International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 924-933 www.ijprajournal.com ISSN: 2249-7781

A Review on Opioid Analgesics and Non-Opioid Analgesics

Diksha Kumari[1], Dr. Gaurav Kumar Sharma[2], Dr. Kaushal Kishore Chandrul[3]
(Student of B.Pharma 4th year[1], HOD of Pharmacy[2], Dean of Pharmacy[3])
Department of Pharmacy, Mewar University, Chittorgarh, Rajasthan, 312901

Date of Submission: 01-08-2021 Date of Acceptance: 11-08-2021

OPIOID ANALGESICS

ABSTRACT-Chronic pain is an international health issue of huge importance that is influenced by both physical and psychological factors. Opioids are useful in treating chronic pain. Opioids are a class of medication used in the management and treatment of pain. It is important for us to understand the basic of opioid pharmacology, like mechanism of action, adverse effect, medicinal uses, pharmacokinetic, pharmacodynamic and drug interaction.

I. INTRODUCTION-

When we have a mild headache or muscle ache, we take over the counter medication for relief. But if our pain is more severe, our doctor might recommend something stronger (like opioid). Opioids are a type of narcotic medication. Opium is a dark brown resinous material obtained from poppy capsule of plant Papaver somniferum. It consists of alkaloids that used as analgesics. Ex: - Morphine, Codeine, Papaverine, Thebaine, Fentanyl.

Opioids act by binding receptors which are found primarily in the central and peripheral nervous system and the gastrointestinal tract. These receptors mediate both the psychoactive and the somatic effect of opioids. Opioid drugs include partial agonist, like anti-diarrhoea drug loperamide and antagonists like naloxegol for opioid-induced constipation, which do not cross the blood-brain barrier, but can move other opioids from binding to those receptors.

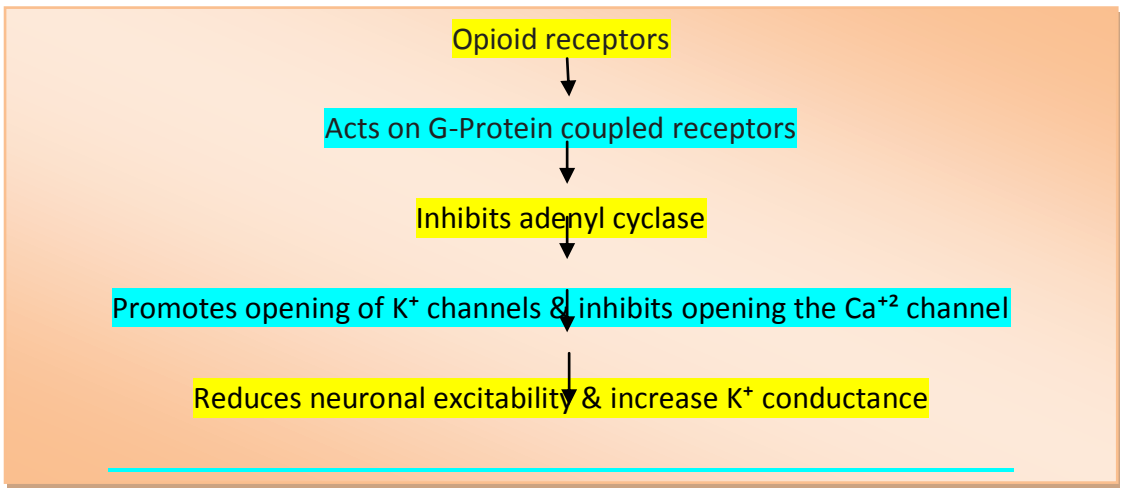
CLASSIFICATION OF OPIOIDS-

► **Natural opium alkaloids**
Morphine, Codeine, Papaverine

► **Semi synthetic opiates**
Diacetylmorphine (heroin), Pholcodine, Benzyl morphine, Ethyl morphine

► **Synthetic Opoids**
Pethidine (Mepiridine), Fentanyl, Methadone, Dextropropoxyphene, Tramadol

MECHANISM OF ACTION-



International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 924-933 www.ijprajournal.com ISSN: 2249-7781

OPIOID RECEPTORS-

All opioid receptors are linked through G-proteins to inhibition of adenylate cyclase. They also facilitate opening of potassium channels (causing hyperpolarisation) and inhibit opening of calcium channels (inhibiting transmitter release).

They are four types:

➢	μ receptor
➢	σ receptor
➢	δ receptor
➢	K receptor

μ-receptors are thought to be responsible for most of the analgesic effects of opioids, and for some main unwanted effects. Most of analgesic opioids are μ-receptor agonists.

