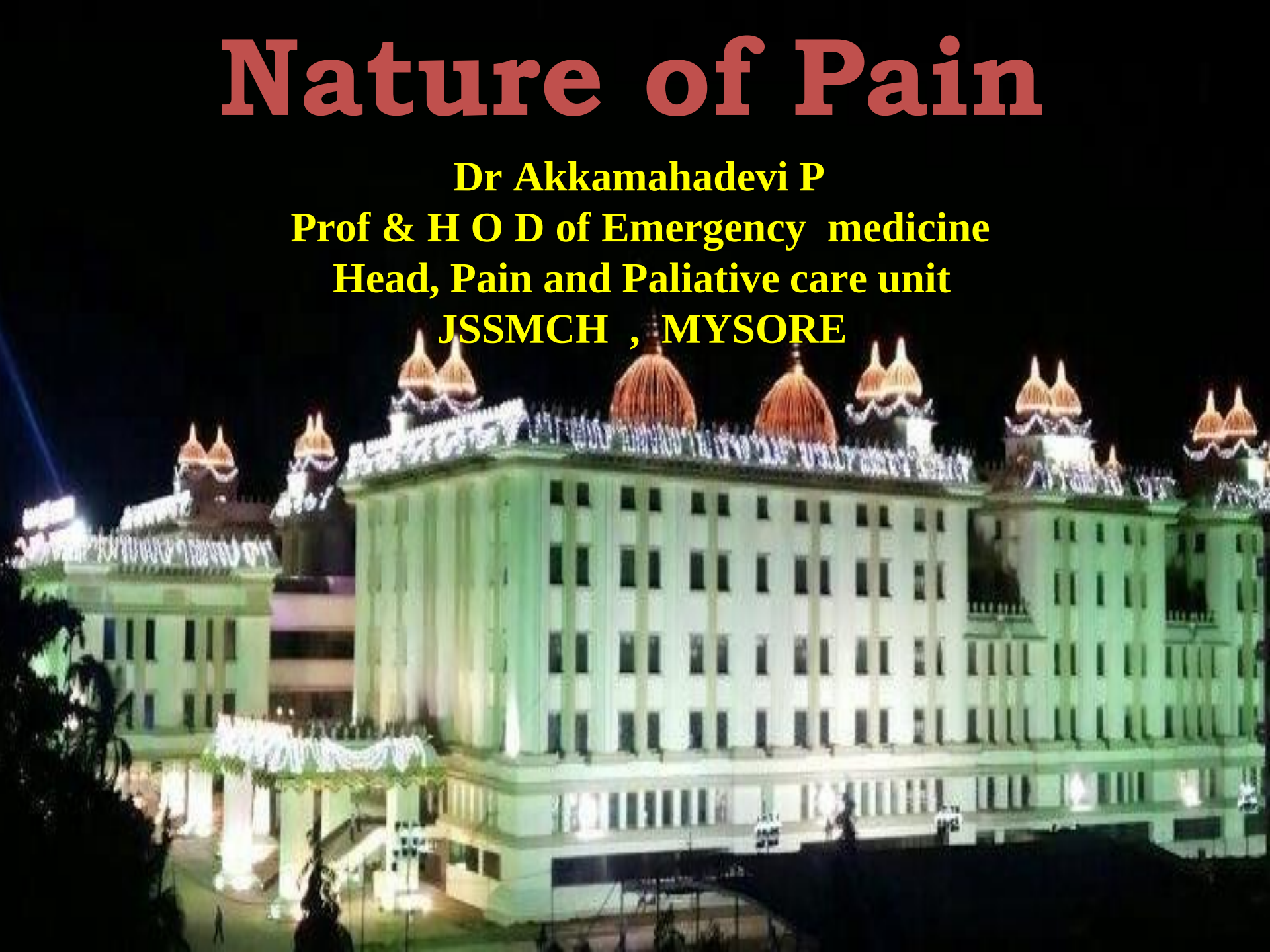
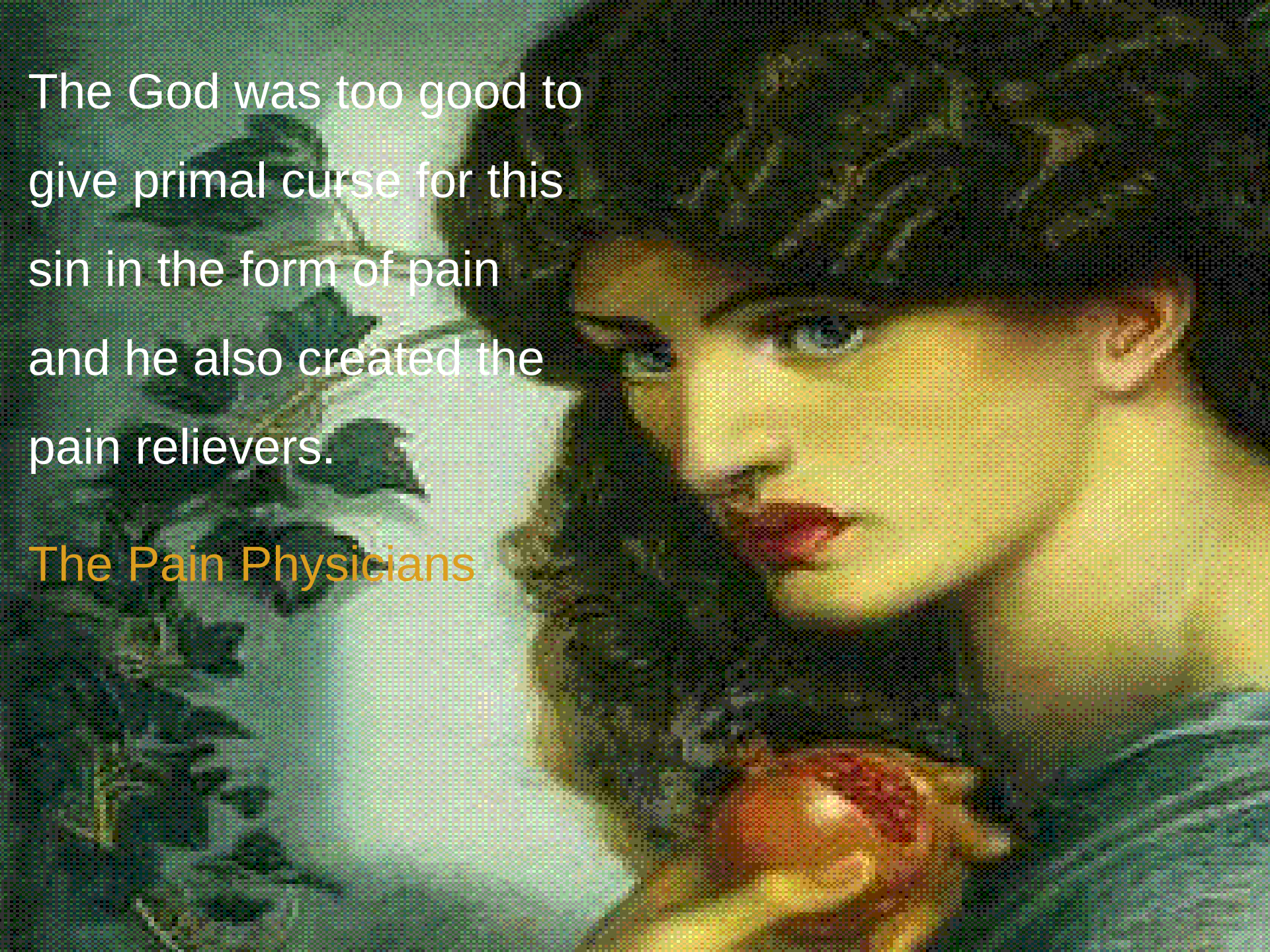
Nature of Pain

Dr Akkamahadevi P
Prof & H O D of Emergency medicine
Head, Pain and Paliative care unit
JSSMCH , MYSORE



God Relieved Adam from Pain, a pain of loneliness


The God was too good to
give primal curse for this
sin in the form of pain
and he also created the
pain relievers.
The Pain Physicians

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1677 – **Countess** of Northemberland – sharpest most uncomfortable pain , deprived her of sleep rarely allowed her only 5-6 mins of peace per hour unable to eat , drink , cough , spit , or wipe her face.


WORST
PAIN IN
THE
WORLD

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Pain is now the 5th vital sign

(Adopted by the American Board for Hospital Accreditation)

Lynch ME et al. Pain Res Manage Vol 11 No 1 Spring 2006

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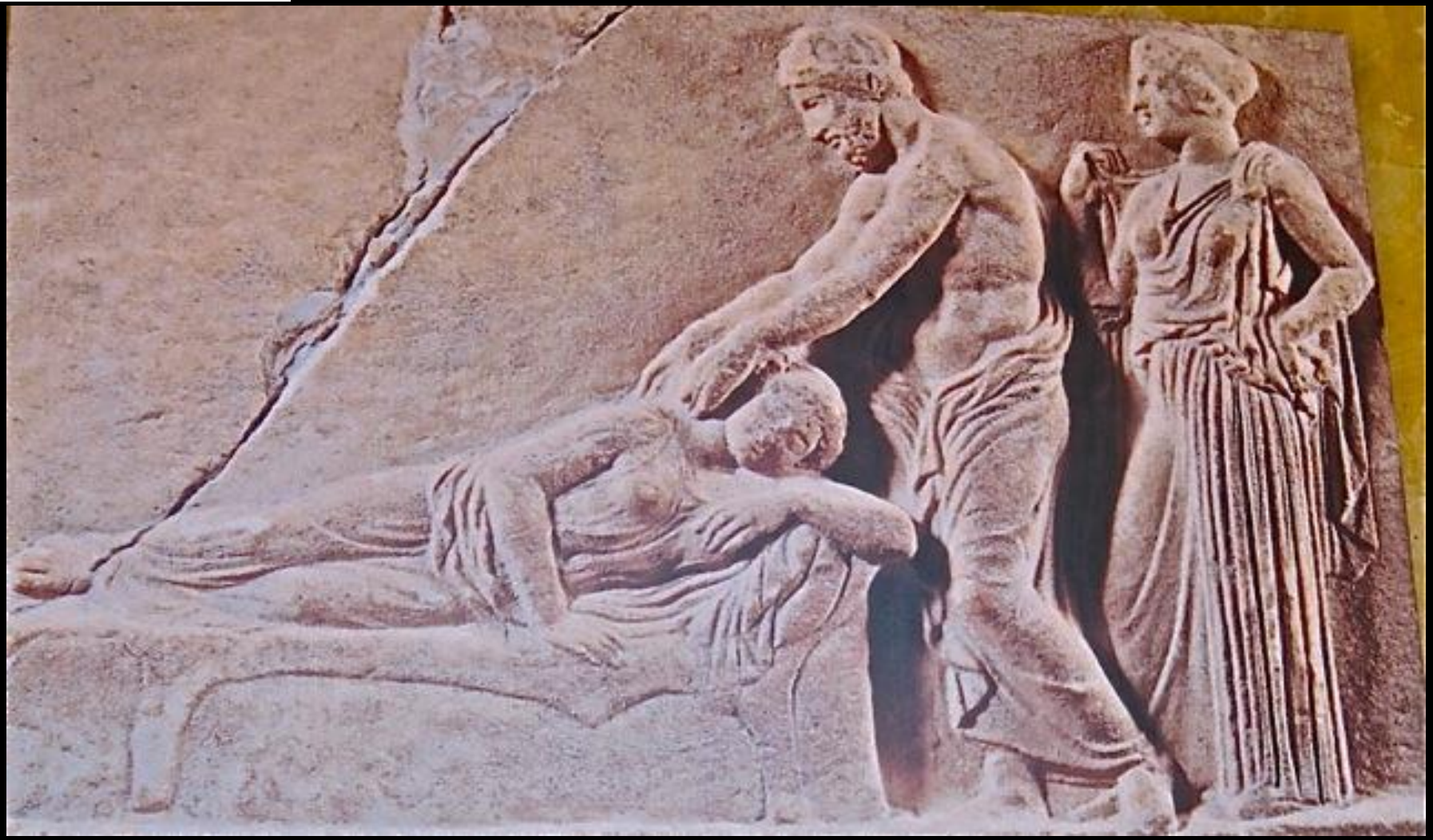
God of medicine

