

Evaluation and Control of Pain in Clinical Settings

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Abstract

Background: Pain is a subjective and an unpleasant sensory and emotional experience associated with actual or potential tissue damage or injury. It can also occur without actual tissue damage, even though the patient refers to it. Pain is a conscious experience, an interpretation of the nociceptive input influenced by memories, emotional, pathological, genetic, and cognitive factors. Pain promotes defensive action and future avoidance behaviour, which requires associating defensive behaviour with resultant changes in pain. Pain has been a predominant health concern for mankind since the dawn of recorded history, and pain control is one of the cardinal objectives of the practice of medicine. It is the most common symptom of disease reported to physicians; more than 80 % of all patients who present to hospitals and clinics do so because of pain. Pain affects the general health, psychological health, social and economic well-being of an individual. The annual cost of uncontrolled chronic pain in the general population is in amount of hundreds of billions of dollars. **Objective:** The work discussed the evaluation tools and protocols, strategies for pain control, and future therapeutic drug targets for pain and analgesia. **Method:** The literature search used for the narrative review employed electronic databases in the search for relevant research articles, and they included scopus, pubmed, medline, google scholar, and the directory of open access journals. Others were the use of standard textbooks and the review of references of identified journal articles. Articles on pain and analgesia were identified and reviewed for selection. The keywords used in the search were: "Pain evaluation, Pain assessment, Pain control, Pharmacotherapy of pain, Pain management, Types and characteristics of pain, Aetiology/ Cause of pain, Classification of pain, Severity of pain, Measurement of pain intensity, Pain evaluation tools, and Novel therapeutic drug targets for pain". The exclusion criteria used, included articles not written in English and those articles that hinged the clinical management of pain on herbal and alternative medicines (e.g., acupuncture, homeopathy etc.). **Result:** One hundred and ninety-seven works, ranging from published journal articles to non-journal articles were identified. A total of 82 research works, monographs and textbooks were selected. The works were extracted and reviewed after screening of the titles and abstracts, and in compliance with the inclusion/ selection criteria. **Conclusions:** Clinical pain is a serious public health concern. Pain evaluation is a multi-strategic observational assessment of a patients' pain experience. The tools (self-report, behavioural and physiological) for pain evaluation have been demonstrated to be clinically effective in assessing acute pain. Pain evaluation is crucial and clinically useful for an effective and successful pain management. Pharmacotherapy is a critical component in the clinical management of pain, including acute, chronic and acute-on-chronic pain.

Keywords: Nociceptor, perception, assessment, analgesia, drug target, pharmacotherapy.

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INTRODUCTION

Clinical pain is a serious public health issue (Tracey and Mantyh, 2007). Globally, it has been estimated that 1:5 adults suffer from pain (Tsang *et al.*, 2008), while another 1:10 adults are diagnosed with chronic pain each year. Pain affects all populations irrespective of age, sex, income and social status, race/ethnicity, or geographical location, and it is not evenly distributed across the globe. Body pain varies

from 8.7 to 42.0 % among adults in different countries (Yeo and Tay, 2009; Cabral *et al.*, 2014; Duenas *et al.*, 2015). The wide discrepancies in the prevalence of pain could be partially explained by methodological, racial/ethnic, or cultural differences (Johannes *et al.*, 2010). Evidence strongly suggests that complaints of pain are more common among the obese (Dario *et al.*, 2015; Okifuji and Hare, 2015), women (Tighe *et al.*, 2014; Boerner *et al.*, 2015; Oliva *et al.*, 2015), middle-

aged persons (Houde *et al.*, 2015; LeResche *et al.*, 2015;), and individuals of lower socioeconomic status (Latza *et al.*, 2000). The experience of pain can be acute, chronic, or intermittent pain, or a combination of the three. Pain is a subjective and an unpleasant sensory and emotional experience associated with actual or potential tissue damage (IASP, 2005; Swieboda *et al.*, 2013). Pain is a disabling condition that is associated with many pathological and emotional states. Pain control is one of the most important therapeutic priorities (Rang *et al.*, 2019). Pain has been a predominant health concern for mankind since the dawn of recorded history, and pain relief is one of the cardinal objectives of the practice of medicine. It is one of the body's most important communication tools, and a protective mechanism to which the body responds to noxious or harmful stimulus (Swieboda *et al.*, 2013). Pain is the most common symptom of disease reported to physicians; more than 80 % of all patients who present to hospitals and clinics do so because of pain (Swieboda *et al.*, 2013; Nagda and Bajwa, 2020). Pain affects both our previous experience of pain and psychosomatic conditions, depending on the relationship between the psyche and the body. The feeling of pain can be caused by irritation of pain receptors – nociceptors (free nerve endings that sense heat, mechanical and chemical tissue damage), and can be found on the skin, muscle, joints, internal organs, and virtually all tissues of the body (Jensen, 2008; Swieboda *et al.*, 2013). Pain can also occur without tissue damage, although the patient refers to it (psychogenic pain). The process leading to pain is a complex phenomenon. Experience of pain is dependent on the strength of the stimulus, individual susceptibility and resistance to pain. Pain promotes defensive action and future avoidance behaviour, which requires associating defensive behaviour with resultant changes in pain (Baliki and Akparian, 2015). Pain receptors are sensitive to mechanical, thermal or chemical stimuli. The application of noxious stimulus to these receptors results in the processing into an electrical signal. This impulse is conducted by nerve fibres into the spinal cord and then to the brain (Swieboda *et al.*, 2013). Chronic pain has been recognised as pain that persists after normal healing period (Bonica, 1953; IASP, 2004), and hence lacks the acute warning function of physiological nociception (Treede, 2011). Usually, pain is regarded as chronic when it lasts or recurs for more than 3- 6 months (Merskey and Bogduk, 1994). Chronic pain is a frequent condition, affecting an estimated 20 % of people worldwide (Brevik *et al.*, 2006; Gureje *et al.*, 2008; Goldberg and Summer, 2011; Institute of Medicine, 2011), and accounts for 15 – 20 % of medical consultations (Mantyselka *et al.*, 2001; Koleva, 2005). Chronic pain should receive greater attention as a global health priority because adequate pain treatment is a human right, and it is the duty of any health care system to provide it (Bond *et al.*, 2006; Goldberg and Summer, 2011). Chronic pain affects several million people globally, altering their physical and emotional

functioning, reducing their quality of life, and impairing the ability to work (Nagda and Bajwa, 2020). It affects general health, psychological health, social and economic well-being. Patients in chronic pain use health services five times more frequently than the rest of the population (Nagda and Bajwa, 2020). The annual cost of unrelieved chronic pain in the general population is in amount of hundreds of billions of dollars. Structured pain assessment using a variety of validated measures can be of important assistance to the diagnosis of pain, direct the treatment, and to evaluate it (Bendinger, 2016). Therefore, for an effective and efficient clinical pain management, pain evaluation is critical.

AETIOLOGY OF PAIN

The causes of pain are manifold, and people respond to it in diverse ways. Acute pain is usually sudden in onset with a limited duration. Most often, it is caused by damage to the tissues such as bone, muscle, ligament, or organs, and the onset is often accompanied by anxiety or emotional distress (WebMD, 2019). Chronic pain may arise from tissue damage, but it is usually attributed to nerve damage. Chronic pain can be caused by the following (Ingraham, 2019):

- Injuries (38%), including road traffic injuries, fall from heights, gunshots and stab injuries (penetrating injuries).
- Musculoskeletal disorders (24%), comprising predominantly of the arthritis (osteo-, gouty, and rheumatoid), the rheumatic diseases, fibromyalgia, and headache syndrome.
- Others (7%), which are mostly malignancies (cancers), abdominal pain, and pain related to major physiological systems.
- Unknown (31%).