- Mu-1
  - Located outside spinal cord
  - Responsible for central interpretation of pain
- Mu-2

Mu (μ)-receptors has two types-

- Located throughout CNS
- Responsible for respiratory depression, spinal analgesia, Physical dependence and Euphoria

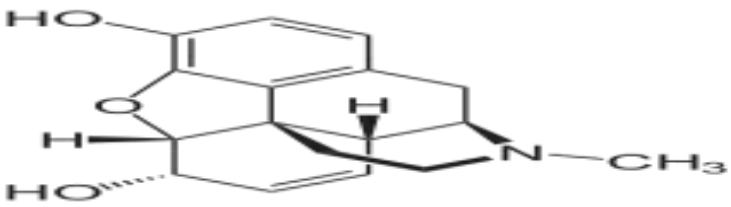
K-receptor contribute to analgesic at the spinal level and may elicit sedation and dysphoria, but produce somewhat few unwanted effects and do not contribute to dependence.

δ-receptor is perhaps more important in the periphery and may also contribute to analgesic.

σ-receptor are not true opioid receptor and it is unclear that what delta actually responsible for but may regulate Mu-receptor activity.

MORPHINE-

Morphine is the major analgesic drug contained in crude opium. It is the prototype strong agonist. It may be given by injection (intravenous or intramuscular) or by mouth, frequently as slow release tablet. It is metabolized to morphin-6-glucronide, which is more effective as an analgesic. It acts directly on the central nervous system (CNS) to increase feeling of satisfaction and warm relaxation and reduce pain.



ADVERSE EFFECT O R SIDE EFFECT OF MORPHINE-

- Nausea, vomiting and abdominal cramp.
- Constipation.
- Sedation and sleepiness.
- Itching and allergic skin reaction causing warmth or flushing.
- Higher dose causes unlikeable symptom such as hallucinations, dizziness and confusions.
- Transmission of HIV/AIDS and Hepatitis B and C among needle users.
- Risk of overdose and poisoning.

USES OF MORPHINE-

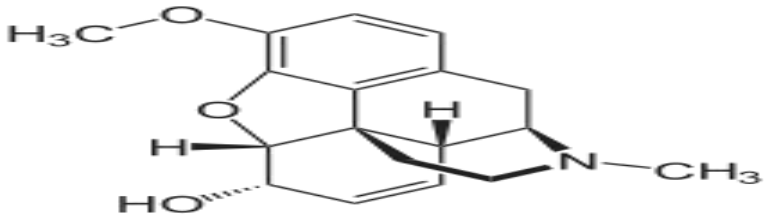
- It can be taken for both acute pain and chronic pain.
- It is used for pain from myocardial infraction, kidney stones and during labor.
- It is used as general anaesthesia to anaesthetize a patient.
- General anaesthesia to anaesthetize a patient.
- Pain relief in terminal cancer patient.
- It has also usually been used in the treatment of acute pulmonary edema.
- It is useful in reducing the symptom of shortness of breath due to both cancer and non cancer causes.

CODEINE-

Codeine is an opioid analgesic used to treat moderate to severe pain when the use of an opioid indicated. It is an opiate and prodrug of morphine used to treat pain, coughing and diarrhoea and commonly abused. It is found in the sap of opium poppy (Papaver somniferum). It is selective against μ-opioid receptor (MOR).Codeine has been found as endogenous compound along with morphine in the brain of non human primates

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 924-933 www.ijprajournal.com ISSN: 2249-7781

with depolarized neurons, indicating that codeine may function as a neurotransmitter in the CNS.



ADVERSE EFFECT OR SIDE EFFECT OF CODEINE-

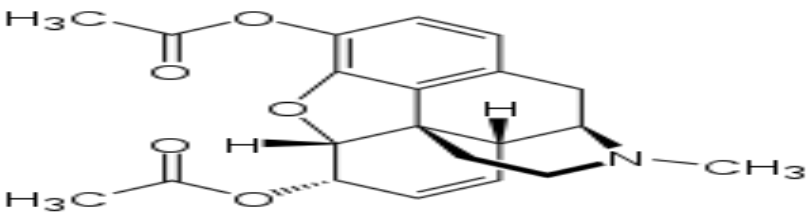
- Nausea or vomiting.
- Constipation.
- Lightheadness, dizziness, sleepiness and sweating.
- Depression or hallucination.
- Allergic reaction.