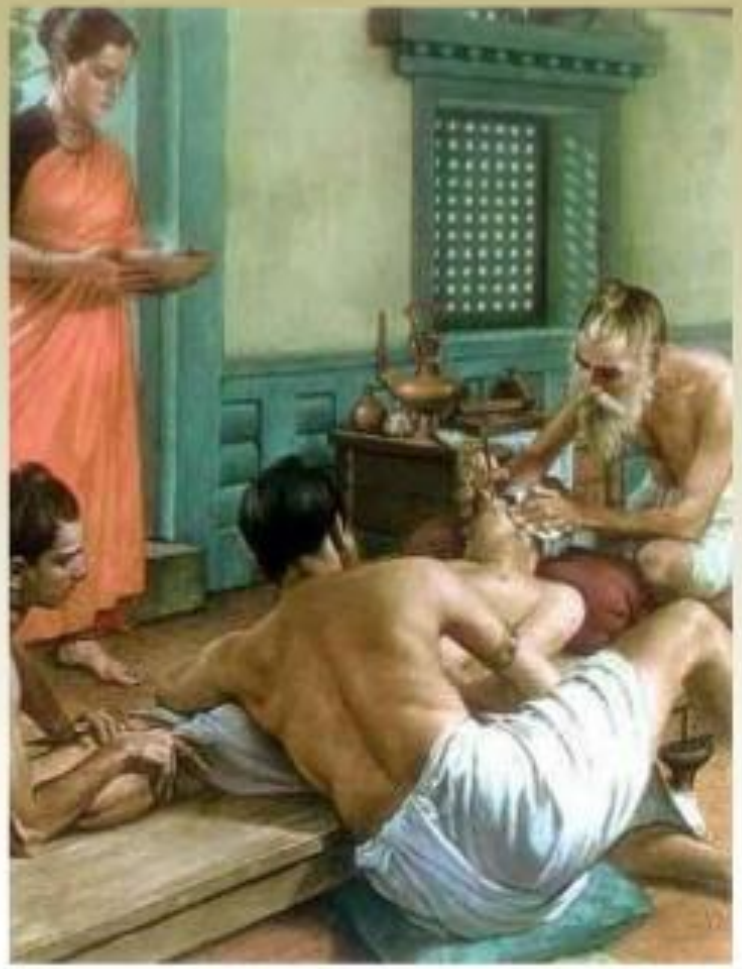


Aesculapius- nepenthe

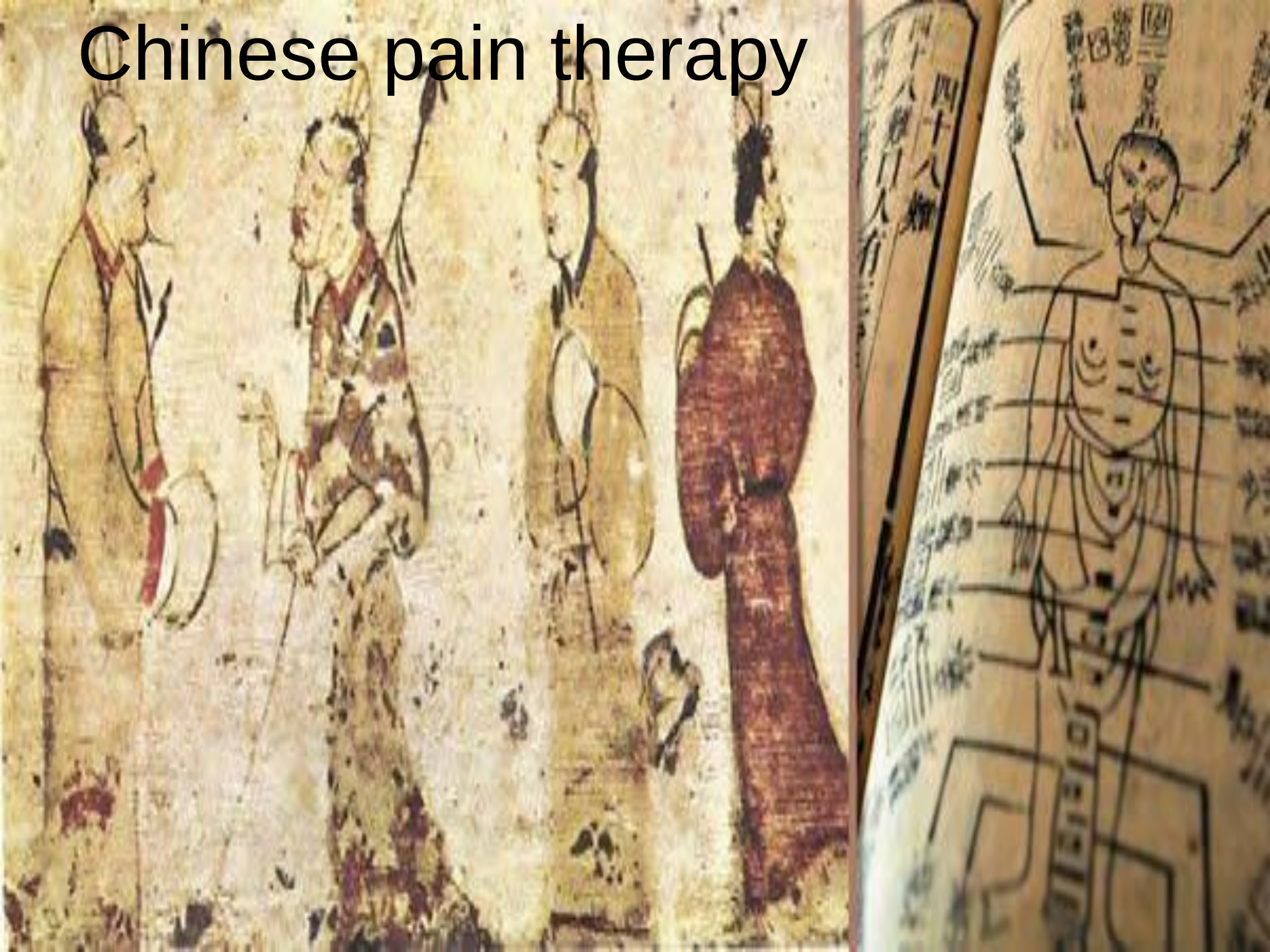
Pain relief in India – olden days

- Sushruta and Charaka mention the use of medicinal liquors
- To produce insensibility to pain (300 BCE)

- In 927 ACE, two surgeons trephined the skull of a king
- Made him insensitive to the operation by administering a drug called Sammohini



Chinese pain therapy



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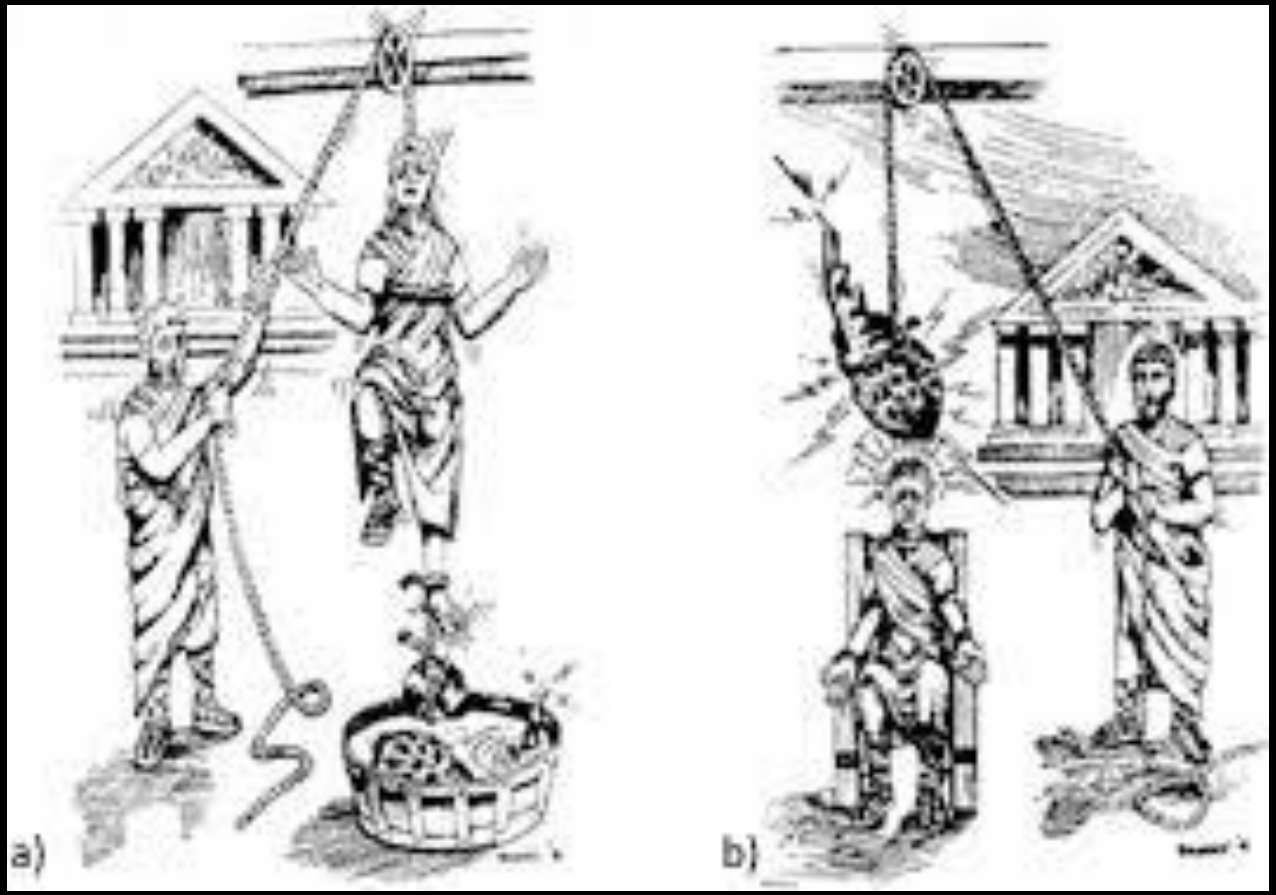

Dioscorides

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SOPORIFIC SPONGE

‘Sleeping potions made from opium and mandragora root which may be used as surgical anaesthetics for such people whom be cut or cauteried’

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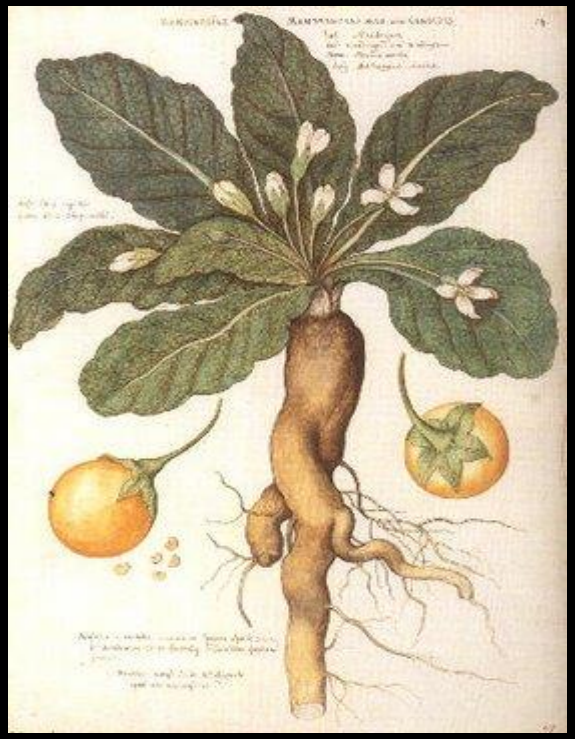
Nature to the rescue..



