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REVIEW ARTICLE

CANCER PAIN AND ANALGESICS: A BRIEF REVIEW

J Mamatha[1], P Simon[2], K R Thilakchand[2], R Vijendra[3], S Rao[2], M S Baliga[2], P L Palatty[1]

[1]*Department of Pharmacology, Amrita Institute Of Medical Sciences, Peeliyadu Road, Ernakulam, Kerala*
[2] *Mangalore Institute of Oncology, Pumpwell, Mangalore, India*
[3] *A.J. Institute of Medical Sciences and Research Centre, 66, Kuntikan, Mangalore, Karnataka*

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ABSTRACT: Cancer, an ailment as old as mankind is still a major issue in almost all parts of the world. Of all the symptoms pain is the most important and fearsome symptom and pain management is an important aspect. Although most pain specialists and oncologists worldwide are well aware of the importance to adequately treat the pain, it was yet established that more than half of cancer patients have insufficient pain control, and about quarter of them actually die in pain. In this review article we attempted to provide the comprehensive information about different options available nowadays for treating cancer pain focusing on most widely used pharmacologic agents and ways to increase the effectiveness of treatment maximally optimizing analgesic regimen and improving compliance.

KEYWORD: analgesic ladder, opioids, NSAIDS

INTRODUCTION:

Pain continues to be a prevalent symptom experienced by cancer patients[1,2]. Decades after the publication of the World Health Organization's analgesic ladder, cancer pain is still a major cause of suffering for patients with cancer that affects millions of people worldwide. Cancer pain still has a prevalence and is neglected and undertreated. [3] Unfortunately, current research as shown that the available options for the successful treatment of cancer pain is being massively underutilized by physicians and many patients suffer from insufficiently controlled pain despite the plethora of available treatment options.[2]The pain associated with cancer is because of several reasons, the tumor per se giving rise to pain is the most common cause of pain, and pain can also be due to metastasis of the tumor to other organs, the tumor pressing on to a nerve root[3]. Thus proper management of pain is the foremost priority in the management of patients with cancer pain. The critical components in the management of pain are the assessment of pain, adopting a standard analgesic regime and integration with other therapies.

From a terminological perspective, pain is defined by the International Association for the Study of Pain (IASP) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[4]However, the IASP goes on to explain nociception as 'the neural process of

Corresponding Author:
Dr PL Palatty,
Department of Pharmacology, Amrita Institute of Medical Sciences,
Peeliyadu Road, Ernakulam, Kerala-682041

encoding noxious stimuli' according to the new 2011 revision of definitions.[5]Pain can be broadly classified as fast pain and slow pain. Fast pain is felt within about 0.1 seconds after a pain stimulus is applied. It is also described by many alternative names like sharp pain, pricking pain, acute pain and electric pain. It is not felt in most of the deeper tissues of the body.[6] Slow pain on the other hand begins only after 1 second after a pain stimulus and increases gradually over many seconds and sometimes can even prolong to minutes. It is also referred as slow burning pain, aching pain, throbbing pain, nauseous pain and even as chronic pain. This usually associated with tissue destruction leading to prolonged, unbearable suffering. It can also occur both in the skin and in almost any deep tissue of organ. [6]

Pain can also be classified as nociceptive that includes somatic and visceral; and non-nociceptive the neuropathic and sympathetic. Nociception basically arises from the stimulation of pain receptors, by the chemical mediators released from damaged cells following anxious stimuli e.g. heat, vibration, cold, stretch or chemicals. Non-nociceptive pain basically arises from peripheral and the central nervous system. The pain in this type is generated by nerve cell dysfunction and specific receptors don't exist here. [6].

Somatic Pain: Somatic pain is usually sharp and well localized, and can often be reproduced by touching or moving the area or tissue involved like skin, muscle, joints, bone and ligaments. They have specific receptor like heat, cold, vibration, stretch, inflammation and oxygen starvation. It can be referred to cutaneous sites from the tissue of origin like the connective tissue and the muscle. [7]

Visceral Pain: Visceral pain is more often poorly localized and feels like a vague dull ache. Itcanbesometimescolickyorcrampinginnature.Theso urceofsuchpainisusually from the internal organs of main body cavities like thorax, abdomen or pelvis.[7]They have specific receptors like receptors for stretch, inflammation and oxygen starvation.

