CHRONIC PAIN

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LECTURE IN DEPT OF PHYSIOTHERAPY
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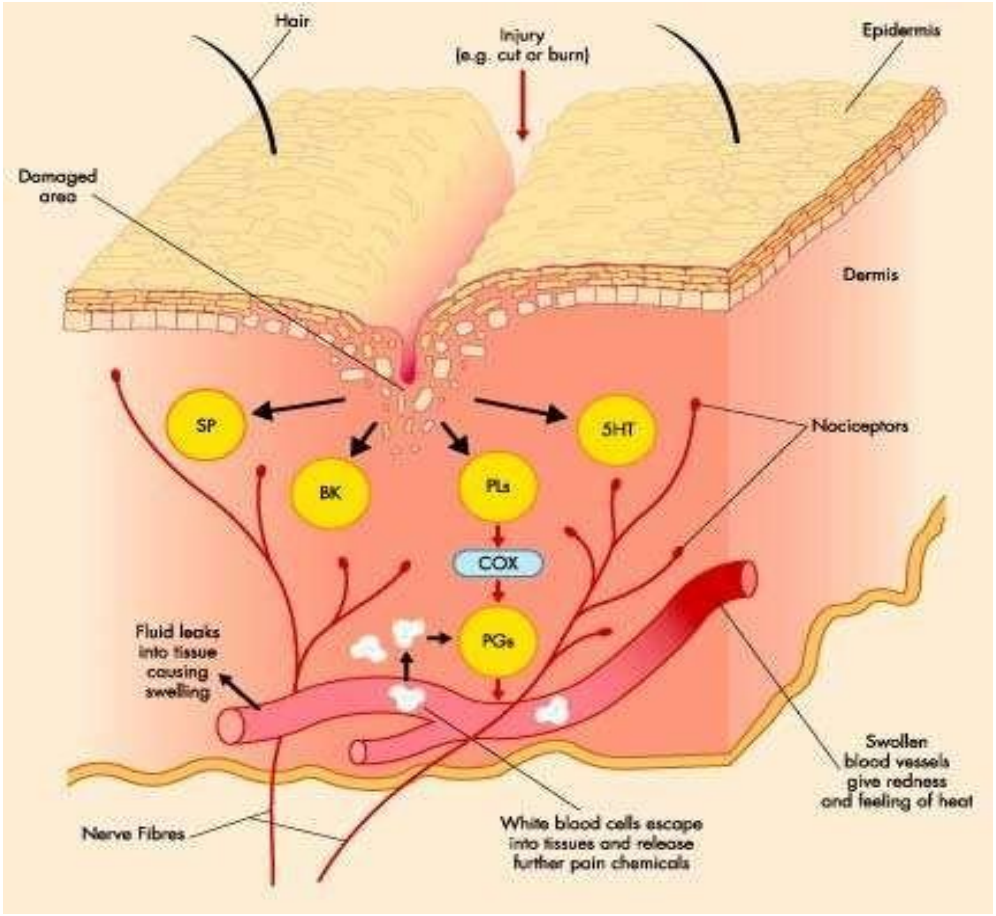
What causes pain?

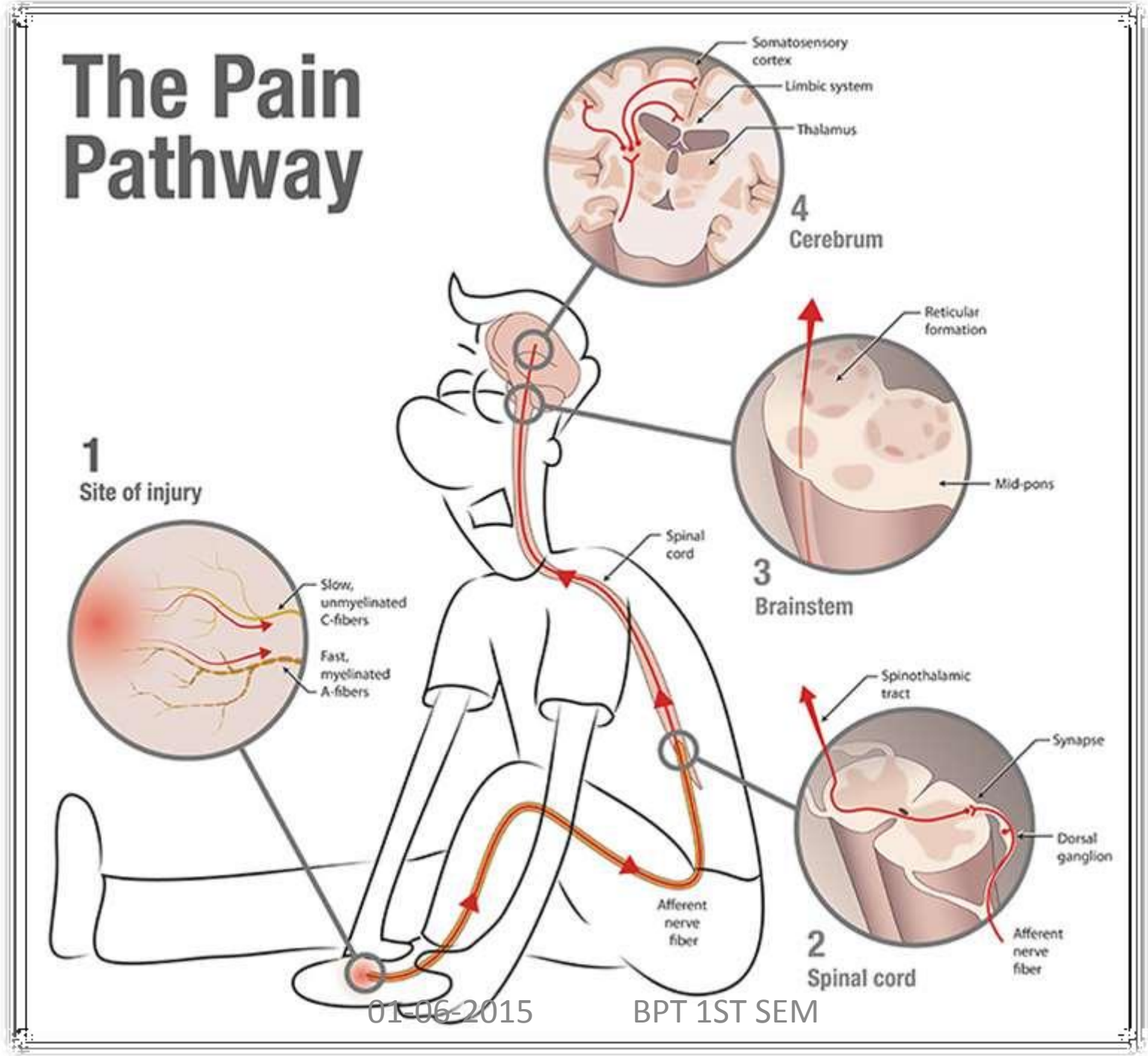


- Trauma/ injury initiates immediate nerve impulses to brain

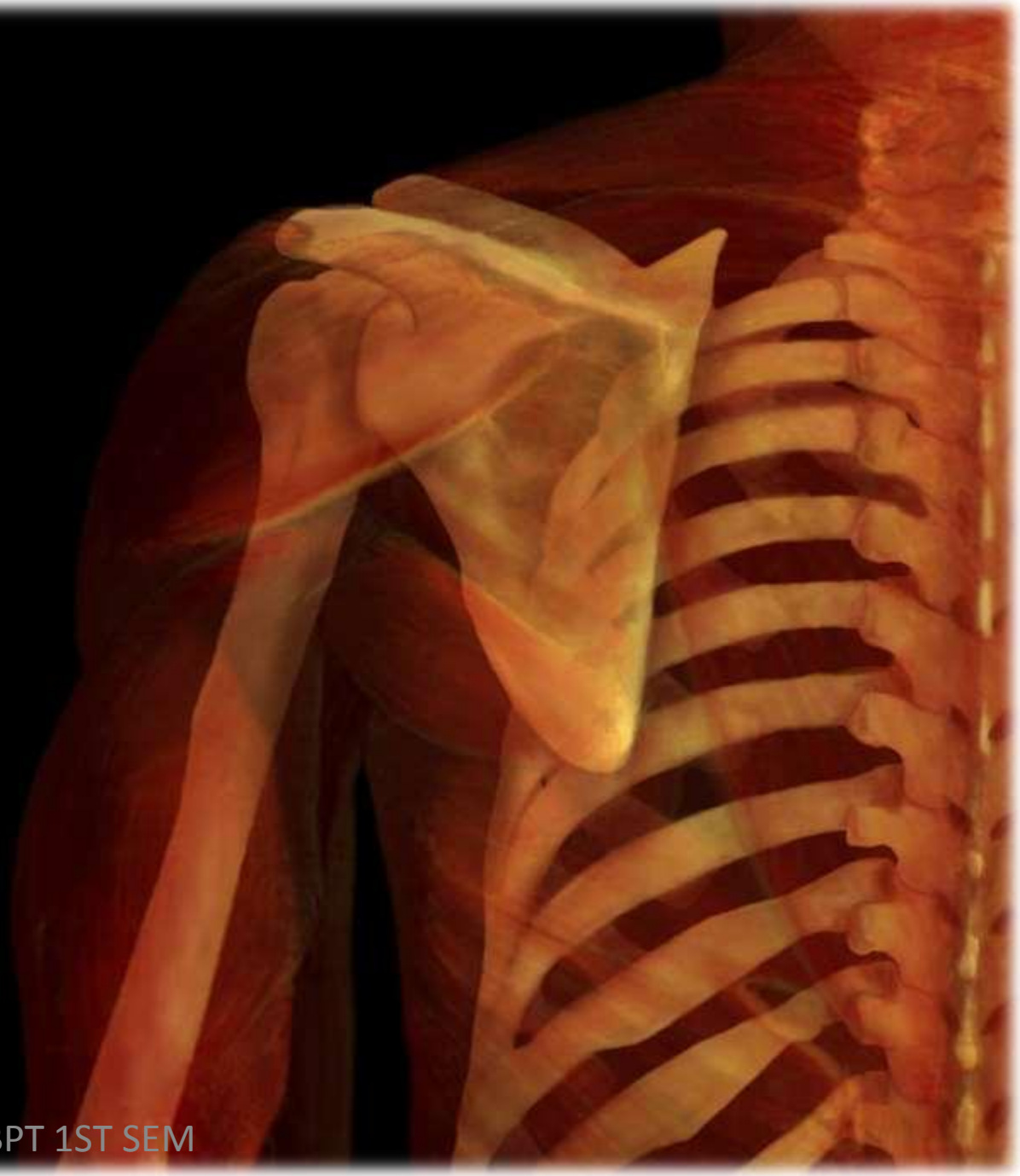
- Injury to cells result in chemical release
  - H^+
  - K^+
  - Substance P
  - Bradykinin
  - 5HT
  - Phospholipids ⇒Prostaglandins

- Blood vessels leak resulting in inflammation

- Stimulate C-fibres (slow response)


The Pain Pathway
Somatosensory cortex
Limbic system
Thalamus
4
Cerebrum
Reticular formation
Mid-pons
3
Brainstem
1
Site of injury
Spinal cord
Slow, unmyelinated C-fibers
Fast, myelinated A-fibers
Spinothalamic tract
Synapse
Dorsal ganglion
Afferent nerve fiber
Afferent nerve fiber
2
Spinal cord

What is Acute & Chronic Pain



Definitions

❖ International Association for Study of Pain Defines pain as

"An unpleasant sensory and emotional experience associated with actual or potential tissue damage and modified by individual Memory, Expectations and Emotions."

