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Nefopam Plus Paracetamol: A Multimodal Approach in Pain Management

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Abstract

Pain is a distressing sensation linked to actual or potential tissue damage. The sole purpose of pain is notifying the body's defense mechanism to react towards a stimulus in order to avoid further tissue damages. The approach to patients with pain begins by identifying the underlying cause and a disease-specific treatment. The first-line pharmacologic agent for the symptomatic treatment of mild to moderate pain is acetaminophen or a non-steroidal anti-inflammatory drug (NSAID). The choice between these two medications depends on the type of pain and patient risk factors for NSAID-related adverse effects. Different NSAIDs have similar analgesic effects. However, cyclooxygenase-2 selective NSAIDs must be used with caution in patients with cardiovascular risk factors and are more expensive than non-selective NSAIDs. If these first-line agents are not sufficient for mild to moderate pain, medications that target separate pathways simultaneously are reasonable choices. Severe acute pain is typically treated with potent opioids. Newer medications with dual actions (e.g., tapentadol) are also an option. There is little evidence that one opioid is superior for pain control, but there are some pharmacologic differences among opioids. Because of growing misuse and diversion of controlled substances, caution should be used when prescribing opioids, even for short-term treatment. Nefopam is a non-opioid, non-steroidal, centrally acting analgesic drug used to prevent postoperative pain, primarily in the context of multimodal analgesia. This review of Nefopam combined with paracetamol reveals enhanced analgesic effect through multi-modal pathways suggesting a role for Nefopam in multimodal analgesia.

Introduction

Pain has been considered as a concept of sensation that we feel as a reaction to the stimulus of our surrounding, putting us in harm's way and acting as a form of defense mechanism that our body has permanently installed into its system [1]. International Association for the Study of Pain (IASP) has revised the definition of pain and accompanying notes in 2020. IASP defines pain as "an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [2].

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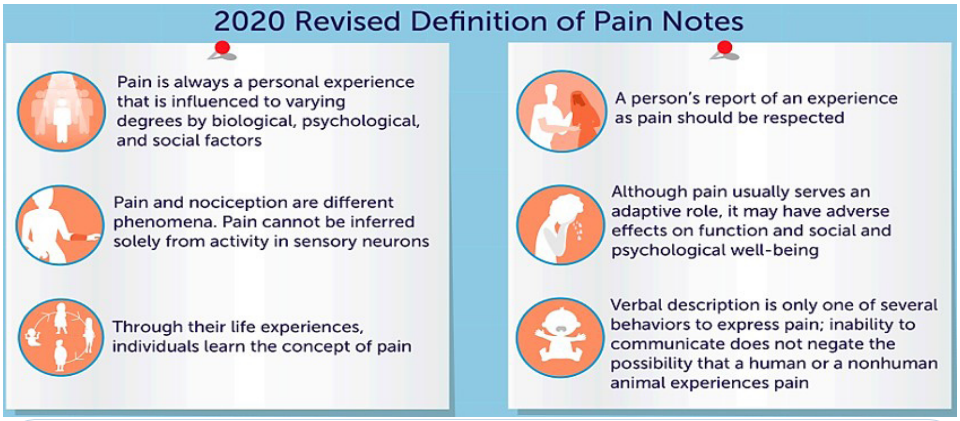

Figure 1: Revised Definition of Pain Notes [2] (Adapted from: Raja SN, Carr DB, Cohen M, Finnerup NB, Flor H, Gibson S, Keefe FJ, Mogil JS, Ringkamp M, Sluka KA, Song XJ, Stevens B, Sullivan MD, Tutelman PR, Ushida T, Vader K. The revised International Association for the Study of Pain definition of pain: concepts, challenges, and compromises. Pain. 2020; 1-7.)

