University of Baghdad **Therapeutic I**
College of Pharmacy **Lec:-**
Department of Clinical Pharmacy **5th Class**

Pain Management

Pain: is a subjective, unpleasant, sensory, and emotional experience associated with actual or potential tissue damage or described in terms of such damage. It may be classified as acute, chronic, or cancer pain.

PATHOPHYSIOLOGY

- **NOCICEPTIVE PAIN**

• Nociceptive pain is either somatic (arising from skin, bone, joint, muscle, or connective tissue) or visceral (arising from internal organs, eg, the large intestine).
• Stimulation of free nerve endings (*nociceptors*) leads to the sensation of pain. These receptors, found in both somatic and visceral structures, are activated by mechanical, thermal, and chemical impulses. Release of bradykinins, prostaglandins, histamine, interleukins, tumor necrosis factor α (TNF-α), serotonin, and substance P may sensitize and/or activate nociceptors.
• The endogenous opiate system consists of neurotransmitters (eg, enkephalins, dynorphins, and β-endorphins) and receptors (eg, μ, δ, and *κ*) that are found throughout the central and peripheral nervous systems (CNS and PNS). Endogenous opioids bind to opioid receptors and modulate the transmission of pain impulses.
• A descending CNS system also controls pain transmission. This system originates in the brain and can inhibit synaptic pain transmission at the dorsal horn. Important neurotransmitters here include endogenous opioids, serotonin, norepinephrine, and γ-aminobutyric acid.

- **PATHOPHYSIOLOGIC PAIN**

• Pathophysiologic pain (eg, postherpetic neuralgia, diabetic neuropathy, fibromyalgia, irritable bowel syndrome, chronic headaches, and some non cardiac chest pain)is often described in terms of chronic pain. It results from damage or abnormal functioning of nerves in the CNS or PNS. Pain circuits sometimes rewire themselves anatomically and biochemically.

❖ Classification of Pain

- **Acute pain:** recent pain that is usually transient in nature lasting for several minutes to several days. Is usually caused by tissue damage and is often associated with some degree of inflammation. The pain is usually self-limiting, decreasing with time as the injury heals. It is described as a linear process, with a beginning and an end. Increased autonomic nervous system activity often accompanies acute pain, causing tachycardia, tachypnea, hypertension, diaphoresis, and mydriasis. Increased anxiety also may occur.
- **Chronic pain** is persistent or episodic pain of a duration or intensity that adversely affects the function or well-being of the patient and can persist after the resolution of an injury. Some define it as lasting more than 6 months.

  a. Chronic nonmalignant pain may be a complication of acute injury in which the healing process does not occur as expected or may be caused by a disease such as a rheumatologicaldisorder (e.g., osteoarthritis, rheumatoid arthritis, fibromyalgia).

  b. The elderly are more likely to experience chronic pain because of the increased prevalence of degenerative disorders in this age group.

  c. The pain is constant, does not improve with time, and is described as a cyclic process (vicious circle).

  d. Compared to acute pain, there is no longer autonomic nervous system stimulation, so the patient may not appear to be in pain. Instead, the patient may be depressed; suffer insomnia, weight loss, and sexual dysfunction; and may not be able to cope with the normal activities of daily living, including family and job-related activities.
- **Chronic cancer pain** occurs in 60% to 90% of patients with cancer. Its characteristics are similar to those of chronic nonmalignant pain. Tumor causes of pain include bone metastasis, compression of nerve structures, occlusion of blood vessels, obstruction of bowel, or infiltration of soft tissue.
- **Breakthrough pain** is the intermittent, transitory increase in pain that occurs at a greater intensity over baseline chronic pain. It may have temporal characteristics, precipitating factors, and predictability.
- **Neuropathic pain** is a result of an injury or malfunction of the nervous system. Neuropathic pain is described as aching, throbbing, burning, shooting, stinging, and tenderness or sensitivity of the skin.
- **Migraine pain** is characterized by a severe headache generally associated with nausea and light and sound sensitivity.