- Pain is whatever the experiencing person says it is.
- Highly subjective.
- The definition avoids tying pain to a stimulus.

❖ Nociception:

- Neural process of encoding noxious stimuli.
- It is not synonymous with pain.

❖ Chronic pain:

- Defined by ASA as “Extending in duration beyond the expected temporal boundary of tissue injury and normal healing, and adversely affecting the function or well being of the individual”
- The IASP sub committee in 1986 defined it as “Pain without apparent biological value that has **persisted beyond the normal tissue healing time** (usually taken to be as three months), and despite the usual customary efforts to diagnose and treat the original condition and injury.”
- The integration of signals from excitatory and inhibitory neurotransmitters with cognitive, emotional, and environmental factors eventually results in the central perception of pain. When the intricate balance of these factors becomes disturbed, chronic pain develops.

- **Allodynia**: Painless stimuli that are experienced as pain eg. clothing, light touch.
- **Dysesthesias**: Unpleasant perception of sensory stimuli to skin
- **Hyperalgesia**: An amplified response to a noxious stimulus
- **Hyperesthesia**: Delayed and explosive response to noxious stimulus applied to affected area.
- **Maldynia**: Maladaptive pain that persists in the absence of ongoing tissue damage or injury.
- **Neuralgia**: Pain in distribution of nerve or nerves.
- **Neuropathy**: A disturbance of function or pathological change in a nerve;
  - On one nerve - mononeuropathy;
  - In several nerves - mononeuropathy multiplex;
  - If diffuse and bilateral - polyneuropathy.
- **Paraesthesia**: Spontaneous pins and needle sensation.
- **Phantom limb**: Pain from a specific site that no longer exists (eg. amputated limb)

Acute Chronic Pain are Different

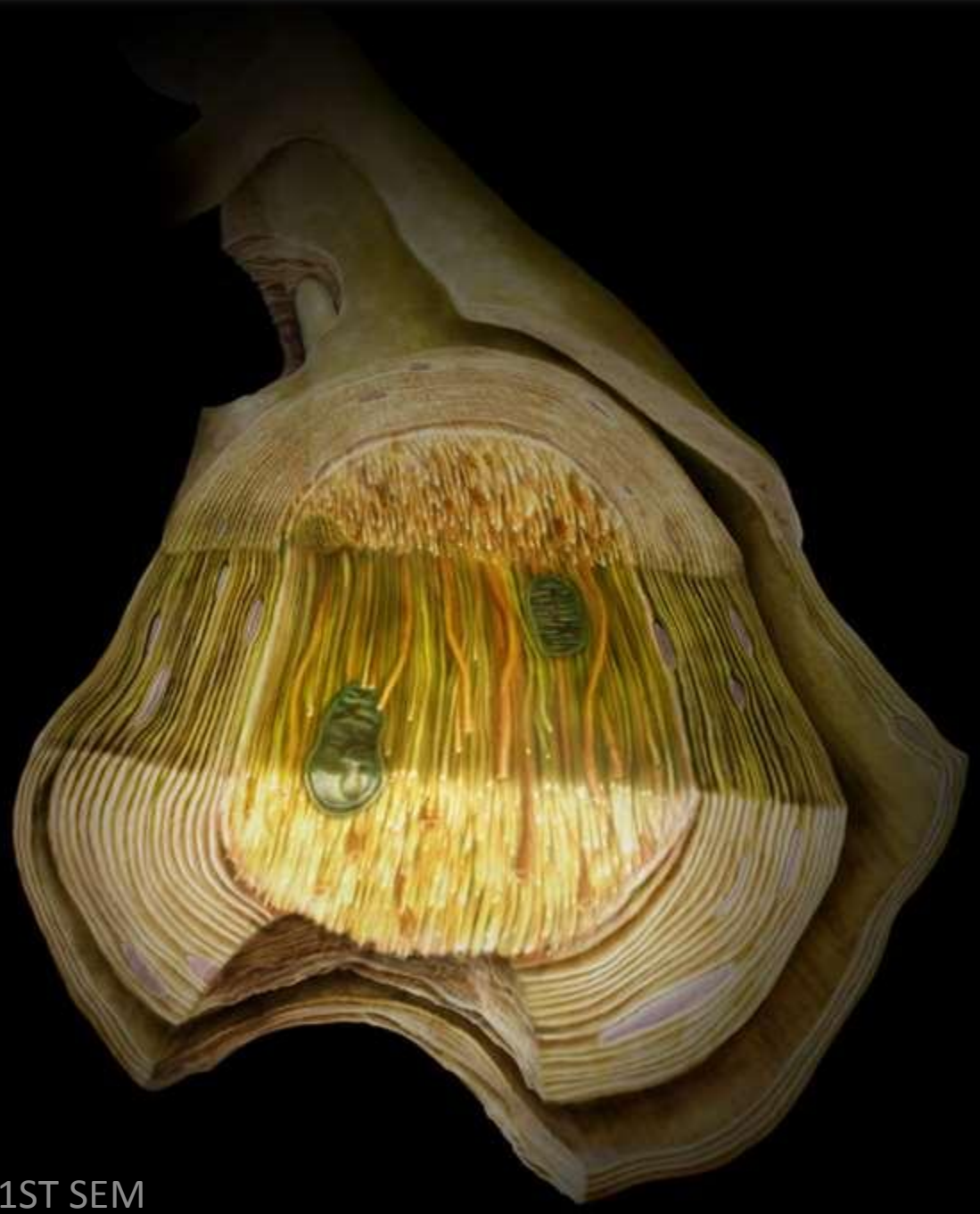
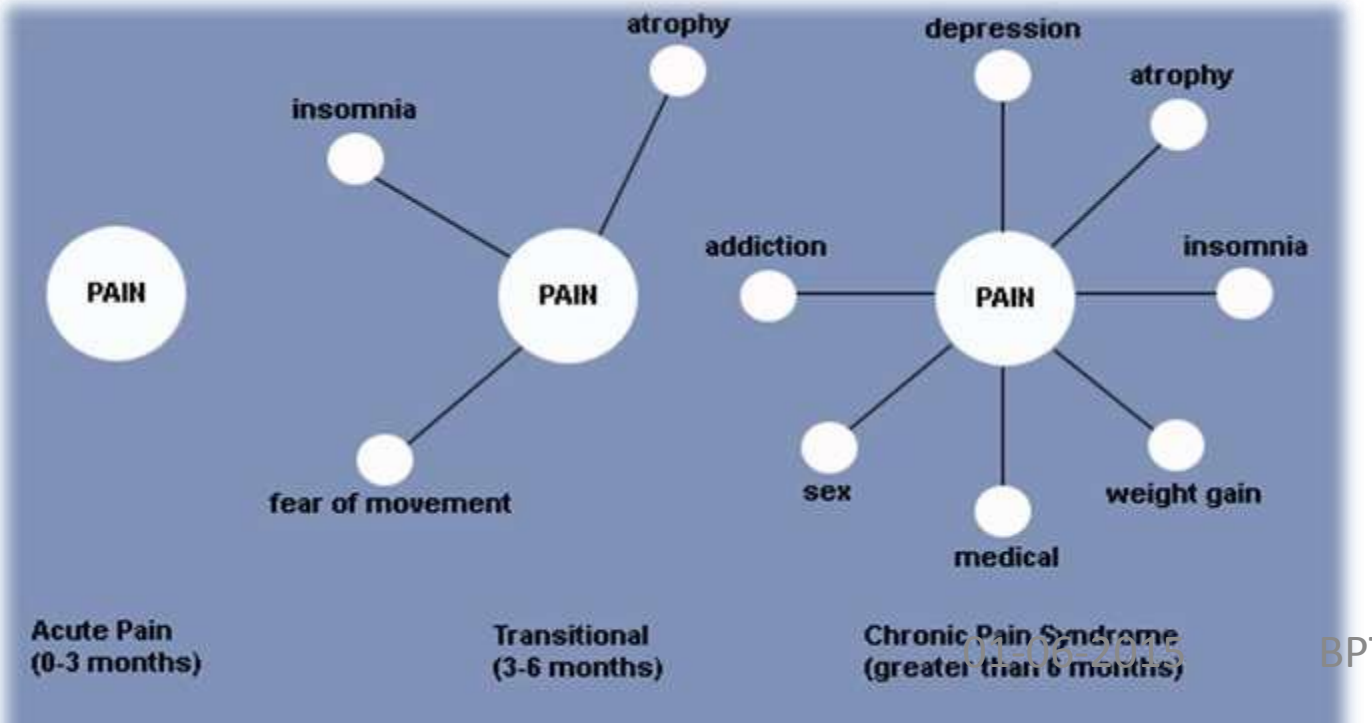


Table 1. Characteristics of Acute vs. Chronic Pain

Characteristic	Acute Pain	Chronic Noncancer Pain	Chronic Malignant Pain
Duration	Hours to weeks	Months to years	Unpredictable
Pathology	Present	Little or none	Usually present
Causes	Surgery, trauma, medical procedures	Arthritis, back pain, headache, AIDS, congestive heart failure, multiple sclerosis	Cancer or cancer treatments
Prognosis	Predictable	Unpredictable	Increasing pain with the possibility of disfigurement or death
Complicating issues	Uncommon	Depression, anxiety, and financial issues	Usually profound; includes loss of control and issues of confronting one's mortality
Nerve conduction	Rapid	Slow	Slow
Treatment	Primarily analgesics	Multimodal	Multimodal

Source: Reference 5.