USES OF CODEINE-

- It is used to help relieve mild to moderate pain.
- It commonly used to treat post-surgical dental pain.
- It is used to relieve coughing.
- It is used to treat diarrhoea and diarrhoea-predominant irritable bowel syndrome.

HEROIN or DIACETYLMORPHINE-

Heroin is an opioid used as recreational drug for its euphoric effects. It is also identified as diamorphine. It is used as a pure hydrochloric salt which is distinguished from black tar heroin. It is typically injected into vein, but it can also be smoked, snorted and inhaled. It may give in intramuscular or subcutaneous injection, as well as orally in the form of tablets.



ADVERSE EFFECT OR SIDE EFFECT OF HEROIN-

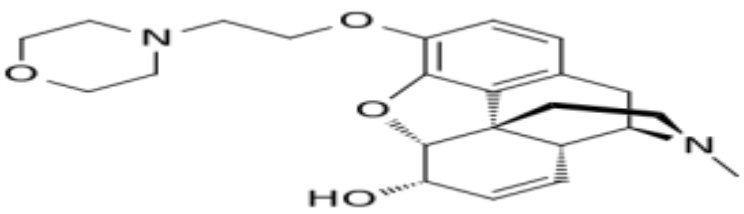
- Respiratory depression.
- Impaired mental function.
- Addiction.
- Blood-borne infection.
- Pneumonia.

USES OF HEROIN-

- It is used to relieve pain during childbirth or heart attack.
- It is used in opioid replacement therapy.

PHOLCODEINE-

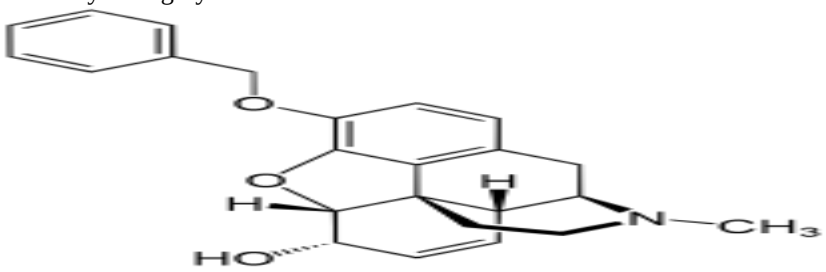
Pholcodine is an opioid antitussive used to suppress unproductive coughing. It has a mild sedative effect but has little or no side effects. It is also known as Morpholinylethylmorphine and Homocodeine. It is found in certain cough lozenges and more commonly as an oral solution. It is now largely replaces the previously more common codeine linctus, as it has much lower potential for dependence.



International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 924-933 www.ijprajournal.com ISSN: 2249-7781

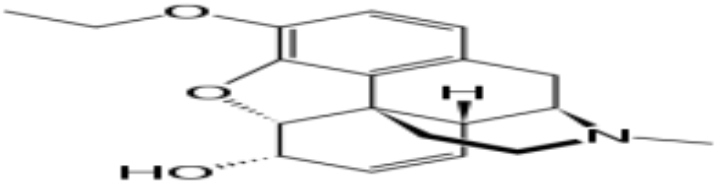
BENZYL MORPHINE-

Benzyl morphine is also known as Peronine. It is a semi synthetic opioid. It is used much same way as codeine, mainly as a moderate strength analgesic for eye surgery as 1 to 2% solution and as a cough suppressant. It is an active metabolite of opioid analgesic myrophine formed in liver. Benzyl morphine is used as a hydrochloride and methylsulfonate.



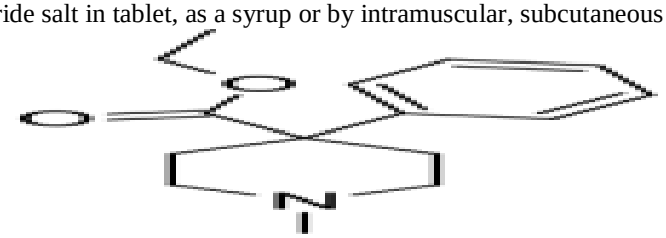
ETHYL MORHINE-

Ethyl morphine is an opioid analgesic and antitussive agent used to decrease coughs caused by cold and lung infection in combination with codeine.



MEPRIDINE or PETHIDINE-

Mepiridine is an opioid agonist with analgesic and sedative properties used to manage severe pain. It is delivered as hydrochloride salt in tablet, as a syrup or by intramuscular, subcutaneous and intravenous injection.



ADVERSE EFFECT OR SIDE EFFECT OF PETHIDINE-

- Dry mouth, unclear vision and tachycardia.
- Overdose of pethidine produce many excitatory effects- tremors, mydraisis, hyperreflexia, delirium, myoclonus and convulsions.

