncture and nontraditional techniques, such as electroacupuncture and dry needling, often result in reported pain improvement [23]. Particularly good results of treatment by acupuncture can be achieved in functional disorders[24]. A common feature in many of the methods used for pain relief is the activation of somatic afferent nerves; for example, through transcutaneous electrical nerve stimulation (TENS), vibration stimulation and massage; receptors or nerve fibres excited in the stimulated tissue[24]. Acupuncture by manual or electrical stimulation is effective at triggering nerve impulses [24]. According to TCM, the needle stimulation in the active acupuncture point needs to produce a specific feeling (called Deqi), which is experienced as numbness, heaviness, radiating paraesthesia, sensation of muscle pain. It is a sign of activation of the thin myelinated A-delta nerve fibres. Low-frequency electrical stimulation (electro acupuncture) of sufficient intensity causes muscle contraction while activating high-threshold and low-threshold mechano-receptors in muscles[24]. Particular significance is attributed to the group of receptors in skeletal muscle with a high-threshold for mechanical stimulation which are innervated with A-delta fibres and C-fibres [24]. These are physiologically activated by strong muscle contraction, which can be functionally excited by dynamic movements [24].

One of the main effects of acupuncture is the release of not only the endogenous opioids, beta-endorphins, enkephalins, dynorphins but also non-opioid compounds, such as serotonin, norepinephrine, GABA and oxytocin which seems to be essential for the induction of functional changes in various organs [24]. Endogenous opioid beta-endorphin is released by two different systems – neural network and blood. The first system includes the hypothalamus and the neural network leading to the midbrain and brainstem and in this way can affect pain sensitivity as well as autonomous functions.There is evidence that the hypothalamus nuclei play a vital role in the mediating effect of acupuncture [24].

Damage in the arcuate nucleus eliminates the analgesic effect of low-frequency but not of high-frequency electro-acupuncture. Acupuncture and pain treatment Low-frequency electrical stimulation induced circulatory changes in multiple tissues. Increase in the beta-endorphin levels was observed in the animal brain tissue both after acupuncture treatment and muscular exercise.Experimental and clinical evidence indicates that acupuncture can also affect the sympathetic nervous system on the hypothalamus hypophysis level[24]. The second system includes the release of the beta endorphin levels into blood. Proopiomelanocortin in the hypophysis produces the equimolar amount of beta-endorphin and ACTH after muscular exercise and also after acupuncture treatment and its modifications in the active acupuncture point.The effects of endorphins are important because endorphins are secreted during both the acupuncture and muscular exercise and may induce changes similar to the effects of morphine agonist and naloxone, which is a non-specific antagonist of beta endorphins [24].

various clinical trials pointed to electrostimulation analgesia in cases of chronic pain where levels of endorphins in cerebrospinal fluid are high and may be suppressed by naloxone. It was also found that the long-term stimulation also weakened the analgesic effect and the increase in endogenous opioids.This was resolved by administration of the L-tryptophan amino acid a precursor of the serotonin biosynthesis in the CNS. The results of some clinical trials in human volunteers and in laboratory animals provide evidence of the involvement of the nervous and endocrine system in acupuncture [24].

Acupuncture was able to reduce the concentration of noradrenaline in the brain and in the blood circulation, it reduced the production of epinephrine in animals exposed to restraint stress; it also induced long-term behavioural and cardiovascular depression and anxiolytic effects commonly observed in animals in captivity [24].

This would suggest that acupuncture is a kind of placebo treatment based on random skin needling.There are many issues in acupuncture research, such as the underlying mechanisms of needling; specificity of acupoints; understanding how individual features of acupuncture transfer into physiological and clinical outcomes. All these issues need to be solved in order to maximize clinical benefits of acupuncture [24].