Neuropathic Pain: Neuropathic pain is described as dull, achy, itchy and burning in quality. This pain might be superficial like the pain experienced on the scalded skin or it can be experiences as a deep rooted pain. It can also be associated with some signs of the central nervous system involvement like tingling sensation, loss of tendon reflexes, hyperalgesia, allodynia, and anesthesia.[1]

Sympathetic Pain: This type of pain occurs more commonly after fractures and soft tissue injuries of the arms and legs which may lead to complex regional pain syndrome due to the over-activity of the sympathetic nervous system and the central or peripheral nervous system. It is characterized by extreme hypersensitivity in the skin around the injury and also peripherally in the limb and is associated with abnormalities of sweating and temperature controlin that area.[8]

Receptors and Nerve Fibres: The pain receptors in the skin and other tissues are all free nerve endings. These receptors are spread about widely in the superficial layers and in the deeper tissues such as periosteum, arterial walls, joint surfaces and the flax and tentorium.[4] Pain is conducted usually by two pathways namely the fast sharp pain pathway or the slow chronic pain pathway.The fast pain pathways comprise of the small type A delta fibres which have a velocity of 6 – 30 m/sec. Whereas the slow chronic pathway comprise of the C- fibres which have a velocity that ranges between 0.5 to 2 min/second. [7]On entering the spinal cord the pain signal takes two paths, the neospinothalamic tract and the paleospinothalamic tract.

Neospinothalamic Tract: The first order neurons here are the A delta fibres which are the myelinated fibers are the carriers of the impulse of pain.[9,10]They terminate in the lamina of the dorsal horn of the spinal cord and excite second order neurons of the neospinothalamic tract, giving rise to long fibres that cross immediately to the opposite side of the cord through the anterior commissure and then turn upwards, passing to the brain in the anterolateral columns.[9,10] A few of these fibres terminate in the reticular area of the brain stem and in the posterior nuclear group of thalamus however most of the fibres pass to the thalamus and terminate in the ventrobasal complex. From the thalamus the signals proceed further to the other basal areas of the brain as well as to the somato sensory cortex.[8] Glutamateis believed to be the

neurotransmitter secreted in the spinal cord at the A delta pain nerve fibre endings.

Paleospinothalamic tract: This tract mainly transmits signals via the C pain fibres, however a few signals are picked up by the A delta fibres. Substance P is believed to be the neurotransmitter secreted by the C-fibres involved in slow pain.[8]The peripheral fibres terminate in the spinal cord in the laminae II and III of the dorsal horns also known as the substantia gelatinosa. [8]The signals then pass through one or more additional short fibre neurons with the dorsal horn and finally enter into the lamina V which is also in the dorsal horn. The last neurons in the series join together giving rise to long axons which join the fibres of the fast pain pathway, which first pass through the anterior commissure to the opposite side and then upwards to the brain in the anterolateral pathway. The paleospinothalamic tract has a wide representation in the brain stem. Only one third or one fourth of its fibres travels to the thalamus where the rest of the fibres are terminating in one of the following areas:

a. The reticular nuclei of the medulla, pons and mesencephalon
b. The tectal area of the mesencephalon deep to the superior and inferior colliculi
c. The preiaqueductal gray region surrounding the aqueduct of sylvius.

From the brain stem pain areas, multiple short fibre neurons relay the pain signals upwards into the intralaminarand ventrolateral nuclei of the thalamus and into certain portions of the hypothalamus and other basal regions of the brain.