❖ **Assessment of pain**

- Evaluation of pain should include a detailed description of the pain and an assessment of its consequences. There should be a full history, psychosocial assessment, medication history and assessment of previous pain problems, paying attention to factors that influence the pain.
- Diagnostic laboratory tests, imaging, including plain radiography, computer tomography (CT) and magnetic resonance imaging (MRI), and diagnostic nerve blocks may aid confirmation of the diagnosis.
- Pain is a subjective phenomenon and quantitative assessment is difficult. The most commonly used instruments are visual analogue and verbal rating scales.
- Visual analogue scales are 10 cm long lines labelled with an extreme at each end; usually 'no pain at all' and 'worst pain imaginable'. The patient is required to mark the severity of the pain between the two extremes of the scale. Verbal rating scales use descriptors such as 'none', 'mild', 'moderate' and 'excruciating'. More elaborate questionnaires such as the Brief Pain Inventory and the McGill Pain Questionnaire help to describe other aspects of the pain, and pain diaries record the influence of activity and medication on pain.

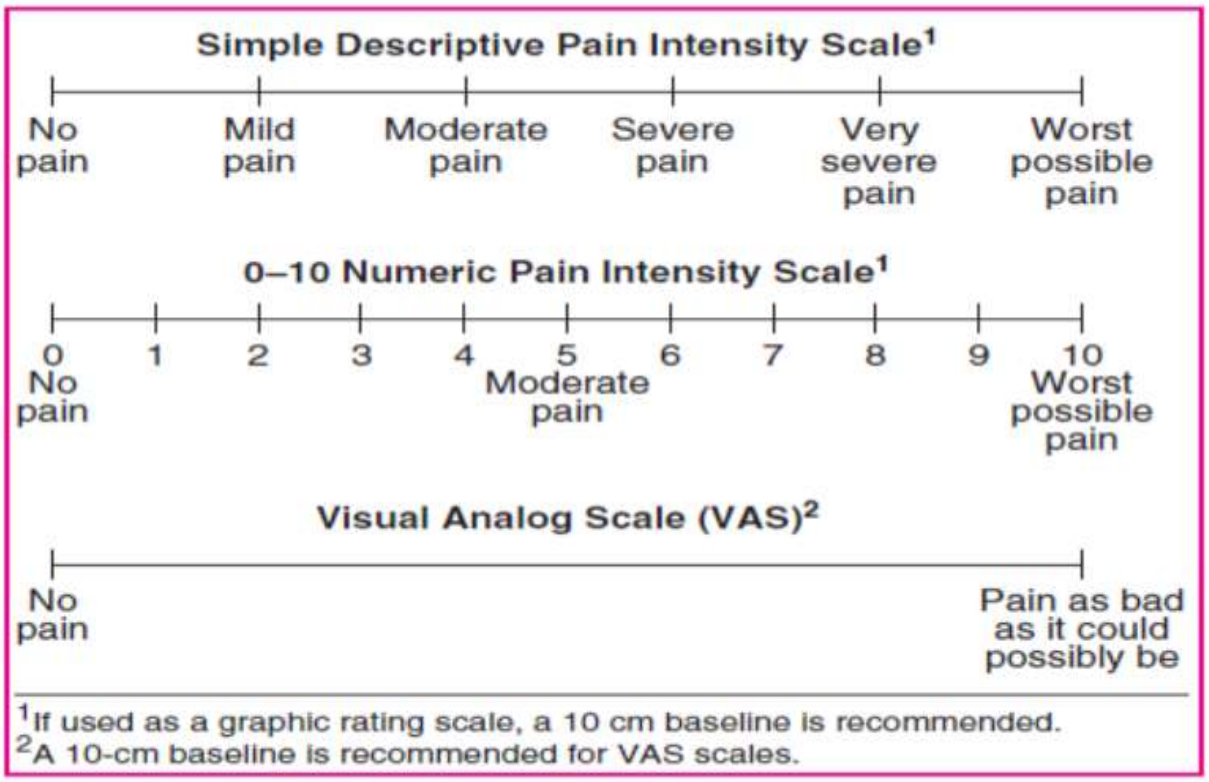

FIGURE 30–1. Pain rating scales.[27]