Description	Acute	Chronic
Cause	Normal response to injury or medical condition	Often unknown or unrelated to medical findings
	Signal of tissue damage or underlying medical condition	Pain is often not a signal of harm
Duration	Short term	Lasts longer than three months
	Pain reduces as body heals	Pain often continues even after healing
Treatment	Often responds to traditional medical treatment	Minimal or no response to traditional medical treatment
Quality of life	Does not affect long-term quality of life	Often interferes with quality of life including sleep, work, recreational activities
	May or may not affect mood	Often accompanied by depression, anger and frustration

Major Categories of Pain

Category	Cause	Symptom	Examples
Physiological	Brief exposure to a noxious stimulus	Rapid, yet brief pain perception	Touching a pin or hot object
Nociceptive/inflammatory	Somatic or visceral tissue injury with mediators impacting on intact nervous tissue	Moderate to severe pain, described as crushing or stabbing; usually worsens after the first 24 hours	Surgical pain, traumatic pain, sickle cell crisis
Neuropathic	Damage or dysfunction of peripheral nerves or CNS	Severe lancinating, burning or electrical shock-like pain	Neuropathy, chronic regional pain syndrome, postherpetic neuralgia
Mixed	Combined somatic and nervous tissue injury	Combinations of symptoms; soft tissue pain plus radicular pain	Low back pain, back surgery pain

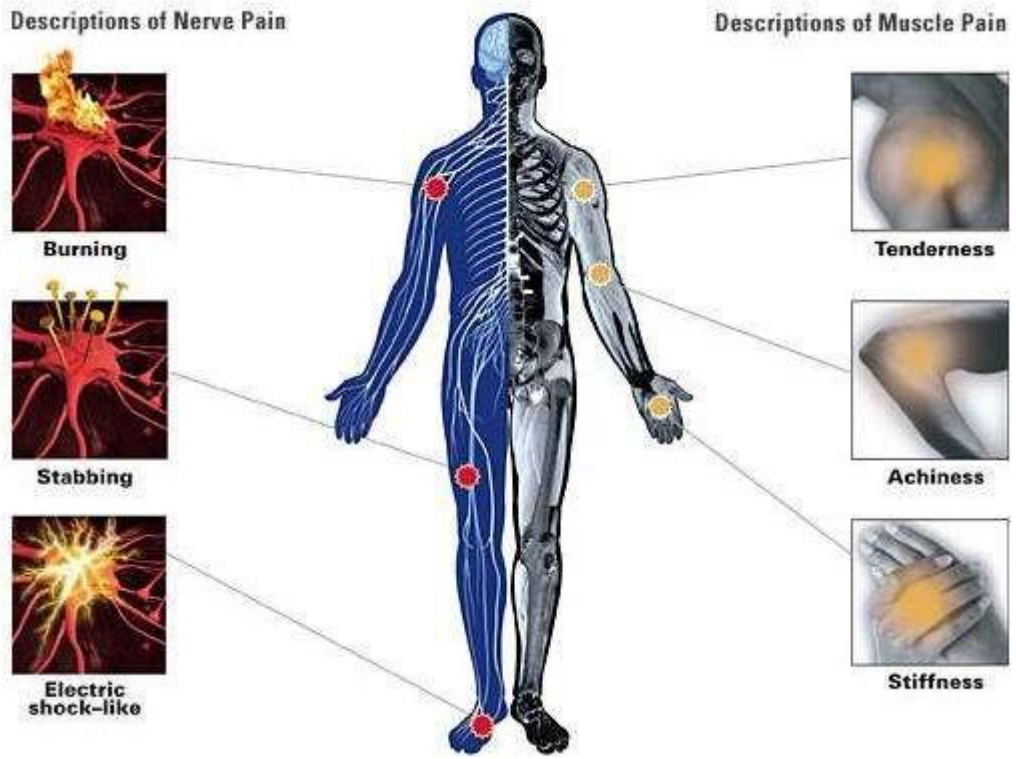
Table 1. Chronic Pain Disorders

Neuropathic Pain	Mixed Pain	Nociceptive Pain
• Peripheral neuropathies (diabetes, HIV)	• Migraine and chronic daily headache	• Mechanical low back pain
• Postherpetic neuralgia	• Fibromyalgia	• Rheumatoid arthritis
• Trigeminal neuralgia	• Phantom limb pain	• Osteoarthritis
• Central post-stroke pain	• Complex regional pain syndrome	• Chronic inflammatory conditions
• Spinal cord injury	• Multiple sclerosis	• Somatoform pain disorder
• Neuropathic low back pain	• Low back pain	• Postoperative pain
	• Myofascial pain syndrome	• Sickle cell crisis
	• Skeletal muscle pain	• Sports/exercise injury

Nociceptive Pain

- **Visceral Pain**: Associated with internal organs.
  - Nature: Crampy, pressure, deep, dull to sharp, diffuse, referred.

- **Somatic pain** : Soft tissues/ myalgic.
  - Nature: Dull to sharp, throbbing, achy, localized



Neuropathic Pain

- Abnormal neural processing by the peripheral or central nervous system
- Signals are amplified or distorted; Synapse receptor numbers are altered; pathways not originally involved become involved
- <u>Patient Description of Neuropathic Pain:</u>
  - Burning, electric, searing, tingling, and migrating or traveling.

Physiological effects of Pain

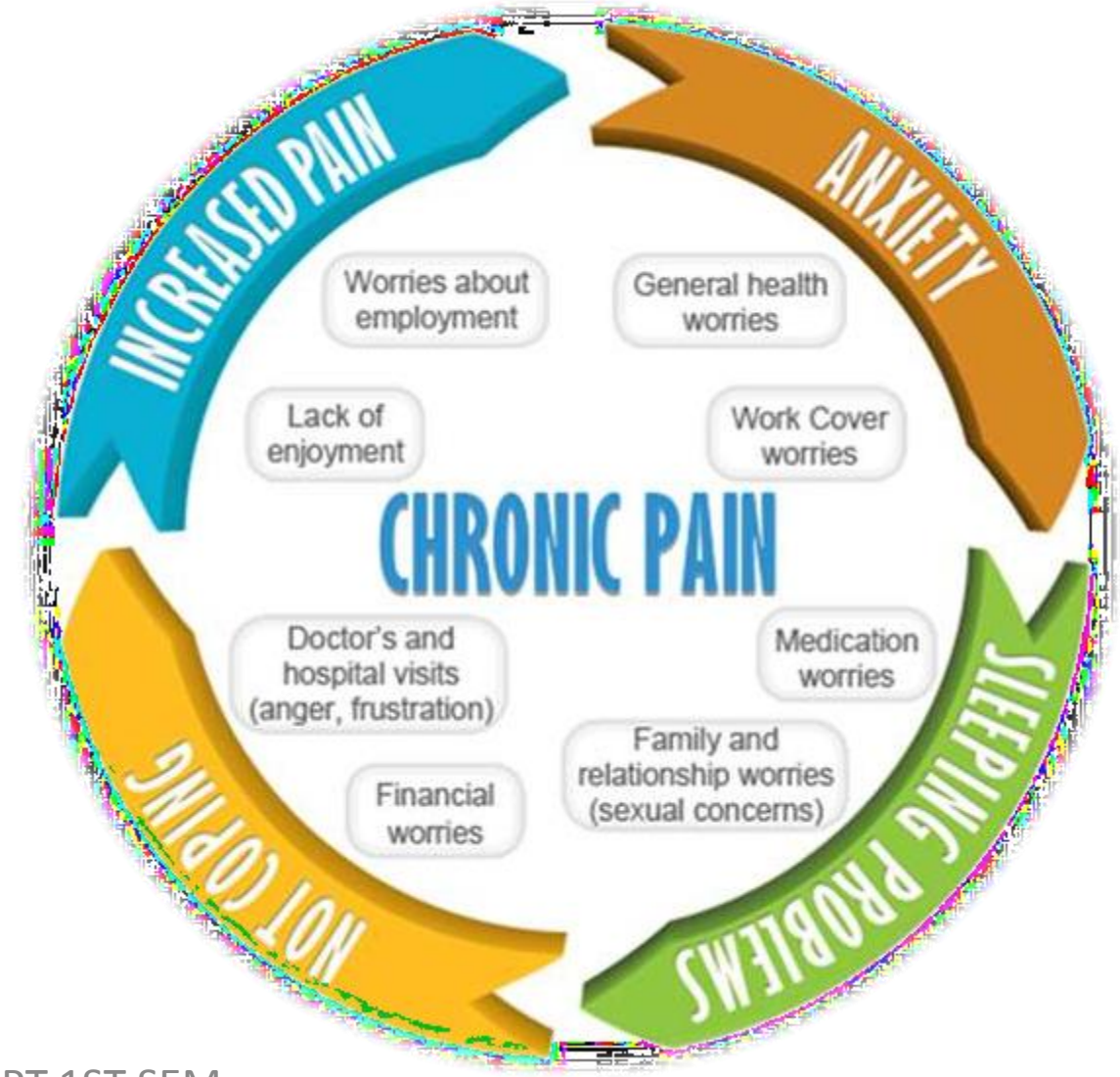
- Increased **catabolic demands**: poor wound healing, weakness, muscle breakdown.
- Decreased limb movement: increased risk of **DVT/PE**
- Shallow breathing, tachypnea, cough suppression with high risk of **pneumonia** & **atelectasis**.
- Increased sodium and water retention (renal)
- Decreased gastrointestinal mobility.
- Tachycardia and elevated blood pressure
- **Negative emotions**: anxiety, depression, Sleep deprivation
- Existential **suffering**: may lead to patients seeking active end of life.