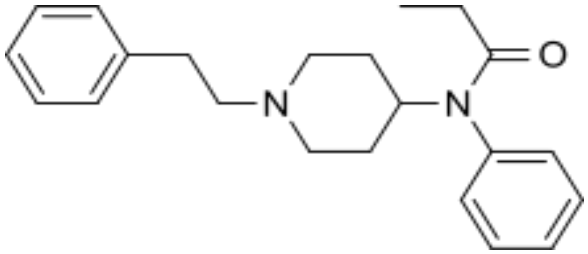
USES OF PETHIDINE-

- Pethidine is most commonly used opioid in labour and delivery.
- It is the preferred painkiller for diverticulitis.
- It is used for the treatment of moderate to severe pain.

FENTANYL-

Fentanyl is a potent synthetic opioid analgesic that is similar to morphine but is 50 to 100 times more potent. It is a Schedule IIprescription drug. It has a rapid onset and its effect normally last under two hours. Medically, it is used by injection, nasal spray, skin patch or absorbed through the cheek as a lozenge or tablet.

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 924-933 www.ijprajournal.com ISSN: 2249-7781



ADVERSE EFFECT OR SIDE EFFECT OF FENTANYL-

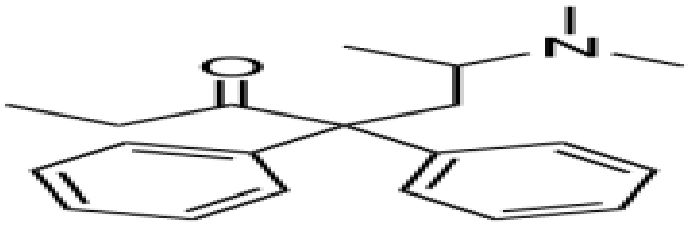
- Sleepiness, anxiety and depression.
- Changes in vision.
- Abnormal thinking and abnormal dreams.
- Irregular menstruation.
- Changes in heartbeat.
- Asthenia and dyspepsia.

USES OF FENTANYL-

- It is used to treat patient with severe pain or to manage pain after surgery.
- It is also used a recreational drug.
- It is frequently used for anaesthesia and to treat pain.
- It is used in the management of chronic pain as well as cancer pain.

METHADONE-

A synthetic opioid, pharmacologically very similar to morphine. It is used for opioid maintenance therapy in opioid dependence and for chronic pain management. It has a slow metabolism and very high fat solubility, making it longer lasting than morphine based drugs. Methadone is one of the more lipid-soluble opioids and is well absorbed from the gastrointestinal tract.



ADVERSE EFFECT AND SIDE EFFECT OF METHADONE-

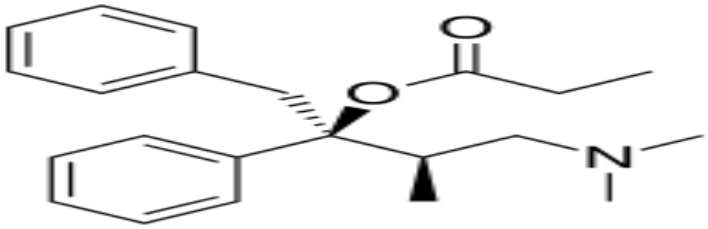
- Flushing and perspiration.
- Dizziness, fainting and weakness.
- Chronic fatigue, sleepiness and exhaustion.
- Constricted pupils.
- Photophobia.
- Hyperventilation syndrome.
- Suicidal ideation.
- Anxiety and panic disorder.

USES OF METHADONE-

- It is used in the treatment of opioid use disorder.
- It is used for the treatment of addiction.
- It is used as analgesic in chronic pain.

DEXTROPROPOXYPHENE-

Dextropropoxyphene is an opioid analgesic used to treat mild to moderate pain. It displays antitussive and local anaesthetic actions. It works by blocking transmission of pain signals to the brain to lower pain perception.