CLASSIFICATION OF PAIN

The classification of pain is a useful guide in the clinical evaluation and control of pain (Dorset Health Care, 2013). Pain can be acute, chronic or acute-on-chronic. Acute pain is transient lasting for 2 – 3 days while chronic pain is usually persistent lasting for 3 – 6 months or even more, and has been described as a disease rather than a symptom of a pathological condition (Bukhari and Kearney, 2009). Acute pain is frequently generated by surgery, but may occur as a result of trauma or as part of a medical illness, such as myocardial infarction or colic (Greenstein, 2009). Acute pain is an adaptive warning of an impending or actual tissue damage. It interrupts behaviour, directs attention to the site of injury, and motivates behaviour to escape from the noxious stimulus (Tracey and Mantyh, 2007). Acute-on-chronic pain is a state where a person that is treated with analgesics for a chronic pain condition suddenly develops acute flare-ups or breakthrough pain. It is found in 70 % of individuals with chronic pain (WebMD, 2019). The intensity of pain may be mild, moderate or severe. More than one type of pain may be found in a patient. For instance, there could be the

presence of both nociceptive and neuropathic pain in a given pathological condition. Acute and chronic pain can be debilitating, and both can affect and be affected by an individual's state of mind. Chronic or intractable pain is a compelling, but typically maladaptive state that is often associated with profound affective (emotional) disturbances in patients (Tracey and Mantyh, 2007). Chronic pain affects more than 20 % of the population worldwide (Breivik *et al.*, 2006; Gureje *et al.*, 2008; Goldberg *et al.*, 2011; Institute of Medicine, 2011), and accounts for up to 20 % of physician visits (Mathyselka *et al.*, 2001; Koleva, 2005). Chronic pain has emerged as a critical component in the global burden of disability (Croft *et al.*, 2010). The cause of chronic pain is often unknown. It develops insidiously and is associated with a sense of hopelessness and helplessness. The nature of chronic pain makes the sufferer more susceptible to the development of psychological and emotional consequences, such as anxiety and depression, because the pain is an on-going process and almost always present and not abating. Psychological distress can amplify the pain (WebMD, 2019). Chronic pain can sometimes be refractory to pharmacological interventions.

TYPES AND CHARACTERISTICS OF PAIN

1. Nociceptive Pain

This type of pain arises due to the stimulation of specific pain receptors (nociceptors) and it is a normal response to potential tissue damage or injury, e.g., skin, visceral organs, muscles, tendons, joints and bones. We have at one time or the other in our lives experienced this type of pain which tends to resolve after a reasonable length of time. Somatic and visceral pain fibres are fully integrated with the skeletal motor and sympathetic systems in the spinal cord, brain stem and higher centres. These synapses are responsible for reflex muscle activity that is associated with pain (Swamy, 2005).

- i. **Somatic Pain:** The type of pain arises from pain receptors (nociceptors) in deep tissues in the body (e.g. bones, muscles and joints). Somatic pain is sharp, gnawing and aching pain, and is usually constant and localised (Njau, 2002; Bukhari and Kearney, 2009).
- ii. **Visceral Pain:** This emanates from the activation of nociceptors in the thorax, abdomen and pelvis. Visceral pain is caused by infiltration, compression and stretching of thorax or abdominal viscera due to a primary or secondary (metastatic) tumour growth (Njau, 2002; Bukhari and Kearney, 2009).

It is a deep pain, somewhat constant and diffused, and not localised or vaguely localised to a viscus. Examples are pain caused by pancreatic cancer or pulmonary metastasis (Njau, 2002).

2. Neuropathic Pain

This pain originates from the CNS either due to a pathological state, injury or dysfunction to the peripheral nervous system (i.e., peripheral nerves - A β , A δ and C-fibres, ganglia, and nerve plexi or plexuses) (Costigan *et al.*, 2009; Colloca *et al.*, 2017), with a burning, constricting, paroxysmal and shooting sensation. It affects 7 – 10 % of the general population. Neuropathy elicits a number of changes in nerves in terms of activity, properties, and transmitter content (Mello and Dickson, 2008). The spectrum of neuropathic pain ranges from neurological deficits which manifest as numbness to hypersensitivity (hyperalgesia or allodynia), and to paraesthesia (tingling sensation) (Dorset Health Care, 2013). The clinical conditions include cerebrovascular disease (stroke), multiple sclerosis, diabetes mellitus, herpes zoster infection (shingles) or mechanical injury. The pathophysiology of neuropathic pain is imprecisely understood. Earlier opinion fingered spontaneous activity in damaged sensory neurones due to over-expression or redistribution of voltage-gated sodium channels (Li *et al.*, 2004; Chahine *et al.*, 2005). However, recent findings suggest that imbalances between excitatory and inhibitory somatosensory signalling, alterations in ion channels and variability in the way that nociceptive information are modulated in the CNS have all been implicated in neuropathic pain (Colloca *et al.*, 2017). The autonomic nervous system (sympathetic division) contributes in part, because of the expression of α -adrenergic receptors and the development of sensitivity to noradrenaline, a characteristic property they do not possess under normal conditions. Therefore, physiological stimuli that evoke sympathetic responses can produce severe pain, a condition clinically described as sympathetically mediated pain. Neuropathic pain is a major cause of disability and distress, and is often times poorly responsive to conventional pharmacological therapy (analgesics), but can be relieved with antidepressants and anti-seizure medicines (Rang *et al.*, 2019).

Abnormal Pain Transmission and Perception

Hyperalgesia and allodynia are consequences of abnormal pain transmission and perception, and are both referred to as hyperaesthesia.

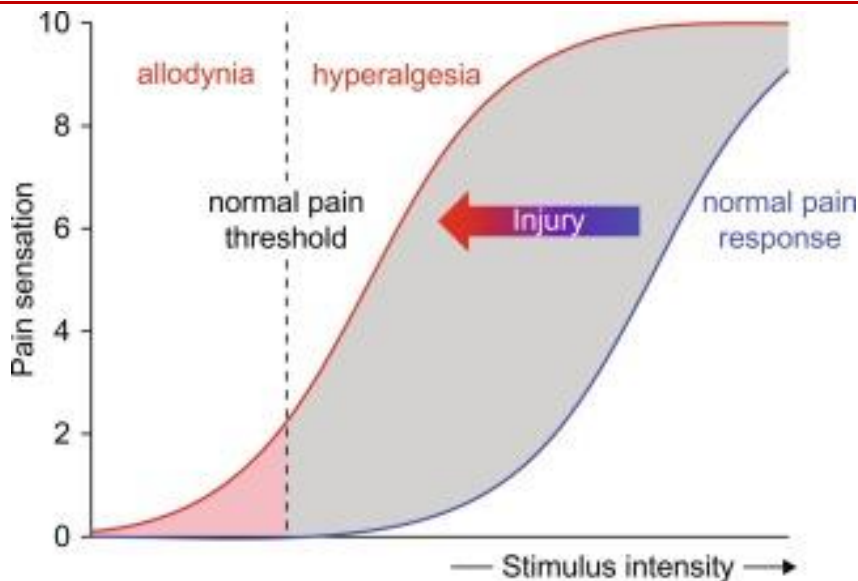


Fig. 1: Illustration of hyperaesthesia (in which tissue injury sensitises the response of nociceptors to innocuous and noxious peripheral stimuli). Adapted from Cervero and Laird (1996)