❖ Management

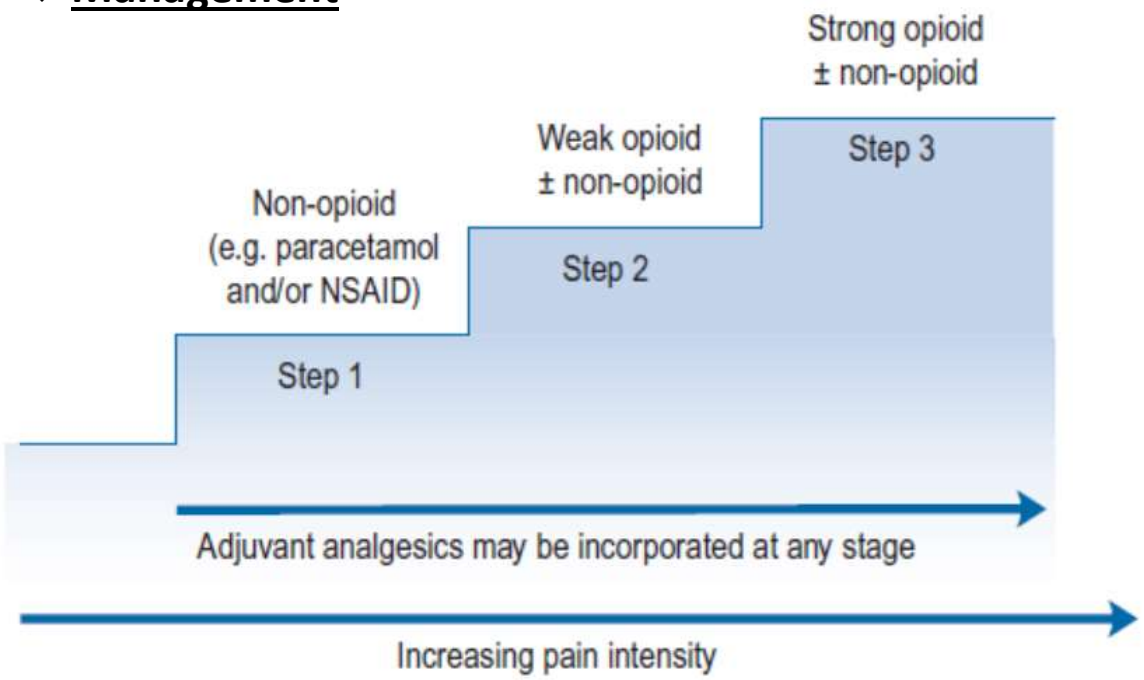

Fig. 33.2 WHO three-step analgesic ladder.

WHO analgesic ladder

-***Step 1***

•Non opioid ±adjuvant : ASA, Paracetamol, NSAIDs/COX-2s±adjuvant

-***Step 2***

•Opioid for mild to moderate pain± nonopioid ± adjuvant:Codeine, Tramadol, oxycodone, ± NSAIDs/COX – 2s± ,adjuvants

-***Step 3***

•Opioid for moderate to severe pain, ± non opioid, ± Adjuvant: Oxycodone, Morphine, Hydromorphine,Fentanyl, methadone, ± NSAIDs/COX – 2s, ± adjuvants

-***Step 4***:

•Nerve block, epidurals, PCA pump, neurolytic nerve blocks.

- **Acute pain** usually results from noxious stimulation as a result of tissue damage or injury. It can be managed effectively using analgesic drugs and is often self-limiting.

o Acute pain Treatment:

→ Most acute pain is nociceptive and responds to

■Nonopioids and opioids
■ Adjuvant analgesics (e.g. local anesthetics)

• Mild somatic pain responds well to

→ Oral non-opioids
■*Paracetamol*
■ Nonsteroidal Anti-inflammatory drugs [NSAIDs])
→ Topical agents (e.g. local anesthetics)
→ physical treatments (e.g. rest, ice, compression, elevation)

• Moderate to moderately severe acute pain is more likely to respond to

→ Opioids

- Non-opioids often combined with opioids to improve pain relief and diminish the risk of side effects.