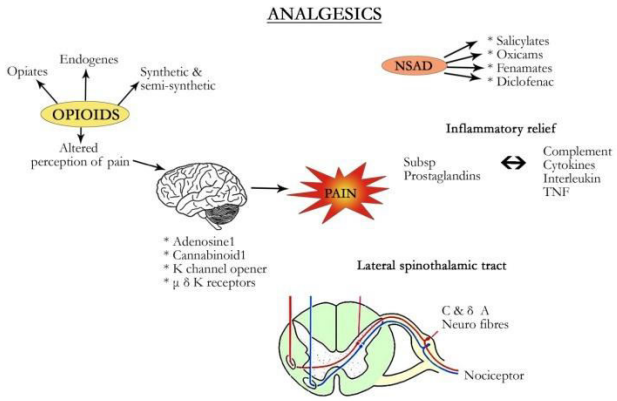

Fig 1.Analgesic Action schematic representation

Mechanisms of Cancer Pain: Bonica and Foley[11] have presented classification schem that are useful in classifying the physical basis of cancer pain. Both include pain associated with direct tumor involvement (bone or nerve infiltration or hollow viscus involvement), pain associated with cancer therapy (postsurgical, chemotherapy, and radiotherapy syndromes), and pain unrelated to cancer. Foley reports that 78% of patients with had pain due to tumor involvement, with 50% due to bone disease, 25% due to nerve compression or infiltration, and 3% due to involvement of hollow viscous. Post therapy pain accounted for 19%, while only 3% had pain due to unrelated causes. In a study of 76 patients with moderate to severe pain, Schwettmann and colleagues found similar percentages of pain mechanisms. When the primary mechanism was considered, 41% had pain due to tumor invasion of bone, 20% due to tumor involvement of nerve, 18% due to soft tissue involvement, 11% due to post-therapy causes, and 7% had pain unrelated to cancer or its treatment. Of the different types of pain, bone pain was most resistant to multimodal paintherapy[12]. Conventionally, pain management is done using opioid analgesics and cyclooxygenase type 2 (COX-2) inhibitors (Table 1)

Table 1: The different class of analgesics used in the treatment of cancer

NSAIDS	Opioid analgesics	Miscellaneous
Acetaminophen Salicylates: acetylated aspirin Salicylate salts: Choline Magnesium Propionic acids: Iburprofen Indolacetic acids: Indomethacin Pyrrolacetic acids: Tolmetin Anthranilic acids: Mefenamic acid Phenylacetic acids: Diclofenac Potassium Enolic acids: Piroxicam Naphtylalkanone: Nabumetone COX – 2 selective: Celecoxib Miscellaneous: Dipyrocetyl	**Endogenous opioids:** endophins, enkephalins, dynorphins, endomorphins Natural opium alkaloids Phenanatherine derivatives: morphine Benzlisoquinoline derivatives: papverine Semisynthetic opium Morphine derivatives: hydromorphine Codeine derivatives: hydrocodone Thebainederivatives: buprenorphine Synthetic opium substitutes: levorphenol Diphenylpropylamine series: methadone Benzomorphans: mepridine Miscellaneous: dextromoramidetartarate	**Antidepressants:** amitryptyline,fluoxetine. VanlafaxineAnticonvulsants: carbamazepine, gabapentin Adrenergic agents: clonidine Nmda receptor antagonist: ketamine, memantine Putative agents: botulinum toxins, talidomide 5-ht agonist: noratriptan, eletriptan Local anasthetics (used with or without adjuvants): lignocaine, ropivacaine Cholinergics: neostigmine magnesium cannabinoids nabilone Muscle relaxants: carisoprodol, methocarbamol
Miscellaneous: Lefetamine Meptazinol Tilidine Tramadol Tapentadol Steroidal analgesics: Flumedroxone	Non opioid, non NSAID: Flupirtine, Nefopam Ziconotide COX and LOX inhibitors: Licofelone	

Opioids: The term opiates refer to compounds that are structurally related to products found in opium, a word derived from ops, the Greek word for juice, natural opiates being derived from the resin of the opium poppy, *Papaversomniferum.* An opiate is any agent that has the pharmacological and the functional properties, of an opiate, irrespective of its structure. The term Narcotic is Greek, derived from the word narkotikos meaning 'to numb'.[12-18]Morphine like alkaloids have been used for analgesia and sedation for centuries. Opium is said to have been mentioned in the Eber's papyrus (1500 BC) and also in the writings of Theophrastus (300 BC) and Galen (2nd century). [18]Though Opium has been used for centuries, it was only after the isolation of morphine as the active ingredient from opium by Serturner in the early 1806 and the introduction of the syringe and hollow needles to clinical practice by Wood in 1853 that opioids were finally permitted to be administered in more precise and measured doses for therapeutic uses.[18]