- i. **Allodynia:** This is the experience of pain due to innocuous stimulus or sensation. It has no biological importance *per se*, but may be an adaptive mechanism to protect the vulnerability of an injury (Sandkuhler, 2009).
- ii. **Hyperalgesia:** It is an increased or severe pain arising from a noxious stimulus that would ordinarily cause a minimal pain, due to lowering of nociceptor threshold level. Hyperalgesia can be primary or secondary. Primary hyperalgesia is caused by peripheral mechanisms (e.g., tissue injury) while secondary hyperalgesia extends beyond the anatomical site of injury to an uninjured tissue or organ. Ankle sprain and burns are classical examples in which allodynia and hyperalgesia are experienced clinically (Rang *et al.*, 2019).
- iii. **Paraesthesia:** This is an unpleasant or painful sensation that arises in the absence of a tactile stimulus (e.g. pins and needles, and electroshock sensations). Paraesthesia is caused by diabetes mellitus (diabetic neuropathy), post-herpetic neuralgia, spinal cord injury, cerebrovascular disease (stroke), phantom pain from limb amputation, nerve disorders, HIV and alcoholism (Dorset Health Care, 2013).

3. Psychogenic Pain

Psychogenic pain, otherwise known as psychalgia or somatoform pain, is pain caused, increased, or prolonged by mental, emotional, or behavioural factors (Psychogenic Pain, 2017). In this type of pain, there is no known physical cause, but the processing of sensitive information in the CNS is disturbed. It may be secondary to tumour infiltration of peripheral nerves or spinal cord, and consequently causing injuries to these structures. Psychogenic pain is paroxysmal, shooting, burning or tingling in nature

(Njau, 2002). The psychological evaluation provides evidence that the pain itself is predominantly sustained by psychological factors. Psychological factors such as social support, hypnotic suggestion, cognitive behavioural therapy, excitement, or distraction can affect pain's intensity or unpleasantness (Eisenberger and Lieberman, 2005; Garland *et al.*, 2020).

GUIDELINES FOR PAIN EVALUATION

The evaluation of pain is a multistrategic observational assessment of a patients' pain experience (Pain Assessment and Management, 2019). It is critical if pain management is to be effective and successful. Pain perception (sensation) is subjective, and thus varies from one individual to another. Self-report is considered the gold standard and most accurate measure of pain. Valid and reliable assessment of pain is necessary for both clinical (analgesic drug) trials and effective pain management. The nature of pain makes objective measurement difficult, if not impossible (Breivik *et al.*, 2008). Acute pain can be reliably assessed, both at rest (necessary for comfort) and during movement (important for function and risk of postoperative complications), with one-dimensional tools such as numerical rating scales or visual analogue scales. These scales are very powerful in detecting changes in pain intensity than a verbal categorical rating scale (Breivik *et al.*, 2008).

Pain Evaluation Tools

The tools used for pain evaluation have been selected based on their validity, reliability and usability, and have been demonstrated to be clinically effective in assessing acute pain (Pain Assessment and Management, 2019). Ethnic, cultural, and language factors may influence expression and assessment of pain (McGrath and Unruh, 2013; Lee *et al.*, 2014). Pain is assessed using self-report, behavioral (vocalisation,

facial expression, body movement), and biological or physiological (heart rate, transcutaneous oxygen, sweating, stress response) measures. Assessing behavioral reactions and physiological reactions to pain are required in non-verbal and young patients (McGrath and Unruh, 2013). The tools are globally recognised by all strata of the clinical specialties. The measures include:

1. **Self-Report:** This is the gold standard for pain measurement (i.e. the patient’s pain story).
2. **Behavioural:** This refers to how the patient behaves or reactions to pain (i.e. the patients’ general behaviour).
3. **Physiological:** This aspect involves the clinical (physical) observation and examination of the patient.

• **SELF-REPORT**

The self-report method of evaluating pain is an invaluable clinical tool to accurately describe, assess and document a patient’s pain. The method also assists in the selection of appropriate pharmacological agent (analgesics) and the assessment of response to treatment (PQRST Pain Assessment Method, 2020). The PQRST assessment questions have been shown to be invaluable clinically.

Provocation/Palliation

- Activity of the individual at onset.
- Cause of pain.
- Relieving factors: Medicines, massage, heat/cold, changing position, physical activity, resting.
- Aggravating factors: Movement, bending, lying down, walking or standing.
- Precipitants/triggers.
- Stress.

- Position of the individual prior to onset of pain.

Quality/Quantity

- Nature/character/description of the pain: Sharp, dull, stabbing, burning, crushing, throbbing, nauseating, shooting, twisting or stretching.

Region/Radiation

- Location: Anatomical site or origin of pain and the region of radiation.

Severity Scale

In severe pain, there is the:

- Interference with activities of daily living.
- Compels the individual to sit down, lie down, and slow down in any activities being performed when the pain occurs.

Measurements of Pain Intensity

The intensity (or severity) of pain can sometimes be underestimated by medical personnel (Prkachin et al., 2007). There are several scales for measuring the intensity of pain in the adult population, and they include: verbal rating scale (VRS), visual analogue scale for Pain (VAS Pain), numeric rating scale for pain (NRS), McGill pain questionnaire (MPQ), short-form McGill pain questionnaire (SF-MPQ), chronic pain grade scale (CPGS), short form-36 bodily pain scale (SF-36 BPS), and measure of intermittent and constant osteoarthritis pain (ICOAP) (Hawker et al., 2011). However, only three of these severity scales was discussed in the work, and they are:

1. Numerical rating scale
2. Verbal rating scale
3. Visual analogue scale

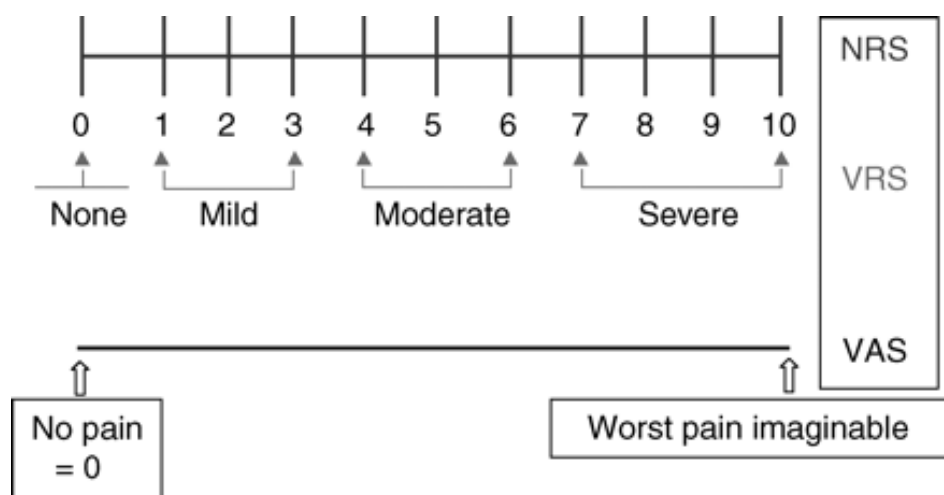


Fig. 2: Scale for Evaluating the Severity of Pain
 Source: Breivik et al., 2008.