- Pain can be modulated using non-pharmacological techniques: for example, stimulationproduced analgesia such as transcutaneous electrical nerve stimulation (TENS), acupuncture and massage, or invasive procedures such as neurosurgery or neurolytic nerve blocks.

ANALGESICS

A. Nonnarcotic analgesics include aspirin, other salicylates, acetaminophen, nonsteroidal anti-inflammatory drugs (NSAIDs), selective cyclooxygenase 2 (COX-2) inhibitors, disease-modifyinganti-rheumatic drugs (DMARDs), and tumor necrosis factor alpha(TNF-inhibitors).

Aspirin products, acetaminophen, and some low-dose NSAIDs such as ibuprofen, ketoprofen, andnaproxen sodium are available as over-the-counter (OTC) products.

2. Therapeutic effects

a. The peripherally acting, nonnarcotic analgesics have several effects in common. These effectsdistinguish these agents from narcotic analgesics.

(1) They are antipyretic.
(2) They are anti-inflammatory (except acetaminophen).
(3) There is a ceiling effect to the analgesia.
(4)They do not cause tolerance.
(5) They do not cause physical or psychological dependence.

Clinical use

- Generally, the nonnarcotic analgesics are used orally to manage mild to moderate pain.
  (1) They are particularly suited for acute pain of skeletal muscle (orthopedic) or oral (dental) origin.
  (2) They are used to treat pain and inflammation associated with osteoarthritis and rheumatoid arthritis.
  (3) They are used in chronic pain and can have an additive effect with narcotic analgesics.
  (4) They also may be effective in managing pain owing to bone metastases.
  (5) They are used for mild to moderate migraine pain.

- The NSAID ketorolac is administered intramuscularly and is useful in moderate-to-severe pain, particularly in cases in which narcotics are undesirable (e.g., with drug addicts, excessive narcotic sedation, respiratory depression).

- Patients may vary in their response and tolerance to nonnarcotic analgesics. If a patient does not respond to the maximum therapeutic dose, then an alternate NSAID should be tried. Likewise, if a patient experiences side effects with one drug, then another agent should be tried.

❖ Guidance on NSAID use

The lowest effective dose of NSAID or COX-2 selective inhibitor should be prescribed for the shortest time necessary. The need for long-term treatment should be reviewed periodically.
Prescribing should be based on the safety profiles of individual NSAIDs or COX-2 selective inhibitors, on individual patient risk profiles, for example, gastro-intestinal and cardiovascular.
Prescribers should not switch between NSAIDs without careful consideration of the overall safety profile of the products and the patient's individual risk factors, as well as the patient's preference
Concomitant aspirin, and possibly other antiplatelet drugs, greatly increases the gastro-intestinal risks of NSAIDs and severely reduces any gastro-intestinal safety advantages of COX-2 selective inhibitors. Aspirin should only be co-prescribed if absolutely necessary.

Adverse effects

a. Gastrointestinal (GI) effects. Most nonnarcotic analgesics cause GI symptoms secondary to prostaglandin inhibition. At normal doses, acetaminophen produce minimal GI upset. Because of their mechanism of action, the COX-2 inhibitors have a GI toxicity similar to placebo. Adalimumab, etanercept, infliximab, and leflunomide have been associated with GI side effects including nausea, abdominal pain, dyspepsia, constipation, vomiting, hematochezia, intestinal perforation, pancreatitis, peritonitis, peptic ulcer, and diarrhea.

(1) The most common GI symptom is dyspepsia, but ulceration, bleeding, or perforation can occur.

(2) Patients most predisposed to severe GI effects include the elderly, patients with a history of ulcers or chronic disease, and those who smoke or use alcohol.

(3) To minimize GI effects, the lowest possible analgesic dose should be used. Aspirin, available as enteric-coated products, may minimize GI upset. Combination therapy with a GI "protectant" (e.g., antacid, H2-antagonist, sucralfate, misoprostol) may be needed.

b. Hematological effects.