Classification: Opioids can be classified as endogenous, naturally occurring, semi synthetic and synthetic. The naturally occurring opioids can be further classified into two main groups namely, Phenanthrene derivatives (morphine, codeine) and Benzoisoquinoline derivatives (parverine, noscapine) (Table 2). Morphine, codeine and papaverine, the only naturally occurring opioids of clinical significance, are obtained from the poppy plant, *Papaversomniferum.*[18]

Table 2: Classification of opiods used in the treatment of pain in cancer patients

Endogenous Opioids: Endophins, Enkephalins, Dynorphins, Endomorphins
Natural opium alkaloids Phenanatherine derivatives: Morphine, Codine, Thebaine, Benxylisoquinolinederivates: Papverine, Narcotine
Semisynthetic opium derivates Morphine derivates Hydromorphine, oxymorphine, heroin
Codeine derivatives: Hydrocodone, Oxycodone, Dihydrocodiene, Pholcodine
ThebaineDerivatives: Buprenorphine
Synthetic opium substitutes Morphinans: Levorphenol, Dextromethorphan
Diphenylpropylamine series Methadone, Propoxyphene
BenzomorphansPentazocine, Phenazocine
Phenylpiperidines Merprindine, Fentanyl, Sufentanil, Alfentanil, REmifentanil, Loperamide,
Diphenoxylate
Miscellaneous Dextromoramidetartarate, Dipipanone HCI

Opioid receptors: In around 1972 Hughes and Kosterlitz discovered the presence of endogenous opioid peptides. Synder and team discovered the presence of specific binding sites in the brain and also identification of these as specific opioid receptors.[19]Depending on various pharmacological observations, multiple receptor types were implicated (Table3).Receptor cloning proved eventually that there were three types of true opioid receptors, termed as mu (μ), Delta (δ) and kappa (k). All these opioid receptors are linked through G-protein coupled receptors to the inhibition of adenylatecyclase.[19] The opioids bind to these receptors and bring about a conformational change in the GPCR structurally, there by initiating the G protein activation/inactivation cycle. Upon receptor activation, the Gi/Go coupling results in a large number of intracellular events:

•Inhibition of adenylcyclase activity
•Reduced opening of voltage-gated Ca2 + channels
•Stimulation of K+ current though several channels including G protein activated inwardly rectifying K+ channels.
•Activation of PKC and PLCb.21
Another type of opioid receptor has been postulated to represent the dysphonic effects of some opiates. These are however not considered as true opioid receptors. They are termed as sigma (σ) receptors..[19-20]

Agonists and Antagonists: Opiates vary in their specificity and efficacy at different types of receptors. Currently recognized are three main categories:

a. **Pureagonists:** This group contains the typical morphine-like-drugs. Most of them have a high affinity towards μ receptors while compared to the other two receptor types.
b. **Partial agonists and mixed agonist-antagonists:** These are a group of drugs that combine a degree of agonist and antagonist activity on different receptors. E.g. Pentazocine and cyclazocine are antagonists at the μ receptor and partial agonists on the δ and κ receptors.
c. **Antagonists:** These groups of drugs block the effect of opiates (Eg Naloxone and Naltrexone).

Mechanism of action of opioids: Opioids produce their action by binding specifically to the various opioid receptors which are all G-protein coupled receptors present on the brain, spinal and sensory nerve endings. They act on multiple receptors (μ1, μ2, δ1, δ2, κ1 & κ2) in varying potencies as agonist, partial agonist or antagonist to produce diverse pharmacological effects (Table 3). The μ receptor agonism mediates analgesia, euphoria, respiratory depression and physical dependence.[19-20] 'α' selective adrenergic agonists would have lesser propensity to produce addiction and respiratory depression.[19-20]Interestingly some studies report gender based differences in analgesia mediated by μ and δ receptors (Table 3).[19-20]

Table 3: Functional effects of the main types of opioid receptors:

	υ	δ	κ
Analgesia			
Supraspinal	+++	-	_
Spinal	++	++	+
Perpheral	++	_	++
Respiratory Depression	+++	++	-
Pupil Constriction	++	-	+
Reduced gastrointestinal motility	++	++	+
Euphoria	+++	-	-
Dysphoria	-	-	+++
Sedation	++	-	++
Physical Dependence	+++	-	+

Neural mechanisms for analgesia: From the ventral tegmental area, the mesolimbic system with D2 dopaminergic and inotropic glutamate projects to the Nucleus accumbens which have GABA-ergic neurons that further project to the ventral pallidum.[19-20]Opioids induce the inhibition of the ventral tegmental area and GABA-ergic interneurons. [19-20]They also act on the nucleus accumbens and reduce GABA mediated inhibition and increases outflow from the ventral pallidum, which results in positive reinforcement.[19-20]Usually opioid analgesics produce their effect by acting on multiple sites.

Supraspinal: Opioids produce analgesia, drowsiness, mood disturbances and disorientation. Some patients report unpleasantness, apathy and reduced physical activity.[20]

Spinal: Opioids inhibit the release of excitatory neurotransmitters from the primary afferents by preventing the opening of the voltage gated calcium channels on the afferent nerve.The post synaptic action of opiates blocks the excitation of dorsal horn neurons directly evoked by glutamate excitatory neurons along with activation of K+ channels. This brings about the profound analgesic action on spinal nociceptive pathway.[20]

Morphine: Morphine is considered as a prototype when describing the action of opioids. The below actions can be observed with other opioid agonists, partial agonists and mixed receptor effects.[20]

Central Effects: The most important CNS effects that occur with opioids are analgesia, euphoria,sedationandrespiratorydepression.Mostofth eseactionsareduetothehigh affinity of μ receptors in the CNS, the primary site of action.[20]

Analgesia: Pain consists of two components, namely the sensory as well as the affective/emotional pain. Unlike NSAIDs it acts by reducing both the aspects of the pain.[20,21]

Euphoria: Patients on intravenous morphine usually experience a euphoric effect characterized by floating sensation with lessened anxiety and distress. However, dysphoria has sometimes been reported.[20]

Sedation: The most common effects of opioids are mental clouding and drowsiness. At standard doses it disrupts the NREM (non rapid eye movement) and REM sleep patterns. Oncombining opioids withanycentral depressant, like sedative hypnotics deep sleep is induced.[20]

Respiratory depression: Opioids result inrespiratory depression by inhibiting the brainstem respiratory mechanism. The opioid induced respiratory depression is dose related and is influenced significantly by the degree of the sensory input. In patients with decreased intracranial

pressure, asthma, chronic obstructive airway diseaseorCorpulmonale,thisdecreaseofrespiratoryfunctionmightnotbetolerated.[20]

Cough suppression: This effect is used mainly in patients with pathological cough and in intubated patients for endotracheal tube tolerance. Unfortunately the use of opioids to suppress cough may allow the accumulation of secretions leading to airway obstruction and atelectasis.[20]

Miosis: Constriction of the pupil is a pharmacological action seen with almost all opioids. This property is not lost even with drug tolerance hence making it a valuable sign in diagnosing opioid overdose.[20]

Truncal rigidity: Truncal rigidity is the intensification of muscle. This usually occurs in rapid administration of highly lipid soluble opioids like fentanyl, sufentanyl, alfentanil, etc. Though originally believed to have been due to spinal cord action,evidenceprovesittobearesultfromanactionatsupraspinallevel. Truncal rigidity can be overcome by the administration of opioid antagonists, which would comprises the analgesic effects also.[20]

Nausea and vomiting: Opioid analgesia cause nausea and vomiting by activating the chemoreceptor trigger zone.[20]

Temperature: Experiments demonstrating the effect of a υ opioid receptor agonists such as morphine causing hyperthermia when administered to the anterior hypothalamus and κ agonist causing hypothermia indicate the homeostatic regulation of body temperature by endogenous opioid peptides in the brain.[20]

Peripheral Effects:

Cardiovascular Effects: Opioids have no effects on the cardiovascular system apart from their ability to causes light ECG changes, bradycardia. The blood pressure in patients with opioid analgesia is well maintained, unless the cardiovascular system is stressed, in which case it may cause hypotension. Opioid analgesics are said to have a minimal effect on the cerebral circulation. This effect may get aggravated in the presence of PCO_2rise as a result of hypotension.[20]

