INTRODUCTION

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Pain

General background

The most widely accepted definition of pain, was that coined in 1979 by the International Association for the Study of Pain, stating that it is" An unpleasant sensory and emotional experience arising from actual or potential tissue damage or described in terms of such damage." Though, later debated and many more arraying definitions were posed, yet fortunately there is a general agreement, that pain bears physical, psychosocial & psychological distress, to the unfortunate victim.[1,2]

Pain is classified depending on which region of the body (superficial, deep, somatic or visceral) is involved, which system dysfunction (headache, back pain, sciatica) is causing the pain, by which etiological factor (trauma, ischemia, cancer, neuralgia) is it precipitated, by which neurochemical modulation (increase bradykinin, prostaglandins, GABA or decrease endorphins, NE, 5HT) is it provoked, by which character pattern (aching, throbbing, burning, stabbing) and intensity (sharp or dull aching) is it presenting and by which time since onset (rapid, insidious) and length of duration (days, weeks, months) does it prevail.[3,4]

Summing all these variables into a single classification seems impossible but simply pain can be arbitrary divided into two main ***types***;[3-8]

1. **Acute Pain:** is of sudden onset, transitory, lasting for hours to days (less than 30 days but can turn to subacute if it lasts up to 6 months) and resolves quickly once the underlying cause is cured (when the noxious stimulus is removed or the underlying damage or pathology has healed spontaneous or by treatment). It is of a clear cause, most often nociceptive (i.e. resulting from injury or inflammation of somatic or visceral tissue). Pain in this case, is considered as a protective response to injury, hence it is beneficial to the patient because it indexes that there is something wrong and motivates the person to get help and without this sensation the individual will ignore his illness resulting in complications and even death. Accordingly, the therapeutic objective is focused to treat the underlying cause.
2. **Chronic Pain:** is of insidious onset, long standing, usually exceeding more than six months duration, yet can last for years or forever. It can either start as acute pain and continues beyond the normal time expected for resolution or persists or recurs for various other reasons or can even arise in absence of any detectable stimuli, damage or disease. It may be nociceptive or neuropathic (i.e. initiated or maintained by a primary lesion or dysfunction along the nervous system). Pain in this case, is considered as a maladaptive response to injury; hence it is not therapeutically beneficial to the patient. Accordingly, the therapeutic objective emphasis upon reducing the pain intensity to give relief, limit disability and improve function.

Pain perception

In order that a noxious stimulus transforms into a painful perception, a group of highly specialized structures are set into a sequential cascade of functional changes: [9-11]

a. ***Recognition*** of the stimulus (when its intensity reaches certain threshold) by a specialized sensing structure ***NOCICEPTORS.*** These are bare sensory peripheral nerve endings of primary afferent neurons that are networking throughout all organs and tissues (except brain). They possess specific biophysical and molecular properties for differential coding of noxious submodalities depending on the differential expression of selective channels that confer sensitivity to heat (as TRPV1), cold (as TRPM8), acidic milieu (as ASICs), and a host of chemical irritants (as TRPA1),[8,10-13] Figure 1.[12]

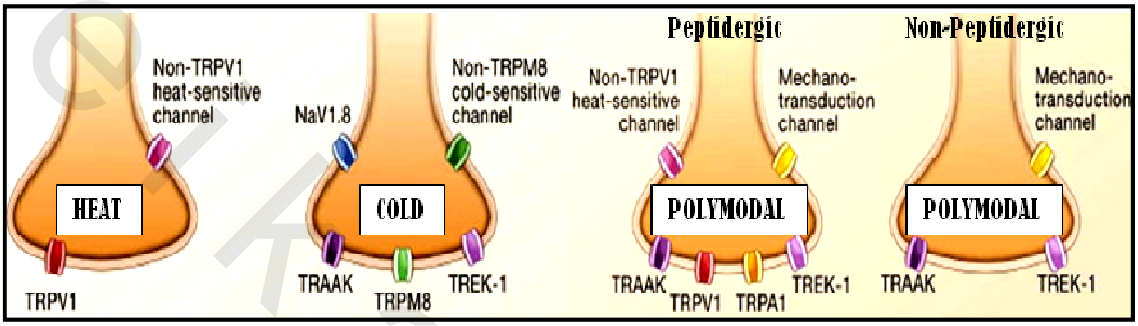

Figure (1): Selective channels in peripheral afferent nociceptor terminals.[12]

b. ***Transduction*** of such stimuli occurs via converting it into a depolarizing current that signal via specific ion channels only expressed within those specialized peripheral terminals. These seem to be activated by a variety of released molecules as; bradykinins, histamine, prostaglandins, leukotrienes, SP, CGRP, purines …etc. [8-9, 12, 14-15]

c. ***Conduction*** refers to the passage of the action potential formed along the peripheral afferent terminals of nociceptors via voltage gated Na channels. These head towards their cell bodies located in dorsal root ganglia (for the body) and in trigeminal ganglion (for the face). From there, signal are further conducted along their central afferent terminal to project to different laminae of the dorsal horn of the spinal cord, where they relay, Figure 2.[16] Fibers that carry such electrical activity are either; [12-14,17-18]