Immunological effects of Pain

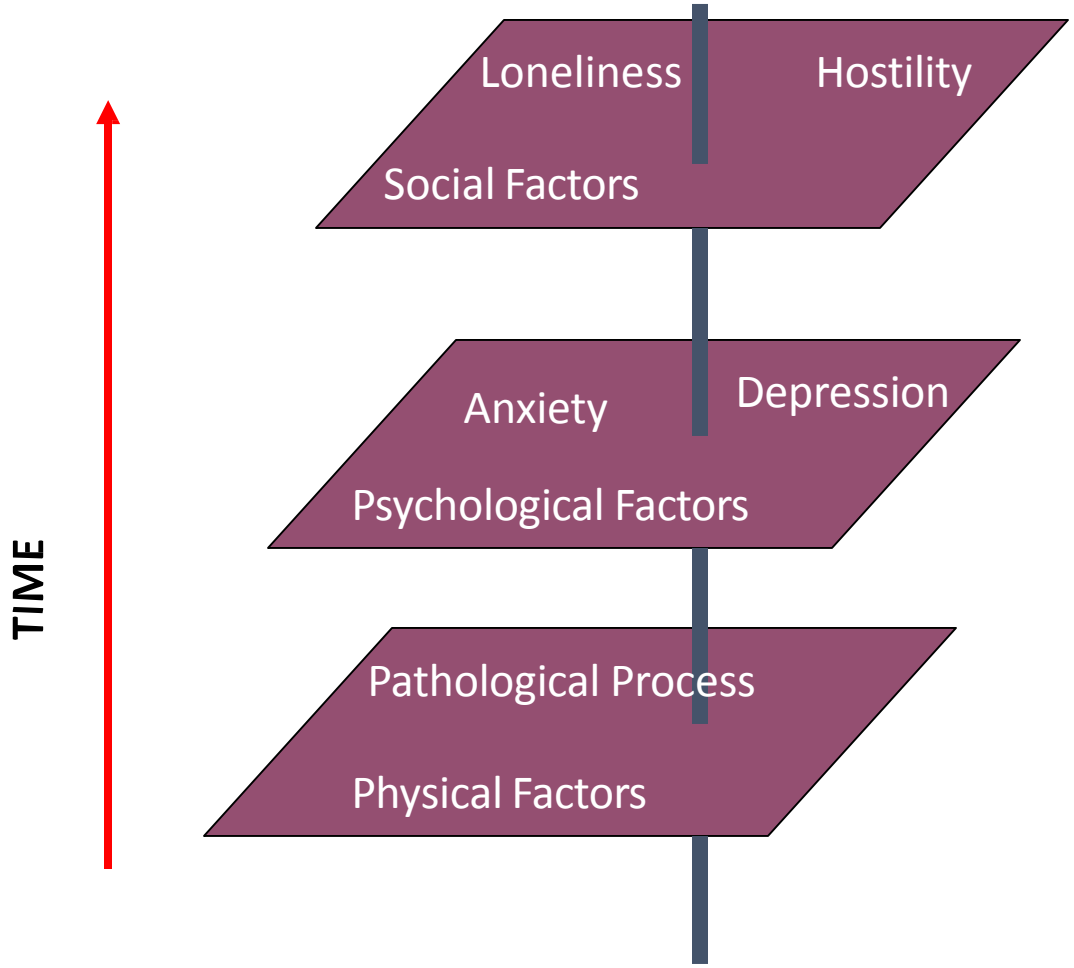
- Decrease natural killer cell counts
- Effects on other lymphocytes(not yet defined).

Biopsychosocial concept of Chronic Pain

- The interplay between biologic, psychological and social factors result in persistence of pain.
- Treating only one aspect of this complex syndrome is insufficient. Therefore a **Biopsychosocial concept** of chronic pain has been adopted.



Dimensions of Chronic Pain



CHRONIC PAIN IS…

MULTI-FACTORIAL

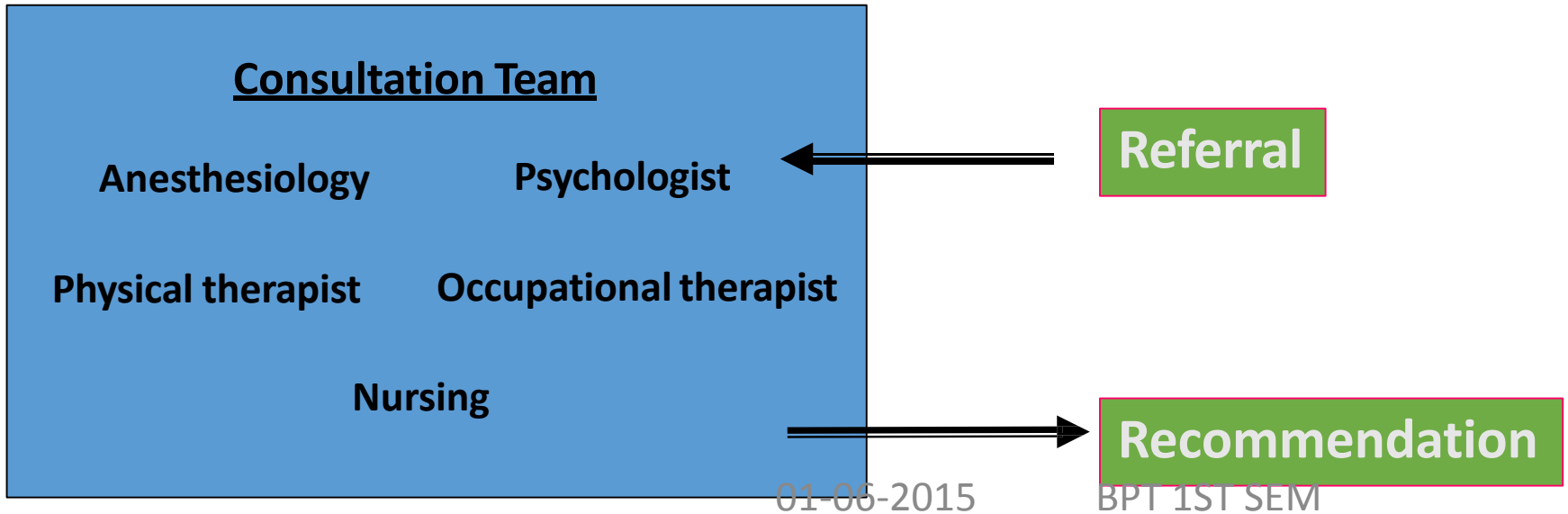
- Psychological factors – depression, anxiety, somatization
- Socioeconomic factors – cultural differences, urban poor, gender
- Spiritual factors – spiritual suffering, meaning of pain
- Physical factors – VERY complex neuroanatomy creating the pain sensation, from pain receptors to afferent nerves to spino-thalamic tract, to thalamus to cortex with modulators all along the way

❖ Therefore best approach is **Multi-disciplinary**.

Pain Consultation Team

- Multidisciplinary group

- It results in increased physical and psychosocial function, reduced health care use and vocational rehabilitation.
- A meta-analysis found such programs offer the most efficacious and cost effective, evidence based treatment of chronic non malignant pain.



EVALUATION OF CHRONIC PAIN

GOALS:

- Determine **Etiology** to better treat this pain
- Determine if correctable, intractable, or potentially dangerous causes
- Determine impact on patient's life
- Take a detailed pain history to aid in controlling this pain

PAIN HISTORY

O Other associated symptoms (nausea with stomach cramps, swelling with somatic pain, depression, anxiety…)

P. Palliative/provocative factors (mobility, touching, eating…)

Q. Quality

R. Region/radiation

S.Severity (0 to 10) T

Timing (when started, continuous/ intermittent, time of day…)

U Untoward effects on activity or quality of life, including psychosocial, spiritual effects.

EVALUATION OF CHRONIC PAIN…

MEDICAL EVALUATION:

- Location, onset.
- Quality, radiation.
- Response to previous treatments.
- H/O past, personal, social, economic, psychological and emotional status.
- Plain radiographs, CT, MRI, bone scans.

PSYCHOLOGICAL EVALUATION:

1. Clinical interview.
2. A structured pain inventory
    a. Mc Gill pain questionnaire.
    b. Psychosocial pain inventory.
    c. Westhaven - Yale multidimensional pain inventory.
    d. Pain profile.

EVALUATION OF CHRONIC PAIN…

- Psychometric testing:

a. Minnesota Multiphasic Pain Inventory(MMPI)

b. Symptom check list-90.

c. Million behavioral pain inventory.

d. The beck depression inventory.

e. The spielberger state-trait anxiety scale.

Electromyography and Nerve conduction studies:

- Useful for confirming diagnosis of entrapment syndromes, neural trauma and poly-neuropathies, radicular syndromes.
- Can **distinguish** between neurogenic and myogenic disorders.

MEASUREMENT OF PAIN

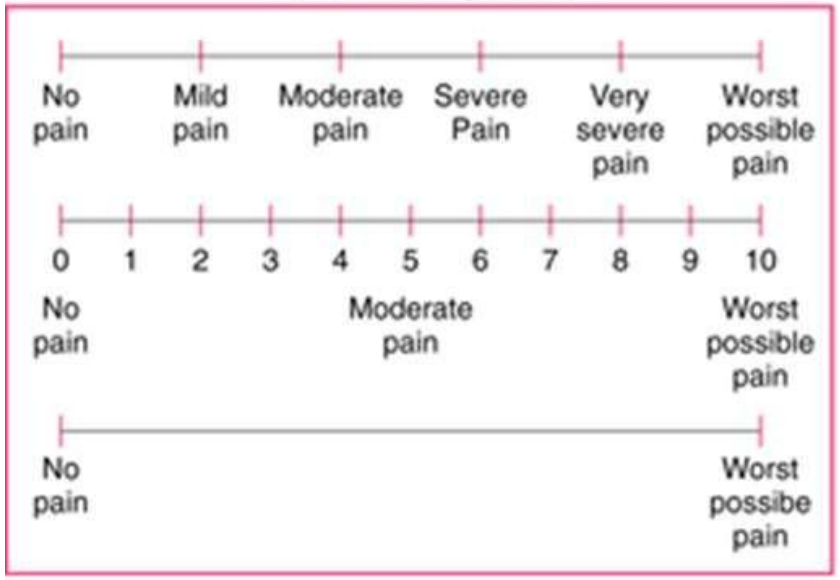
- Reliable quantitation of pain severity helps determine therapeutic interventions and evaluate the efficacy of treatments.
- PAIN SCALES:

- Numerical rating scale.
- Faces rating scale
- Visual analog scale.
- McGill pain questionnaire.

Can pain-intensity scales be used ?