Numerical Rating Scale

Severity of pain on a scale of 0-10: 0=Absence of pain, 1-3=Mild pain, 4-6=Moderate pain, 7-9=Severe pain, 10=Very severe pain (i.e., unbearable or worst pain possible).

Verbal Rating Scale

The verbal categories mild, moderate, and severe pain may correspond to different values on the VAS in the same patient on different occasions, whereas the NRS and VAS values generally agreed well (Breivik *et al.*, 2000). Therefore, a categorical pain scale should be used only as a coarse (or approximate) screening tool, and more accurate pain intensity assessment should rely on an NRS or VAS, even in routine clinical valuation.

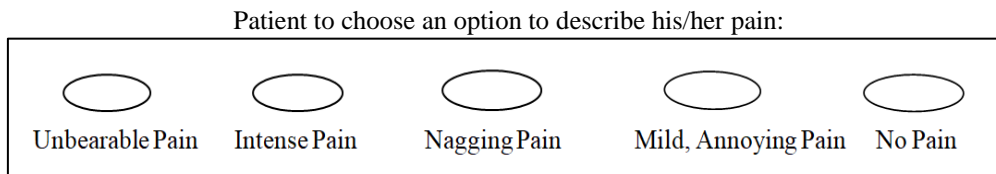
Visual Analogue Scale

The visual analogue scale (VAS) is a common, reproducible tool in the assessment of pain and analgesia (Kelly, 2001). The scale is a continuous line anchored by verbal descriptors, one for each extreme of pain, where a higher score indicates greater pain intensity. VAS is usually 10 cm in length with no

intermediate descriptors as to avoid marking of scores around a preferred numerical value. When applied as a pain descriptor, these anchors are often 'no pain' and 'worst possible or imaginable pain'. Cut-off levels for pain classification have been recommended as no pain (0 - 4 mm), mild pain (5 - 44 mm), moderate pain (45 - 74 mm) and severe pain (75 - 100 mm) (Hawker *et al.*, 2011). The VAS is a psychometrical response scale which can be used in questionnaires. VAS is a clinical tool for subjective characteristics or attitudes that cannot be measured directly. It is the most common pain scale for quantification of endometriosis-related pain and skin graft donor site-related pain (Sinha *et al.*, 2017). VAS and NRS have been described as the best adapted pain scales for the measurement of pain in endometriosis.

Types of Visual Analogue Scale

- **Semantic Differential (Non-Slider) Scale:** This consists of circles at equal distances and according to the desired option; the respondent will have to select the circle.



- **Slider Visual Analogue Scale:** In this scale, the respondents indicate their level of agreement using a slider which has adjectives corresponding to the issue being discussed as the two extremes ('Unbearable Pain' at one end and 'No Pain' at the other end) of the scale as well as other intermediate terms (just as in the Non-slider) that connect the duo.

Timing

- **Period of onset/Duration:** At what time did the pain start (i.e. ten days ago, six months ago, two years ago etc.).
- **Nature and circumstances of onset:** Gradual or sudden; Type of activity being performed at onset of pain.
- **Frequency:** Hourly, half-hourly, daily, weekly, monthly.
- **Disruption of sleep:** Awakened from sleep,
- **Periodicity of pain:** Is the pain present in the early morning, afternoon (daytime), night?
- **Seasonality:** The weather cycle or period of the year: Spring, summer, autumn, winter; dry or rainy season.
- **Associations:** Is it related to meals (before, during or after)?; Does the pain evoke other symptoms and/or signs?

Documentation of Pain

It is important that careful and complete documentation of pain is carried out, so as to ensure that patients receive the highest quality of medical care. These should be documented on the clinical observation chart as stated below:

- i. Patient understands of the pain scale: Describe the patient's ability to assess pain level using the 0-10 pain scale.
- ii. Patient satisfaction with pain level with current treatment modality: Determine the patient's pain level prior and post commencement of analgesics to know if the patient is satisfied with the treatment or otherwise, and to examine interventions adopted in times of unsatisfactory treatment of patient's pain level.
- iii. Timely re-assessment following any interventions and response to treatment: State the patient's response to pain therapy.
- iv. Communication with the doctor: Report any changes in clinical condition to the physician.
- v. Patient education provided and the patient's response to learning: Ensure that patient actually understands (one-on-one communication) all that has been thought regarding his/her pain level and the management of same.

• PHYSIOLOGICAL METHOD

Physiological tool alone is inadequate as an indicator of pain measurement. A clinical tool that encompasses self-reports, behavioural and physical (physiological) is recommended. However, in severely debilitated and unconscious patients, physiological indicators of pain can be invaluable in the examination of a patient's pain experience (Pain Assessment and Management, 2019).

Physiological signs of pain:

- a.) Tachycardia can occur
- b.) Respiratory rate and depth of breathing may change from normal to an increase, decrease or a change pattern.
- c.) Hypertension may ensue
- d.) Oxygen saturation decline
- e.) Sweating
- f.) High blood glucose
- g.) Poor organ perfusion
- h.) Decreased gastric acid secretion
- i.) Decreased gastrointestinal motility
- j.) Pallor or flushing
- k.) Pupillary dilatation

CLINICAL MANAGEMENT OF PAIN

An understanding of the neurophysiology of pain is important for pain management, because it provides informed decisions regarding diagnosis and treatment (Cohen, 2017). Interventions to provide the required relief in patients (nerve blocks, implantable devices) can be performed at regional anatomical sites. With the emergence of new therapeutic modalities and pharmacological agents to provide analgesia (i.e., reduction, elimination or prevention of pain), the clinician with this fundamental knowledge will be better equipped to understand their mechanism(s) and clinical applications (Cohen, 2017).

Pharmacotherapy of Pain

The classical or typical analgesic medicines, notably the non-steroidal anti-inflammatory drugs (NSAIDs) or non-opioids and the opioids, whose prototypes are aspirin (acetylsalicylic acid) and morphine respectively, have been in clinical use for several decades, although many other compounds that act by the same mechanism have been developed (Rang *et al.*, 2019). Prescription analgesic medicines provide stronger and better relief from pain than over-the-counter agents (e.g., paracetamol, NSAIDs or their combination).

Classification of Analgesic Drugs

1. Non-Opioids: Paracetamol (acetaminophen) is a non-NSAID, non-opioid medicine with antipyretic and analgesic properties, but with a weak/little or

no anti-inflammatory activity. Also included in this group are the NSAIDs (e.g., aspirin, diclofenac, naproxen, piroxicam etc.).