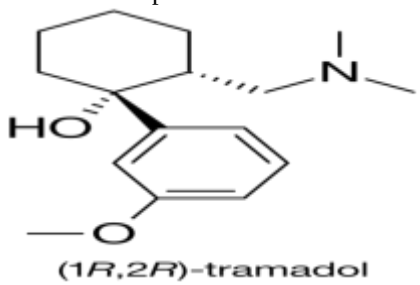
International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 924-933 www.ijprajournal.com ISSN: 2249-7781

ADVERSE EFFECT AND SIDE EFFECT OF DEXTROPROPOXYPHENE-

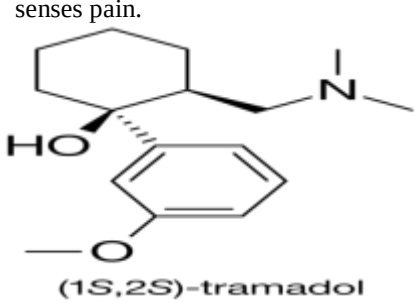
- Nausea.
- Constipation.
- Sore throat.
- Sleepiness.
- Itching.
- Tremors.
- Diarrhoea

USES OF DEXTROPROPOXYPHENE-

- It is used to treat mild pain.



(1*R*,2*R*)-tramadol



(1*S*,2*S*)-tramadol

ADVERSE EFFECT OR SIDE EFFECT OF TRAMADOL-

- Headache and dizziness.
- Nausea and vomiting.
- Severe sleepiness.
- Unusual tiredness.
- Difficulty with breathing
- Loss of consciousness.
- Hives, itching and skin rash.
- Bloating.
- Blurred vision.

USES OF TRAMADOL-

- It is used to treat mild to severe pain.
- It is mainly use for treatment of chronic pain.
- It has less sedative effect.
- It is also used to treat long-standing pain when weak painkillers no longer work.
- It is helpful in relieving the symptoms in restless legs syndrome.
- It is used to ease the with drawl symptoms in people addicted to opioids.

TRAMADOL-

Tramadol is opioid analgesic which used to help relieve moderate to moderately severe pain. It comes in both immediate release and extended release forms. It works by changing how your brain senses pain.

NON-OPIOID ANALGESICS

ABSTRACT:-

Non-opioid analgesics including both selective and non-selective cyclooxygenase (COX) inhibitors and acetaminophen are the most commonly used treatments for pain. It is essential for us to understand the basic of non-opioid pharmacology like mechanism of action, adverse effect, medicinal uses, pharmacokinetic, pharmacodynamic and drug-interaction.

INTRODUCTION:-

Non-opioid analgesic are over the counter (OTC) and prescription medication used to ease pain. They have become increasingly emphasized in a variety of clinical settings as a preferred, safe and effective first line therapy substitute to opioid medication for mild to moderate pain acute and chronic pain. The most common opioid analgesics are acetaminophen, aspirin and non-steroidal anti-inflammatory drugs (NSAIDs).

Most non-opioids are taken by mouth. Some are given by injection or IV before, during or after a surgical procedure.

CLASSIFICATION OF NON-OPIOIDS:-

- **Non-selective cox inhibitors**
  - Salicylates
    - Aspirin
    - Salicylamide
    - Benorylate
  - Pyrazole derivatives
    - Phenyl butazone
    - Oxyphenyl-butazone
  - Propionic acid derivatives
    - Ibuprofen
    - Naproxen
  - Indole derivatives
    - Indomethacin
    - Sulindac
  - Anthralinnic acid derivatives
    - Mefenamic acid
    - Flufenamic acid
  - Aryl acetic acid derivatives
    - Diclofenac
    - Tolmetin
  - Oxicam derivatives
    - Piroxicam
    - Tenoxicam

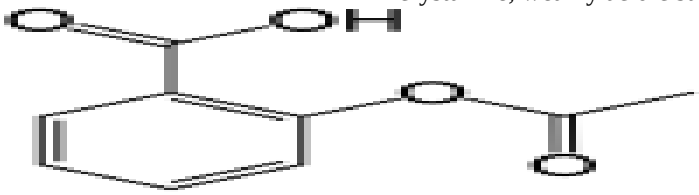
International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 924-933 www.ijprajournal.com ISSN: 2249-7781

► **Prefential COX-2 inhibitors**
- Nimesulide
- Meloxicam
- Nabumetone

► **Selective COX-2 inhibitors**
- Valdecoxib
- Celecoxib
- Rofecoxib

ASPIRIN-

Aspirin also known as acetylsalicylic acid. It is general drug for relieving minor aches, pains and fever. It is a non steroidal anti-inflammatory drugs (NSAID). It contains salicylate which found in plants such as the willow tree and myrtle. It has analgesic, antipyretic and anti-inflammatory actions. It can be given by mouth, rectal, lysine acetylsalicylate may be given intravenously or intramuscularly. It can give soon after a heart attack decreases the risk of death. It also suppress the normal functioning of platelets. It is a white, crystalline, weakly acidic substance.