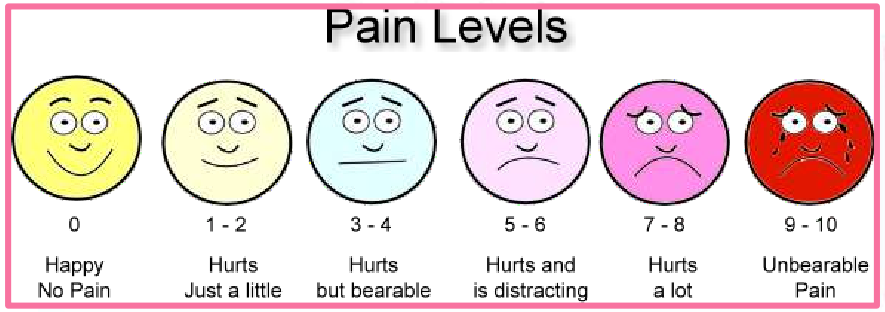
- Yes- but, limited by cognitive changes, impaired vision, physical limitation
- No specific scale more “user friendly”

Visual Analog Scale



Word Descriptor Scale

0 = No pain
1 = Mild pain
2 = Distressing pain
3 = Severe pain
4 = Horrible pain
5 = Excruciating pain



Verbal Scale

“On a scale of 0 to 10, with 0 meaning no pain and 10 meaning the worst pain you can imagine, how much pain are you having now?”

Functional Pain Scale

0 = No pain
1 = Tolerable and pain does not prevent any activities
2 = Tolerable and pain prevents some activities
3 = Intolerable and pain does not prevent use of telephone, TV viewing, or reading.
4 = Intolerable and pain prevents use of telephone, TV viewing, or reading.
5 = Intolerable and pain prevents verbal communication


Pain relief

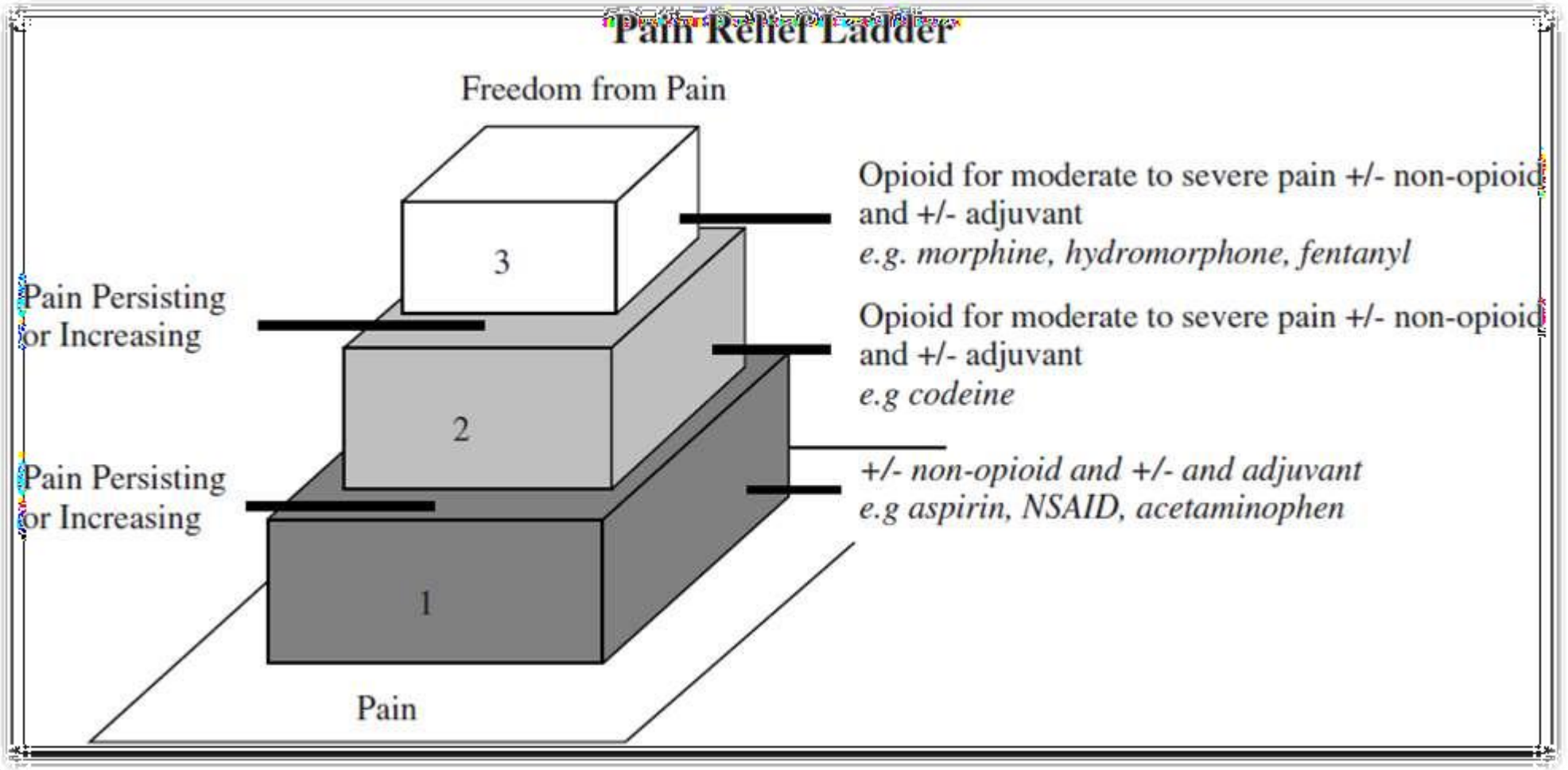
Chronic Pain Management Goals

- Improvements in **nociception**, **not** curing.
- There is **no magic bullet**, no single cure
- Decrease pain and suffering
- **Rehabilitation**: Reconditioning & Prevention
- **Coping**: Management of Residual Pain

Step Ladder Approach

"Divine is the task to relieve pain."
-Hippocrates

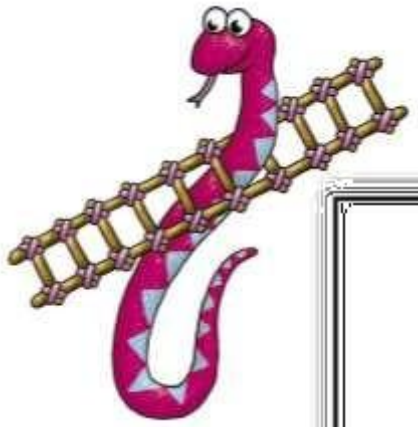
- The World Health Organization (WHO) in 1986 developed a stepwise approach to analgesic dosing. The WHO three-step "ladder" correlated analgesic selection and dosing in relation to the intensity of the pain complaint
- The WHO "pain ladder" was initially created for treating **cancer pain** but is now commonly used as a paradigm for treating all types of pain.
- While simplistic in nature, it was considered to be a successful therapeutic advance as it provided an **organized approach** to pain assessment and management on a global scale.

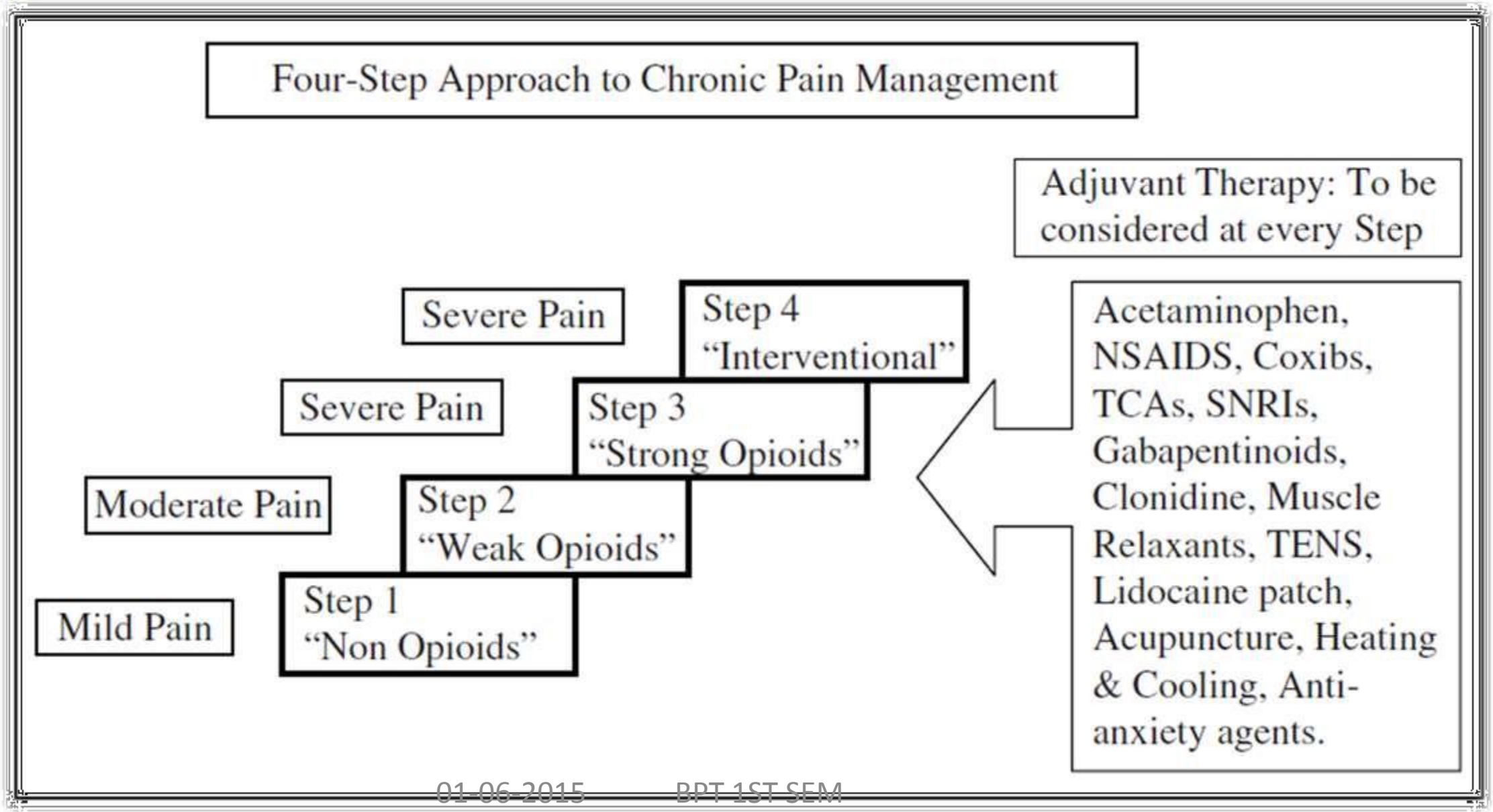


The major drawback :