Most nonnarcotic analgesics inhibit platelet aggregation. The effect is produced by reversible inhibition of prostaglandin synthetase. Aspirin is an irreversible inhibitor.

Acetaminophen and choline magnesium trisalicylate lack antiplatelet effects.

TNF-_ inhibitors have been associated with anemia, aplastic anemia, leukopenia, neutropenia, pancytopenia, and thrombocytopenia. Leflunomide has been associated with anemia and ecchymosis.

(1) The effect of the NSAIDs correlates to the presence of an efective serum concentration.

(2) Use of anticoagulants (e.g., heparin, warfarin [Coumadin]) is relatively contraindicated in combination with aspirin or NSAIDs.

c. Renal effects.

NSAIDs can produce renal dysfunction. Etanercept has not been shown to affect renal function.

(1) The mechanism of NSAID-induced renal dysfunction includes prostaglandin inhibition, interstitial nephritis, impaired renin secretion, and enhanced tubular water/sodium reabsorption.

(2) Many risk factors have been implicated, including congestive heart failure (CHF), chronic renal failure (CRF), cirrhosis, dehydration, diuretic use, and atherosclerotic disease in elderly patients.

(3) Renal dysfunction is commonly manifested as abrupt onset oliguria with sodium/water retention. The effect reverses after discontinuation of the NSAID.

d. Malignancies and lymphoproliferative disorders. Agents that block TNF-_ may affect host defenses against malignancies because TNF-_ mediates inflammation and modulates cellular immune response. Lymphomas have occurred more frequently in patients receiving TNF-_-blocking agents than in controls.

e. Infections. Opportunistic and serious infections leading to sepsis and death have been associated with leflunomide and the TNF-_-blocking agents.

Drug interactions. Salicylates have two clinically significant drug interactions.

a. Oral anticoagulants. Aspirin should be carefully monitored, if used, in anticoagulated patients because it inhibits platelet function and can cause gastric mucosal damage. This can significantly increase the risk of bleeding in anticoagulated patients. Also, doses of more than3 g/day of aspirin produces hypoprothrombinemia. Choline magnesium trisalicylate or acetaminophen can be used if a nonnarcotic is needed in an anticoagulated patient.

b. Methotrexate. Salicylates may enhance the toxicity of methotrexate. The primary mechanism is blockage of methotrexate renal tubular secretion by salicylates. The resultant methotrexate toxicity has been reported as pancytopenia or hepatotoxicity. Salicylates should be avoided in patients receiving methotrexate.

c. TNF-_-blocking agents. Anakinra (Kineret), a recombinant interleukin-1 (IL-1) receptor antagonist, has been observed to cause an increased risk of serious infections as neutropenia when used concomitantly with etanercept in patients with rheumatoid arthritis. Consequently, its use is not recommended concomitantly with any TNF-_-blocking agent.

❖ Narcotic analgesics

Include the opioid drugs. Because of their abuse potential, opioids are classified as controlled drugs. Special regulations control their prescribing.

2. Clinical use

a. Opioid analgesics are used for the management of moderate-to-severe pain (acute or chronic pain) of somatic or visceral origin.

b. The use of narcotics should be individualized for each patient. The optimal analgesic dose varies from patient to patient. Each analgesic regimen should be titrated by increasing the dose up to the appearance

of limiting adverse effects. Changing to another analgesic should occur only after an adequate therapeutic trial.

c. The appropriate route of administration should be selected for each patient.

(1) Oral administration is the preferred route, particularly for patients with chronic, stable pain. Controlled-release morphine and oxycodone tablets are available for convenience in controlling continuous pain, particularly in those patients with cancer.

(2) Intramuscular and subcutaneous administration are very commonly used in the postoperative period. Fluctuations in absorption may occur, particularly in elderly or cachectic patients.

(3) Intravenous (IV) bolus administration has the most rapid, predictable onset of effect.

(4) IV infusion is used to titrate pain relief rapidly, particularly in patients with unstable chronic pain. Morphine is most commonly used, often with supplemental IV bolus doses for breakthrough pain.