Mandrake plant and root

Indian Hemp

Poppy plant(opium)

Pythian priestess of Apollo

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And the so called “HUMBUG”

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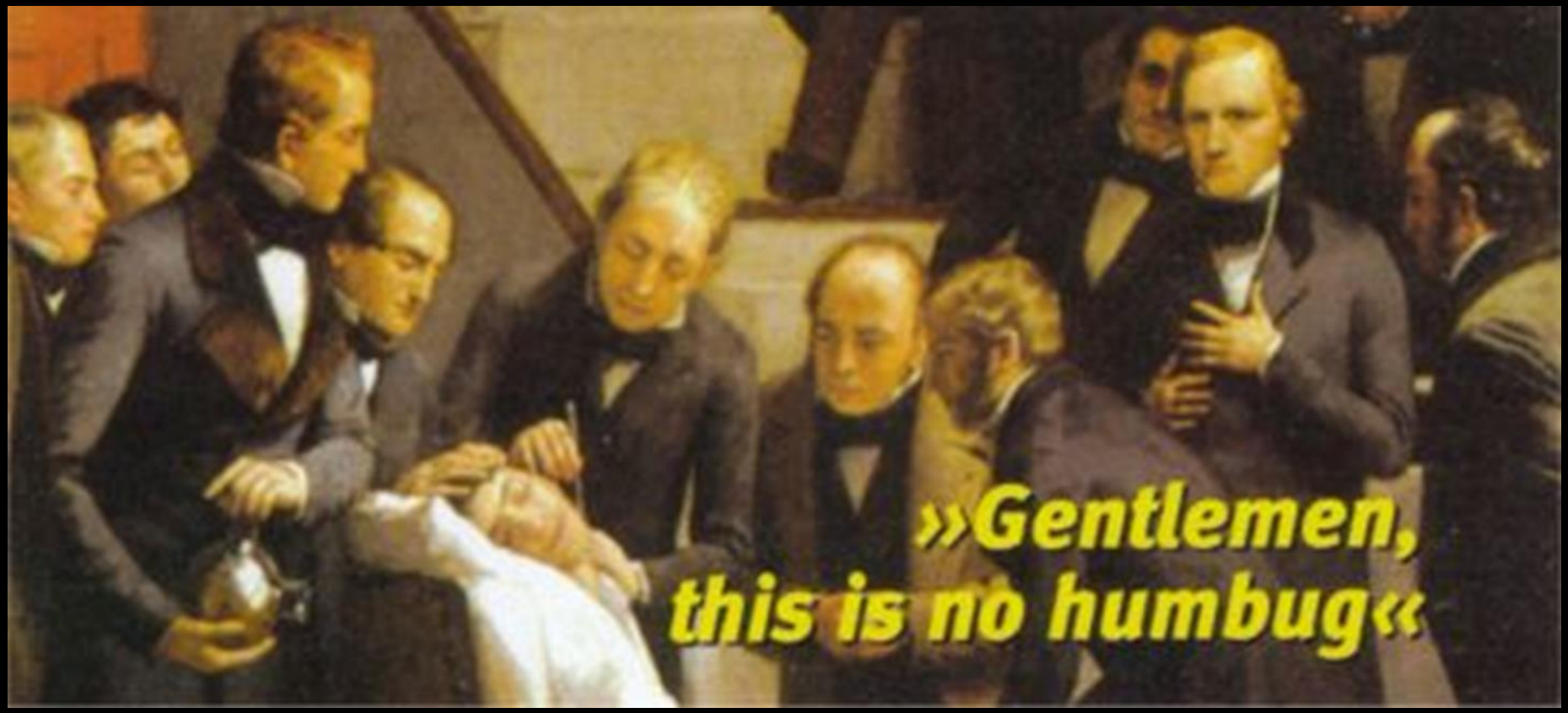
This is no Humbug..



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1953- John bonica- father of pain medicine

1965- R. Melzak and P D Wall- gate control theory

1974- international association for the study of pain

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PAIN

Derived from Latin word "*peone*" meaning "penalty" or "punishment"

"Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"

-IASP

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CLASSIFICATION

BASED ON DURATION:

- ACUTE: useful, physiologic process
  - warns the individual about the disease states/ harmful situations

- CHRONIC: pathological with altered anatomy and neural pathways.

  - Duration longer than 3 months

    Expected time to tissue healing

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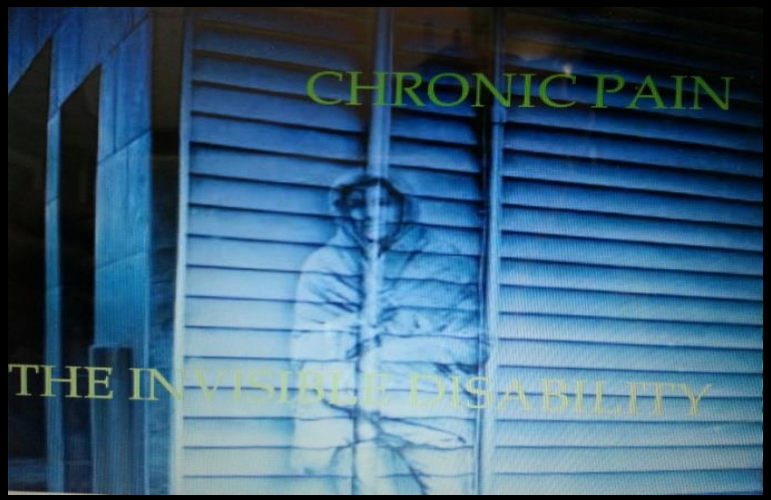
ACUTE

- Sudden onset
- Useful / protective
- Diagnosed and treated easily
- Adaptive

CHRONIC

- Insidious onset
- Useless/destructive
- Remodelling of brain and PNS
- Maladaptive



BASED ON PATHOPHYSIOLOGY

NOCICEPTIVE:

Normal nerves transmit information to the central nervous system about trauma to tissues

NEUROPATHIC:

Damage or dysfunction of nerves in the peripheral or central nervous system

Neuralgia

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Nociceptive

- Physiological
- Predictable
- response to an adverse stimulus
  - Eg.- trauma, acute illness
- Well localised, sharp or dull pain

Neuropathic

- Nervous system damage
- Pathological
- Tissue injury may not be obvious
- No protective function
- Burning, pricking, shocking, itching, shooting
- Not well localised

BASED ON CAUSE

- Cancer
- Non cancer

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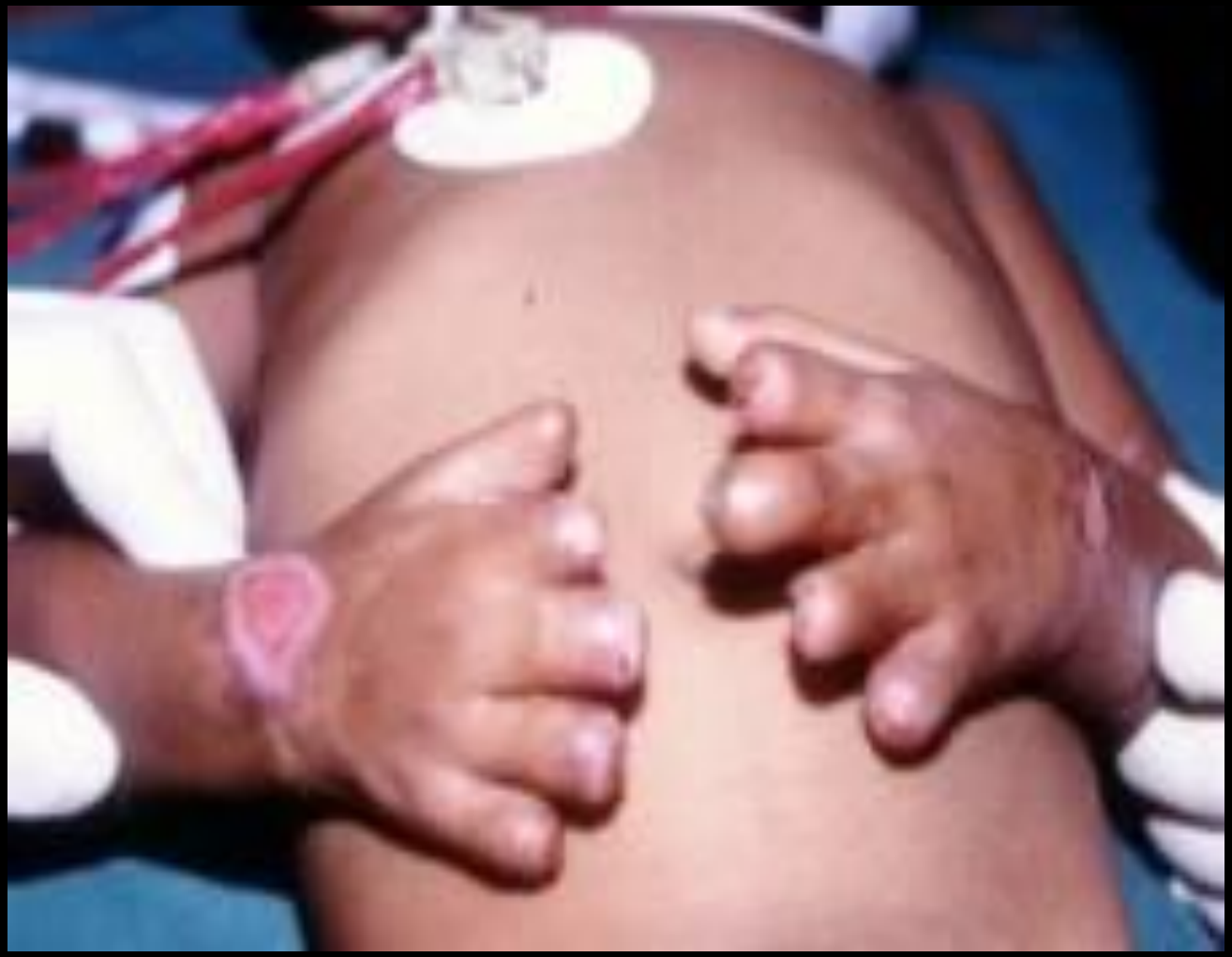
CONGENITAL ABSENCE OF PAIN



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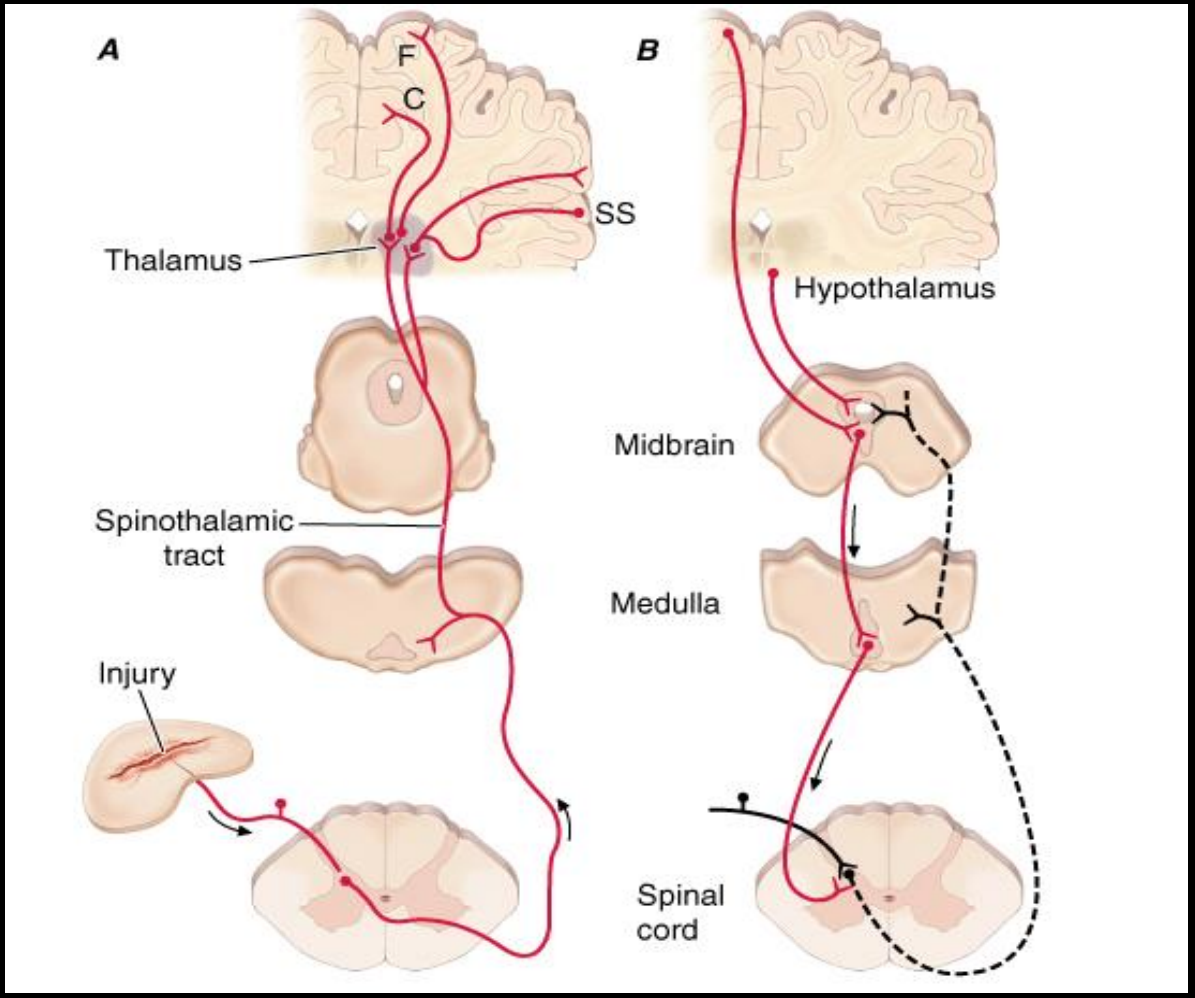
PAIN PATHWAYS