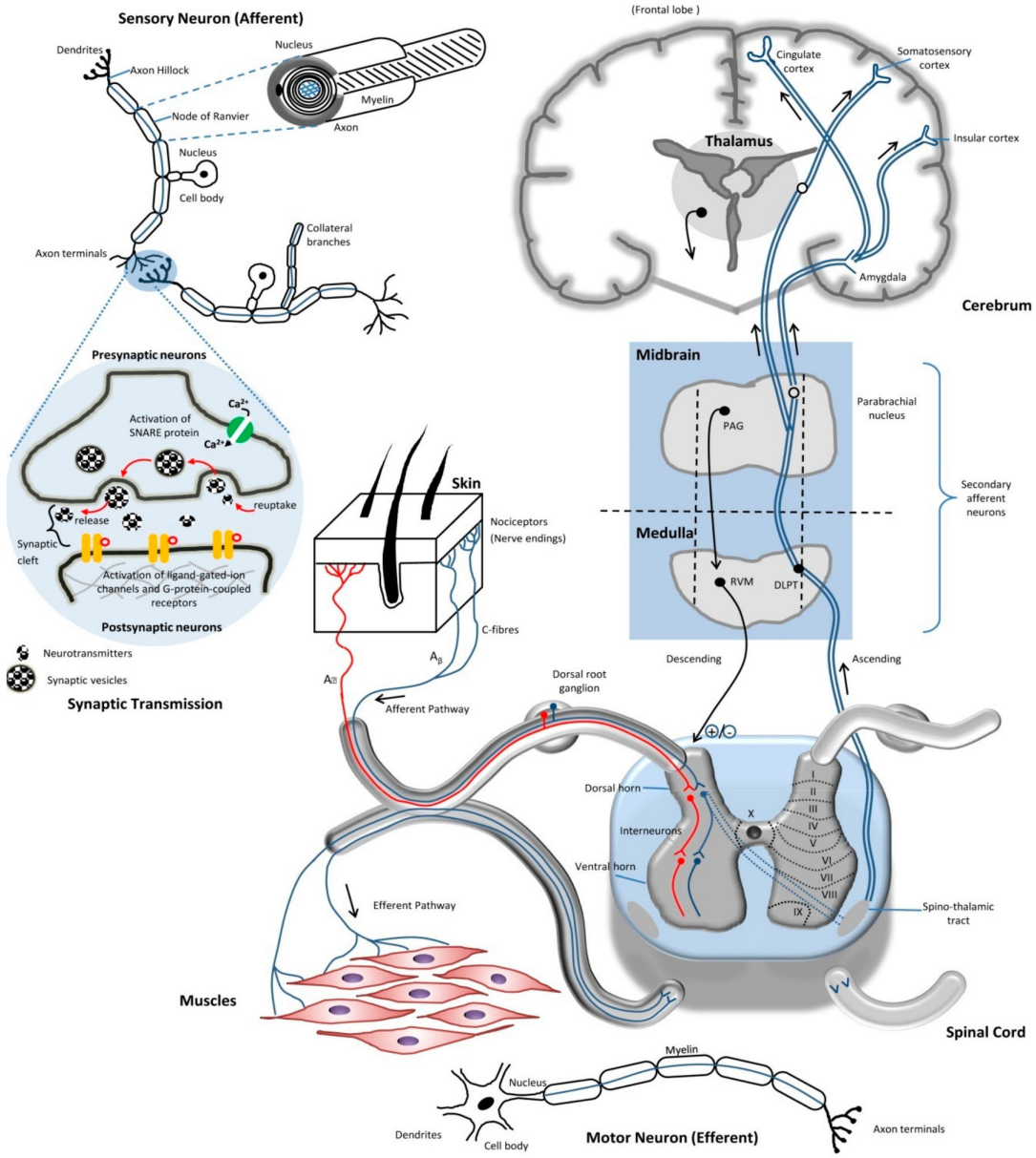

Figure 1: The basic route of pain transmission upon noxious stimuli in ascending and descending order, and the illustration of synaptic transmission in synaptic cleft [1]. (Adapted from: Yam MF, Loh YC, Tan CS, Khadijah Adam S, Abdul Manan N, Basir R. General Pathways of Pain Sensation and the Major Neurotransmitters Involved in Pain Regulation. Int J Mol Sci. 2018 Jul 24; 19(8): 2164.)

The sensation of pain is associated with the activation of the receptors in the primary afferent fibers, which is inclusive of the unmyelinated C-fiber and myelinated Aσ-fiber. Both nociceptors remain silent during homeostasis in the absence of pain and are activated when there is a potential of noxious stimulus. The perception of a series of sensory events is required for the brain in order to detect pain and produce a response towards the threat [1].

Perception of pain

There are generally 3 main stages in the perception of pain.

First stage is pain sensitivity, followed by the second stage where the signals are transmitted from the periphery to the Dorsal Horn (DH), which is located in the spinal cord via the Peripheral Nervous System (PNS). Lastly, the third stage is to perform the transmission of the signals to the higher brain via the Central Nervous System (CNS). Typically, there are two routes for signal transmissions to be conducted: ascending and descending pathways. The pathway that goes upward carrying sensory information from the body via the spinal cord towards the brain is defined as the ascending pathway, whereas the nerves that goes downward from the brain to the reflex organs via the spinal cord is known as the descending pathway [1].

Both the CNS and PNS are involved in the mechanism and pathways of all variations of pain perception. The PNS comprises nerves and ganglia that are located outside the brain and spinal cord, mainly functioning to connect the CNS to organs and limbs in our body. On the other hand, CNS is composed of spinal cord and brain, mainly responsible for integrating and interpreting information sent from the PNS, and subsequently coordinating all the activities in our bodies, before sending response towards the effector organs [1].

Basic mechanisms of pain

Fundamentally, the basic pain mechanism undergoes three events - transduction, transmission and modulation when there is a presence of noxious stimuli. Transduction occurs along the nociceptive pathway in the following order:

1. Stimulus events are converted to chemical tissue events;
2. Chemical tissue and synaptic cleft events are then changed into electrical events in the neurons; and
3. Electrical events in the neurons are transduced as chemical events at the synapses.

After the completion of transduction, the following mechanism is transmission. It takes place by transmitting the electrical events along the neuronal pathways, while neurotransmitters in the synaptic cleft transmit information from a post-synaptic terminal of one cell to a pre-synaptic terminal of another. Meanwhile, the modulation event takes place at all level of nociceptive pathways through the primary afferent neuron, dorsal horn and higher brain center by up- or down-regulation. All these lead to one end result, and the pathway of pain has been initiated and completed, thus allowing us to feel the painful sensation triggered by the stimulus. The basic illustration on pain transmission is illustrated in Figure 2 [1].

Types of pain

Typically, pain can be classified into three types-nociceptive, neuropathic and inflammatory pain, based on three characteristics, such as symptoms, mechanisms and syndromes.

Nociceptive pain

Nociception used interchangeably with nociperception is the response of our bodies' sensory nervous systems towards actual or potentially harmful stimuli. The sensory endings that are activated by such stimuli are known as nociceptors, which are mainly responsible for the first stage of pain sensations. Fundamentally, the Aδ- and C-fibers are two types of primary afferent nociceptors responding to noxious stimuli presented in our bodies'. Both these nociceptors have specialized free nerve endings that are widely located in the skin, muscle, joint capsule, bone and some major internal organs. They are functionally used to detect potentially damaging chemical, mechanical and thermal stimuli that might put us in harm's way [1].

The major nociceptive pain can be categorized into two types including visceral somatic pain (which is further classified into two kinds: deep somatic and superficial pain). Both the Aδ- and C-fibers are mostly found in superficial organs, such as the skin, whereas other deep somatic structures, such as muscles and joints, are mainly supplied with C-fibers. Aδ-fibers are activated under thermal or mechanical stimuli and result in a short-lasting-pricking type of pain sensation. However, the activation of C-fibers is stimulated by thermal, mechanical or chemical stimuli, which often results in poor localization and dull pain sensation. There are three major roles for the receptors in the primary afferent neurons, which are excitatory, sensitizing and inhibitory response. Once these receptors are being stimulated and have reached the pain threshold, the resulting impulses are propagated along the afferent fibers towards the dorsal horn (PNS) and medulla (cranial) [1].