- 2. Opioids:** Opioid medicines may be natural (e.g., morphine and codeine), semi-synthetic (e.g., oxycodone, hydrocodone, hydromorphone and oxymorphone) and synthetic (e.g., fentanyl, methadone and tramadol). These agents alter pain perception and have potential for addiction. As a consequence, they are not prescribed for routine chronic pain management, although they can be administered for short duration after caesarean surgery, other surgical operations, as well as traumatic injuries, such as fall from height and road traffic injury.
- 3. Non-Classical:** Other agents used in pain therapy, especially chronic pain have also been referred to as atypical, adjuvants or co-analgesics, and describe any drugs with a primary clinical application or use other than pain, but can be employed in certain clinical pain conditions due to its analgesic properties (Dworkin *et al.*, 2003; Sharma, 2019).
 - a) **Corticosteroids:** Steroids possess strong anti-inflammatory activity. They inhibit the biosynthesis of inflammatory mediators that induce irritation and inflammation. Clinical conditions like migraine headache, arthritis and back pain can be treated with prednisone or prednisolone in combination with other medications.
 - b) **Antiseizure Drugs:** Carbamazepine, oxcarbazepine, lamotrigine and phenytoin are antiseizure medications indicated in pain of trigeminal neuralgia. Others include clonazepam (benzodiazepine), gabapentin, pregabalin (second generation antiseizure drug) (MFMER, 2020). These drugs interrupt pain impulses to the brain, and in so doing, provide relief for nerve pain and fibromyalgia. They can be administered singly or in combination with NSAIDs and/or opioids in chronic pain conditions (e.g., neuropathic pain).
 - c) **Antidepressants:** The tricyclic antidepressants (e.g., imipramine, amitriptyline etc.) can be used as monotherapy, but they are usually co-administered. Antidepressants have demonstrated clinical efficacy in certain types of pain, especially neuropathic pain.
 - d) **Muscle Relaxants:** Myorelaxants reduce pain by relaxing tight muscles. They also relieve the spasm of skeletal muscles (e.g., baclofen), hence they are clinically referred to as spasmolytics or neurospasmolytics or antispastic drugs.

Table 1: A Step-wise Clinical Approach to Analgesia

| Stage | Treatment | Examples |
|-----------------------------------|--------------------------------------|--|
| Rung 1.(Mild to Moderate Pain) | Non-opioids ± Adjuvants | Paracetamol, NSAIDs |
| Rung 2. (Moderate to Severe Pain) | Weak opioids+Non-opioids ± Adjuvants | Codeine, Dihydrocodeine, Tramadol |
| Rung 3. (Severe Pain) | Strong opioids | Morphine, Hydromorphone, Fentanyl, Methadone |

Therapeutic Adjuvants: Carbamazepine, Corticosteroids, Biphosphonates

Source: Cancer Pain Relief and Palliative Care, World Health Organisation, 1990.

Table 2: Classification and Characterisation of Analgesic Medicines

| Drug Class | Mode of Action | Adverse Effects | Other Information |
|--|---|--|---|
| Paracetamol | Weak inhibitor of COX enzyme; Acts centrally. | Rashes and blood disorders | Maximum of 4 g in 24 h |
| NSAIDs (Non-selective) e.g., ibuprofen | Inhibit COX-1 & 2 Enzyme; Enzyme synthesise PGs. PGs block pain, fever, inflammation and protect the gastric mucosal lining. | Gastrointestinal bleeding, nausea, vomiting, diarrhoea, rash, renal failure, hypersensitivity, hepatic failure | Good for dental and menstrual pains, arthralgia. Adjuvant in the WHO analgesic ladder. |
| NSAIDs (Selective) e.g. celecoxib | Inhibit COX-2 enzyme only. | Nausea, vomiting, abdominal pain, cardiotoxicity. | GI side effects are less relative to the non-selective NSAIDs. |
| Opioids | Bind to specific CNS receptors; can be agonists, partial agonists or antagonists. Three distinct sub-types of opioid receptors (μ , δ , κ). Most strong opioids are μ -receptor agonists. | Reduced GI motility, Anticholinergic side effects (dry mouth, blurred vision, urinary retention, constipation and drowsiness), nausea, vomiting, respiratory depression. | Tolerance to side effects. Patients on regular (strong) opioids should receive anti-emetics and laxatives concomitantly. |
| Morphine | Acts all over the CNS. | | Variety of short/ long acting solid and liquid formulations. Diamorphine is ideal for subcutaneous infusion. Respiratory depression, an opioid toxicity may ensue requiring naloxone (opioid antagonist) for its reversal. |
| Codeine | Structurally related to morphine. | | Potent cough suppressant with a short duration of action. |
| Fentanyl | | | Synthetic opioid with rapid onset and short duration of action when administered intravenously. Metabolised in the liver. Transdermal route by-passes first-pass effect and leads to dermal depot. Has low molecular weight, high solubility, long half-life; steady-state concentration achieved within 36 – 48 h; elimination half-life is ≥ 17 h. Caution should be exercised when changing from intravenous or oral to transdermal route. May take up to 72 h for depot clearance. |
| Hydromorphone | | | Controlled- and fast-release formulations are available. 7-fold more potent than the prototype agent (morphine). Has fewer side effects. Hydromorphone is an alternative to morphine for patients who manifest with confusion, hallucinations, vivid dreams, and loss of concentration. |

Source: Bukhari and Kearney, 2009

Table 3: Potencies of Oral Opioids

| Oral Opioids | Potency Ratio to Morphine |
|----------------|---------------------------|
| Codeine | 0.05 |
| Dihydrocodeine | 0.10 |
| Pethidine | 0.10 |
| Morphine | 1.00 |

Conversion of Approximate Equivalent Dose of Morphine: Dihydrocodeine, 30 mg (oral) is equivalent to Morphine, 5 mg (oral).

Source: Njau, 2002

FUTURE THERAPEUTIC DRUG TARGETS FOR PAIN

Drug discovery and development efforts in the biomedical and pharmaceutical sciences, as well as the clinical sciences increasingly rely on the use of unbiased (i.e., hypothesis-generating, omics) approaches, such as genomics, in contrast to the more traditional candidate (i.e., hypothesis-testing) approaches (Insel *et al.*, 2019). The search for better novel therapeutic drug targets has continued vigorously despite the multitude of clinically effective analgesic medicines. The rationale for this un-relentless effort may not be unconnected with safety concerns and the side effects profile of currently available agents. The NSAIDs cause gastric erosion and bleeding among other untoward effects, while the opioids are associated with the risks of tolerance, dependence and addiction, as well as respiratory depression. Accumulating knowledge and recent understanding of the various chemical mediators and signalling pathways implicated in pain perception indicates that there is an avalanche of new concepts and approaches to the control of pain and analgesia. Many of these novel therapeutic modalities are currently under exploration (Hill, 2006; Dray, 2008).

- i. **Nerve Growth Factor:** NGF is a mediator of inflammatory and neuropathic pain (Hefti *et al.*, 2006). It is a novel therapeutic target of critical importance. Monoclonal antibodies (i.e., identical immunoglobulins, generated from a single B-cell clone) to NGF or its receptor, TrKA (tropomyosin receptor kinase A) is presently under investigation. TrKA is also known as high affinity NGF receptor (Malenka *et al.*, 2009).
- ii. **TRP Channel Ligands:** Transient receptor potential (TRP) channels are a group of membrane proteins involved in the transduction of many chemical and physical stimuli. These channels modulate ion entry, mediate several neural signalling processes involved in the perception of temperature, pressure, and pH, including smell, taste, vision, and pain sensation (Muller *et al.*, 2019). TRPV1 (also referred to as capsaicin receptor) agonists and antagonists possess analgesic property (Rang *et al.*, 2019). Many diseases involve TRP channel dysfunction, including neuropathic pain, inflammation, and pulmonary disorders. In the search for novel therapies for these pathological conditions, it was discovered that cannabinoids can modulate a

certain subset of TRP channels. The TRP vanilloid (TRPV), TRP ankyrin (TRPA), and TRP melastatin (TRPM) subfamilies were all found to contain channels that can be modulated by several endogenous, phytogetic, and synthetic cannabinoids (Muller *et al.*, 2019).