- ❖ **Adverse effects of opioids**

The adverse effects of opioids are nearly all dose related, andtolerance develops to the majority with long-term use.

- ✓ **Respiratory depression**

Respiratory depression is potentially dangerous in patientswith impaired respiratory function, but tolerance develops rapidly with regular dosing. It can be reversed by naloxone.

- ✓ **Sedation**

Sedation is usually mild and self-limiting. Smaller doses, givenmore frequently, may counteract the problem. Rarely, dexamfetamineor methylphenidate has been used to counteract thiseffect.

- ✓ **Nausea and vomiting**

Antiemetics should be co-prescribed routinely with opioidsfor the first 10 days. Choice of antiemetic will depend uponthe cause, and a single drug will be sufficient in two-thirds ofpatients. Where nausea is persistent, additional causes shouldbe sought and prescribing reviewed. If another antiemetic is used, it should have a different mode of action.

- ✓ **Constipation**

Opioids reduce intestinal secretions and peristalsis, causing a dry stool and constipation. Unlike other adverse effects constipation tends not to

improve with long-term use, and when opioids are used on a long-term basis most patients need a stool softener (e.g. docusate sodium) and a stimulant laxative (e.g. senna) regularly. Dosage should be titrated to give a comfortable stool. High-fiber diets and bulking agents do not work very well in preventing constipation in patients on opioids.

- ✓ **Tolerance, dependence and addiction**

Persistent treatment with opioids often causes tolerance to the analgesic effect, although the mechanism remains unclear (Holden et al., 2005). When this occurs the dosage should be increased or, alternatively, another opioid can be substituted, since cross-tolerance is not usually complete. Addiction is very rare when opioids are prescribed for pain relief.

- ✓ **Smooth muscle spasm**

Opioids cause spasm of the sphincter of Oddi in the biliary tract and may cause biliary colic, as well as urinary sphincter spasm and urinary retention. Thus, in biliary or renal colic, it may be preferable to use another drug without these effects.

Pethidine was believed to be the most effective in these circumstances but the evidence for this has been questioned (Thompson, 2001).

Opioid use in cancer pain

Morphine is the first-line opioid used for the management of cancer pain and may be given in immediate or modified release oral formulations. If not tolerated, alternatives such as oxycodone or hydromorphone, both having relatively long half-lives, may be considered. Optimal dosage is determined on an individual basis for each patient by titration against the pain.

Notes for opioids*:*

- ✓ **Opioid- naïve:** Patient previously not on opioid or who have been receiving opioid for less than 7 days.
- ✓ **Renal failure:** All the opioids except fentanyl produce metabolites, which can accumulate. Dosing interval should be increased by approximately 50%.
- ✓ **Liver failure:** Most opioid may have decreased clearance, however no specific dose adjustment can be recommended.

- ❖ **Combination Analgesics**

Combinations of opioids and non-opioids often result inenhanced analgesia and lower dose of each. Combinationanalgesics are frequently used in moderate pain. However, insevere pain, the non-opioid component reaches maximumdosage, and thus, the usefulness of non-

opioids in this situationis limited. Additionally, the combination products areshort-acting and often not suitable for chronic therapy.
Single agents offer greater dosing flexibility than combinationproducts.

Diabetic peripheral polyneuropathy.
Nerve damage and neuropathy is one of the long-term complications of diabetes mellitus and is most prevalent in elderly patients with type II diabetes. Often patients describe numbness but also experience a burning sensation on their feet. The sensory loss can result in painless foot ulcers. Tricyclic antidepressants or serotonin noradrenaline reuptake inhibitors (duloxetine or venlafaxine), and anti-epileptics, such as gabapentin and pregabalin, have been demonstrated to be beneficial.
Nonpharmacological pain management.

- Emotional support as part of routine holistic palliative care;
- Physical therapies e.g. heat and massage for muscle spasm, physiotherapy inputfor maintenance of function and splinting;
- Occupational therapy input for lifestyle adaptation;Activities of daily living/ work modifications
- Meditation and visualization;
- TENS (transcutaneous nerve stimulator); or
- Acupuncture.

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