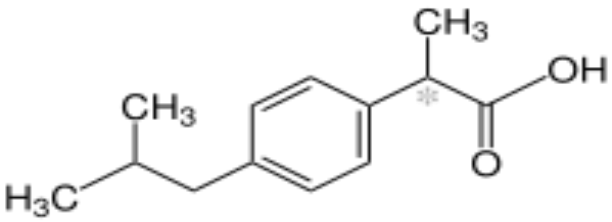


SIDE EFFECT OR ADVERSE EFFECT OF ASPIRIN-
- ► Nausea, vomiting and epigastric distress
- ► Increases blood loss in stools
- ► Rashes, urticaria and rhinorrhea
- ► Asthma and anaphylactoid reaction
- ► Dizziness, tinnitus and vertigo
- ► Mental confusion and hyperventilation
- ► Electrolyte imbalance

USES OF ASPIRIN-
- ► It is used to treat pain and fever.
- ► It is also used to treat rheumatic fever, rheumatic arthritis and osteoarthritis.
- ► It is used as an anti-inflammatory agent.
- ► It is used in veterinary medicine as an anticoagulant or to relieve pain.

IBUPROFEN-

Ibuprofen is a non-steroidal anti-inflammatory drugs. It works by reducing hormones that cause inflammation and pain in the body. It is a general treatment for relieving the symptoms of fever and pain. It is a type of medication with analgesic, fever-reducing. It may be given by mouth and intravenously.



SIDE EFFECT AND ADVERSE EFFECT OF IBUPROFEN-
- ► Heartburn and rashes
- ► Gastrointestinal bleeding
- ► Asthma
- ► Heart failure and kidney failure
- ► Headache and dizziness
- ► Nausea and vomiting
- ► Diarrhoea and constipation
- ► Edema or fluid retention

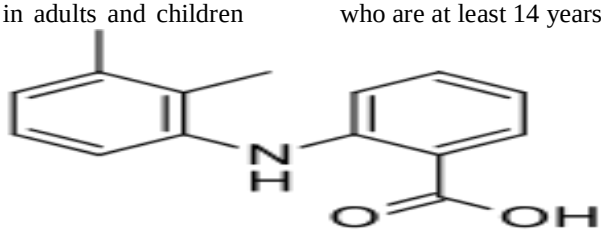
USES OF IBUPROFEN-
- ► It is used for treating pain, fever and inflammation.
- ► It is also used to treat painful menstrual period, migraine and rheumatoid arthritis.
- ► It may be also use to close a patent ductus arteriosus in a premature baby.
- ► It is used for anti-inflammatory disease such as juvenile idiopathic arthritis.

MEFENAMIC ACID-

Mefenamic acid is a non-steroidal anti-inflammatory drug which is a part of the anthranilic acid derivatives class. It works by stopping the body's production of a substance that causes pain, fever and inflammation. It is used short-term to

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 924-933 www.ijprajournal.com ISSN: 2249-7781

treat mild to moderate pain in adults and children who are at least 14 years old.



SIDE EFFECT OR ADVERSE EFFECT OF MEFENAMIC ACID-

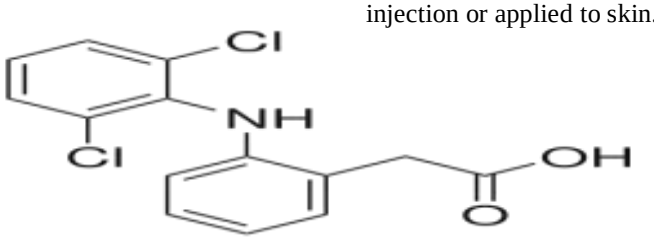
- Headaches, nervousness and vomiting
- Diarrhoea and peptic ulcer
- Gastrointestinal perforation
- Hematemesis
- Skin reaction
- Blood cell disorder
- Liver disease and pale skin
- Cloudy, discoloured or bloody urine

USES OF MEFENAMIC ACID-

- It is used for short-term treatment of mild to moderate pain.
- It is used to reduce pain and blood loss from menstrual periods.
- It is used to treat pain and inflammation in rheumatoid arthritis and osteoarthritis.
- It is used to treat acute pain including muscle and back pain.
- It is also prescribed for menorrhagia.

DICLOFENAC-

Diclofenac is a non-steroidal anti-inflammatory drug. This drug works by reducing substances in the body that cause pain and inflammation. It is taken by mouth, rectally in a suppository, used by injection or applied to skin.