- iii. **Sodium Ion Channels:** A number of sodium ion channel isoforms have been implicated in modulating nociception and pain sensations. Eight of the nine mammalian isoforms have been identified in peripheral sensory neurones (with the exception of Na_v1.4). While Na_v1.7, Na_v1.8, and Na_v1.9 are preferentially expressed in nociceptive neurones, several of the other isoforms have been implicated as possible therapeutic targets for regulating pain (Cummings *et al.*, 2020). Voltage-gated sodium ion channels play diverse roles in sensory neurone electrogenesis and are critical targets for potential analgesics (Cummings *et al.*, 2020). Na⁺ channel antagonists are currently being developed. These therapeutic candidates include lacosamide (antiseizure), ralfinamide (in clinical trial). Ralfinamide blocks Na⁺ channels and inhibits monoamine oxidase enzyme (Rang *et al.*, 2019). It has also demonstrated antinociceptive activity in experimental models of pain.
- iv. **Potassium Voltage-gated Channels:** Retigabine is a potassium voltage-gated channel (KCNQ) opener that inhibits primary afferent nerve fibre (C- and A δ -fibres) mediated nociceptive responses in the spinal dorsal horns in both naïve and neuropathic rat models. The suppression of KCNQ/M channels in primary dorsal root ganglion neurones plays a crucial role in the development of bone cancer pain and osteoarthritic pain (Zheng *et al.*, 2013; Zhang *et al.*, 2019).
- v. **Acetylcholine Receptor:** The nicotinic receptor agonist (e.g., epibatidine), is a chlorinated alkaloid derivative from the skin of the poisonous frog (*Epipedobates tricolor*). Epibatidine significantly demonstrated greater analgesic potency than morphine in assays of acute thermal pain. Derivatives of epibatidine with better side effects profile are being evaluated for possible clinical utility.
- vi. **Neuropeptides:** Somatostatin, a tetradecapeptide is present in high concentrations in many sites in the CNS, especially the dorsal horn of the spinal cord. The concentration of somatostatin in rexed laminae II and III of the dorsal horn shows that

somatostatin has important functions in modulating the transmission of somatosensory signals. Calcitonin is a peptide hormone which regulates calcium homeostasis. Calcitonin possesses analgesic properties, primarily *via* receptor mediated modulation of serotonergic pain pathway in the CNS (Visser *et al.*, 2005). Calcitonin and somatostatin have robust analgesic activity when administered parenterally (intrathecally). Clinical studies indicate that these agents may prove efficacious in the treatment of certain hormone-dependent disorders (e.g., endometriosis-related pains).

- vii. NMDA Receptor:** Facilitation of nociceptive transmission in the dorsal horn of the spinal cord can be inhibited by NMDA receptor blockers (e.g., ketamine). Dextromethophan and other NMDA receptor antagonists have demonstrated to be effective analgesics in clinical studies (Bennett, 2000; Carlsson *et al.*, 2004; Eisenberg *et al.*, 2007).
- viii. Nuclear Receptor:** REV-ERB α and REV-ERB β were originally identified as orphan receptors (i.e., proteins similar to other receptors, but whose endogenous ligands are yet to be identified). Both REV-ERB α and REV-ERB β constitutively silence transcription, and have been found to bind to haem. They function as ligand-dependent (i.e., haem-dependent) silencers of transcription (Kojetin and Burris, 2014). These nuclear receptors have vital roles in many physiological functions, including development, circadian rhythm, metabolism and immune function. Synthetic REV-ERB agonists alter the circadian rhythm and have beneficial effects on the metabolic profile in obese mice. REV-ERB agonists increase oxidative metabolism in the skeletal muscle and improve exercise endurance in mice (Kojetin and Burris, 2014). A study conducted to determine if activating the nuclear receptor (REV-ERBs) in specialised spinal cord cells, the neuroglial cells (e.g., astrocytes) resulted in analgesia in rodent models (American Laboratory, 2019). Nuclear receptor, therefore, may be a potential novel target for analgesia which could be of critical importance in chronic pain management.

CONCLUSIONS

Pain is a disabling state that is associated with many pathological and emotional conditions. It is one of the body's most important communication tools, and a protective mechanism to which the body responds to noxious or harmful stimuli. Pain evaluation and control are some of the fundamental objectives of the practice of human medicine. The evaluation of pain is an invaluable clinical tool to accurately describe, assess and document a patient's pain. Pain evaluation also offers tremendous assistance to the clinician in order to prioritise and optimise treatment through careful selection of appropriate therapeutic drugs (medicines)

that will abort pain and enhance the quality of life of patients. More therapeutic drug targets for pain and analgesia will emerge in the future due to the side effects profile and poor responsiveness of certain chronic pain conditions to the currently available analgesic medicines.

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CONFLICTS OF INTEREST

There was no competing interests to declare.

REFERENCES

- American Laboratory (2019): Findings on Pain Receptor Could Lead to New Treatment for Chronic Pain.
- Amico, D. (2016): Health and Physical Assessment in Nursing. Boston: Pearson. p. 173.
- Baliki, M. N., & Apkarian, A. V. (2015): Nociception, Pain, Negative Moods, and Behaviour Selection. *Neurone* 5, 87(3), 474 – 491.
- Bendinger, T. (2016): Measurement in Pain Medicine. *British Journal of Anaesthesia Education*, 16(9), 310–315.
- Bennett, G. J. (2000). NMDA-Receptor Antagonists: Evolving Role in Analgesia. Update on the Neurophysiology of Pain Transmission and Modulation: Focus on the NMDA Receptor. *Journal of Pain and Symptom Management*, 19, S2 – S6.
- Boerner, K. E., Schinkel, M., & Chambers, C. T. (2015), It is not as Simple as Boys versus Girls: The Role of Sex Differences in Pain Across the Lifespan. *Pain Management*, 5(1), 1 – 4.
- Bond, M., Breivik, H., Jensen, T. S., Scholten, W., Soyannwo, O., & Treede, R. D. (2006). Pain Associated with Neurological Disorders. In: Aarli J.A., Dua T., Janca A. and Muscetta A. (eds.) *Neurological Disorders: Public Health Challenges*. Geneva: WHO Press, p. 127 – 139.
- Bonica, J. J. (1953). *The Management of Pain*. Philadelphia, PA: Lea and Febirger.
- Breivik, E. K., Björnsson, G. A., & Skovlund, E. (2000). A Comparison of Pain Rating Scales by Sampling from Clinical Trial Data. *Clinical Journal of Pain*, 16, 22 – 28.
- Breivik, H., Borchgrevink, P. C., Allen, S. M., Rosseland, L. A., Romundstad, L., Breivik Hals, E. K., Kvarstein, G., & Stubhaug, A. (2008). Assessment of pain. *British Journal of Anaesthesia*, 101, 17 – 24.
- Breivik, H., Collett, B., Ventafridda, V., Cohen, R., & Gallacher, D. (2006). Survey of Chronic Pain in Europe: Prevalence, Impact on Daily Life, and Treatment. *European Journal of Pain*, 10(4), 287 – 333.