- ✓ Approximately 20–25% of patients did not respond to potent opioids, and continued to suffer severe pain.
- ✓ Comorbid conditions, including obesity, sleep apnea, and chronic obstructive pulmonary disease, and mental health issues such as anxiety, depression, and posttraumatic stress, further complicate pain management and reduce caregiver comfort in prescribing opioids

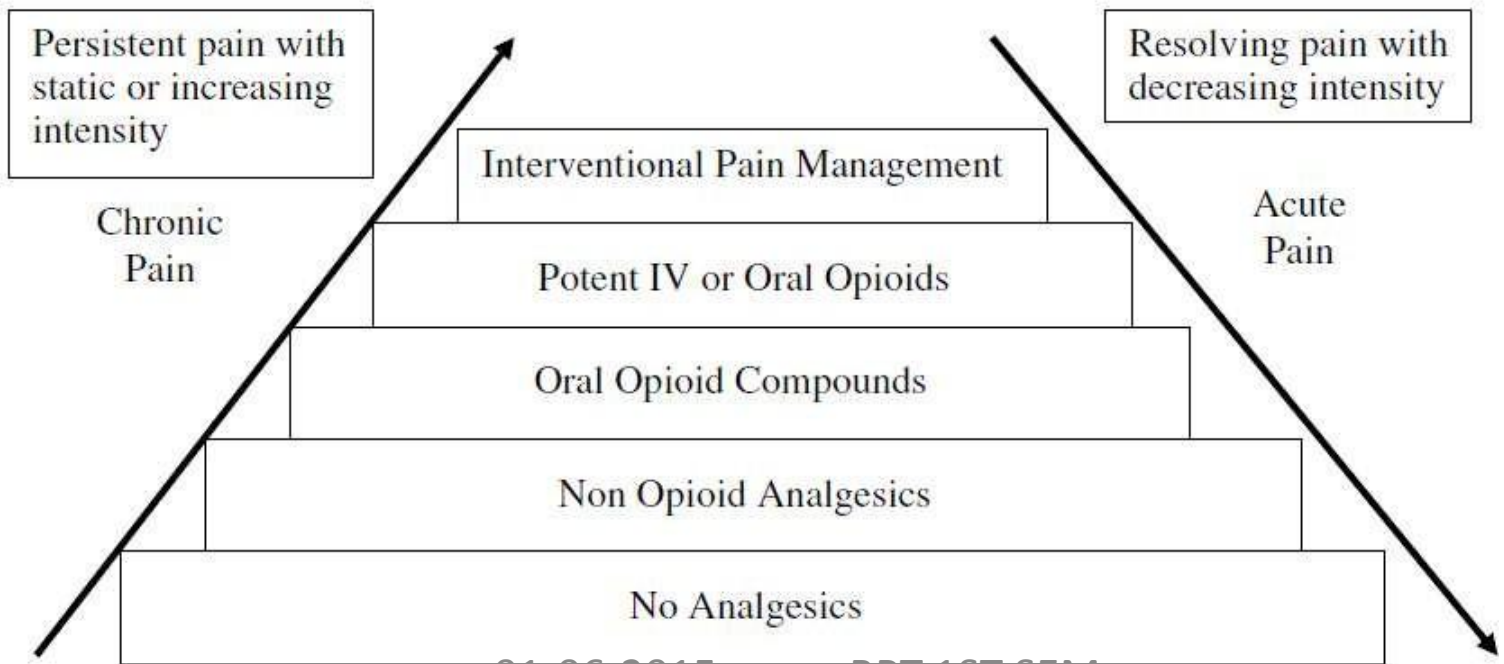
- With the advent of Anaesthesiology and multi-specialty based pain clinics and caregiver specialization in interventional pain management, a **four-step analgesic approach** was developed to more effectively treat patients with chronic pain.
- The first three steps of this care plan are similar to the WHO analgesic ladder; however, a new fourth step, termed the **interventional step**, utilizes invasive techniques that are placed and managed by pain specialists.
- Interventional therapy includes implantable analgesic pumps, peripheral and epidural stimulators, regional and neuraxial steroids, and neurolysis. Such therapy may provide measurable reductions in pain intensity and opioid sparing effects that are particularly beneficial to highly tolerant patients, the elderly, and those suffering intolerable dose-related adverse events




Four-Step Approach to Chronic Pain Management
Adjuvant Therapy: To be considered at every Step
Severe Pain
Step 4 "Interventional"
Severe Pain
Step 3 "Strong Opioids"
Moderate Pain
Step 2 "Weak Opioids"
Mild Pain
Step 1 "Non Opioids"
Acetaminophen, NSAIDS, Coxibs, TCAs, SNRIs, Gabapentinoids, Clonidine, Muscle Relaxants, TENS, Lidocaine patch, Acupuncture, Heating & Cooling, Anti-anxiety agents.

Big Difference

Acute and Chronic Pain: Temporal Differences in Intensity and Management



Moving toward a "flexible approach" to pain management

- The previously described three- and four-step ladders are widely employed for managing malignancy related and other terminal pain states; **however,** the time has come to rethink and possibly discard these traditional stepwise approaches.
- Application of flexible and more individualized treatment plans would be particularly beneficial for patients suffering benign chronic pain.
- For certain individuals, care plans that include non-opioid-based multimodal analgesia and early application of interventional pain management may be superior to progressive increases in opioid dosing.
- Instead of being considered as a "last resort", interventional pain management can be employed at an early stage of care
- Such therapy, while invasive and expensive, would be encouraged in setting where patients might benefit from improved pain relief and significant opioid-sparing effects.

A more flexible approach

A Flexible, Non stepwise Approach to Chronic Pain Management.

Opioid Supplementation for Severe to Very Severe Pain

Sustained Plus Immediate Release Potent Opioids (Morphine, oxycodone, hydrocodone, oxymorphone)

Dual Acting Analgesics (Tramadol, Tapentadol) Buprenorphine,

Opioid Supplementation for Moderate to Severe Pain

Pharmacological Pain Management

Inflammatory Pain
NSAIDs, Coxibs

Somatic Pain
Acetaminophen, Clonidine, Topical Analgesics, Muscle relaxants

Neuropathic Pain
Gabapentinoids, NE reuptake inhibitors, Lidoderm patch

Psychosocial Adjuncts
Antidepressants, Antianxiety Agents, Psychotherapy, Physical therapy, TENS Acupuncture, Chiropractic, Massage

Interventional Pain Management

Joint blocks
Epidural steroids
Facet blocks
Neurolysis
Sympathetic blockade
Ganglionic/plexus blockade
Plexus destruction
Spinal stimulators
Peripheral stimulators
Intrathecal pumps
DREZ Lesions

Patients Requiring Chronic Pain Management


CHRONIC PAIN TREATMENT CONTINUUM
LEVEL 3
PAIN THERAPIES
Spinal Cord Stimulation
Neuroablation
Surgery
Implantable Drug Pumps
LEVEL 2
PAIN THERAPIES
Thermal Procedures
Neurolysis
Systemic Opioids
Nerve Blocks
LEVEL 1
PAIN THERAPIES
Cognitive & Behavioral Modification
TENS
Rehabilitation Therapy
NSAIDS
Over-the-Counter Pain Medications
Exercise Programs
DIAGNOSIS

THERAPEUTIC MODALITIES

TCAs and SSRIs
Amitriptyline, Nortriptyline
Duloxetine

Topical Agents
Capsaicin, 5% Lidocaine Patch

Regional Nerve Blockade
Stellate ganglion block,
Lumbar sympathectomy,
Peripheral nerve block

Non Pharmacological Approaches
Behavioral modification
Cognitive Therapy
Physical Therapy
Nutritional Counseling

Anticonvulsant Agents
Pregabalin, Gabapentin, Carbamazepine

Opioids
Tramadol, Tapentadol,
Hydrocodone, Oxycodone,
Methadone

Interventional Techniques
Peripheral neural stimulation,
Spinal cord stimulation,
Neuroablation

NMDA Inhibitors
Ketamine,
Amantidine,
Memantiine

Non-Pharmacological

- Ice, heat
- Physical therapy
- Behavior Modification
- Cognitive therapy
- Nutrition Therapy
- Massage
- Acupuncture
- Yoga
- Chiropractic/osteopathic manipulations
- Topical agents (Ben Gay/Icy Hot – with menthol, salcylates, Capcaicin)
- Local injections (steroids, lidocaine)
- Glucosamine shown to help with osteoarthritis

PHARMACOLOGIC CONTROL OF PAIN

- About half of hospitalized patients who have pain are under-medicated.
- Children are at particular risk of poor pain control methods.
- Medications are given as:
  - PRN (Pro re nata) – “as needed”
  - As a prescribed schedule

Multimodal Analgesic approach

- The multimodal analgesic approach aims to reduce opioid-related adverse effects Peri-operatively.
- Multimodal analgesia combines different classes of analgesics and methods of pain management to provide superior pain relief than any one class or method alone.
- The basic principle is that using various classes of medications will simultaneously and synergistically inhibit the different pain receptor pathways.
- The combination reduces the dose of each analgesic and thereby decreases the incidence of side effects of any particular medication used.

Drug options...

- NSAIDS, COX INHIBITORS AND ACETAMINOPHEN
- OPIOIDS
- ANTI CONVULSANTS
- ANTI DEPRESSANTS
- CORTICOSTEROIDS
- LOCAL ANAESTHETICS – Systemic administration.