SIDE EFFECT AND ADVERSE EFFECT OF DICLOFENAC-

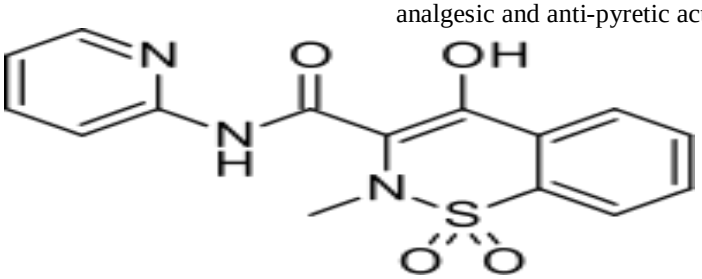
- Nausea and vomiting
- Headache and vertigo
- Heart attack or stroke
- Kidney disease
- Liver disease
- Increased blood pressure
- Swelling or pain in arms and legs

USES OF DICLOFENAC-

- It is used to treat pain and inflammatory disease.
- It is used to treat chronic pain related with cancer.
- It is used to treat rheumatoid arthritis and osteoarthritis.
- It is used to treat dysmenorrhoea.
- It is used for post traumatic & post operative inflammatory condition.
- It is used for toothache.
- It is used for spondylitis.
- It is used to treat mild to moderate pain.

PIROXICAM-

Piroxicam is a non-steroidal anti-inflammatory drugs (NSAID) of the oxicam class. It is used to reduce the symptoms of painful inflammatory condition like arthritis. It works by preventing production of endogenous prostaglandin which are involved in the medication of pain, stiffness, tenderness and swelling. It has good analgesic and anti-pyretic action.



International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 924-933 www.ijprajournal.com ISSN: 2249-7781

SIDE EFFECT AND ADVERSE EFFECT OF PIROXICAM-

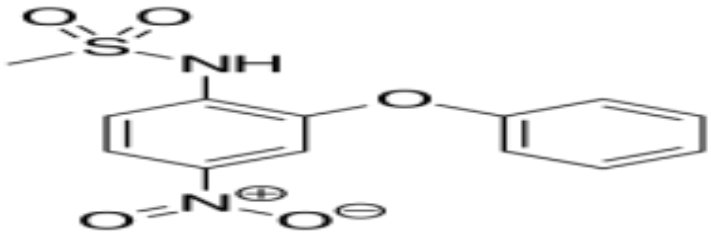
- Nausea and headache
- Diarrhoea
- Dizziness and nervousness
- Insomnia and vertigo
- High blood pressure
- Oedema
- Kidney failure
- Liver damage
- Skin reaction
- Liver damage

USES OF PIROXICAM-

- It is used to treat pain or inflammation caused by osteoarthritis and rheumatoid arthritis.
- It is used in the treatment of primary dysmenorrhoea.
- It is used to treat post-operative pain.
- It is used as an analgesic.
- It is used to treat ankylosing spondylitis.
- It is also used to relieve muscle pain and swelling.
- It is used to treat pain after surgery or childbirth.

NIMESULIDE-

Nimesulide is a non-steroidal anti-inflammatory drug (NSAID). It works by blocking the release of certain chemical messenger that cause pain and inflammation (redness and swelling).It is a medication which used for pain relief and for the prevention of fever. It works by blocking the production of prostaglandins.



SIDE EFFECT AND ADVERSE EFFECT OF NIMESULIDE-

- Stomach discomforts and cramps
- Nausea and vomiting
- Dizziness
- Skin rashes
- Diarrhoea
- Elevated liver enzymes
- Blood clotting disorder
- Bitterness in mouth

USES OF NIMESULIDE-

- It is used for the treatment of acute pain related with menstruation and osteoarthritis.
- It is also used for mild to moderate pain.
- It is used to treat joint pain, muscle strains and sprains.
- It is used for primary dysmenorrhoea in adolescents.
- It is used to pain relief and for the prevention of fever.

II. CONCLUSION-

Opioid analgesic and non-opioid analgesic are definitely useful in reducing pain and improving the quality of life but have their own spectrum of adverse effects. Both analgesic are used to treat different types of pain on different way. Opoid analgesic can be used by prescription but non-opioid analgesic can be used without prescription because it is over the counter medicine.