Gastrointestinal tract: Constipation has been recognized as an effect of opioids that doesn't diminish with continued use. Opioid receptors are concentrated in the gastrointestinal tract. In the stomach, it leads to reduced gastric emptying and increased tone, along with reduced gastric acid secretion. In the small intestine, there may be a decrease in the amplitude of non-propulsive contractions, along with an increase in resting tone and resting spasms. In the large intestine, the propulsive peristaltic waves are decreased and the tone is increased. Due to all these effects the colonic transit time is increased causing constipation.[20]

Biliary tract: Opioids act on the biliary smooth muscle causing contraction resulting in biliary colic. There might also be increased levels of plasma amylase and plasma lipase due to the constriction of the sphincter of Oddi.[20]

Renal: Opioids the renal plasma flow and can compromise renal function. They also increase the urethral and bladder tone and also sphincter tone which could precipitate urinary retention especially in postoperative patients.[20]

Uterus: Opioids decrease the uterine tone, by both peripheral and central actions and hence could prolong labor.[20]

Neuroendocrine: Opioid analgesics stimulate the release of ADH, prolactin and somatotropin but inhibit the release of luteinizing hormone.[20]

Prutitus: Flushing and warming of the skin, is accompanied by sweating and itching seen in therapeutic doses of opioid analgesics. [20]

Miscellaneous: Opioids also modulate the immune system effects on the lymphocyte proliferation, antibody production and chemotaxis. Endogenous opioids also play a role in tissue injury by countering the inflammatory pain.[20]

Toxicity profile of morphine:

Tolerance: Tolerance to opioids is developed over the frequent exposure to the drug for over a period of 2 to 3 weeks. The development of tolerance is increased when large doses are given over a short period of time and is decreased when small doses are given over a long period of time.[20] The rate at which tolerance appears and disappears largely depends on the compound used, duration of use and also may vary from individual to individual using the same opioid analgesic. E.g. tolerance to sedation and respiratory depression dissipates within a few days after the drug is stopped, whereas tolerance to emetic effects persist for several months after the withdrawal of the drug. Tolerance can also develop to mixed agonist-antagonist opioids; however, they are much less. Such effects include hallucination, sedations, hypothermia and respiratory depression.[20] Cross-tolerance is also another important characteristic of opioid analgesics. This is most commonly seen with μ receptor agonists. Morphine and its congener's exhibit cross tolerance. Opioid rotation, a concept developed through clinical observation finds that by rotating the opioid better effect can be maintained and tolerance decreased.[20]

Physical Dependence: Exaggerated rebound from pharmacological effects is noted in opioids on sudden withdrawal of opioids. The withdrawal/ abstinencesyndrome is characterized by rhinorrhea, lacrimation, yawning, chills, gooseflesh, hyperventilation, hyperthermia, mydriasis, muscular aches, vomiting, diarrhea, anxiety and hostility. The duration, intensity and time of onset depend on the drug being used and also its half-life. For e.g morphine starts 6 – 10 hours after the last dose, followed by a peak fall in between 36 – 48 hrs and then a gradual fall of symptoms with most of it disappearing within 5days. An antagonist precipitated withdrawal may also be seen in a subject by administrating naloxone or any other antagonist. Following the injection, signs and symptoms similar to withdrawal appear within 3 minutes which peak by 10–20 minutes and subsides by 1 hour.[20]

Psychological dependence: The primary reason for the opioid abuse includes the sense of euphoria, sedation, indifference to stimuli, abdominal effects especially when administered intravenously. These cause the individual to be physiologically dependent on these drugs.[20]

Diagnosis and treatment of opioid over dosage: An overdose of opioids usually cause CNS depression and may lead to coma, which can be reversed by an intravenous injection of Nalaxone. This should be supported by other supportive measures like ventilatory support.[20]