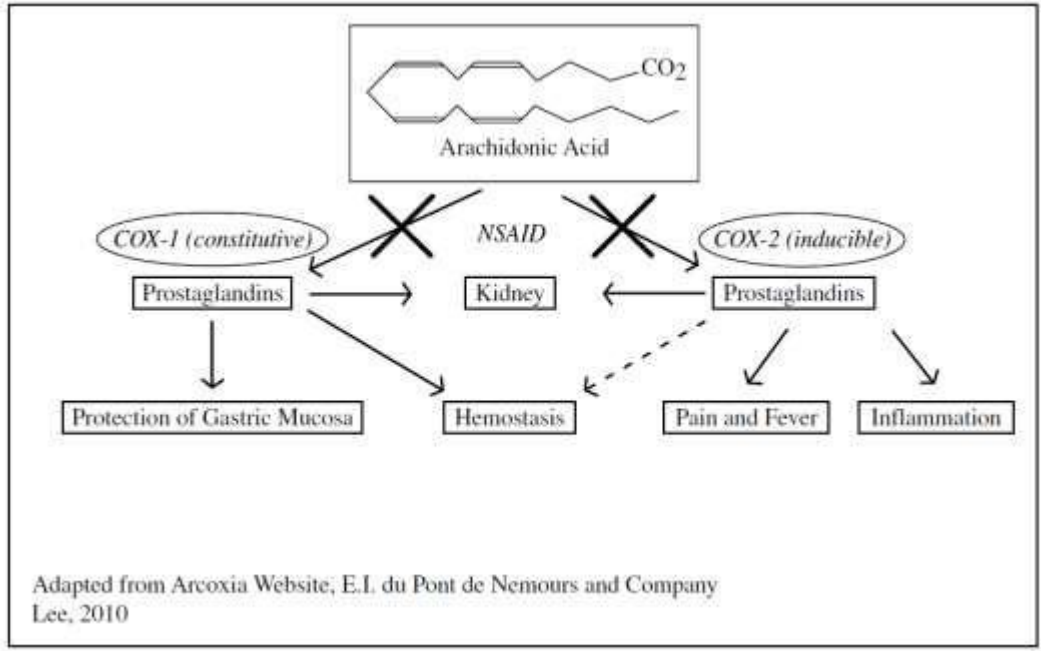
TABLE 64-1 ANALGESIC DRUGS, TARGETS, MECHANISMS, AND SIDE EFFECTS

Drugs	Targets	Mechanisms	Functional Consequences	Side Effects
Opioids	G-protein coupled μ, δ, κ receptors	↓ cAMP ↓ Ca^{2+} currents ↑ K^+ currents	↓ Excitability of peripheral and central neurons ↓ Release of excitatory neurotransmitters	μ, δ: Sedation, nausea, euphoria/reward, respiratory depression, constipation κ: Dysphoria/aversion, diuresis, sedation
NSAIDs	Cyclooxygenases (COX-1, COX-2)	↓ Prostaglandins ↓ Thromboxanes	↓ Sensitization of sensory neurons ↑ Inhibition of spinal neurons	Nonselective: gastrointestinal ulcers, perforation, bleeding, renal impairment COX-2: thrombosis, myocardial infarction, stroke
Serotonin agonists	G-protein coupled 5-HT receptors 5-HT_3: ion channels	↓ cAMP (5-HT_1) ↑ cAMP ($5\text{-HT}_{4\text{-}7}$) ↑ PLC (5-HT_2)	↓ Release of excitatory neuropeptides ↓ Neurogenic inflammation ↑ Vasoconstriction	Myocardial infarction, stroke, peripheral vascular occlusion
Antiepileptics	Na^+, Ca^{2+} channels GABA receptors	↓ Na^+ currents ↓ Ca^{2+} currents ↑ GABA receptor activity	↓ Excitability of peripheral and central neurons ↓ Release of excitatory neurotransmitters	Sedation, dizziness, cognitive impairment, ataxia, hepatotoxicity, thrombocytopenia
Antidepressants	Norepinephrine/5-HT transporters Na^+, K^+ channels	↓ Norepinephrine/5-HT reuptake ↓ Na^+ currents ↑ K^+ currents	↓ Excitability of peripheral and central neurons	Cardiac arrhythmia, myocardial infarction, sedation, nausea, dry mouth, constipation, dizziness, sleep disturbance, blurred vision

Ca^{2+}, Calcium; *cAMP*, cyclic adenosine monophosphate; *GABA*, γ-aminobutyric acid; *5-HT*, 5-hydroxytryptamine (serotonin); *K^+*, potassium; *Na^+*, sodium; *NSAIDs*, nonsteroidal antiinflammatory drugs; *PLC*, phospholipase C.

Nonselective Non-Steroidal Anti-inflammatory Drugs, COX-2 Inhibitors, And Acetaminophen

- Amongst the most commonly used Analgesics
- In the Peri-operative setting, these analgesics are gaining recognition as an important alternative and/or adjunct to the historically mostly opioid-based analgesia.
- Aside from their important role in multimodal analgesic therapy, they have also been extensively studied in Pre-emptive analgesia.



Adapted from Arcoxia Website, E.I. du Pont de Nemours and Company
Lee, 2010

NSAID (Aspirin, ibuprofen, indomethacin, diclofenac)

- 40-60% of NSAID use is by older people
- Avoid chronic use in high risk patients
- Not for use in chronic background analgesia
- Use in selected pts with good indications
  - Bone pain
  - Inflammatory pain
  - Somatic pain with poor response to other analgesics
- Be aware of S/E: impaired platelet function, Gastric ulcers, Nephrotoxicity, formation of highly reactive metabolite.
- PRESCRIBE FOR LIMITED DURATION

ACETAMINOPHEN

(Paracetamol)

- First-line agent for Headache, fever, Arthritis, back pain, etc.
- Safe alternative to NSAID's for non-inflammatory pain
- Safe given q4h to max 4000 mg/day
- Caution with liver disease or heavy Ethanol ingestion or G6PD Deficiency
- Rapid onset (20-30 mins)
- Do not EXCEED :
  - 4 gm/day > 10 days in healthy pts.
  - 3.2 gm/day for chronic use in healthy pts.
  - 2.6 gm/day for chronic use in non-healthy pts.

Efficacy of IV acetaminophen 1 g versus other IV analgesics in post-operative pain

Dose	Comparable efficacy
IV acetaminophen 1 g	Ketorolac 30 mg
	Diclofenac 100 mg
	Metamizol 2.5 g
	Morphine 10 mg

Efficacy may depend on type of surgery performed.

OPIOIDS

- Individualize route, dosage, and schedule
- Administer analgesics regularly (not PRN) if pain is present most of day
- Become familiar with dose / time course of several strong opioids
- Give infants / children adequate opioid dose
- Follow patients closely, particularly when beginning or changing analgesic regimens
- When changing to a new opioid or different route
  - Use equi-analgesic dosing table to estimate new dose
  - Modify estimate based on clinical situation

- Recognize and treat side effects
- Be aware of potential hazards of meperidine / mixed agonist-antagonists - particularly Pentazocine
- Do not use placebos to assess nature of pain
- Watch for development of:
  - Tolerance - treat appropriately
  - Physical dependence – prevent withdrawal
- Do not label a patient psychologically dependent, “addicted”, if you mean physically dependent on / tolerant to opioids
- Be alert to psychological side of patient .

CAUTIONS IN OPIOID USE

- 80% of the time dose needs to be increased because the disease is advancing; 20% because of tolerance.
- Mixed or partial agonists have a ceiling, neurotoxicity, and can induce withdrawal if on other opioids.
- Methadone – q8-24hr drug, may be better with neuropathies & addiction because inhibits the NMDA receptor in the brain, though half-life 6-100hrs so watch for accumulation.
- Meperidine – neurotoxic metabolite can build up in 1 wk; in 1 day with renal failure
- Oral, sublingual, rectal short acting meds peak within 1 hr., IV/SC peak within 10 minutes. Choose oral if they can do it.
- To taper drug, decrease by 25% a day.

OPIOID SIDE EFFECTS

- Constipation is a given, no tolerance develops, use stimulants.
- Nausea/vomiting – tolerance can occur in 2-5 days, Prochlorperazine/ metoclopramide can help.
- Sedation – tolerance can occur in 2-3 days, changing drug can help if persists.
- Clonic jerks – usually high doses; change drug or benzodiazepam can help
- Respiratory suppression in toxic doses.

PHYSICAL vs. PSYCHOLOGIC DEPENDENCE

PHYSICAL DEPENDENCE:

- Tolerance (20-40%) – up-regulate opioid receptors to need higher dose for sustained effect
- Withdrawal (20-40%) – after 2 wks, withdrawing drug leads to adrenaline response (sweating, tachycardia, tachypnea, cramps, diarrhea, hypertension); avoid by decreasing drug 25% a day.

PSYCHOLOGIC DEPENDENCE:

- Addiction (0.1% in CA pain) – a need to get "high" where drug controls your life, compulsive uncontrolled behavior to get the drug; lie, cheat, steal.

Benefits and Drawback

Benefits
1. Rapid onset of analgesia for moderate, severe and very severe pain
2. Highly effective analgesia (no analgesic dose ceiling)
3. Selective analgesia: reduction in pain suffering, minimal effects on pain localization
4. No effects on key organs: cardiac, renal, hepatic, and hemostatic safety
5. Multiple agents and routes of administration are available
6. Relatively inexpensive (morphine, oxycodone)
Drawbacks
1. Annoying adverse effects: nausea, pruritus, sedation, constipation
2. Clinically significant adverse effects: illeus, bowel obstruction, severe vomiting, confusion, dysphoria
3. Life-threatening effects: airway obstruction, respiratory depression, respiratory arrest
4. Social effects: dose escalation, physical dependence, diversion and abuse, addiction
5. May be expensive (sustained-release opioids, oral buccal preparations)

Opioid Dosing regimen

Drug	Equianalgesic Potency*		Comments
	Oral	Parenteral	
Morphine	30 mg	10 mg	Long-acting forms may be given orally every 8 to 12 hours. Some long-acting dosage forms may be given rectally. Metabolites may cause myoclonus in patients with renal failure.
Hydromorphone	7.5 mg	1.5 mg	Potent opioid. Good agent for patients with renal dysfunction.
Oxycodone	20 mg	–	Long-acting form may be given orally/rectally every 8 to 12 hours.
Methadone	5 mg	**	Half-life > 24 hrs, so dosing adjustments should be made cautiously. Given every 6 to 8 hrs for pain management. May have role in management of neuropathic pain. Equi-alanalgesic ratios change with oral morphine doses > 100 mg/day – consult a specialist. Some N-methyl-D-asparatate (NMDA) antagonist activity. For the experienced practitioner only. Pharmakenetics are highly variable and there is non-dose related cardiotoxicity. ECG monitoring is recommended prior to initiation of methadone, at 30 days, and annually due to the possibility of QTc interval prolongation and other cardiac dysrythmias.
Levorphanol	4 mg	2 mg	Potent opioid with some NMDA antagonist activity.
Meperidine	300 mg	75 mg	Metabolized to normeperidine, a CNS stimulant, which may cause seizures in patients with renal failure.
Fentanyl***	–	100 mcg	Available as transdermal patch (see conversion below) and buccal products.
Codeine	200 mg	130 mg	5-10% of Caucasians lack the enzyme to metabolize codeine to morphine. May cause more nausea and constipation than other opioids. Profound narcosis has occurred in chronic renal failure patients.
Hydrocodone	30 mg	–	Often combined with non-opioid analgesics, which limits the total dose per day.
Oxymorphone	10 mg	1 mg	Oral administration with food or alcohol may result in excessive sedation.
Nalbuphine	–	10 mg	May precipitate withdrawal in opioid-dependent patients.
Butorphanol	–	2 mg	Available as nasal spray.
Pentazocine	50 mg	30 mg	Mixed agonist/antagonist. May precipitate withdrawal in opioid-dependent patients.
Buprenorphine	–	0.4 mg	Mixed agonist/antagonist. May precipitate withdrawal in opioid-dependent patients.
Tapentadol	No equianalgesic dosing recommendations		Synthetic opioid with some inhibition of norepinephrine reuptake. Only extended-release formulation is FDA approved for chronic pain.