Neuropathic pain

Neuropathic pain is commonly described as a nerve injury or nerve impairment and is often associated with allodynia. It triggers a pain response from a stimulus that is deemed as non-painful in normal conditions, due to sensitization process from said repetitive stimulation. This condition can be described as "pathologic" pain, because neuropathic pain actually serves no purpose in terms of defense system for our body, and the pain could be in the form of continuous sensation or episodic incidents. The major causes of this type of pain could be primarily due to inflammation or metabolic diseases, such as diabetes, trauma, toxins, tumors, primary neurological diseases and herpes zoster infection. The central sensitization plays a rather important role in this process. Neuropathic pain can be caused by the damage of the nerve, affecting the somatosensory nervous system, and may be generated by the disorders of the PNS or CNS [1].

The neurochemistry of the damaged axons can be altered due to the initiations of complex reaction upon compression, stretching, or transaction of the periphery nerves, followed by a spontaneous hyper-excitability on the site. During neuropathic pain, nociceptors demonstrate a dynamic expression of ion channels, such as Na_v channels. In fact, Na_v channels are the major channels in regulation of the neuronal excitability, initiation and propagation of the action potentials. The Na+ current in the Dorsal Root Ganglion (DRG) can be classified into three types, namely, fast Tetrodotoxin - Sensitive (TTX-S), slow Tetrodotoxin - Resistant (TTX-R) with high-activation thresholds and persistent TTX-R with lower activation thresholds. TTX is a potent neurotoxin and acts as a Na_v channel blocker whereby its binding with the Na_v channels inhibits the firing of action potentials generated in the neurons [1].

Inflammatory pain

Inflammation is a natural biological response produced by the tissues within our body as a reaction to the harmful stimuli in order to eradicate the necrotic cells and initiate the tissue repairing process. Neutrophils are usually the first respondents of an inflammatory response and gather at the site of injury via the bloodstream, followed by the release of other chemical mediators. Inflammation may lead to three major responses: hyperalgesia, allodynia and sympathetic maintained pain. An inflammation can also induce mast cell degranulation, which subsequently leads to the release of Platelet Activating Factor (PAF) and stimulates the release of 5-HT from the circulating platelet. The cardinal signs of inflammation include the hot inflamed site due to increase in blood flow towards the region, redness and swelling due to vascular permeability pain caused by the activation and sensitization of primary afferent neurons and lasting loss of function. The localized inflammatory response then induces the release of free Arachidonic Acid (AA) from the phospholipids, which are converted into Prostaglandins (PG) via the Cyclooxygenase (COX) pathways [1].

Pain from inflammation can be further classified into 2 types: Chronic and acute pain. Acute Inflammatory Pain is intense and occurs for a short duration of time, initiated as a response to harmful stimuli normally mediated by the Aδ-fibers. Leukocytes and plasma from the blood stream are accumulated at the site of injury to assist in the inflammatory process. However, prolonged inflammation, better known as chronic inflammatory pain, lasts beyond the expected period of healing and is typically mediated by C-fibers [1].

Pain pathways

Painful stimuli cause the opening of ion channels and flux of ions across cell membranes within the peripheral nociceptive afferent. Sufficiently strong stimuli result in depolarization and generation of action potentials that are conducted via peripheral afferents to the dorsal horn of the spinal cord. Each action potential evokes the release of excitatory neurotransmitters (e.g., glutamate), neuropeptides (e.g., substance P) and neuromodulators (e.g., Brain-Derived Neurotrophic Factor (BDNF)) from axon terminals into the synapse within the dorsal horn. These neurotransmitters/modulators then bind to and activate receptors on the post-synaptic nerve terminal, including N-methyl-D-aspartic acid (NMDA), a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), G-protein-coupled receptors and tyrosine kinase receptors. If the pre-synaptic action potentials occur at a sufficient frequency and duration, the activity in the post-synaptic terminal will also increase, propagating another action potential. The impulse generated in the dorsal horn travel through ascending pathways (e.g., the spinothalamic tract) and ultimately to the brain, where the signals are processed and pain is perceived [3].

Peripheral nociceptive afferent activity can be augmented if tissue damage has occurred due to release of pro-inflammatory factors, including bradykinin, prostaglandin E2, nerve growth factor and tumor necrosis factor alpha (TNF-α). These mediators, when bound to specific receptors on neuronal terminals, initiate a cascade of events that results in an altered state of sensitivity. Specifically, these inflammatory mediators can depolarize primary afferents directly by activating sodium ion channels, though in most cases they sensitize the nerve terminal (i.e., lower the threshold for activation) rather than directly activating it. Furthermore, glial cells (i.e., Schwann cells, microglia, astrocytes and oligodendrocytes), which have traditionally been thought of as support cells, are now known to have a key role in the initiation and maintenance of increased nociception following peripheral tissue injury. Under normal conditions, glial cells are quiescent. However, upon activation by tissue damage or inflammation, glial cells are capable of releasing a variety of nociceptive sensitizing agents, such as TNF-α, interleukin (IL)-1, nitric oxide, arachidonic acid and excitatory amino acids, which directly increase nerve excitability, indicating a role for these cells in the initiation and maintenance of enhanced pain states, including neuropathic pain [3].

In addition to the sensitization that can occur in periphery, neurons in the CNS can undergo changes that increase their excitability, often as a result of continued impulse activity in the periphery, a situation known as 'central sensitization'. Activation of the NMDA receptor appears to play a role in increasing CNS excitability. During central sensitization, phosphorylation of NMDA receptors causes their translocation from intracellular stores to the synaptic membrane and increases their responsiveness to the excitatory neurotransmitter glutamate. This activity-induced central hyper-excitability can cause activation of pain pathways by stimuli that are normally sub-threshold (allodynia) or cause exaggerated responses to normally supra-threshold stimuli (hyperalgesia) [3].