1. **Medium diameter myelinated (Aδ) afferents** that conduct at fast rate (5-20 m/s). They mediate well-localized acute, brief, sharp, pricking, fast pain sensations. They project to lamina I as well as to deeper dorsal horn (lamina V).
   N.B. differentiates from A-δ fibers that respond to innocuous mechanical stimulation (i.e. light touch).
2. **Small diameter unmyelinated "C" fibers** that conduct at low rate (0.5–2.0 m/s). They convey poor localized, slow, 'dull' burning, aching, and longer lasting pain sensations. They project more superficially to laminae I (most peptidergic C fibers) and II (nonpeptidergic afferents).

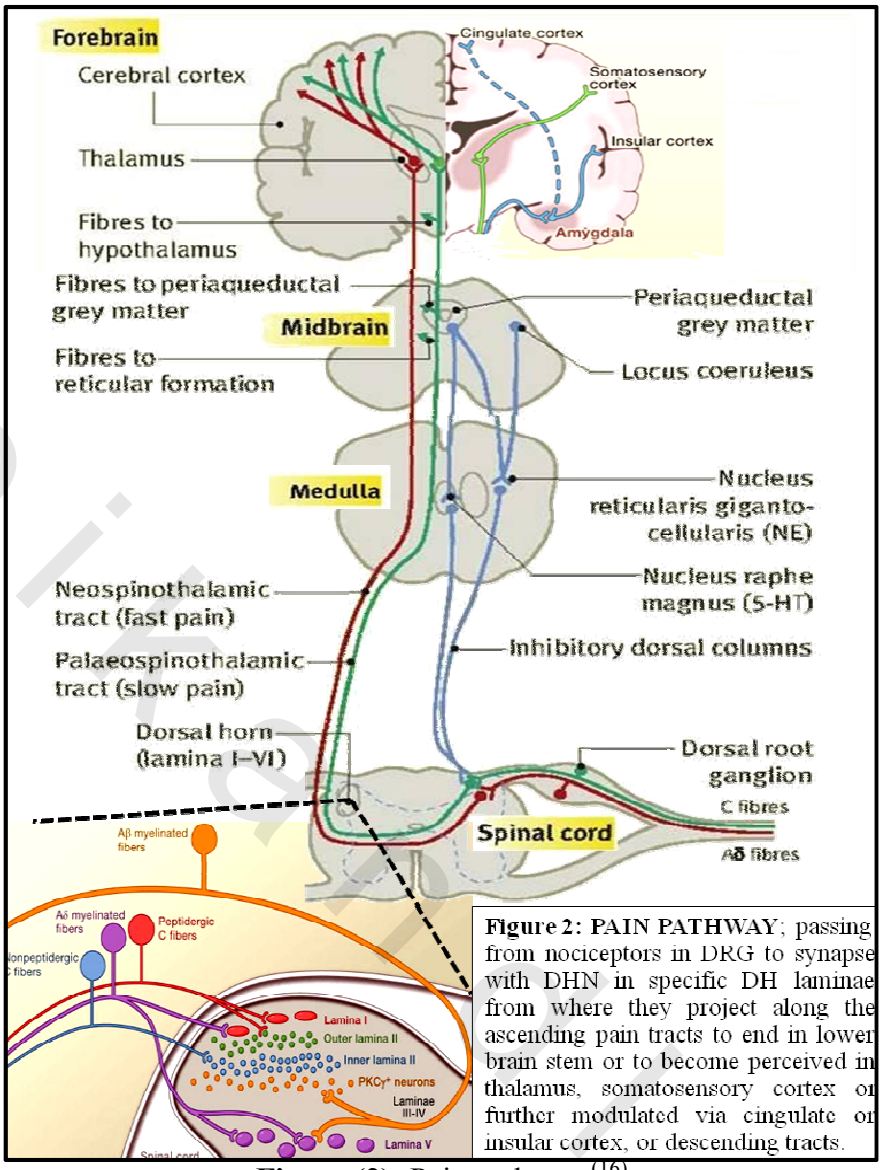

Figure (2): Pain pathway.[16]

d. ***Transmission*** is the process of synaptic transfer of signals from primary to secondary afferent projection neurons within the dorsal horn. It involves the release of neurotransmitters as glutamates (by Aδfast fibers), SP (by C slow fibers) and other tachykinins as neurokinin A and B …etc. [9-10, 13-14, 19]