ANTI-CONVULSANTS

- Used most commonly in **neuropathic pain** resulting from lesion to peripheral (diabetes, herpes) or central nervous system (Stroke).
- **M/A**: Sodium channel and calcium channel blockade, Glutamate release reduction and action on NMDA/AMPA receptors, Peripheral fibroblast and anti inflammatory activity.
- Various Drugs and uses:
  - **Gabapentin**- Post-herpetic neuralgia (PHN), Partial seizures, and also Reduce chronic post-operative neuropathic pain, Phantom pain, Complex regional pain syndrome (CRPS), cancer pain.
  - **Pregabalin**- Diabetic peripheral neuropathy, PHN and Fibromyalgia
  - **Carbamazepine**- Epilepsy, Trigeminal neuralgia, Glossopharyngeal neuralgia, Diabetic neuropathy.
  - **Lamotrigine**- Diabetic neuropathy and Trigeminal neuralgia
- **S/E**: Impairment in mental status(MC) and motor function, Hepatotoxicity, thrombocytopenia, dermatological and haematological reactions.

ANTI- DEPRESSENTS

- Used in treatment of Neuropathic pain, Headache and other conditions.
- Action due to blockade of Presynaptic reuptake of serotonin, norepinephrine or both.
- Serious side effects , include **Arrhythmias** due to block of cardiac ion channels by TCA. It also blocks histamine, cholinergic and adrenergic receptor sites leading to Sedation, Nausea, Dry mouth, Constipation, dizziness, confusion, sleep disturbance and urinary retention .
- Ex. Amitriptyline, imipramine, duloxetine, Desipramine, Nortriptyline, Clomipramine, Doxepine, Fluoxetine, Paroxetine.
- Antidepressants are frequently co-administered with Anti-epileptics.

Serotonergic Drugs

- Serotonin (5-hydroxytryptamine [5-HT]) is a monoamine NT found in sympathetic nervous system.
- Triptans **inhibit neurogenic inflammation** through 5-HT_{1D} receptors on trigeminal afferents. The activation of vascular 5-HT_{1B} receptors constricts meningeal (and coronary) vessels.
- Triptans can be applied orally, subcutaneously, or transnasally, and these drugs have been used in the treatment of migraine.
- All triptans narrow coronary arteries through 5-HT1B receptors by up to 20% at clinical doses and should not be administered to patients with risk factors for coronary, cerebrovascular, or peripheral vascular disease. Some triptans have the potential for significant drug-drug interactions.
- Rational use of triptans should be restricted to patients with disability associated with migraine

Corticosteroids

- Glucocorticoids are extensively used in pain management for their anti inflammatory and possibly analgesic actions.
- Can be given topically, orally, parenterally.

Table 96.1. Clinical effects of glucocorticoid actions

Anti-inflammatory
Anti-edema
Analgesia
Antiemesis
Antipyretic
Euphoria
Increased alertness
Increased energy
Restlessness
Increased appetite

Topical Analgesic

- Topical NSAIDs
- Topical Tricyclic (doxepin)
- Capsaicin
- Topical formulation of Local Anaesthetics
- Topical applied or injected Opioids

Other Analgesics and Adjuvants

- Mexiletine
- α_{2-} Agonists like clonidine reduce NT release and decrease postsynaptic transmission.
- Cannabinoids
- Benzodiazepines
- Baclofen – a $GABA_B$ receptor agonist
- Botulinum toxin – inhibits Ach release at NMJ.
- Ziconotide- blocks N-type voltage sensitive Ca^{2+} channel.

Role of Invasive Procedures

- Optimal pharmacologic management can achieve adequate pain control in 80-85% of patients
  - The need for more invasive modalities should be infrequent
  - When indicated, results may be gratifying
- Intractable pain*
- Intractable side effects*

**Symptoms that persists despite carefully individualized patient management*

Interventional pain management

When systemic or topical pharmacotherapy and other non-invasive approaches provide inadequate relief in patients with Neuropathic Pain, interventional approaches may be used, including sympathetic blockade with local anesthetics, intraspinal drug delivery, spinal cord stimulation, peripheral subcutaneous nerve stimulation, or stimulation of specific central nervous system structures, and various neuroablative procedures (e.g. dorsal rhizotomy, neurolytic nerve block, intracranial lesioning). Neuroablative procedures are not reversible and should be reserved for carefully and properly selected patients with intractable pain.

- Nerve blocks
- Transcutaneous electrical stimulation (TENS) for chronic pain
- Spinal cord stimulation

Nerve Block

- The interruption, interference, or blockade of painful stimuli has been used in the management of pain for several decades.
- Acute, chronic, and post-operative pain can be diminished with various types of regional anaesthesia or specific nerve blocks. In the setting of chronic pain management, various peripheral nerve blocks can be diagnostic, prognostic, or therapeutic in nature.
- Nerve blocks are generally most useful when a specific nerve or limb is affected. Neural blockade may help differentiate a peripheral source of pain from a neuroma or entrapped nerve root, identify sources of referred pain, or assist in distinguishing somatic from visceral pain.
- Sympathetic ganglion blocks are widely employed for diagnostic and therapeutic purposes: e.g. diagnosis of sympathetically maintained pain; neuropathic pain, including phantom limb pain; complex regional pain syndrome; and ischemic pain.
- Controlled evidence supports the use of neurolytic blocks in patients with low back pain, head, neck and shoulder pain, fibromyalgia, complex regional pain syndrome, and cancer pain

Transcutaneous electrical stimulation (TENS)

- TENS is used in a variety of clinical settings to treat a range of acute and chronic pain conditions and has become popular with patients and healthcare professionals of different disciplines.
- By applying peripheral stimuli, in the case of TENS, electrical stimulation directly over the area of pain, sensory information from larger-diameter (non-pain-carrying) afferents is activated, and affects the processing of pain impulses within the dorsal horn of the spinal cord.
- TENS is generally believed to be a safe and relatively **non-invasive intervention** that can be used to alleviate many different types of pain, including neuropathic pain (primarily diabetic peripheral neuropathy).

Spinal cord stimulation

- Also called dorsal coloumn stimulation.
- Produces analgesia by directly stimulating large A beta fibers in dorsal coloumns of the spinal cord.
- **Mechanism** – activation of descending modulating systems and inhibition of sympathetic outflow.
- **Indications**:
  - Sympathetically mediated pain
  - Spinal cord lesions
  - Phantom limb pain
  - Failed back surgery syndrome.
- Technique:
  - Electrodes placed epidurally and connected to an external generator.
  - Complications: infection, lead migration, lead breakage.

Diagnosis	Evidence-Based	Also Used
Neuropathic pain	1st line: TCAs[9] 2nd line: Anticonvulsants[9] gabapentin + GABA antagonist, lioresal (Baclofen)[11]	
Dysesthetic and paroxysmal lancinating pain		Anticonvulsants[11]
CRPS (complex regional pain syndrome); formerly reflex sympathetic dystrophy		Steroids (prednisone)[12] antidepressants[12] anticonvulsants[12] calcitonin[12] opiods[12]
DPN (diabetic peripheral neuropathy)	FDA approved: duloxetine (Cymbalta), pregabalin (Lyrica)[13]	TCAs, especially amitriptyline[7]
PHN (post herpetic neuropathy)	FDA approved: pregabalin (Lyrica), gabapentin (Neurontin)[13]	Capsaicin cream[14] TCAs – amitriptyline[14] Clonidine[14]
Trigeminal neuralgia	FDA approved: carbamazepine (Tegretol)[13]	Dilantin[14,15]
Glossopharngeal neuralgia	FDA approved: carbamazepine (Tegretol)[11]	Baclofen[10]
RLS (restless leg syndrome)	FDA approved: ropinirole (Requip), pramipexole (Mirapex)[13]	Carbamazepine (Tegretol)[9] clonidine (Catapress)[14]
Primary fibromyalgia syndrome	FDA approved: pregabalin (Lyrica)[13]	Capsaicin[14] antiinflammatories[3] antidepressants[15]
Phantom limb pain		TCAs – amitriptyline[14]
Lumbar discogenic pain		NSAIDs[15] antidepressants[15] anticonvulsants[15]
Migraine prophylaxis	FDA approved: topiramate (Topamax) propranolol (Inderal) timolol (Blocadren) divalproex (Depakote)[13]	TCAs –amitriptyline[14] Gabapentin (Neurontin)[14] valproic acid (Depakene)[14] phenytoin (Dilantin)[16]

- **Neuropathic pain**
  - Disease-specific measures
    - Tighter glucose control in diabetes
    - Use of disease-modifying agents in MS
    - Surgery, chemotherapy, or radiation therapy for nerve decompression
    - Infection control (e.g., in HIV infection, herpes zoster, Lyme disease)
  - Symptom management
    - Local or regional treatment
      - Topical agents
        - Capsaicin
        - Lidocaine patches
        - Anesthetic creams
      - Regional anesthetics
        - Sympathetic blocks
        - Epidural/ intrathecal blocks
        - Selective nerve root blocks
        - Epidural/ intrathecal pumps
      - Stimulation-based therapy
        - TENS
        - Acupuncture
        - Spinal cord stimulation
        - Massage
      - Physical rehabilitation measures
        - Splinting
        - Manipulation
        - Assistive devices
        - Range-of-motion exercises
        - Ergonomic methods
      - Ablative procedures
        - Phenol/alcohol nerve ablation
        - Cordotomy/ rhizotomy
        - Radiofrequency nerve root ablations
    - Systemic treatment
      - Drug therapy
        - Anticonvulsants
        - Tricyclic anti depressants SNRIs
        - Corticosteroids
        - Opioids
      - Behavioral therapy
        - Biofeedback
        - Hypnosis
        - Guided imagery
        - Other relaxation techniques
        - Cognitive-behavioral therapy

Lastly…

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YEAR
AGAINST
NEUROPATHIC
PAIN

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Thank You