- Bukhari, N., & Kearney, D. (2009). FASTtrack Therapeutics, 1st Edition, Pharmaceutical Press, India, pp. 156 – 158.
- Cabral, D. M., Bracher, E. S., Depintor, J. D., & Eluf-Neto, J. (2014). Chronic Pain Prevalence and Associated Factors in a Segment of the Population of Sao Paulo City. *Journal of Pain*, 15(11), 1081 – 1091
- Carlsson, K. C., Hoem, N. O., Moberg, E. R., & Mathisen, L. C. (2004). Analgesic Effect of Dextromethorphan in Neuropathic Pain. *Acta Anaesthesiologica Scandinavica*, 48, 328 – 336.
- Cervero, F., & Laird, J. M. A. (1996). Mechanisms of touch-evoked pain (allodynia): a new model. *Pain*, 68(1), 13 – 23.
- Chahine, M., Ziane, R., Vijayaragavan, K., & Okamura, Y. (2005). Regulation of Na^v Channels in Sensory Neurons. *Trends in Pharmacological Sciences*, 26, 496 – 502.
- Cohen, R. I. (2017). Anatomy and Physiology of Pain. In: Bajwa, Z.H., Wootton, R.J. and Warfield, C.A.(eds.). *Principles and Practice of Pain Medicine*, 3rd Edition, McGraw Hill Education.
- Colloca, L., Ludman, T., Bouhassira, D., Baron, R., Dickenson, A. H., Yarnitsky, D., Freeman, R., Truini, A., Attal, N., Finnerup, N. B., Eccleston, C., Kalso, E., Bennett, D. I., Dworkin, R. H., & Raja, S.N. (2017). Neuropathic pain. *Nature Review and Discovery Primers*, 3, 17002.
- Costigan, M., Cholz, J., & Woolf, C. J. (2009). Neuropathic pain: A maladaptive response of the nervous system to damage. *Annual Review of Neuroscience*, 32, 1 – 32.
- Croft, P., Blyth, F. M., & van der Windt, D. (2010). The Global Occurrence of Chronic Pain: An Introduction. In: Croft P., Blyth F.M. and van der Windt D. (eds.). *Chronic Pain Epidemiology: From Aetiology to Public Health*. Oxford: Oxford University Press; p. 9 - 18.
- Cummings, T. R., Waxman, S. G., & Wood, J. N. (2020). Sodium Channels and Pain. In: Wood, J.N. (ed.). *The Oxford Handbook of the Neurology of Pain*.
- Dario, A. B., Ferreira, M. L., Refshauge, K., Sánchez-Romera, J. F., Luque-Suarez, A., Hopper, J. L., ... & Ferreira, P. H. (2016). Are obesity and body fat distribution associated with low back pain in women? A population-based study of 1128 Spanish twins. *European Spine Journal*, 25, 1188-1195.
- Dorset Health Care (2013). Trying to understand pain when there is no obvious explanation. Dorset Health Care University National Health Service, Dorset Community Health Service.
- Dray, A. (2008). Neuropathic Pain: Emerging Treatments. *British Journal of Anaesthesia*, 101, 48 – 58.
- Duenas, M., Ojeda, B., Salazar, A., Mico, J. A., & Failde, I. (2015). A Nationwide Study of Chronic Pain Prevalence in the General Spanish Population: Identifying Clinical Subgroups through Cluster Analysis. *Pain Medicine (Malden, Mass.)*, 16(4), 811 – 822.
- Dworkin, R. H., Backonja, M., Rowbotham, M. C., Allen, R. R., Argoff, C. R., Bennett, G. J., ... & Weinstein, S. M. (2003). Advances in neuropathic pain: diagnosis, mechanisms, and treatment recommendations. *Archives of neurology*, 60(11), 1524-1534.
- Eisenberg, E., Pud, D., Koltun, L., & Loven, D. (2007). Effect of early administration of the N-methyl-d-aspartate receptor antagonist amantadine on the development of post mastectomy pain syndrome, a prospective pilot study. *Journal of Pain*, 8, 223 - 229.
- Eisenberger, N. I., & Lieberman, M. (2005). Why it hurts to be left out: The neurocognitive overlap between physical and social pain. In: Williams, K.D. (ed.). *The Social Outcast: Ostracism, Social Exclusion, Rejection, & Bullying* (Sydney Symposium of Social Psychology). East Sussex: Psychology Press. p. 210.
- Garland, E. L., Brintz, C. E., Hanley, A. W., Roseen, E. J., Atchley, R. M., Gaylord, S. A., ... & Keefe, F. J. (2020). Mind-body therapies for opioid-treated pain: A systematic review and meta-analysis. *JAMA internal medicine*, 180(1), 91-105.
- Goldberg, D. S., & Summer, J. M. (2011). Pain As A Global Public Health Priority. *BMC Public Health*, 11, 770.
- Greenstein, B. (2009). *Narcotic Analgesics*. Trounce's Clinical Pharmacology for Nurses, 18th Edition, Churchill Livingstone, London, pp. 131 - 144.
- Gureje, O., Von Korff, M., Kola, L., Demyttenaere, K., He, Y., Posada-Villa, J., ... & Alonso, J. (2008). The relation between multiple pains and mental disorders: results from the World Mental Health Surveys. *PAIN@*, 135(1-2), 82-91.
- Hawker, G. A., Mian, S., Kendzerska, T., & French, M. (2011). Measures of Adult Pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care and Research* 63 Suppl. 11 (S11), S240 - S252.
- Hefti, F. F., Rosenthal, A., Walicke, P. A., Wyatt, S., Vergara, G., Shelton, D. L., & Davies, A. M. (2006). Novel Class of Pain Drugs Based on Antagonism of NGF. *Trends in Pharmacological Sciences*, 27, 85 – 91
- Hill, R. G. (2006). Analgesic Drugs in Development. In: McMahon S.B. and Koltzenburgh M. (eds.), *Wall and Melzack's*