Signals further ***project*** from these dorsal horn neurons (DHN), as major outputs that constitute the ascending pain pathways, to finally relay supraspinal where their information is processed and perceived, Figure 2. [12,16] After these ascending pathways comprise: [12-14,19-22]

1. **Neospinothalamic tract;** arise from laminae I and V where Aδ carry "fast spontaneous pain" to somatosensory area in the cerebral cortex.
2. **Paleospinothalamic tract;** arise indirectly from laminae II and III (substancia geletinosa) that has inter-neuronal connections with lamina V from where C fibers carry "slow increasing dull pain" to thalamus and lower brainstem regions (medulla, pons, periaquidactal grey matter, midbrain tectum).

e. ***Perception*** is the process of integrating the relayed signals and translating them to actual sensory experience of appreciation or conscious awareness. It occurs either within the somatosensory cortex which is responsible for sensory-discriminative pain perception integrating it with emotional aspects arising from the anterior cingulate gyrus and insular cortex. It also occurs within the thalamus and lower brain stem areas which are responsible for the poorly localized pain perception integrating that with emotional/motivational perspective arising in forebrain. [12, 19, 23-24]

But how this interpretation process occurs, is still debatable and is explained by many theories, the most known is the "gate control theory" proposed by Melzack and Wall in the 1960's followed by its new version posed in 1999 which is "neuromatrix theory". [11,17, 25-29]

1. **The "Gate Control Theory"** postulates that nociceptive pain is "gated" by non-nociceptive stimuli. For instance, neural mechanisms in DHN act like a gate "opening" and "closing" i.e. permitting or shutting down respectively flow of impulses, thus altering level of firing projected via ascending tracts that are perceived. This alteration is controlled by ramifications from small adjacent cells which tend to either excite or inhibit DHN. Thus large-fiber inputs (such as gentle rubbing) tend to close the gate while small-fiber inputs (such as pinching) generally open it. Vice versa, gating alteration is also profoundly influenced by facilitatory or inhibitory descending pathways from the brain.
2. **The "Neuromatrix Theory"** states that each individual has a genetically built-in network of neurons called the "body-self neuromatrix." that is unique to him and is affected by all facets of the person's physical, psychological, and cognitive makeup, as well as his experience. As a subsequence, pain perception will not reflect a simple one-to-one relationship between tissue damage and nociceptive firing but that individual's set-up will also have a say.

Pain regulation and modulation

a. Facilitation and Sensitization; this can be achieved through increased firing of peripheral or central nociceptor terminals to modulate the ascending nociceptive pathways. It can be also achieved by suppressing inhibitory or activating excitatory interneurones or via activating DHN firing by descending facilitatory pathways. [8-9,11-12]

- Peripheral Sensitization; is the increase in sensitivity of peripheral terminals of nociceptors. It is caused either by inflammatory molecules released during inflammation following tissue damage, or by persistence of noxious stimulation allowing C fibres to react by peripherally releasing neuropeptides creating neurogenic inflammation. This will activate "silent" neurons and sensitize nociceptors. The downstream signaling cascade of such triggers will increase in the concentration of both sodium and calcium ion channels within the plasma membrane of nociceptors and will phosphorylate them i.e. lowering their threshold for activation and increasing their rate of firing. This phenomenon is a pathophysiological mechanisms underlying inflammatory and neuropathic pain perception i.e. ***in hyperalgesia*** (painful stimuli are perceived more intensely) and ***in allodynia*** (normally non-painful stimuli, such as pressure stimuli, are experienced as pain), [9,11,29-30] Figure 3. [31]
- Central Sensitization (called windup); is the increase in efficiency of transferring action potentials at the synapse between nociceptors and DHN or supraspinal neurons. It may be initiated by a brief but intense nociceptive signal or it may be caused by sensitized nociceptors that fire ectopically. In such a cascade nociceptors initiate the

drive by increasing glutamate release that is coupled with a concomitant increase in NMDA receptors density within post-synaptic membranes of DHN. Also there is downstream alteration in Na, Ca influx and K outflux allowing more depolarization with release of Mg block to later permit subthreshold inputs from nociceptors to continue exciting DHN. The increased glutamates may also reduce opioid responsiveness (e.g. analgesic tolerance and/or opioid hyperalgesia). This phenomenon is a pathophysiological mechanisms underlying neuropathic more than inflammatory pain perception,[8-9, 11-12,32-36] Figure 3. [31]