Table 1: The pain-mediated intracellular effectors and their signaling mechanism pathways [1].
(Adapted from: Yam MF, Loh YC, Tan CS, Khadijah Adam S, Abdul Manan N, Basir R. General Pathways of Pain Sensation and the Major Neurotransmitters Involved in Pain Regulation. Int J Mol Sci. 2018 Jul 24; 19(8): 2164.)

Intracellular Effectors		
G-protei11-co11 pled receptors (Metabotropic)		
PLC/IP3, DAG/PKC	Gq<X-protein-coup led receptors	Excitatory
Inhibit NE release, Inhibit AC/cAMP/PKA	Gi<X-protein-coupled receptors	Inhibitory
Activate AC/cAMP/PKA	G5<X-protein-coupled receptors	Excitatory
sGC/cGMP	NO-signaling cascade	Inhibitory
Ligand-gated ion c/umnels (Ionotropic)		
	GABAA	Inhibitory
	SNSNav	Excitatory
Ca^{2+}	vocc	Excitatory
K•	Kv	Inhibitory
Protons (H+)	ASIC,VRl	Excitatory

Two important properties of receptors include (1) the recognition of extracellular molecules;and (2) transduction of the signals down the cascades for excitatory/inhibitory ph-umacological response via (a) the ions movement across the membrane; (b) phosphory lation of protein kinases; *(c)* changesof transmitters released; (d) protein syntlwsis regulation; and (e) enzymatic activity. PKA and PKC can interact and sensitize SNSNa, and VR! receptors. AC: Adenylyl Cyclase; ASIC: Acid-Sensing Ion Channels; Ca^{2+}: Calcium Ion; Camp: Cyclic Adenosine Monophosphate; Cgmp: Cyclic Guanosine Monophosphate; CJ-: Chloride Ion; DAG: Diacylglycerol; GABAA: Y-Aminobutyric Acid Type A; IP3: Inositol Triphosphate; K^+: Potassium Ion; K,: Voltage-Activated Potassium Channels; Na^+: Sodium Ion; Nav: Voltage-Activated Nn^+ Channels; NE: Norepinephrine; NO: Nitric Oxide; PKA: Protein Kinase A; PKC: Protein Kinase C; PLC: Phospholipnse C; Sgc: Soluble Gu= Ylyl Cyclase; SNS: Sensory Neurone Specific; VOCC: Voltage-<>Pe Rated Calcium Channels; VR!: Vanilloid Receptor For Cnpsaicin.

Pharmacological interventions with distinct analgesic mechanisms of action

Various analgesic agents are used for the management of pain, each having distinct mechanisms and sites of anti-nociceptive activity. The complexity of pain and the myriad neuronal mechanisms that contribute to its transmission and modulation provide many potential targets for pharmacological intervention. Additionally, certain classes of analgesic agents may be more effective than others for specific types of pain. Therefore, an understanding of the mechanisms by which each drug class produces analgesia is important to clinical decision-making by enabling rational drug selection [3].

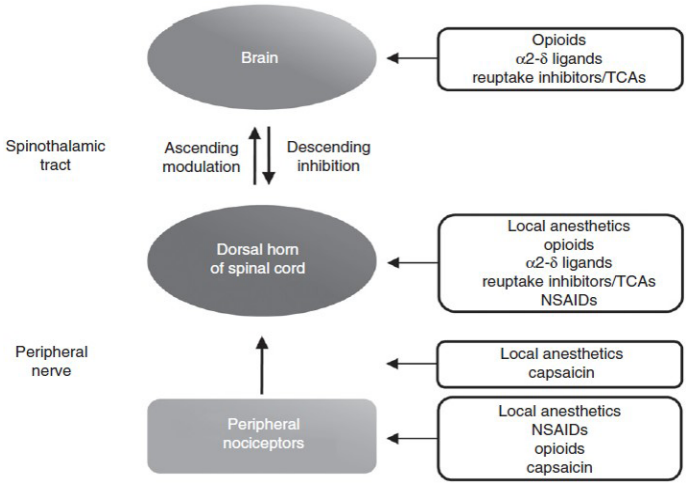

Figure 3: The complexity of the mechanisms that relay stimuli from the periphery to the brain allow for multiple opportunities to mitigate pain using different analgesics that interrupt pain pathways at different points [3]. (Adapted from: Argoff C. Mechanisms of pain transmission and pharmacologic management. Curr Med Res Opin. 2011 Oct; 27(10): 2019-31.)

Local anesthetics

Local anesthetics such as lidocaine and bupivacaine exert their effects through blockade of neuronal membrane sodium channels within tissues at the site of application, thus inhibiting nociceptive signal conduction. Local anesthetics have also been shown to be effective in the management of acute, postoperative pain [3].

Non-steroidal anti-inflammatory drugs (NSAIDs)

NSAIDs are most commonly used for the management of acute and chronic musculoskeletal and post-surgical pain. The primary mechanism of NSAID-induced analgesia is thought to be these agents' inhibition of the enzyme cyclooxygenase, which thereby reduces the production of inflammatory mediators, including the prostaglandins. However, a variety of NSAIDs have also demonstrated the ability to inhibit the expression of or directly block acid-sensitive ion channels within membranes of nociceptive neurons; this may also contribute to their analgesic effects. NSAIDs may provide satisfactory analgesia as monotherapy for mild to moderate pain, but they are primarily used as adjunct therapy in cases of severe pain [3].

NSAIDs should be used cautiously in several patient populations. Risk factors for gastrointestinal bleeding and peptic ulcer disease associated with NSAID use include a history of gastrointestinal bleeding, peptic ulcer, older age, smoking or alcohol use, and longer duration of NSAID use. Indomethacin and ketorolac should not be used in older adults because of the increased risk of these gastrointestinal adverse effects. Concomitant use of NSAIDs and low-dose aspirin is associated with an increased risk of upper gastrointestinal bleeding. Renal insufficiency associated with NSAID use is related to inhibition of renal prostaglandin synthesis, which can present as azotemia and hyperkalemia. Use of NSAIDs in patients with impaired renal function, decreased creatinine clearance, or azotemia can result in acute renal failure [4].