Nociceptive impulses

Pain modulation

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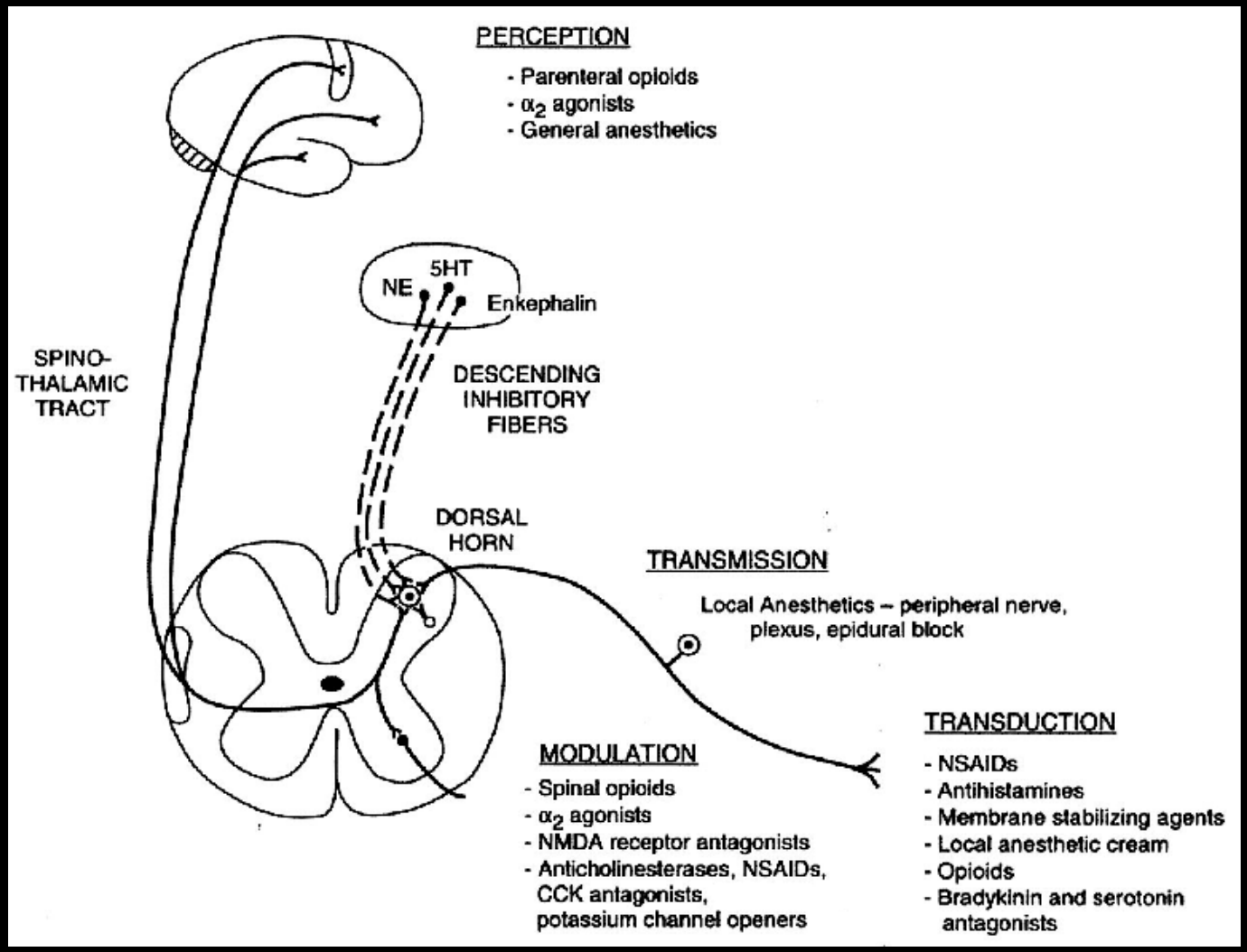
Events Involved

- **Transduction:** conversion of one form of energy to another
- **Transmission:** electrical event transmitted along neuronal pathways whereas molecules in synapse transmit from one cell surface to another
- **Modulation:** adjustment of events, by up- or downregulation
    - This can occur at all levels of the pathway
- **Perception:** awareness or understanding the sensory information


PERCEPTION
- Parenteral opioids
- α_2 agonists
- General anesthetics
5HT
NE
Enkephalin
SPINO-THALAMIC TRACT
DESCENDING INHIBITORY FIBERS
DORSAL HORN
TRANSMISSION
Local Anesthetics – peripheral nerve, plexus, epidural block
TRANSDUCTION
- NSAIDs
- Antihistamines
- Membrane stabilizing agents
- Local anesthetic cream
- Opioids
- Bradykinin and serotonin antagonists
MODULATION
- Spinal opioids
- α_2 agonists
- NMDA receptor antagonists
- Anticholinesterases, NSAIDs, CCK antagonists, potassium channel openers

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RAT APPROACH

- Recognize
- Assess
- Treat

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Chronic Pain is a Disease State

Painting : " *Sharp Pain*"
by Baruch Elron

The Relief of Pain should be a Human Right

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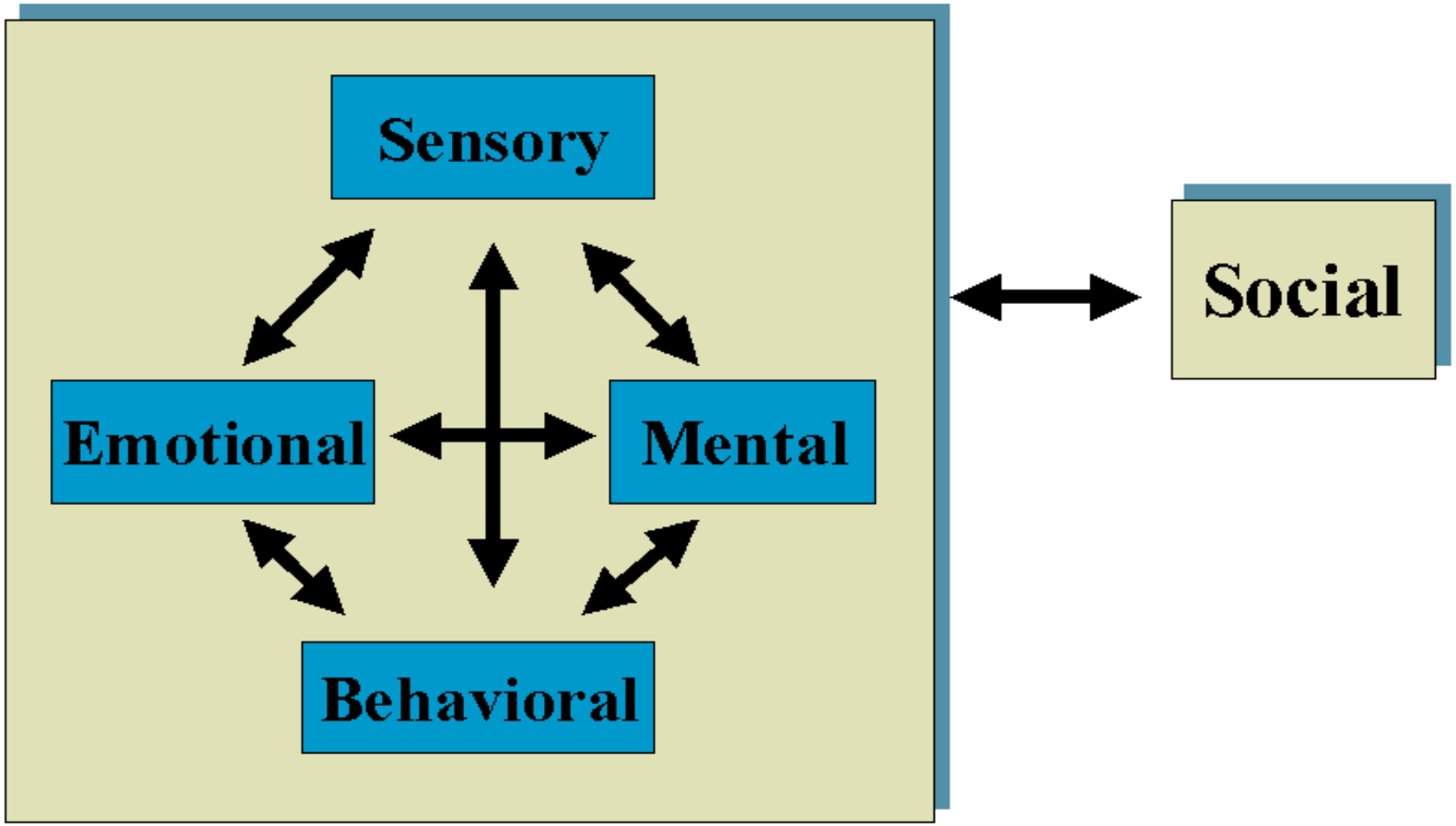
MORTALITY?
MORBIDITY!