Opioid Antagonists: Opioid antagonists basically consists of three drugs namely, naloxone, naltrexone and nalmefene. All these three drugs are morphine derivatives and have a high affinity towards the μ opioid receptors, with a lower affinity to the other receptors. Naloxone has a short duration of action when given via the intravenous route and is metabolized by glucoronide conjugation. Naltrexone on the other hand has a longerhalf-lifeof10hoursandiswellabsorbedafteroraladministration.However,it may undergo rapid first pass metabolism. [20] Nalmefeneis a new entity which is a derivative of naloxone and resembles it, but has alonger half life of 8–10hours.[20] In case of opioid over dosage, intravenous administration of opioid antagonists reverses the process and normalizes respiration, level of consciousness, pupilsize, bowel activity, and awareness of pain. However, itshould be noted that in case of subjects who appear normal and who are dependent on opioids, antagonists can precipitate an abstinencesyndrome. [19]

Non opioid analgesics: Apart from the various opioid analgesics there are various non-opioid analgesics that could be used to relieve pain. [20, 21]The Major classes of drugs which belong to this category are the NSAIDS (Table 4). [20, 21] In contrast to the opoid analgesics, the NSAIDS relieve pain without interacting with the opoid receptors, they have antipyretic effect, possess anti-inflammatory property, have antiplatelet activity, do not cause sedation and are non addictive.[22]Below is an account of the various NSAIDS used in the management of pain due to cancer.

Table 4: Classification of NSAIDs.

Acetaminophen	**Pyrrolacetic acids Ketorolac Tolmetin**
Salicylates Acetylated Aspirin Modified Diflunisal	Anthranilic acids Mefenamic acid
Salicylate salts Choline Magnesium Trisalicylate	Phenylacetic acids Diclofenac Potassium
Propionic acids Ibuprofen Naproxen Naproxen Sodium Fenoprofen Ketoprofen Oxaprozin	Enolic acids Meloxicam Piroxicam
Indolaceticacids IndomethacinSulindac Etodolac	Naphtylalkanone Nabumetone
	COX – 2 selective Celecoxib RofecoxibVadecoxib

Mechanism of action of NSAIDS

Whenever the tissue is injured, tissues release prostaglandins (PGs), and these are the mediators of inflammation which sensitize the pain receptors. The principal therapeutic effects of NSAIDs derive from their ability to inhibit PG production. The NSAIDS bring about their action by inhibiting the COX enzyme to prevent the synthesis of PGs [20-22].There are two forms of COX, COX-1 and COX-2. COX-1, expressed constitutively in most cells, is the dominant source of prostaglandins for housekeeping functions, such as gastric epithelial cytoprotection and hemostasis.[20-22] Conversely, COX-2, induced by cytokines, shear stress, and tumor promoters, and is the more importantsourceofprostaglandinsformationininflammationandperhapsincancer. [20-22]However, both enzymes contribute to the generation of autoregulatory and homeostatic prostaglandins, and both can contribute to prostaglandin formation in syndromes of human inflammation and pain. [20-22] Importantly, COX-1 is expressed as the dominant, constitutive iso forming a stricepithelial cells and is thought to be the major source of cytoprotective PG formation. Inhibition of COX-1 at this site is thought to account largely for the gastric adverse events that complicate therapy with NSAIDs, thus providing the rationale for the development of NSAIDs specific for inhibition of COX-2.[19-22]the prostaglandins induce hyperalgesia, by affecting the transducing property of the free nerve endings so that the stimuli that normally does not elicit pain is able to do so. NSAIDS block the pain sensitizing mechanism induced by bradykinin, TNF□, interleukins primarily by inhibiting COX-2. [18]They are effective against the peripheral component of pain and pain associated with inflammation.[20]