Misuse of drugs

The nomenclature around the illicit use of drugs remains confusing, but the recent *International Statistical Classification of Diseases* and Related Health Problems (*ICD-10*, released by the World Health Organization in 2016) uses "dependence syndrome" as the preferred term. Other terms such as "addiction," "substance use disorder," and "substance misuse" relate to the same condition, but for the purpose of clarity and simplicity we use "dependence syndrome" [35]. *Dependence syndrome: A cluster of behavioural, cognitive, and physiological phenomena that develop after repeated substance use and that typically include a strong desire to take the drug, difficulties in controlling its use, persisting in its use despite harmful consequences, a higher priority given to drug use than to other activities and obligations, increased tolerance, and sometimes a physical withdrawal state.* Controlled dependence: where they are on clinically supervised maintenance or replacement regimen. Currently abstinent: currently abstinent are no longer physically dependent on the drug but are particularly vulnerable to relapse, owing to the chronic changes induced by drug use

Senses

Globally, the United Nations estimate that around 250 million people (5% of the world's adult population) used an illicit drug at least once in 2014, whereas the number of people classified as having a drug use disorder is estimated to be 29 million. opioids are used less often than cannabis, cocaine, or amphetamine but contribute to 82% of fatal overdoses. Alcohol is one of the most frequently used drugs, with Germany citing 1 in 5 perioperative patients having an alcohol use disorder. Recent figures suggest that there are 1.3 million high-risk opioid users in the European Union. Approximately 435,000 people in the United States use heroin, whereas almost 5 times that number 1.9 million meet criteria for prescription opioid use disorder.

Assessment and Screening of patients

It is essential to establish good patient–clinician rapport to promote an atmosphere of trust and understanding. This will allow an open discussion to accurately ascertain which drugs the patient is currently taking, address the patient's anxieties, manage expectations, and plan care collaboratively, thus reducing discord between the patient and the health care team. On or before admission, clinicians should reconcile the patient's medicines with the patient's primary care physician and/or drug and alcohol worker. In preparation for discharge, the team should arrange community support to provide follow-up and manage the process of analgesia reduction during the recovery phase. There is a high prevalence of psychiatric comorbidities in those with drug dependence, with more than 50% of patients showing evidence of significant psychopathology, particularly anxiety disorders and affective disorders, including depression. Such comorbidities may further complicate patients' behaviour and their interaction with staff while in the hospital.

Concerns in treatingpain in patients with drug dependence syndrome:

Patient concerns

- The fear of withdrawal, such as when the usual opioids used in substitution therapy are not given promptly. These anxieties are most obvious after long waits in the emergency department or immediately after admission to the hospital, when the drug has not yet been prescribed or released by the pharmacy. If doses are omitted or delayed, there will be a re-emergence of withdrawal symptoms and drug cravings.
- The fear of pain not being taken seriously, with restricted access to analgesia and pain left unrelieved.
- The fear of discrimination, often based on previous poor hospital experiences, leading to clinician distrust.
- In those currently abstinent, the fear of relapse if re-exposed to opioids or untreated pain.

Clinician concerns

Mistrust of those with addiction.

- Overtreatment of pain, leading to opioid-induced ventilatory impairment.
- The possibility that reports of pain may be fabricated to acquire opioids for euphoria.
- The diversion of prescribed opioids.

- Fear that patients may leave the hospital against medical advice (elopement) and not completing essential medical care (e.g., infection control).

Discharge

Discharge planning begins at admissionto ensure that the patient is discharged into a safe and supportive environment. Referral to a hospital social worker should be undertaken on awareness of a patient with a drug dependence syndrome to allow sufficient time to explore any community housing needs and to inform the discharge plan. Good communication with primary care clinicians, dispensing pharmacists, and drug treatment services is essential to ensure that patients re-engage with support services and maintain their prehospital management. Where opioids for analgesia are needed on discharge, decisions on how to provide that safely will be based on the services available in individual hospitals. Immediate-release formulations would be most appropriate for the ongoing treatment of acute pain, but they carry a higher risk of diversion or overdose. Some hospitals may be able to offer frequent outpatient appointments in the time immediately after discharge so that limited doses of short-acting opioids can be given and weaned under close supervision. Where this intense control is not available, supervised consumption of long-acting preparations may be the safest and most appropriate way of providing short-term pain relief and preventing diversion, with a clear and specific plan to guide dose reduction.

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