- Textbook of Pain, 5th Edition, Elsevier, Edinburgh, pp. 541 – 552.
- Houde, F., Cabana, F., & Leonard, G. (2016). Does Age Affect the Relationship between Pain and Disability? A Descriptive Study in Individuals Suffering from Chronic Low Back Pain. *Journal of Geriatric Physician and Therapeutics*, 39(3), 140 – 145.
 - IASP (2004): Chronic Pain. International Association for the Study of Pain.
 - IASP (2005): Definition of Pain. International Association for the Study of Pain.
 - Ingraham, P. (2019): Surprising Causes of Pain: Trying to understand pain when there is no obvious explanation. PainScience.com.
 - Insel, P. A., Amara, S. G., Blaschke, T. F., & Meyer, U. A. (2019). Introduction to the Theme: New Therapeutic Targets. *Annual Review of Pharmacology and Toxicology*, 59, 15 – 20.
 - Institute of Medicine (2011): Relieving Pain in America: A Blueprint for Transforming Prevention, Care, Education, and Research. Washington, DC: The National Academies Press.
 - Jensen, M. P. (2008). The Neurophysiology of Pain Perception and Hypnotic Analgesia: Implications for Clinical Practice. *American Journal of Clinical Hypnosis*, 51(2), 123 – 148.
 - Johannes, C. B., Le, T. K., Zhou, X., Johnston, J. A., & Dworkin, R. H. (2010). The Prevalence of Chronic Pain in United States Adults: Results of an Internet-based Survey. *Journal of Pain*, 11(11), 1230 – 1239.
 - Kelly, A. M. (2001). The minimum clinically significant difference in visual analogue scale pain score does not differ with severity of pain. *Emergency Medicine Journal*, 18(3), 205 – 207.
 - Kojetin, D. J., & Burris, T. P. (2014). REV-ERB and ROR Nuclear Receptors As Drug Targets. *Nature Reviews Drug Discovery*, 13, 197-216.
 - Koleva, D. (2005). Pain in Primary Care: An Italian Survey. *European Journal of Public Health*, 15, 475 – 479.
 - Latza, U., Kohlmann, T., Deck, R., & Raspe, H. (2000). Influence of Occupational Factors on the Relation between Socioeconomic Status and Self-reported Back Pain in a Population-based Sample of German Adults with Back Pain. *Spine*, 25(11), 1390 – 1397.
 - Lee, G. Y., Yamada, J., Kyolo, O., Shorkey, A., & Stevens, B. (2014). Pediatric Clinical Practice Guidelines for Acute Procedural Pain: A Systematic Review. *Paediatrics*, 133(3), 500 - 515.
 - LeResche, L., Saunders, K., Dublin, S., Thielke, S., Merrill, J. O., Shortreed, S. M., ... & Von Korff, M. R. (2015). Sex and age differences in global pain status among patients using opioids long term for chronic noncancer pain. *Journal of women's health*, 24(8), 629-635.
 - Li, C. Y., Song, Y. H., Higuera, E. S., & Luo, Z. D. (2004). Spinal Dorsal Horn Calcium Channel alpha-2-delta-1 subunit Up-regulation Contributes to Peripheral Nerve Injury-induced Tactile Allodynia. *Journal of Neuroscience*, 24, 8494 – 8499.
 - Malenka, R. C., Nestler, E. J., & Hyman, S. E. (2009). Atypical Neurotransmitters. In: Sydor A. and Brown R.Y. (eds.). *Molecular Neuropharmacology: A Foundation for Clinical Neuroscience* (2nd ed.). New York: McGraw-Hill Medical.
 - Mäntyselkä, P., Kumpusalo, E., Ahonen, R., Kumpusalo, A., Kauhanen, J., Viinamäki, H., ... & Takala, J. (2001). Pain as a reason to visit the doctor: a study in Finnish primary health care. *Pain*, 89(2-3), 175-180.
 - McGrath, P. J., & Unruh, A. M. (2013). Measurement and Assessment of Paediatric Pain. In: McMahon S.B., Koltzenburg M., Tracey I. and Turk, D.C. (eds.). *Wall and Melzack's Textbook of Pain*, 6th Ed. Philadelphia, Pa.: Elsevier Saunders: pp. 320 - 327.
 - Mello, R. D., & Dickenson, A. H. (2008). Spinal cord mechanisms of pain. *British Journal of Anaesthesia*, 101(1), 8 - 16.
 - Merskey, H., & Bogduk, N. (1994). Classification of chronic pain, 2nd Edition. Seattle: IASP: 209 – 214.
 - MFMER (2020): 1998 - 2020 Mayo Foundation for Medical Education and Research.
 - Muller, C., Morales, P., & Reggio, P. H. (2019). Cannabinoid Ligands Targeting TRP Channels. *Frontiers in Molecular Neuroscience*, 11, 487.
 - Nagda, J. V., & Bajwa, Z. H. (2020). Definitions and Classification of Pain: Principles and Practice of Pain Medicine. Access Anaesthesiology.
 - Njau, E. (2002). *Pharmacology and Therapeutics. A Manual for Health Personnel in Rural Africa*. African Medical and Research Foundation, 2nd Edition, English Press, Nairobi, pp. 171 – 179.
 - Okifuji, A., & Hare, B. D. (2015). The Association between Chronic Pain and Obesity. *Journal of Pain Research*, 8, 399 – 408.
 - Oliva, E. M., Midboe, A. M., Lewis, E. T., Henderson, P. T., Dalton, A. L., Im, J. J., ... & Trafton, J. A. (2015). Sex differences in chronic pain management practices for patients receiving opioids from the Veterans Health Administration. *Pain Medicine*, 16(1), 112-118.
 - Pain Assessment and Management (2019): The Royal Children's Hospital, Melbourne, Australia.
 - PQRST Pain Assessment Method (2020.): Crozer-Keystone Health System.
 - Prkachin, K. M., Solomon, P. E., & Ross, J. (2007). Underestimation of Pain by Health-Care Providers: Towards a Model of the Process of Inferring Pain in Others. *The Canadian Journal of Nursing Research*, 39(2), 88 – 106.

- Psychogenic Pain. (2017). Cleveland Clinic.
- Rang, H. P., Dale, M. M., Ritter, J. M., Flower, R. J., & Henderson, G. (2019). *Analgesic Drugs*. Rang and Dale's Pharmacology, 7th Edition, Elsevier Churchill Livingstone, London.
- Sandkuhler, J. (2009). Models and Mechanisms of Hyperalgesia and Allodynia. *Physiology Review*, 89, 707 – 758.
- Sharma, N. (2019). *Atypical Analgesics in Chronic Pain Management*. A web resource.
- Sinha, S., Schreiner, A. J., Biernaskie, J., Nickerson, D., & Gabriel, V. A. (2017). Treating pain on skin graft donor sites: review and clinical recommendations. *Journal of Trauma and Acute Care Surgery*, 83(5), 954-964.
- Swamy, K. V. M. (2005). *Physiology of Pain*. Update in Anaesthesia.
- Swieboda, P., Filip, R., Prystupa, A., & Drozd, M. (2013). Assessment of Pain: Types, Mechanism and Treatment. *Annals of Agriculture, Environment and Medicine*, 1, 2 - 7.
- Taylor, C. (2015). *Fundamentals of nursing, the art and science of person-centered nursing care*. Philadelphia: Wolters Kluwer Health. p. 244.
- Tighe, P. J., Riley, J. L., & Fillingim, R. B. (2014). Sex Differences in the Incidence of Severe Pain Events Following Surgery: A Review of 333,000 Pain Scores. *Pain Medicine (Malden, Mass.)*, 15(8), 1390 – 1404.
- Tracey, I., & Mantyh, P. W. (2007). The Cerebral Signature for Pain Perception and Its Modulation. *Neuron*, 55(3), 377 – 391.
- Treede, R. D. (2011). Entstehung der Schmerzchronifizierung. In: Baron R., Koppert W., Strumpf M. And Willweber-Strumpf A. (eds.). *Praktische Schmerztherapie*. Heidelberg: Springer., p. 3 – 13.
- Tsang, A., Von Korff, M., Lee, S., Alonso, J., Karam, E., Angermeyer, M. C., ... & Watanabe, M. (2008). Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. *The journal of pain*, 9(10), 883-891.
- Venes, D. (2013). *Taber's Cyclopedic Medical Dictionary*. Philadelphia: Davis F.A. p. 1716.
- Visser, E. J. (2005). A Review of Calcitonin and its Use in the Treatment of Acute Pain. *Acute Pain*, 7(4), 185 – 189.
- WebMD (2019). *Pain Types and Classifications*. Pain Management Guide.
- World Health Organisation (1990). *Cancer Pain Relief and Palliative Care*.
- Yeo, S. N., & Tay, K. H. (2009). Pain Prevalence in Singapore. *Annals of Academic Medicine Singapore*, 38(11), 937 – 942.
- Zhang, F., Liu, Y., Zhang, D., Fan, X., Shao, D., & Li, H. (2013). Suppression of KCNQ/M Potassium Channel in Dorsal Root Ganglia Neurons Contributes to the Development of Osteoarthritic Pain. *Pharmacology*, 103(5-6), 257 - 262.
- Zheng, Q., Fang, D., Liu, M., Cai, J., Wan, Y., Han, J. S., & Xing, G. G. (2013). Suppression of KCNQ/M (Kv7) Potassium Channels in Dorsal Root Ganglion Neurons Contributes to the Development of Bone Cancer Pain in a Rat Model. *Pain*, 154(3), 434 - 448.