- **loss of work**
- **anger**
- **anxiety**
- **depression**

Biopsychosocial Interactions



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PREVELENCE

- 50%-suffer chronic pain
- 5-8% -cancer
- 40%-musculoskeletal & joint dysfunction
- 35%-neck and backache
- 10%-headache

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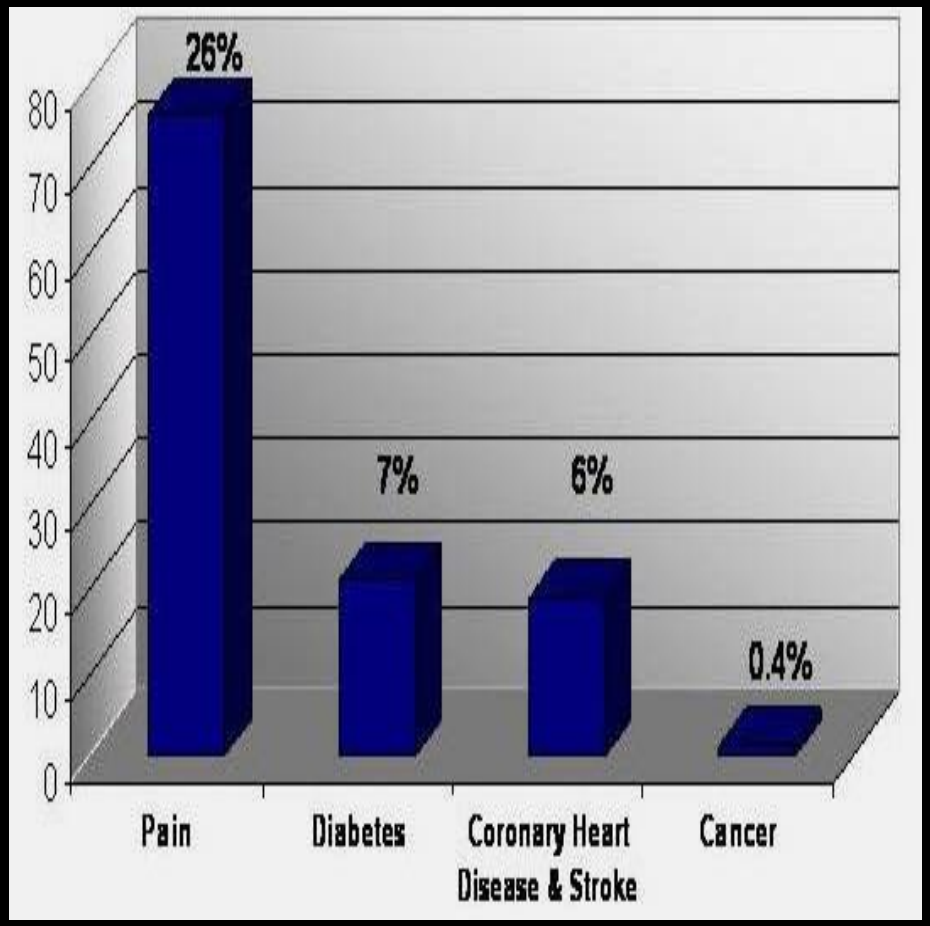
Prevalence of Chronic Pain



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Public health

"Disease that hinders happiness and harms public health."

- Most common symptom reported to physician(80%).
- Decrease in quality of life, impairs the ability to work.
- Use health services upto 5 times more frequently.
- Cost of unrelieved pain in the U. S
  - >50 billion dollars
  - >550 million work days/ year

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WHO

“ Persistent pain is a major public health problem accounts for untold suffering and lost productivity around the world.”

National institute of health designates pain as

“One of the most significant public health problems.”

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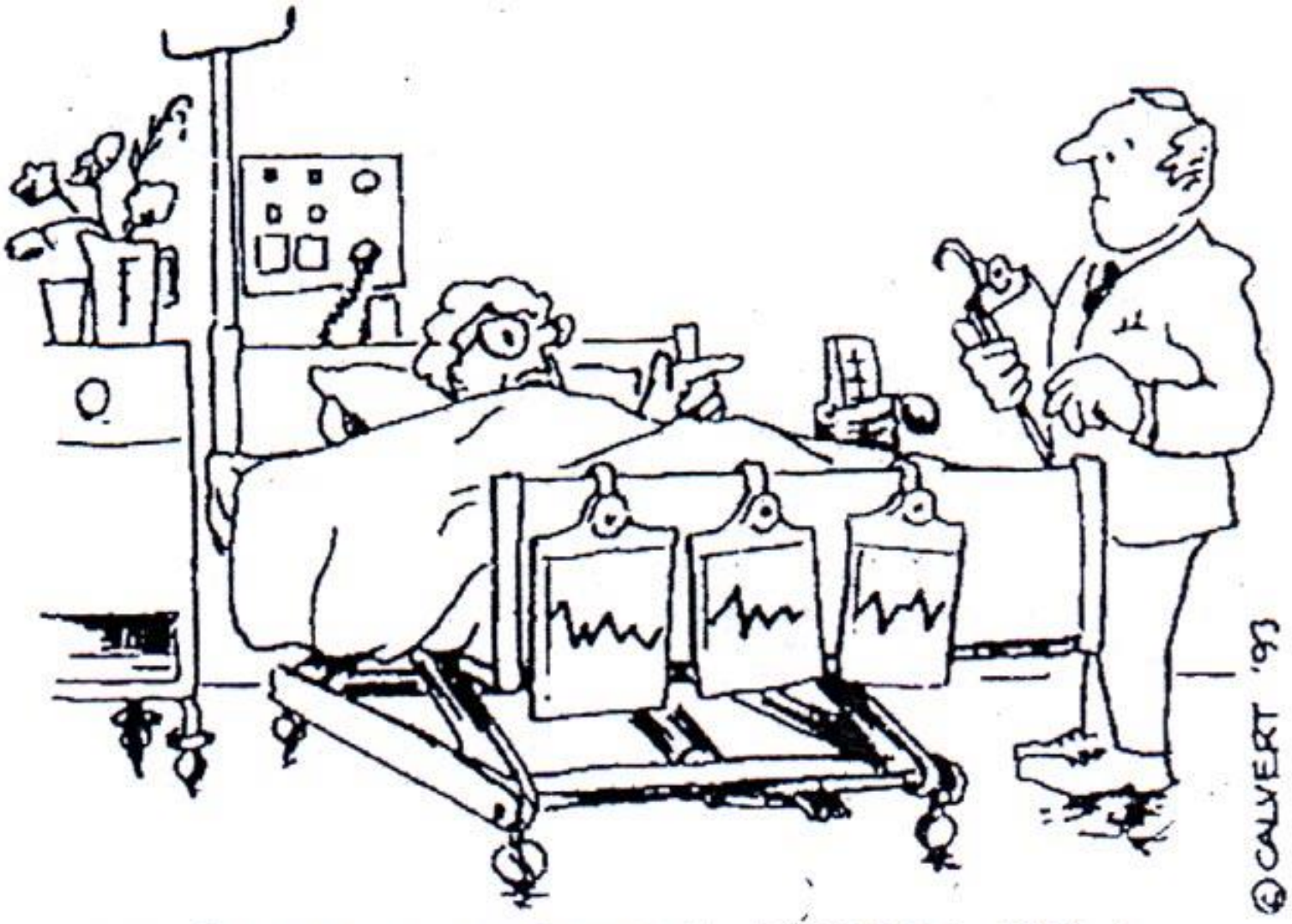
DO WE TREAT ACUTE PAIN EFFICIENTLY?

NO



NO. I'M NOT A LONG TERM PATIENT. I'M A SHORT TERM PATIENT YOU **STILL** HAVEN'T SUCCESSFULLY TREATED.

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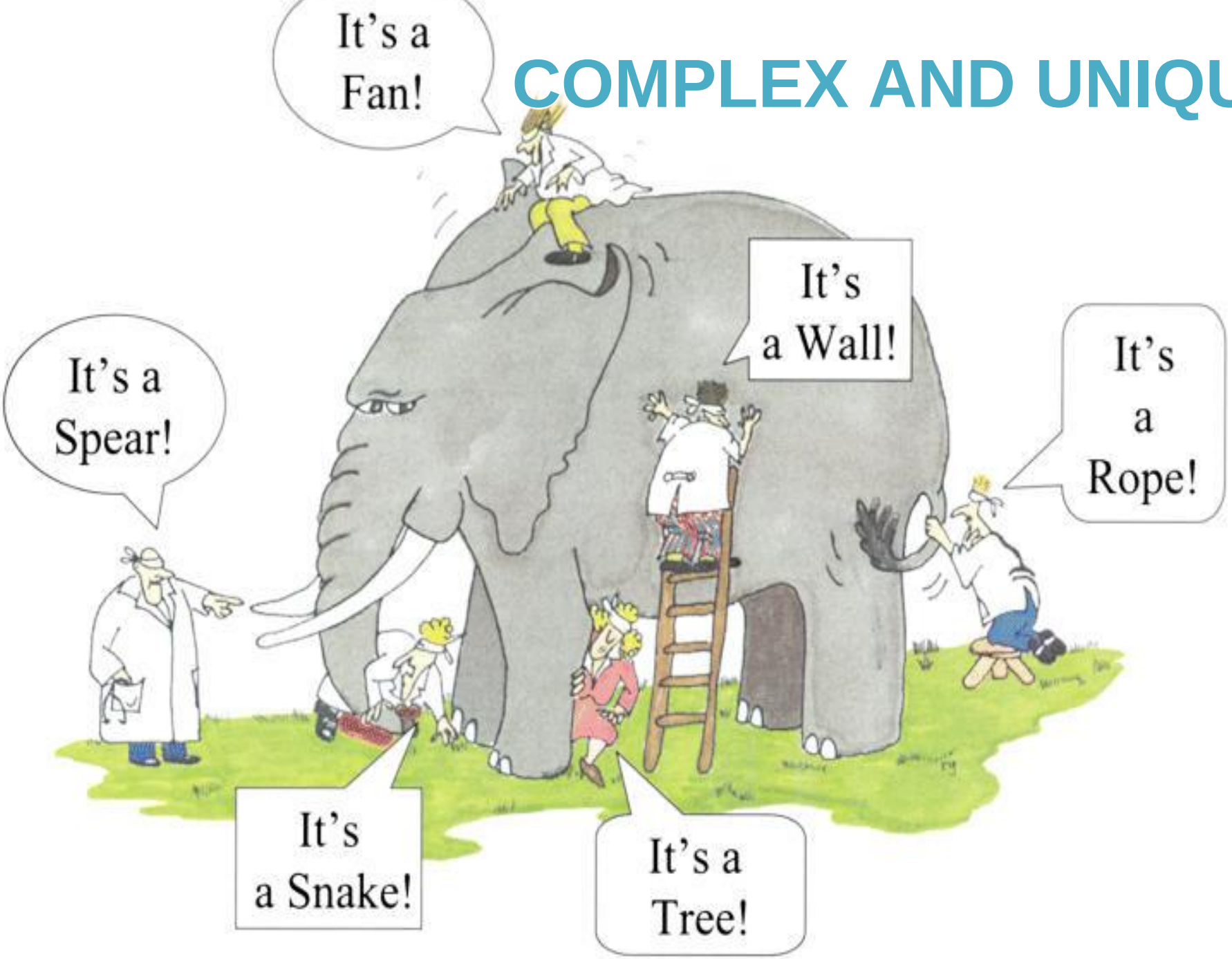
Then what about chronic pain?

"A NEGLECTED AREA"

COMPLEX AND UNIQUE



Usual tendancy of doctors is to dismiss pain or say that it is all in the patients head

BUT

It is not what is in patients head but rather what is no in the doctors head. What the mind does not know th eyes cannot see

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Who is best suited for pain practice?

- **Anaesthesiologist ?**
- **Orthopaedic surgeon ??**
- **Interventional radiologist ???**
- **Physiotherapist ??**

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MAJORITY – **ANAESTHESIOLOGISTS**

- Subspeciality
- **Enormous effort over the last** half century

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World war

- "Long after the trace of the effects of a wound has gone, ..neuralgic symptoms are apt to linger, and too many carry with them throughout long years this final reminder of the battle-field."

Interdisciplinary management

- Bonica-world war II
  - Pain physicians
  - Psychologist
  - Physical therapist
  - Occupational therapist

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Requisites for pain practice?

- **Sympathy & Empathy**
- **Understanding and knowledge of pain**
- **Diagnostic modalities – X- Ray, CT, MRI, Doppler, Bone scan, PET scan etc**
- **Therapeutic modalities- Drugs, blocks and advanced modalities.**

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PROBLEMS OF PAIN PRACTICE

Lack of awareness amongst

- Consultants,
- family physicians,
- Media
- General public

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PROBLEMS OF PAIN PRACTICE

Lack of

- Infrastructure for pain procedures, C ARM, Table for C ARM
- Availability of versatile pumps, needles and catheter sets for pain
- Pharmaceutical industry
- Preservative free drugs, LA, Opioids, Baclofen, Clonidine etc

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Issues

- Patients
- Doctors
- Political
- Ethical
- Legal

Patient issues

“Pain upsets and destroys the person who feels it.”- Aristotle

22% of chronic pain patients have changed doctors at least 3 times in search of pain relief.