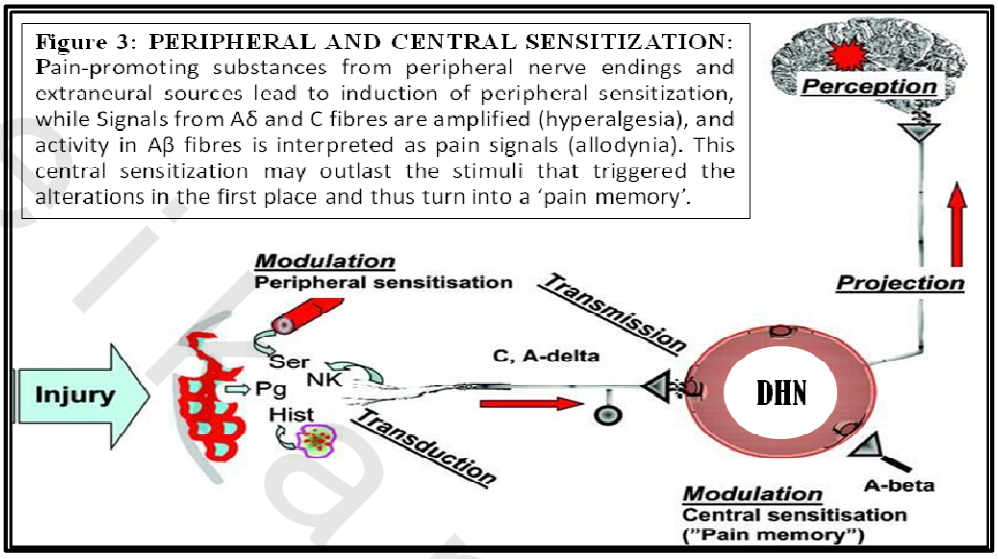

Figure (3): Peripheral and central sensitization.[31]

- Descending Facilitatory Pathways; arise mainly from rostral ventromedial medulla in response to nociceptive firing projecting to it from damaged nerves directly or indirectly. This leads to the release of many substances as glutamates, SP, CGRP, purines, tachykinins that subsidiary lead to activation microglial cells there. The latter respond by IL-18 release to activate astrocytes to produce more cytokines that in turn activate a subset of descending 5HT neurons that project as descending facilitatory fibres back to the spinal cord or trigeminal nucleus where they activate 5-HT3 receptors and thereby enhance pain transmission. This descending facilitatory activation is incriminated in the pathophysiology of neuropathic pain perception.[37-40]

b. Inhibitory Modulation; this can be achieved via inhibition of transmitter release by peripheral or central terminal of nociceptors, to decrease firing along ascending pathways.

It can also be achieved by excitation of inhibitory or inihibtion of excitatory interneurons or via inhibiting of projection neurons firing by descending inhibitory pathways. [9, 12, 35]

- Descending Inhibitory Pathways; arise mainly from periaqueductal grey matter to project downstream to nucleus raphe magnus (release 5HT) or locus coeruleus and nucleus reticularis giganto cellularis (release NE) to synapse on DHN or block signals sent by excitatory neurons to the dorsal horn via nociceptors. Endorphines acting on opioid receptor is the main modulator of this natural analgesic system by releasing the descending pathways from their GABAergic inhibition to allow NE and 5HT to suppress the DHN. However GABA reigns supreme within the spinal cord as it is the transmitter released by the inhibitory interneurones.[9,12,35,41-43]

Pathophysiological pain syndromes

Pain can be encompassed under four distinguished syndrome states namely; nociceptive, inflammatory, neuropathic or dysfunctional. The last two states, belong to chronic type of pain, are maladaptive in the sense, that pain neither protects nor supports healing and repair, but rather represents malfunction of the somatosensory apparatus i.e. a disease in its own right.[12,31,36,44-45] The character of each is detailed in Figure 4:[46]