Acetaminophen

Acetaminophen has similar analgesic and antipyretic properties to NSAIDs, but lacks anti-inflammatory properties. Although the complete mechanism of action is not understood, acetaminophen is thought to inhibit cyclooxygenase- mediated activation of prostaglandins primarily in the CNS. In addition, acetaminophen has been suggested to act on the serotonergic inhibitory descending pathway and the endogenous opioid pathway. Acetaminophen is recommended for use in multidrug therapies for severe pain. Acetaminophen is considered to have a safety profile comparable to NSAIDs at therapeutic doses, although overuse has been associated with liver damage. Multiple clinical trials have shown that acetaminophen in combination with various NSAIDs offers significantly greater pain relief than placebo or either monotherapy alone for treatment of post-surgical pain, and that these multidrug therapies had similar side effects to their constituent monotherapies [3].

Anticonvulsant drugs

Certain anticonvulsant drugs, such as the so-called α_2-δ ligands, are also effective analgesics, and their use in the management of neuropathic pain has been extensively studied in such conditions as painful diabetic neuropathy and PHN. Although the exact mechanism by which α_2-δ ligands promote analgesia remains unclear, these agents are known to bind to the α_2-δ subunit of voltage-dependent calcium channels within neuronal membranes, which is thought to inhibit the release of excitatory neurotransmitter by pre-synaptic neurons. In addition, α_2-δ ligands may activate descending inhibitory pathways, resulting in an increase in spinal norepinephrine concentration [3].

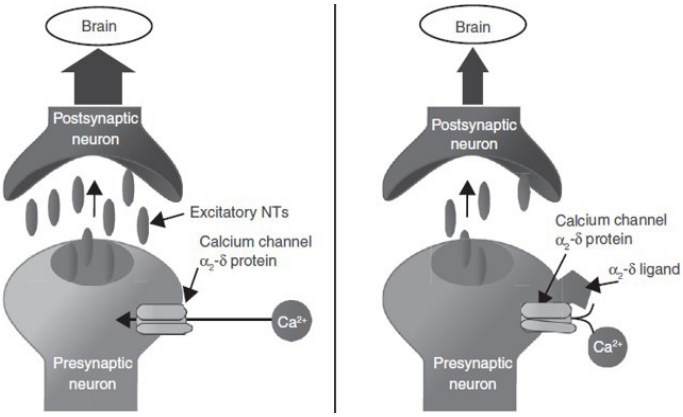

Figure 4: The α_2-δ ligands are believed to promote analgesia by binding to the α_2-δ subunit of voltage-dependent calcium (Ca^{2+}) channels on presynaptic neurons and inhibiting the release of excitatory neurotransmitters (e.g., glutamate, NMDA), thereby limiting the excitation of the post-synaptic neuron [3]. (Adapted from: Argoff C. Mechanisms of pain transmission and pharmacologic management. Curr Med Res Opin. 2011 Oct; 27(10): 2019-31.).

Clinical trials have shown that treatment with α_2-δ ligands leads to a ≥50% reduction in pain intensity in approximately 26% to 50% of patients with chronic neuropathic pain conditions, including PHN and diabetic neuropathy. The most commonly reported side effects included dizziness, somnolence, peripheral edema, headache and dry mouth[3].

Moderate to severe pain management

Opioids

Opioids are a mainstay of therapy for the management of moderate to severe nociceptive pain, which is pain caused by activation of peripheral afferent terminals by noxious thermal, chemical or mechanical stimuli. In most published guidelines, opioids are generally considered second-line therapy for neuropathic pain conditions, such as diabetic peripheral neuropathy and PHN. While several clinical studies have demonstrated the efficacy of opioids in pain conditions having a predominantly neuropathic etiology, evidence for their utility in these conditions is inconsistent, and high rates of treatment discontinuation due to side effects have been reported. The analgesic effects of opioids are mediated through the activation of μ-opioid receptors in the CNS that can inhibit afferent nociceptive impulse transmission, as well as activation of μ-opioid receptors within the midbrain and brainstem to activate descending inhibitory pathways or suppress descending facilitatory pain pathways [3].

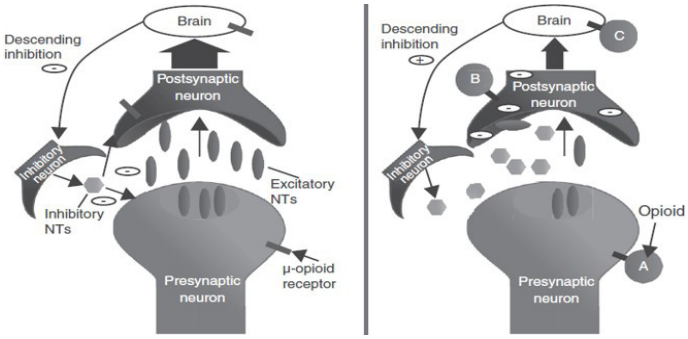

Figure 5: Opioids are believed to promote analgesia in a variety of ways, including: (A) decreasing pre-synaptic release of excitatory neurotransmitters, (B) decreasing post-synaptic neuronal excitability, and (C) promoting descending inhibition [3] (Adapted from: Argoff C. Mechanisms of pain transmission and pharmacologic management. Curr Med Res Opin. 2011 Oct; 27(10): 2019-31.)

In addition to their centrally mediated analgesic effects, it has been proposed that at least a portion of opioid-mediated analgesia can be attributed to their binding at peripheral μ-opioid receptors, especially in painful inflammatory conditions [3].

Limitations of Opioids: Opioid binding to peripheral μ-opioid receptors is associated with certain characteristic side effects, including nausea, vomiting, constipation and pruritus, which may affect adherence to analgesic therapy [3].