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Patients

- Expect 100% pain relief
- Not regular
- Over dose or inadequate dose
- Plan their own schedule
- Anger, anxiety & depression
- Culture- affects behaviour & attitude
- Race
- Access to treatment centres and multi disciplinary care

Doctors

“ Under treatment of chronic pain may largely result from physician’ s under education regarding its management.” - Pain Medicine , Gregory Turner and Debru Waner

- >50% patients in the hospital- undertreated

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Over come by

- Advanced training and knowledge.
- Medical schools- curriculum.
- Expansion of fellowships.
- Establish research forum and web learning.
- Multi disciplinary approach to evaluation, diagnosis, treatment and rehabilitation.
- Clinical experience.

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Politics of pain

- Neglected area of governmental concern
- Controversy surrounds chronic pain and opiods
- Strongest of pain killer “opiods” are feared and stigmatized
- Insufficient data to support the use of chronic pain
- Doctors hesitate close monitoring
- Fear of investigation and prosecution

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Solution

- Liberalization of law on opioid availability.
- Educate health care providers.
- Studies :
  - Less than a tenth of one percent of pain patients become addicts(NIH).
  - Opioids improved function status.

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"Anyone who said 'ouch' is entitled to receive opioids in whatever dose they seem to need."

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Legal issues

- Greater risk of being sued for malpractice.
- Pain practitioners are physicians and not technicians
- Thorough evaluation, consent, record keeping.
- Follow protocol based therapies.
- Do not perform unfamiliar procedures.

Ethical issues

“Physicians involved in pain management have an ethical obligation to treat pain as effective as possible.”

Principles:

- Autonomy (patient informed and involved in decision making)
- Beneficience (do good)
- Non maleficience (do no harm)
- Justice (balancing the needs of individuals with those of society)

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Goals

- Reduction of pain intensity
- Improvement of quality of life
- Improvement of psychological functioning
- Reduction of healthcare utilization
- Promotion of return to work/school class and/or role within the family/society

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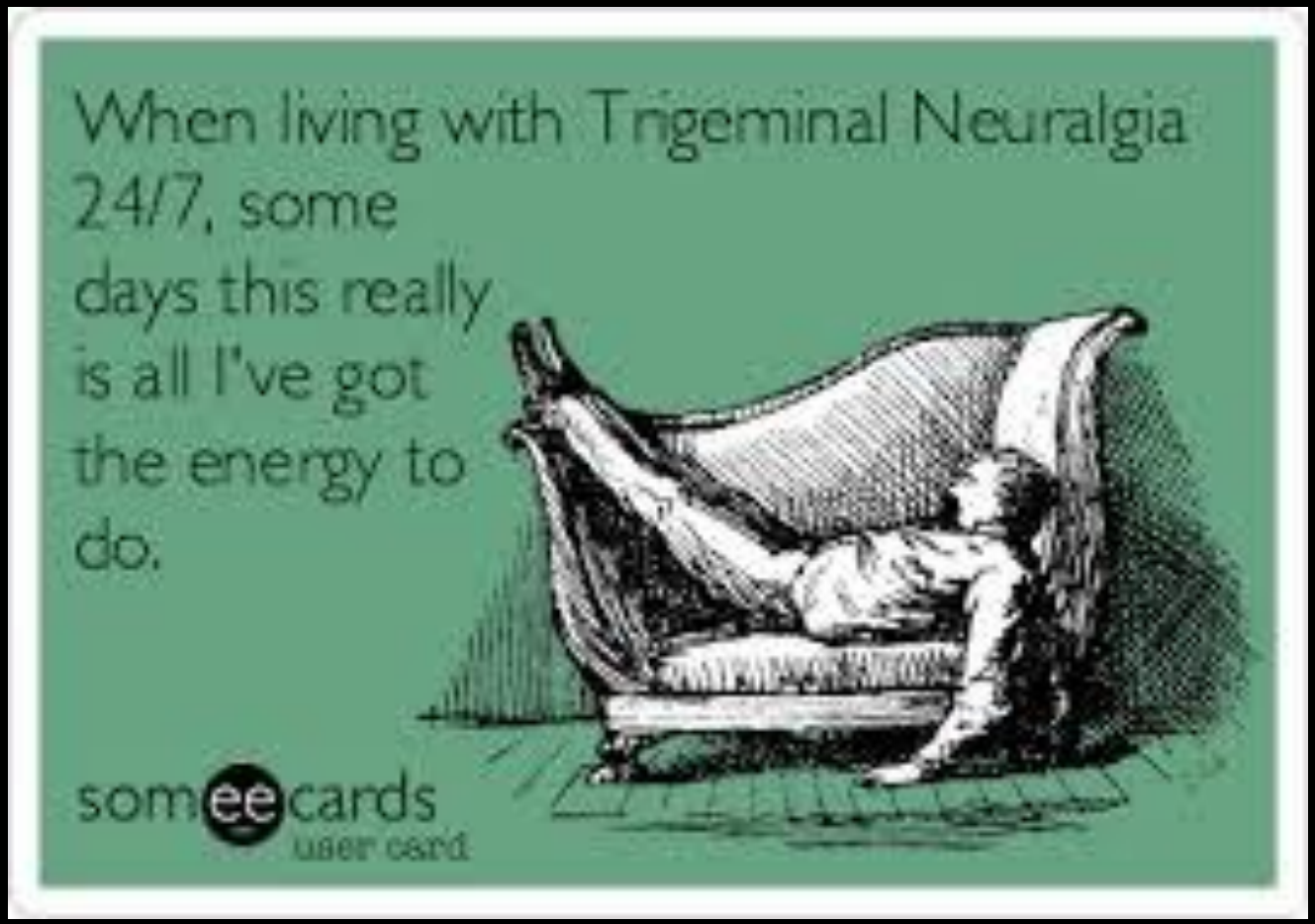
TRIGEMINAL NEURALGIA : TIC Doulourex



A big puzzle for pain physicians

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TRIGEMINAL NEURALGIA

Middle age , 2 : 1

Unilateral , Bilateral (1- 5) – MS

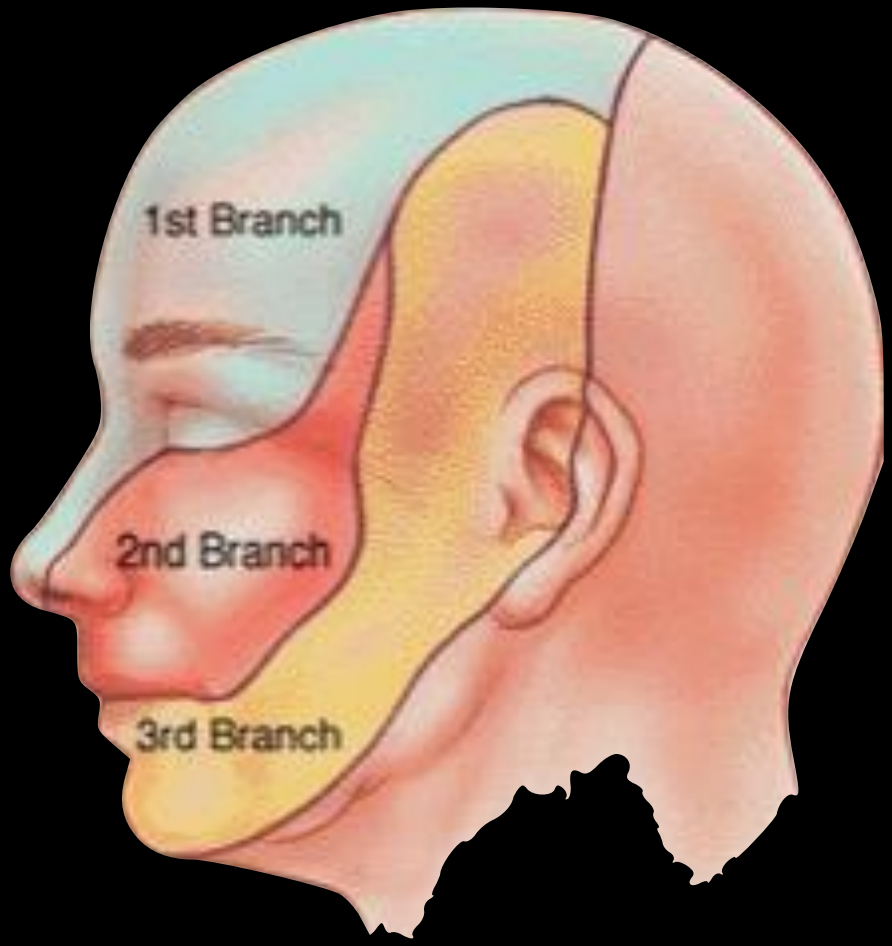
Right side (60 %) Left side (39 %)

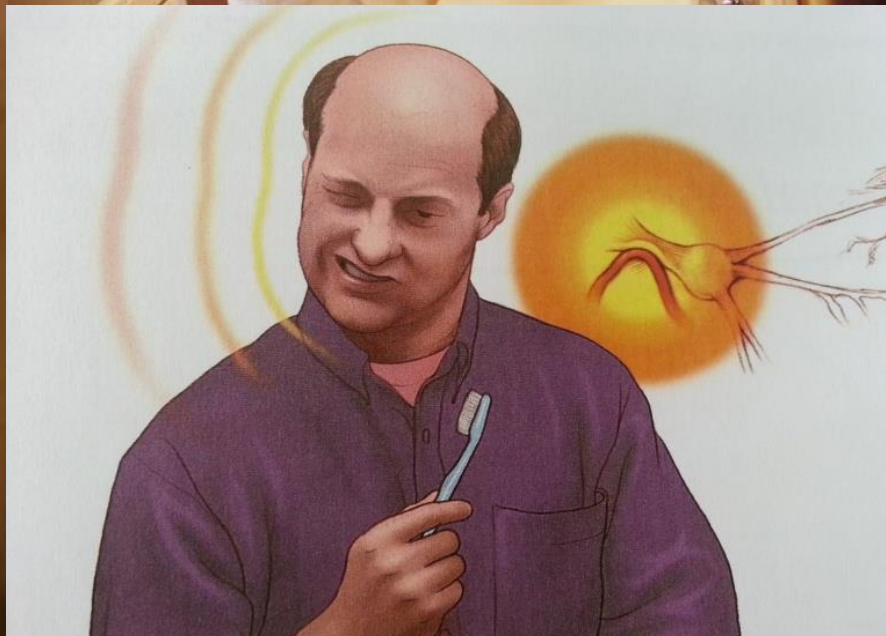
Maxillary 20 % , Mandibular 77 % ,

Ophthalmic 2 % , Ophthalmic and

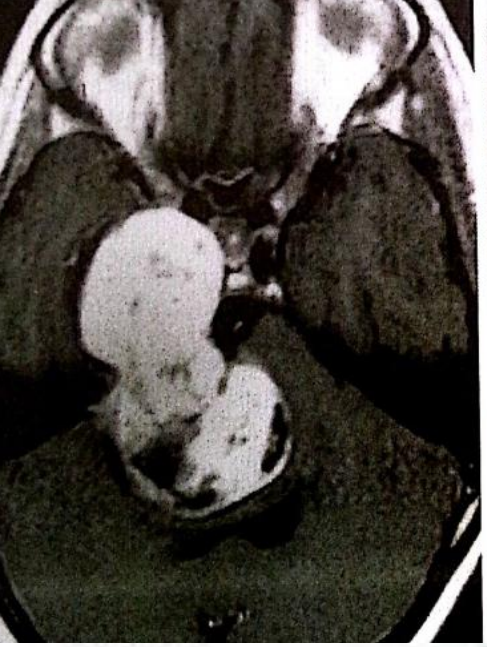
Mandibular 14 % , Maxillary and Mandibular

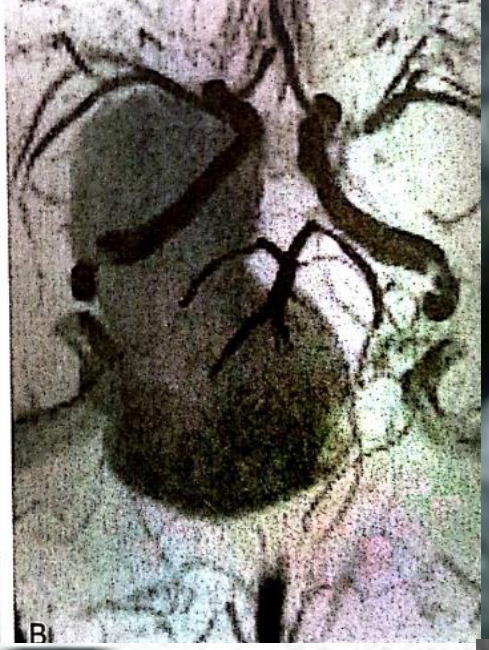
42 % , All three 5 %.