- **Nociceptive Pain;** detects noxious inflicts. If it is induced by potentially injurious inflicts that cannot be ignored (e.g. intense thermal, mechanical or chemical stimuli), that provoke withdrawal reflexes, then it is considered to be still physiological. This is because it intends to prevent or minimize the possibility of tissue injury, being rapidly perceived and of very short duration. However, if it is induced by actual tissue damage as that following surgical, traumatic, or disease-related injuries…etc then it is pathological and usually progress to also enroll an inflammatory state in most instances. If so, then the intent of pain imperatively shifts to address the consequences of damage. It is rapidly perceived, with intensity proportional to both its magnitude and the amount of released mediators that subsequently follows,[11,13,36,45-47] Figure 4.[46]
- **Inflammatory Pain;** occurs in the context of healing from tissue injury. Thus, while aiding in repair, a profound change in sensory responsiveness occurs. It no longer acts just as a detector for noxious stimuli, but is activated also by low-threshold innocuous inputs. The resultant response thus becomes exaggerated and prolonged; i.e. sensitized. This heightened sensitivity (windup), occurs in both inflamed (as primary hyperalgesia) and contiguous non-inflamed (as secondary hyperalgesia) areas, as a result of plasticity in peripheral nociceptors and in central nociceptive pathways. Typically, it should disappear after resolution of the initial injury. However, it may turn chronic,[9,31,34,36,45-46,48-49] Figure 4.[46]
- **Dysfunctional Pain;** occurs in situations in which there is no identifiable noxious stimulus nor any detectable inflammation or damage to the nervous system. The causes of its manifestation or persistence are even non obvious, but may result from an autonomous amplification of nociceptive signals inside the CNS, with disturbed balance of excitation and inhibition in central circuits, and altered sensory processing. Fibromyalgia, IBS, are examples,[36,45,50-52] Figure 4.[46]
- **Neuropathic Pain;** occurs primarily due to neural damage. It starts adaptive to a peripheral or central nervous system lesion (traumatic, metabolic, neurotoxic, collagenic, vascular, and infectious or tumor invasion…etc.). It then persists for prolonged periods because its initiator cause is either progressing and continues to damage the nervous system or on the contrary has even long disappeared but did create a maladaptive neuronal plasticity that cascaded changes to insure the sustainability of such pains. In such a scenario, two interdependent processes are contributing namely; the balance between compensatory and decompensatory reactions to the neural damage and the genetic setup that either enhances or protects an individual from the establishment of such pains,[12,34-36,52-53] Figure 4.[46]

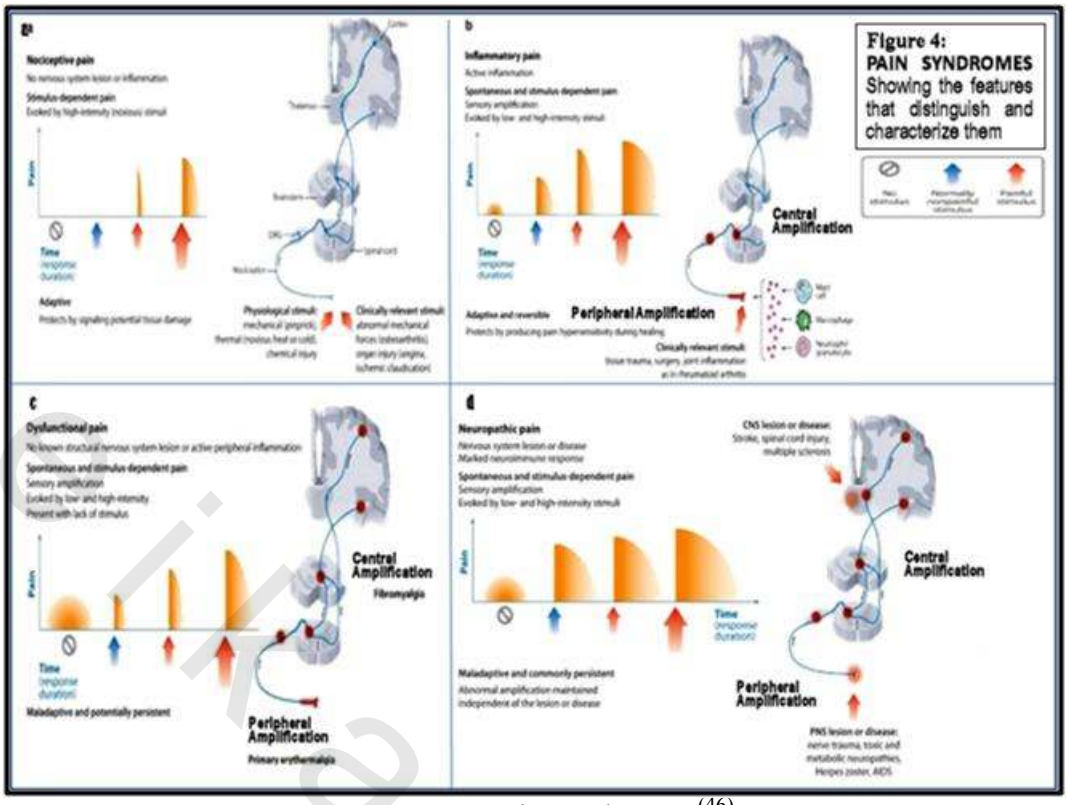

Figure (4): Pain syndromes.[46]