REFERENCES-

[1]. Opoid analgesics, Jamison RN Mao J,, Mayo Clinic proceedings, 2015 Jul [Pubmed PMID: 26141334]
[2]. Zollner C, Stein C, Opoids. Handbook of experimental pharmacology, 2007; [PubMed PMID: 17087119]
[3]. Essentials of Medical Pharmacology- 7th edition by KD Tripathi.
[4]. Goodman & Gilman's the Pharmacological basis of Therapeutics 12th edition by Laurence Brunton.
[5]. Rang & Dales Pharmacology, 6th edition.
[6]. Lippincott's Pharmacology, 5th edition.
[7]. Lippincott's Illustrated reviews: Pharmacology 6th edition by Richard A Harvey.
[8]. Reuben DB, Alvanzo AA, Ashikaga T, et al. National Institutesof Health Pathways to Prevention Workshop: the role of opioids in the treatment of chronic pain. Ann Intern Med. 2015;162(4):295-300.
[9]. https://www.webmd.com/pain-management/guide/narcotic-pain-medications

International Journal of Pharmaceutical Research and Applications
Volume 6, Issue 4 July-Aug 2021, pp: 924-933 www.ijprajournal.com ISSN: 2249-7781

[10]. https://www.google.com/search?q=%EF%82%AB+https://slideshare.net/BikashAdhikari+26/opioid-analgesics-opioid-dependence&s https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4590096/pell=1&sa=X&ved=2ahUKEwjIuI3VzI3yAhWwyTgGHXKlBUsQBSgAegQIARAx
[11]. https://www.slideshare.net/sidrahena/opioid-receptors-opioid-analgesics
[12]. Vital Signs: Changes in Opioid Prescribing in the United States, 2006-2015, Guy GP Jr, Zhang K, Bohm MK, Losby J, Lewis B, Young R, Murphy LB, Dowell D,, MMWR. Morbidity and mortality weekly report, 2017 Jul 7 [PubMed PMID:28683056]
[13]. Basic opioid pharmacology – NCBI-NIH, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4590096/
[14]. A Systematic Review of NMDA Reeptor Antagonists for Treatment of Neuropathic Pain in Clinical Practice., Aiyer R, Mehta N, Gungor S, Gulati A., The Clinical Journal of pain, 2017 Sep 1
[15]. Dowell D, Haegrich TM, Chou R, CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. JAMA. 2016 Apr 19;
[16]. Bohnhert AS, Valenstein M, Bair MJ, et al. Association between opioid prescribing pattern and opioid overdose-related deaths. JAMA. 2011;305(13):1315-1321
[17]. Pini LA, Vitale G, Sandrini M. Serotonin and opiate involvement in the antinociceptive effect of acetylsalicylic acid. Pharmacology. 1997;54;84-91
[18]. Opioid Analgesic and Antagonists, https://accesspharmacy.mhmedical.com/content.aspx?bookid=1568&sectionid=95702914
[19]. Opioid pharmacology- Pain physician, https://www.painphysicianjournal.com/current/pdf?article=OTg3&journal=42
[20]. Non-opioid treatments for chronic pain, https://www.cdc.gov/drugoverdose/prescribing/guideline.html
[21]. American Academy of Pain Medicine. AAPM facts and figures on pain. https://www.painmed.org/patient/facts.html. Feb 25,2011.
[22]. Munir MA, Enany N, Zhang JM. Non-opioid analgesics. Anaesthesiology Clin. 2007;25(4):761-764
[23]. US Food and Drug Administration. COX-2 selective and non-selective non-steroidal anti-inflammatory drugs. https://www.fda.gov/cder/drug/infopage/COX
[24]. https://www.slideshare.net/DrPrahladPatki/opioid-amp-nonopioids
[25]. Gage, Tommy W. **Mosby's Dental Drug Reference**. Mosby-Year Book, Inc.1994.
[26]. Holoryd, Sam V. **Clinical Pharmacology in dental** practice. 4th ed. The C.V. Mosby Company. 1988.
[27]. https://breastcancer.org/treatment/pain/meds/narcotics
[28]. Non-opioid analgesics https://www.slideshare.net/sungyeonlee/non opioid-analgesics-55865366
[29]. Nimesulide, https://link.springer.com/article/10.2165/00003495-199448030-00008
[30]. Effects of Nimesulide, https://link.springer.com/article/10.2165%2F00003088-199835040-00001
[31]. https://medicoverhospitals.in/medicine/nimesulide
[32]. Nimesulide for external use, https://patents.google.com/patent/EP0782855B1/en
[33]. "Diclofenac". Drugs.com. Retrieved 22 December 2018. https://www.drugs.com/international/diclofenac.html
[34]. https://www.webmd.com/drugs/2/drug-4284-4049/diclofenac-oral/diclofenac-sodium-enteric-coated-tablet-oral/details
[35]. Diclofenac uses, dosage & side effects. https://www.drugs.com/diclofenac.html