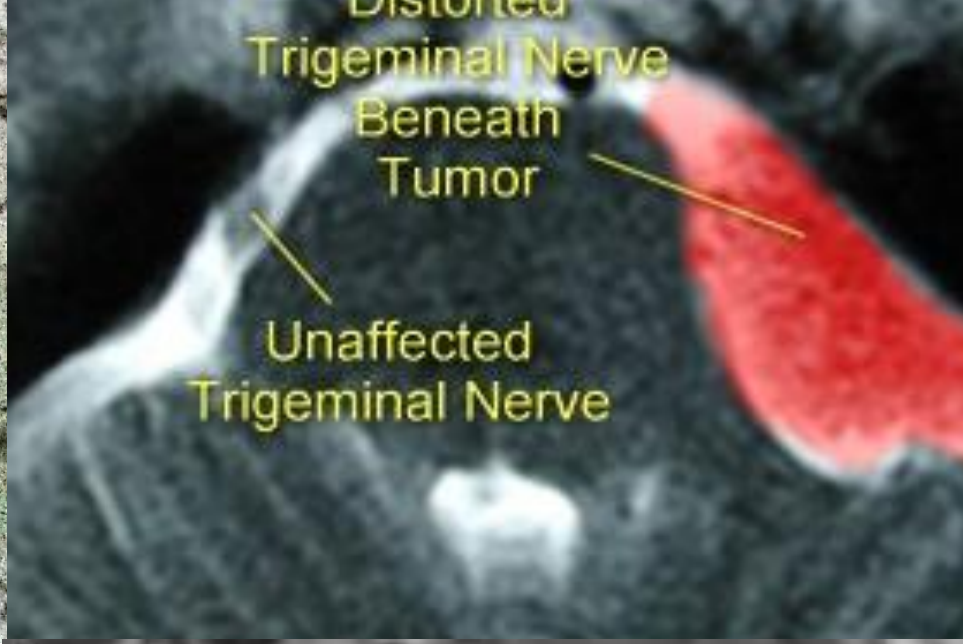


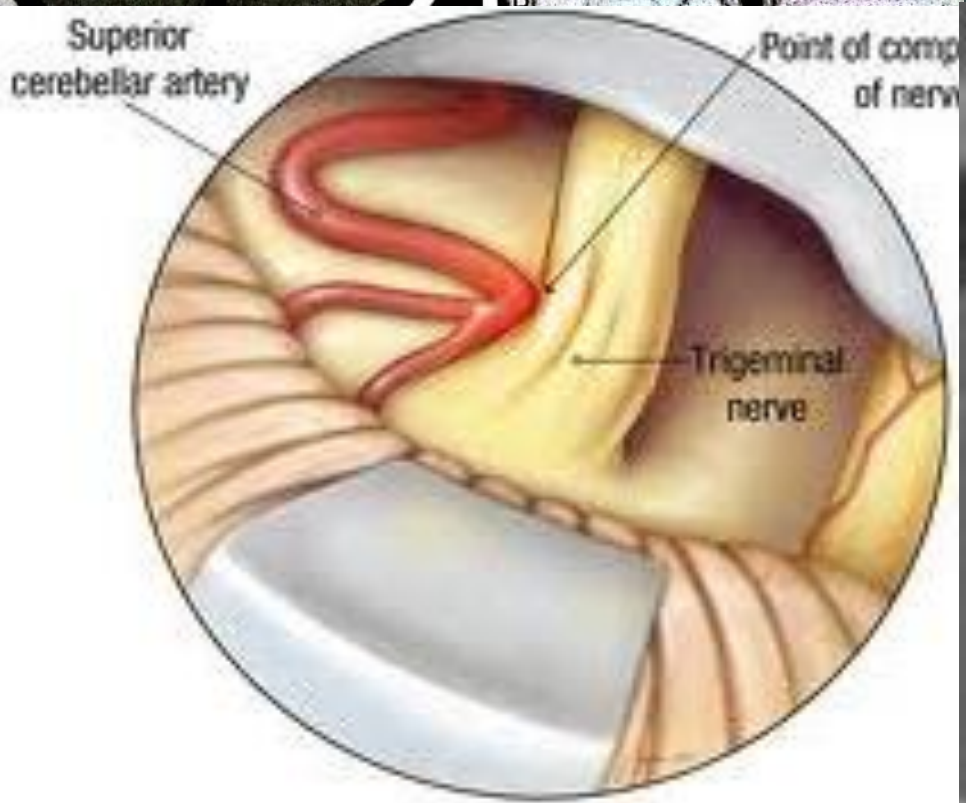


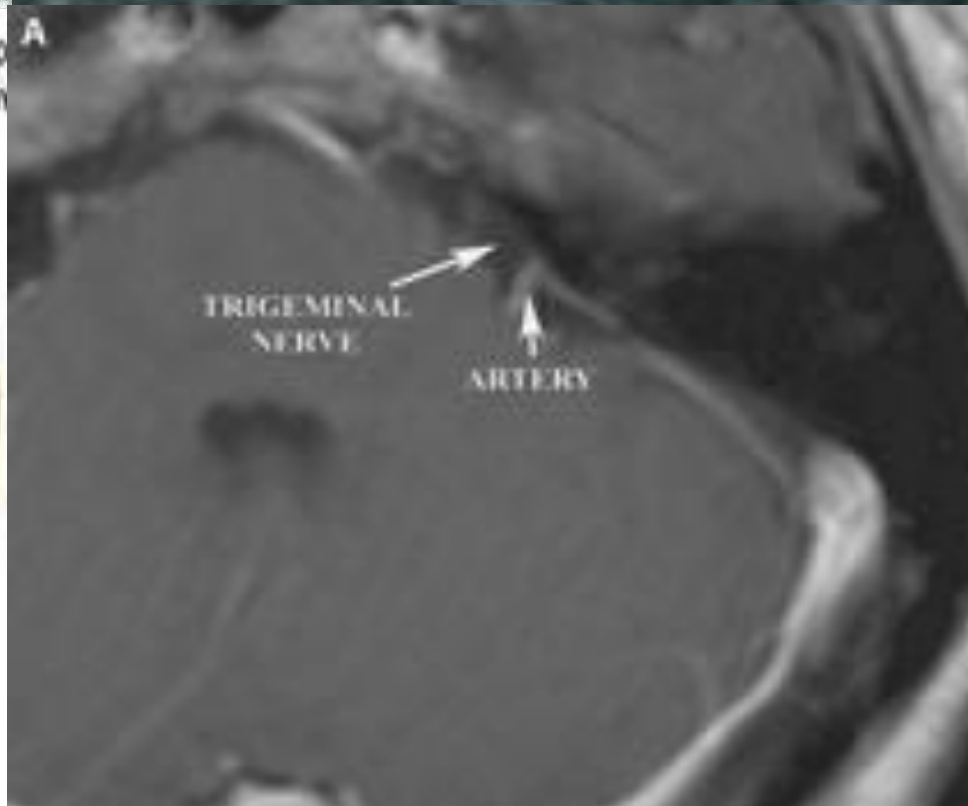

WORST
PAIN IN
THE
WORLD





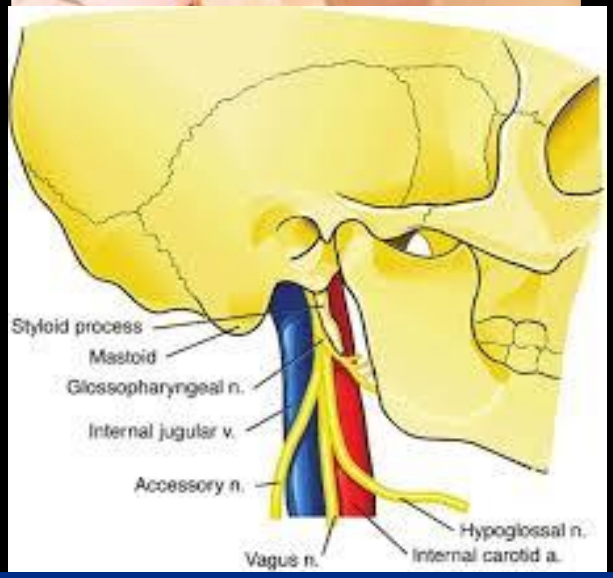

Distorted
Trigeminal Nerve
Beneath
Tumor
Unaffected
Trigeminal Nerve


Superior
cerebellar artery
Point of comp
of nerv
Trigeminal
nerve


A
TRIGEMINAL
NERVE
ARTERY

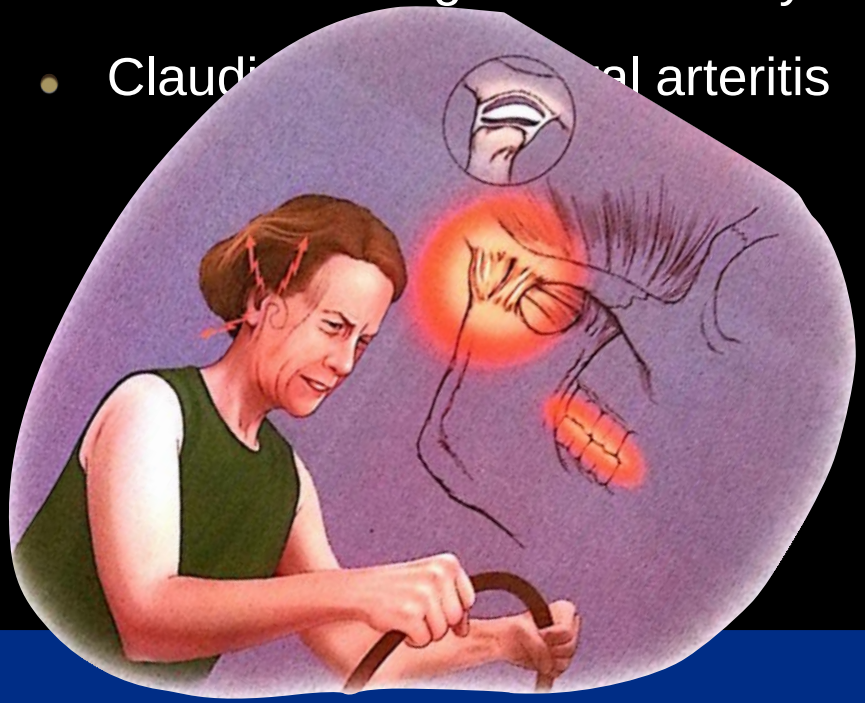
GLOSSOPHARYNGEAL NEURALGIA

- Pain in the distribution of glossopharyngeal nerve.
- Rare condition , 1/100,000.
- Women , old age
- Posterior part of tongue , pharynx , tonsil .
- **Idiopathic** – Compression by blood vessels.
- **Secondary** – Tumors of posterior tongue , tonsils hypoparynx .
- Sharp , stabbing , shooting .