General lines of management of pain

Acute pain usually resolves by drugs that are prescribed by the treating physician, while chronic pain needs an interdisciplinary approach conducted by a team that work together not only to relieve the pain but to improve the quality of life of those living with pain. The typical pain management team includes medical practitioners, clinical psychologists, physiotherapists, occupational therapists, and nurse practitioners.[54]

The drugs that are used to treat pain fall under 2 major groups; [16,31,39,46,52,55-58]

- Analgesics; whether opioids or non-opioids (Acetaminophen, NSAIDs, Coxibs)
- Other pain controlling drugs; Antiepileptics, Antidepressants, Local anesthetics, α_2 adrenergic agonist, NMDA receptor antagonists, Cannabinoid antagonists, Capsaicin, CGRP antagonist,…..etc.

Most drugs are used systemic (parenteral or oral), only some can be applied topical. Selectively, local anaesthetics and some analgesics are moreover used to induce nerve or regional block or spinal and epidural analgesia.

Other approaches to treat pain, some of which have sound medical reference standards while others do not. The commonest that are enrolled include;[54,59,60]

- Physiotherapy; Cryotherapy, Exercise, Hot pack , Occupational therapy, Physical therapy, neurostimulation and transcutaneous electrical nerve stimulation.
- Acupuncture; application of needles to precise points on the body according to Chinese Oriental Medicine.

- Cognitive-Behavioral Therapy; a wide variety of coping skills and relaxation methods to help prepare for and cope with pain. It is used for postoperative pain, cancer pain, and the pain of childbirth.
- Prolotherapy; injecting an otherwise non-pharmacological and non-active irritant solution into the body for the purpose of strengthening weakened tissue.
- Biofeedback; the use of special electronic machine to train patients to become aware of, to follow, and to gain control over certain bodily functions including pain.

Pre-emptive analgesia

By definition; Pre-emptive analgesia is a treatment that is initiated before surgical procedures (before onset of noxious stimulus) in order to reduce pain perception post procedural. It has become a popular adjunct to conventional postoperative pain control.[31]

Its rational resides on the hypothesis that the most effective way to eliminate or reduce postoperative pain is to prevent pain signals evoked by tissue damage, from triggering nociceptive afferent firing, thus aborting their sensitization to peripheral and central pain pathways,[34,61] Figure 5.[62]