Opioid use is associated with multiple adverse effects that range from mild to severe. Addiction and respiratory depression are severe opioid side-effects with serious consequences. Opioid-Induced Respiratory Depression (OIRD) is potentially lethal, especially when the opioid is abused/overdosed, used in combination with sedatives (e.g. sleep medication, alcohol), or is combined with illicit substances. Although reversal strategies may be effective under certain circumstances, there are conditions at which reversal is less efficacious and sometimes even impossible [5].

Opioids produce their respiratory depressant effects by activating opioid receptors expressed on neurones within the respiratory networks of the brainstem. Additionally, there are some sites outside the central nervous system that contain opioid receptors and that might be involved in OIRD (such as the carotid bodies). Various centres in the brainstem contain opioid receptors and their activation is associated with bradypnoea, including the pre-Botzinger complex, parabrachial nucleus, and dorsal rostral pons. All opioids that are currently prescribed for the treatment of acute or chronic pain that active the μ-opioid receptor will cause analgesia linked to respiratory depression. The magnitude of OIRD, however, varies depending on the degree of activation of the various intracellular pathways by the opioid agonist. Among a series of pathways, μ-opioid receptors engage two important signaling pathways, the G-protein and β-arrestin pathways. The former pathway is associated with analgesia, the latter with opioid side-effects, including respiratory depression. Opioids that are biased towards activation of G-protein pathway are so-called 'biased ligands' [5].

As opioids are most effective in alleviating moderate to severe pain, we are convinced that opioid therapy will remain the cornerstone of modern pain therapy. Still, the current crisis mandates that we modify pain therapy strategies to increase safety (but without losing efficacy). Possible strategies include use of effective opioid alternatives, radical changes in prescription behavior and the return to well-defined indications, the development and use of opioids with less adverse effects (most importantly opioids with less addictive and respiratory effects, such as biased ligand opioids, allosteric modulators of the opioid receptor, bi - or multifunctional opioids) and co-treatment with opioid and non-opioid drugs that prevent adverse (respiratory) effects [5].

Monoamine re-uptake inhibitors

Monoamine re-uptake inhibitors are considered first-line therapy for neuropathic pain based on numerous clinical trials in conditions having a predominantly neuropathic component. These agents are believed to exert their analgesic effects primarily by increasing the activity of descending pain-suppressing pathways [3].

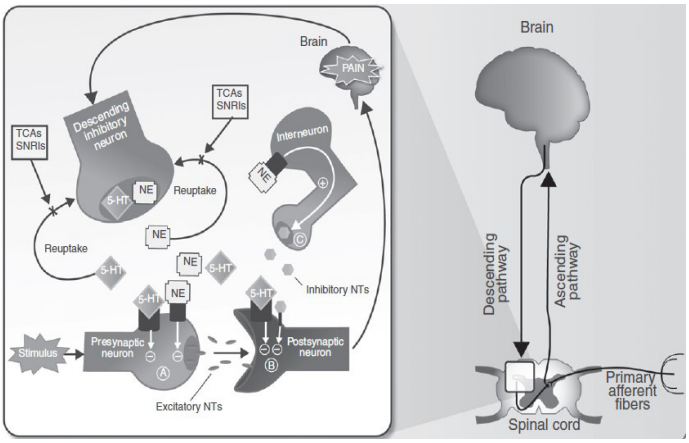

Figure 6: Monoamine re-uptake inhibitors such as tricyclic antidepressants (TCAs) and serotonin and norepinephrine re-uptake inhibitors (SNRIs) are believed to promote analgesia by increasing the synaptic concentration of norepinephrine (NE) and/or serotonin (5-HT) within the dorsal horn, thereby (A) inhibiting the release of excitatory neurotransmitter by pre-synaptic neurons; (B) reducing the excitation of post-synaptic neurons; and (C) promoting the release of other inhibitory neurotransmitters by interneurons [3]. (Adapted from: Argoff C. Mechanisms of pain transmission and pharmacologic management. Curr Med Res Opin. 2011 Oct; 27(10): 2019-31.)

Agents belonging to this class of analgesics include tricyclic antidepressants (TCAs; e.g., amitriptyline, clomipramine, desipramine, imipramine and maprotiline), as well as serotonin and norepinephrine re-uptake inhibitors (SNRIs; e.g., duloxetine and milnacipran). Evidence from clinical studies indicates that agents that inhibit norepinephrine re-uptake, either selectively or in addition to inhibiting serotonin re-uptake provide more effective analgesia than those agents that selectively inhibit serotonin re-uptake. In a systematic review of pooled data from eight studies in patients with neuropathic pain, TCAs provided significant pain relief compared with placebo, while pooled data from three trials using selective serotonin reuptake inhibitors (SSRIs; e.g., citalopram, fluoxetine and paroxetine) showed no benefit of active treatment over placebo [3].

Limitations of Monoamine re-uptake inhibitors: The clinical utility of TCAs and SNRIs is limited, however, by a number of issues. While these agents have documented analgesic efficacy in patients with neuropathic pain, their efficacy as single agent therapy for nociceptive pain is less well established. The use of TCAs and SNRIs for pain management may also be limited by anticholinergic side effects, including dry mouth, constipation, blurred vision, confusion, fatigue and potential cardiac toxicity, which can lead to analgesic discontinuation.[3]

Dual-action medications

Tapentadol

A recent alternative to traditional strong opioids is Tapentadol; licensed for both moderate to severe acute pain requiring opioids and severe chronic pain including cancer pain. Tapentadol is a weak μ-opioid receptor agonist (18 times less potent binding affinity than morphine) and a noradrenaline reuptake inhibitor. The two distinct pharmacological actions are thought to synergistically enhance the descending inhibitory pain pathway [6].

Limitations of Tapentadol: Although tapentadol is a weak opioid, its side-effect profile is similar to strong opioids [6]. The main adverse effects of Tapentadol are gastrointestinal and central, the most common being nausea (30%), followed by vomiting (18%), drowsiness (15%) and dizziness (24%). Another recognized adverse effect due to the continuous use of MOR agonists in men is the opioid-induced androgen deficiency, leading to erectile dysfunction, reduction in sperm counts, testicular atrophy, and hair rarefaction. Studies have shown that Tapentadol presented a relatively lesser magnitude of these effects [7]. Tapentadol should be used cautiously with serotonergic medications because of the risk of serotonin syndrome [4].