Nonanalgesic actions of NSAIDS: NSAIDS reduce the body temperature in fever by blocking the effect of pyrogens including TNF alpha, interleukins. [18] NSAIDs act as anti-inflammatory agents by including inhibition of expression ICAM 1on the surface of endothelial cells thus disrupting chemotaxis. They also prevent generation of superoxide and free radicals. NSAIDs lower the uterine PG levels and therefore excellent relief inpatients suffering from dysmennorhea.[18] By inhibiting the proaggregatory effect of TXA 2 NSAIDs exert their anti-platelet action and inhibit platelet aggregation. It inhibits the synthesis of PGE2 which is responsible for the patency of the ductusarteriosis and closes it. NSAIDs can cause gastricmucosal damage by inhibiting COX-1 mediated synthesis of gastro protective PGE2 and PGI2. NSAIDs can produce COX-1 dependent impairment of renal blood flow and reduction of GFR and worsen renal in sufficiency. Renal effects are marked in patients with hypovolemic and CHF and in patients with hepaticcirrhosis.[18]Analgesic nephropathy can happen after heavy ingestion of analgesicsover a period of time and the pathologic features are papillary necrosis, tubular atrophy and in worse cases can even result in renal fibrosis.[20-24]

Adverse effects of NSAIDs: Adverse effects are generally quite similar for all of the NSAIDs. [20] They are:

- **Central nervous system:** Headaches, tinnitus, and dizziness.
- **Cardiovascular:** Fluid retention hypertension, edema, and rarely, congestive heart failure.
- **Gastrointestinal:** Abdominal pain, dysplasia, nausea, vomiting, and rarely, ulcers orbleeding.
- **Hematologic:**Rarethrombocytopenia,neutropenia,orevenaplasticanemia.
- **Hepatic:** Abnormal liver function tests and rare liverfailure.
- **Pulmonary:**Asthma.
- **Rashes:** All types,pruritus.
- **Renal:** Renal insufficiency, renal failure, hyperkalemia, and proteinuria.[21]

WHO analgesic ladder: At a practical clinical level non opioid analgesics are considered effective, and are often used as one component in the ladder of analgesic treatments for cancer. But the general consensus is that a combination of A plus B may be no better than A alone.[20] However a second argument is that the combination may be better, but that increased toxicity results. The third school of thought is that they are better, but cost considerations make them too expensive and that the individual drugs should be used in a complicated process of titration.[25] It is important to know the pharmacokinetic and the pharmacodynamic profile of the drug to establish its practical use in clinical practice. In 1986 the World Health Organization (WHO) presented the analgesic ladder as a framework that physicians could use when developing treatment plans for cancer pain.[25] This stepwise approach for managing pain has served as a catalyst for increasing awareness around the world of the importance of treating cancer pain. The analgesic ladder proposed the use of a limited number of relatively inexpensive medications, such as morphine, in a stepwise approach. [25]It helped legitimize the use of opioids for treatment of cancer pain and encouraged numerous worldwide teaching campaigns on the use, benefits, and side effects of narcotics in the treatment of pain.[26]The cornerstone of the WHO protocol rests on 5 simple recommendations for the correct use of analgesics to make the prescribed treatments effective.

- Oral administration of analgesics.
- Analgesics should be given at regular intervals.
- Analgesics should be prescribed according to pain intensity as evaluated by a scale of intensity of pain.
- Dosing of pain medication should be adapted to the individual.
- Analgesics should be prescribed with a constant concern for detail.

Due to some drawbacks in the existing guidelines in the pain ladder in matters related to treatment of severe acute pain, the WHO has adopted some changes in the ladder. The newer version of the analgesic ladder is as below. The new fourth step is recommended for the treatment of crises of chronic pain.Interventionalpainliteraturesuggeststhatthereis moderateevidencefortheuse of trans for aminal epidural steroid injections, lumbar percutaneous adhesiolysis, and spinal endoscopy for painful lumbar radiculopathy, and limited evidence for intradiscal treatments in low back pain. [25-27]The new adaptation of the analgesic ladder adds new opioids, such as tramadol, oxycodone, hydromorphone, and buprenorphine, and also new ways of administering them, such as by transdermal patch, that did not exist in 1986. Adjuvant medications include steroids, anxiolytics, antidepressants, hypnotics, anticonvulsants, antiepileptic-like gabapentinoids (gabapentin and pregabalin), membrane stabilizers, sodium channel blockers, and *N*-methyl-d-aspartate receptor antagonists for the treatment of neuropathic pain. This version of the analgesic ladder can be used in a bidirectional fashion: the slower upward pathway for chronic pain and cancer pain, and the faster downward direction for intense acute pain, uncontrolled chronic pain, and break through pain.[25-27]

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