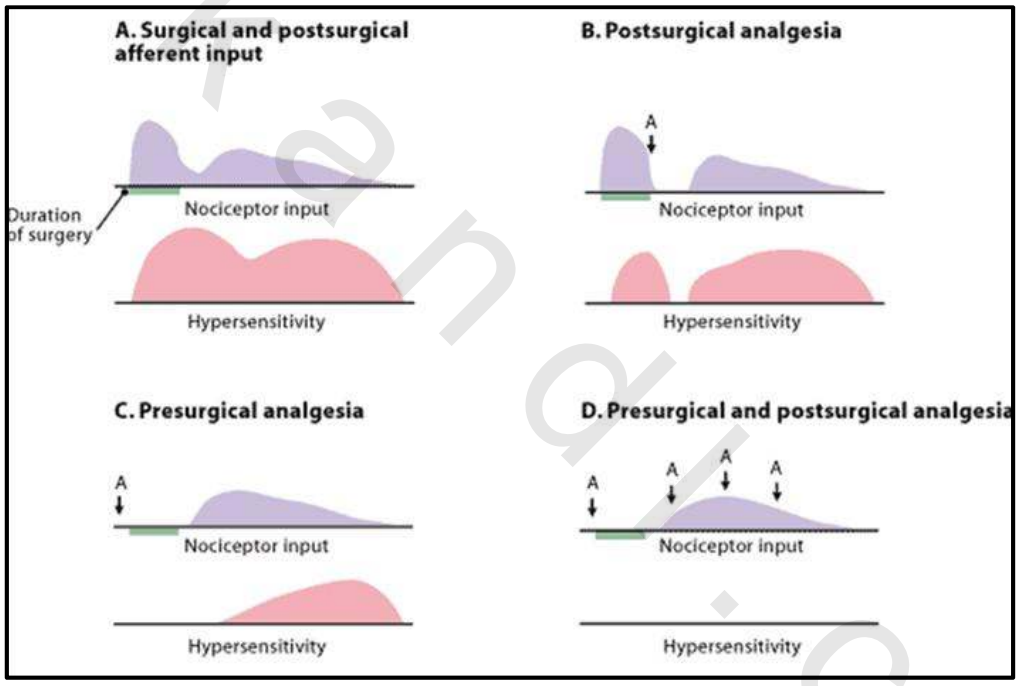

Figure (5): Preemptive analgesia; emphasizing on how it can prevent sensitization of the nervous system throughout the perioperative period.[62]

Clinically, this "protective nociceptive strategy" predicts not only less pain during the initial postoperative period than a similar analgesic treatment initiated only after the procedure but has also the ability to reduce pain intensity during the days that follow. It was even cleared that when adequate drug dosing were administered to appropriately selected patients, benefits could be observed as long as one year following surgery.[63]

The strategies adopted to conduct preemptive analgesia include interventions at one or more sites along the pain pathway namely by; infiltration with local anesthetics, induction of nerve, epidural, or subarachnoid block or using intravenous analgesics or anti-inflammatory drugs.[64-67]

Focusing on laparoscopic gynecology, a variety of preemptive analgesic regimens has been previously assessed. For instance, some reported a decrease in wound hyperalgesia post procedural when intravenous opiates were used before the incision.[68]

Others claimed that sub hepatic bupivacaine instillation either before or immediately after creation of pneumoperitoneum is more effective than its administration before withdrawal of the trocars.[69] A series of studies enrolled the use of different anti-inflammatory drugs (diclofinate, parecoxib, valdecoxib…etc.) pivoting on their ability to reduce inflammatory response that triggers peripheral nociceptor modulation and subsequent attenuation of central sensitization. However all such studies yielded varying results depending on timing, dosing, duration…etc. of prototype drug used versus quality and nature of pain relief gained. [34,70] These explanations set for the controversial benefits that exists, invited researchers to expand on other antihyperalgesics pharmacotherapeutic modalities as dextro-methorphan, gabapentinoids, NMDA receptor antagonist ...etc. that have just been or are still scrutinized. This is in attempt to reach a consensus regimen of clear efficacy to over last postoperative pain control and prevent its progress to chronic pain. [57-58]

Pregabalin

The gabapentinoids; gabapentin and its developmental successor pregabalin are structural derivatives of the inhibitory neurotransmitter GABA although they do not bind to $GABA_A$, $GABA_B$ or benzodiazepine receptors, nor do they metabolically convert into GABA, or alter its uptake or degradation.[71-73]

They were originally developed as spasmolytic agents.[74,75] Their anticonvulsant, anxiolytic and sleep-modulating utility permitted their use as adjuncts for management of generalized or partial epileptic seizures resistant to conventional therapies.[74,75] Their therapeutic armamentarium was furthermore expanded over time to control chronic pain conditions [*diabetic neuropathy, post herpetic neuralgia, central neuropathic pain, and fibromyalgia*] as well as some acute pain conditions [inflammatory or insional injuries (especially laparoscopic and daycare surgeries)].[76-78]

Pregabalin pharmacology

Pharmacokinetically; unlike its predecessor gabapantin, pregabalin absorption is non- saturable, resulting in an advantage of having ***linear pharmacokinetic profile***.[75,79]

It ***absorbs*** rapidly when administered on an empty stomach, with average ***bio-availability*** exceeding 90%, reaching peak plasma concentrations within one hour. This absorption decreases when given with food permitting a decrease in C_{max} by approximately 25 to 30% and a delay in T_{max} to approximately 2.5 hours.[75,79.80]

The drug ***distributes*** non bound to plasma proteins, crosses blood brain and placental barriers and is found in milk. Its volume of distribution in humans after an oral dose is approximately 0.56 L/kg.[73,75,79,81]

Drug ***metabolism*** is negligible, i.e. sparsely metabolizes into N-methyl pregabalin. It is approximately 98% is excreted unchanged in urine signifying that drug ***excretion*** is primarily renal with an elimination that is nearly proportional to creatinine clearance. Thus a 50% reduction in pregabalin daily dose is recommended in patients with creatinine clearance between 30 and 60 mL/min.[73,79-83]

The $t_{1/2}$ range from 5-6.5 hrs, with the merit of being of longer duration of action than gabapantin, so requires less frequent daily dosing.[78-80,83]