Tramadol

Considered Tapentadol closest competitor, since they share certain chemical superficial structural similarities, Tramadol also has more than one mechanism of action, with agonist action on opioid receptors, minimum NRI effect and significant effect in inhibiting serotonin reuptake, binding to MOR, KOR and DOR with low affinity, being, therefore, less effective than other opioids to treat intense pain.[7] It is effective for acute pain (e.g., osteoarthritis) in clinical trials, but the benefits are small and it is considered a second-tier medication [4].

Limitations of Tramadol: Tramadol should be used cautiously, if at all, in patients at risk of seizures[4]. Many pharmacological interactions can be triggered by Tramadol since some antiarrhythmic, antidepressants, antipsychotics, antiparasitic drugs and tamoxifen are a substrate for CYP9. In animal models, Tapentadol showed to be 2 to 5 times more potent than tramadol. Even assuming a conservative conversion rate of 1: 2 between Tapentadol and Tramadol based on the maximum daily recommended dose of 400mg for Tramadol, this dose would reach only 40% of the analgesic effect of the maximum daily dose of Tapentadol. A factor that could explain the lower potency and clinical efficacy of Tramadol, in spite of its affinity with MOR be more intense, would be the fact that Tramadol does not cross the blood-brain barrier in the same ratio that its dose is increased, while Tapentadol crosses it, following its concentration gradient [7].

Most common adverse events with single or multiple dose oral or parenteral administration of tramadol are nausea (6.1%), dizziness (4.6%), drowsiness (2.4%), tiredness (2.3%), sweating (1.9%), vomiting (1.7%) and dry mouth (1.6%). Adverse events occur in ≈15% of patients. Unlike other opioids, notably morphine, tramadol does not cause clinically relevant respiratory depression at recommended therapeutic doses. The incidence of seizures in patients receiving tramadol is estimated to be <1%. [8].

Nefopam

Nefopam hydrochloride is a benzoxazocine derivative and belongs to the category of a non-opioid, non-steroidal, and centrally-acting analgesic drug. It was developed in 1960s and was known as fenazocine at that time. Initially classified as an antidepressant, fenazocine was later renamed as Nefopam in 1970. Nefopam bears structural resemblance to antihistaminic orphenadrine and diphenhydramine [9].

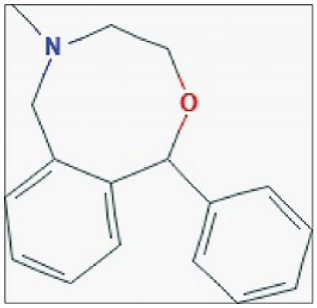

Figure 7: Chemical structure of Nefopam.

Per orally, Nefopam can be prescribed with a dose of 90–180 mg/day in divided doses, 3–6 times a day. For treating chronic neuropathic pain, the duration of therapy is for a longer duration [9].

Mechanism of action

The exact mechanisms of analgesic action of Nefopam are not fully understood and complex [9]. Nefopam is chemically distinct and pharmacologically unrelated to any of the presently known analgesics. Nefopam does not bind to opioid receptors, does not cause respiratory depression, has no effect on platelet function and does not induce an anti-inflammatory effect. In animals, Nefopam induces anti-nociception and counteracts central hyperalgesia. Its main mechanisms of analgesic action involve the inhibition of serotonin, norepinephrine and dopamine reuptake and effects on the glutamatergic pathway via modulations of calcium and sodium channels that leads to decreased activation of postsynaptic glutamatergic receptors, such as N-methyl-D-aspartate (NMDA) receptors, which are involved in the development of hyperalgesia [10].

Multimodal analgesic approach

Results from clinical trials as well as observations from years of direct patient care suggest that use of a single pharmacologic agent for the treatment of various chronic pain states is likely, if it is successful, to provide approximately a 30% reduction in pain intensity. Actually, this should not be surprising given the complexity of pain and the variety of physiological mechanisms involved. Single-agent regimens may not provide optimal analgesia for certain types of pain because they address a limited number of therapeutic targets in the pain transmission and modulatory pathways. Multidrug analgesic approaches take advantage of complementary mechanisms of different drug classes to enhance analgesia and/or reduce side effects by lowering the required dose of one or more agents. The practice of combining different classes of analgesic agents is common and has been integrated into clinical practice guidelines for the treatment of both acute and chronic pain [3].

Numerous clinical studies that combined opioid and non-opioid agents have documented the value of multidrug therapy by demonstrating that this approach reduced consumption of opioid analgesics and lowered the incidence of opioid-associated side effects without sacrificing efficacy, and in some instances, provided superior analgesia. Some clinical trials investigating the utility of multidrug analgesia have involved treating patients with different drug combinations administered at varying intervals [3].

The use of combination therapy in clinical practice is advocated by a number of guidelines for pain management. According to the American Society of Anesthesiologists Task Force on Acute Pain Management, ''The literature supports the administration of two analgesic agents that act by different mechanisms via a single route for providing superior analgesic efficacy with equivalent or reduced adverse effects''. While the use of multidrug analgesia has not been as thoroughly investigated in chronic pain as in acute pain, the Evidence-Based Recommendations for Pharmacologic Management of Neuropathic Pain and the American Society of Anesthesiologists Task Force on Chronic Pain Management Practice Guidelines both endorse multidrug therapy for a variety of chronic pain states [3].

Despite the clear benefits provided by multidrug approaches to pain management, potential complications must be evaluated. Multiple pharmacologic agents can complicate medication regimens and contribute to reduced patient compliance. Single-pill combination therapy has been shown to improve long-term adherence over two-pill administration in other therapeutic areas. Proper communication between physicians and patients when employing a combination approach is important for increased adherence and optimal analgesia. [3].