Pharmacodynamically; Pregabalin, act by binding selectively to the α2-δ subunit of presynaptic, voltage-gated calcium channels (widely distributed throughout the central and peripheral nervous system).[73,79,84-87] This subunit is mainly extracellular with a single transmembrane domain and five intracellular carboxyl terminal amino acids. It consists of two disulfide-linked peptides (α2 and δ) that are encoded by the same gene.[88,89] It is highly glycosylated, and when expressed with other Ca channel subunits, it is likely involved in VGCC assembly, stabilization and cellular trafficking. It also increases and stabilizes current amplitude, channel binding sites and binding affinity for N-type VGCC ligands.[88-90]

Pregabalin binding to such subunit, will transiently inhibit Ca influx, thereby reducing release of several neurotransmitters like glutamate, norepinephrine, serotonin, dopamine, substance P and CGRP.[75,79,91,92] This inhibitory modulation of neuronal excitability, occurs particularly in areas dense in synaptic connections such as the neocortex, amygdala, and hippocampus. In contrast, pregabalin it does not bind to other types of Ca channels, especially those controlling cardiovascular functions.[73,75,93, 94]

The binding of pregabalin to the α2-δ subunit was found to be 6 times more potent than that of gabapantin which reasons why it is 3–10 times more potent antiepileptic and 2–4 times more potent analgesic than gabapentin.[79,95] This simply means that it provides equivalent efficacy at much lower doses, with the promise of less dose-related adverse effects.[96]

Adverse drug reactions are mild-to-moderate, mostly dose dependent, usually transient especially on short term use. In clinical trials, the most frequently reported were dizziness in 29% and somnolence in 22%.[97] Dry mouth, blurred vision, peripheral edema, vertigo, irritability and weight gain, …etc are less commonly retrieved (<10%) while case reports of myoclonus, asterixis, gynecomastia, depression, suicidal thoughts, …etc. are infrequent or rare.[73,79,98-100] Withdrawal manifestations as seizures, restlessness, insomnia, and anxiety appear upon abrupt discontinuation after long-term use, which calls for the need of gradual withdrawal over a week. Overdosing frequently occurs in patients with impending renal failure, so therapeutic drug monitoring may be needed to monitor therapy or confirm toxicity. If so is the case, a 4-hs hemodialysis treatment, will reduce plasma pregabalin concentrations to approximately 50 %.[73,75,81,84]

Pregabalin is contraindicated in patients with known hypersensitivity to any of its components.[73]

No kinetic drug-drug interactions have been identified,[73,101] yet minimal potential dynamic interactions may occur if given with CNS depressants as opioids (pregabalin is synergistic with opioids in lower doses), benzodiazepines, barbiturates, ethanol.[73,102]

Pregabalin in pain control

Since its launch, pregabalin was approved (2004) for treatment of neuropathic pain associated with diabetic peripheral neuropathy and postherpetic neuralgia. Thereafter it was approved (2007) as first drug treatment of fibromyalgia.[73,75,103-105] In such domains, many clinical trials did confirm its efficacy and safety when used alone in or in combination to control such chronic pain syndromes.[106]

In parallelism, its role in control of acute pain, especially acute post-operative pain, were assessed in several randomized controlled trials, which included the use of pregabalin in the setting of a heterogenous group of surgeries performed under general anesthesia, spinal anesthesia, or daycare surgery in doses varying from 50-600 mg/day.[79]

Their rational resided on realizing how sensitization of DHN during acute pain possibly plays a role in the development of chronic pain after surgery, where by upregulation of α2δ subunit of VGCC there, was implicated in such sensitization process. It seemed that by decreasing such DHN hyperexcitability (induced by the traumatic followed by inflammatory tissue damage), via reducing release of several excitatory neurotransmitters, pregabalin would possess the potentiality of controlling postoperative pain.[79,107-110]

The collective results reported from those heterogenous clinical trials cleared that perioperative use of pregabalin decreased postoperative pain scores and opioid consumption in the first 24hours in some of them. While the others, debated pregabalin ability to significantly reduce pain intensity, though few proved that it can still reduce opiate consumption during the first post-operative day. However, there was no clear consensus, as to which surgeries would better benefit from this modality of pain control post-operative.[79,106]

Within those aforementioned surgeries, one approved and the other denied pregabalin utility in controlling acute post-operative pain evoked by laparoscopic gynecology. When contrasting between them, the doses of pregabalin used, the quality of pain assessed, the methodology by which pain was scored, the type of rescue.[73]