Given the multitude of pain transmission and modulatory pathways that can undergo neuroplastic changes and contribute to central sensitization, multidrug analgesia that targets different points along these pathways may be a rational treatment approach. Multidrug analgesia may also provide beneficial effects compared with single-agent regimens by providing equal or superior analgesia with lower doses of the individual agents, which may reduce the incidence of side effects. Data from numerous clinical trials and meta-analyses support this concept, and multidrug strategies are endorsed in current guidelines for the management of both acute and chronic pain [3].

Nefopam and paracetamol combination

Combination between Nefopam and Paracetamol involves the inhibition of central cyclooxygenase COX-2 and COX-3 enzymes and the modulation of the serotonergic system. The main mechanisms of analgesic action for Nefopam involve inhibition of serotonin, norepinephrine and dopamine reuptake and the modulation of the glutamatergic pathway. Therefore, Paracetamol and Nefopam share at least one mechanism of action: the modulation of the serotonergic system. However, both drugs act other systems through mechanisms that are not shared: the cyclooxygenase pathway for Paracetamol and the glutamatergic pathway for Nefopam [10].

In a study by Li Q *et al,* the data demonstrated that acetaminophen may enhance the anti-nociceptive activity of Nefopam [11]. In a clinical study exploring Nefopam-Paracetamol combinations during tonsillectomy, the median effective doses of these drugs were determined, and an isobolographic analysis revealed a strong synergy [12]. In addition, in clinical practice, the combination of Nefopam and Paracetamol is currently used to control moderate post-operative pain [12].

A study by Al-Awwady AN *et al* recommends use of Paracetamol Nefopam combination for immediate postoperative pain control for elective laparoscopic cholecystectomy in the absence of contraindications. The study compared Paracetamol alone (group A), Paracetamol and Nefopam (group B) or Paracetamol and Tramadol (group C) combinations for intra and immediate postoperative pain control for laparoscopic cholecystectomy. The pain score assessment revealed that the mean score was significantly lower in group B at immediate postoperative checkup and it remained significantly lower at each subsequent 5 min. interval checkups till the last measurement at 30 min. postoperatively. The pain score tended to increase in the other two groups, in all comparisons. The mean pain scores during the whole postoperative period follow up (0-30 min) revealed that the mean pain score of group B was significantly lower than that in each of the two other groups (A and C) and the effect size was large respectively [13].

Table 2: Comparison of pain scores of the studied groups [13].

Pain core	A (N=30)		B (N=30)		C (N=30)		*P*
	Mean	SD	Mean	SD	Mean	SD	
0	5.3	1.8	2.6	1.1	4.2	0.7	<0.001
5	5.0	1.4	2.6	1.2	4.5	0.9	<0.001
10	5.5	1.0	2.1	1.0	5.1	1.0	<0.001
15	5.9	.05	1.9	0.6	5.6	0.8	<0.001
20	5.9	0.4	1.9	0.7	5.6	0.8	<0.001
25	6.3	1.1	1.9	0.7	5.8	1.1	<0.001
30	6.3	1.2	1.9	0.7	5.9	1.2	<0.001

Adapted from: Al-Awwady AN. Comparison of Paracetamol vs. Paracetamol Nefopam Combination vs. Paracetamol Tramadol Combination Intravenous Infusion for Intraoperative and Immediate Postoperative Analgesia for Laparoscopic Cholecystectomy. La Prensa Medica Argentina. 2020; 106(S1).

The study concluded that the use of Paracetamol plus Nefopam combination during induction of anesthesia is more effective for intra and immediate post-operative pain control for elective laparoscopic cholecystectomy than paracetamol alone or paracetamol plus Tramadol combination [13].

In conclusion, in addition to its specific mechanism of action, Nefopam displays a number of 'clinical' characteristics that support its use as a unique analgesic. 'Unlike NSAIDs, Nefopam has no effect on platelet function, and (in contrast to opioids) does not increase the risk of respiratory depression. In addition, Nefopam has been shown to result in decreased morphine consumption when used as a co-analgesic following abdominal surgery'. These efficacy and safety properties strongly suggest a role for Nefopam in treatments combining it with opioid and non-opioid drugs during multimodal analgesia regimens [10].

Combined role of nefopam and paracetamol [10, 14-16]

- Nefopam stimulates α-2 receptor and decrease the release of substance P
- Nefopam blocks the sodium channel and decrease the release of glutamate
- Nefopam & Paracetamol together block the reuptake of serotonin and increase its concentration in synaptic cleft to induce endogenous analgesic mechanism
- Paracetamol increase the concentration of Dynorphin in synaptic cleft and decrease the pain sensitization established centrally
- Paracetamol decreases the concentration of COX-3 in hypothalamus and decrease pain sensation

Rationale of Nefopam and Paracetamol combination

✓ Nefopam (non-narcotic analgesic) acts centrally with supraspinal and spinal sites of action.

✓ Nefopam inhibits catecholamine, serotonin, and dopamine reuptake, and directly interacts with alpha2-adrenoreceptors.

✓ It also modulates glutaminergic transmission pre-synaptically via inhibition of voltage-sensitive sodium channels.

✓ Paracetamol inhibit brain cyclooxygenase (COX) 3.

✓ Paracetamol exerts its anti-nociceptive effect through the opioidergic system, modulating dynorphin release in the CNS.

✓ Paracetamol indirectly activates spinal $5HT_3$ receptors and there is evidence for a central serotoninergic action.

✓ The analgesic efficacy of Nefopam and of Paracetamol has been demonstrated in the postoperative period.

✓ Smaller doses of each drug could be used in combination, this would reduce side-effects while maintaining analgesic efficacy.

Conclusion

- Combination of Nefopam and Paracetamol will provide quick onset of action.
- Being non-opioid, tolerability profile of Nefodol will be better than conventional therapy in the management of pain.
- Multi-target property of combination will provide benefit in decreasing severity of pain intensity.
- Combination can result in synergistic (supra-additive) effects, thereby allowing dose reduction of each drug, and therefore a reduction of adverse effects.

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