TEMPEROMANDIBULAR JOINT DYSFUNCTION

- Pain arising from temperomandibular joint.
- Myofacial pain syndrome.
- 8:1 female to male .
- Pain in muscles , joints , clicking , sticking or trismus , fullness in ear .
- Clicking or popping noise in the TMJ.
- Restricted mandibular range (<35 mm).
- Ridged buccal mucosa , crenated tongue , masseteric hypertrophy.
- Arthritic changes in the X-ray .
- Claud[illegible]al arteritis

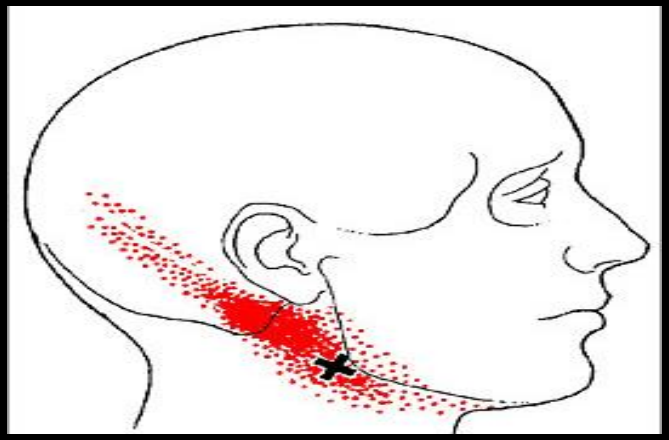


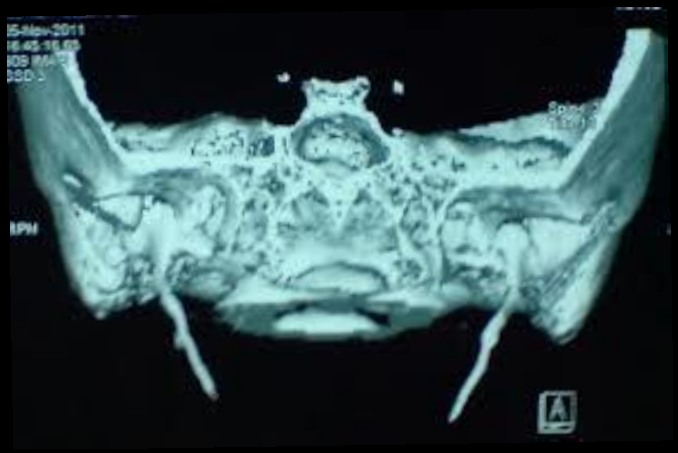
ATYPICAL FACIAL PAIN OR PERSISTANT IDIOPATHIC FACIAL PAIN

- Continuous pain in the maxillary region .
- Cannot be provoked ,
- not paroxysmal (cluster headache)
- Diagnosis by exclusion –
  - middle aged women , unilateral or bilateral , aching or cramping , continuous , stress triggers , depression and sleep disturbances .
- Overlaps division of trigeminal nerve.
- No triggering points

EAGLES SYNDROME :

- Stylohyoid syndrome
- Pressure over the ICA and surrounding structures.
- Elongated styloid process
- ***Typical*** – after tonsilectomy sensation of foreign body in pharynx , pain in ears , dyspahagia ,
- ***Atypical*** – similar to carotidynia , tenderness , precipitated by palpation in tonsillar fossa
- Rx – Nerve block
    - Surgical option





BURNING MOUTH SYNDROME

- Burning discomfort or pain
- Clinically normal mucosa .
- Glossodynia , somatodynia, pyrosis
- Women after menopause
- Treatment : Spontaneous remission,
  - nutrition.

Phantom Pain

- Deafferentation pain .
- Constant , dull , deep ache , occasionally sharp .

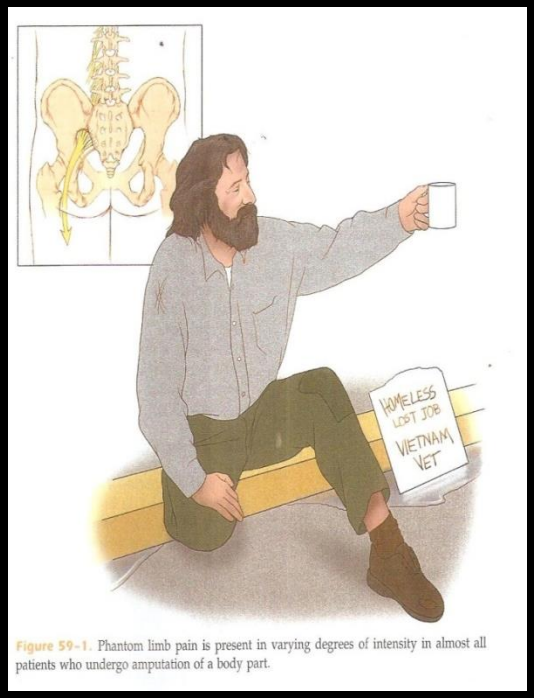
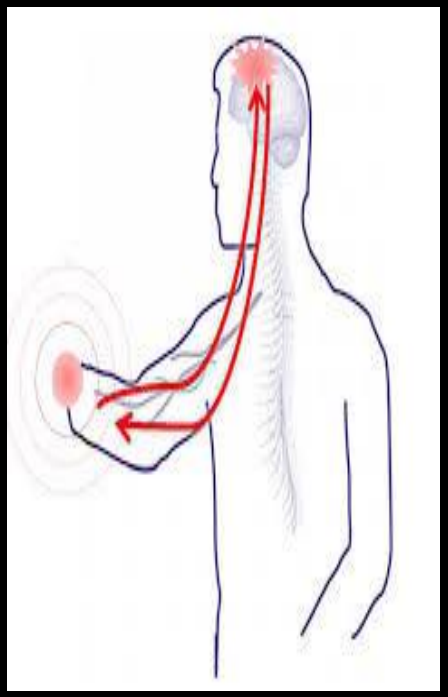


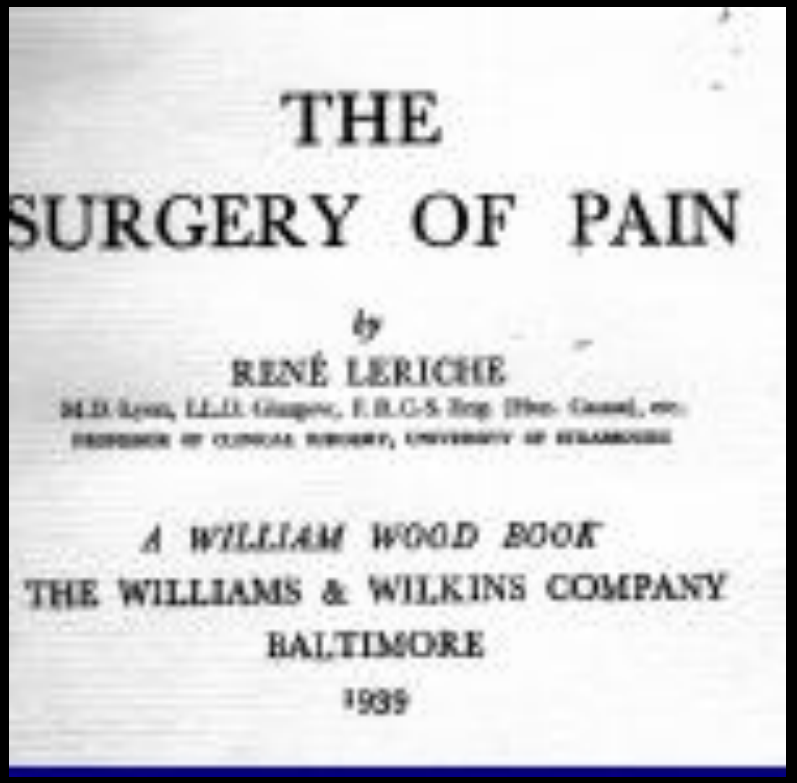
Figure 59-1. Phantom limb pain is present in varying degrees of intensity in almost all patients who undergo amputation of a body part.



Post-traumatic spreading neuralgia

A lady, aged37, receive a gift of a hare. She cut it up, with a view to make a well-know marinade,..she pricked her index finger with a spicule of bone.

By next day, all trace of injury had vanished and it was forgotten. The hare was eaten, but it had its revenge!


THE
SURGERY OF PAIN
by
RENÉ LERICHE
A WILLIAM WOOD BOOK
THE WILLIAMS & WILKINS COMPANY
BALTIMORE
1939

COMPLEX REGIONAL PAIN SYNDROME (CRPS) , FACE

- Common denomination – trauma , injury , infection , cancer , artheritis , dental extraction .
- Burning
- Allodynia , hyperalgesia.
- Sudomotor , vasomotor changes (Trophic skin changes).
- D/D- Dental or sinus pain
- Atypical facial pain / TGN

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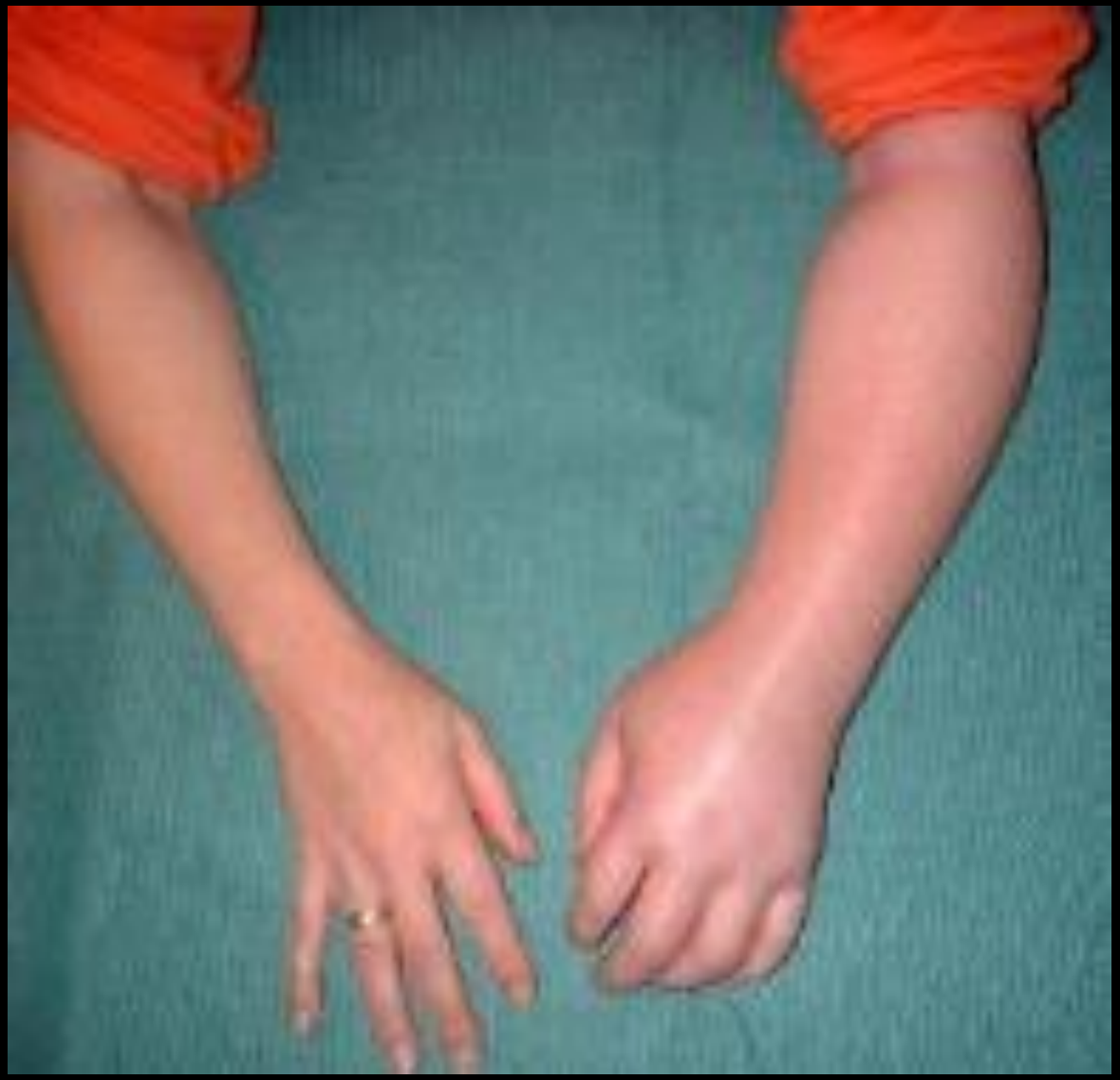
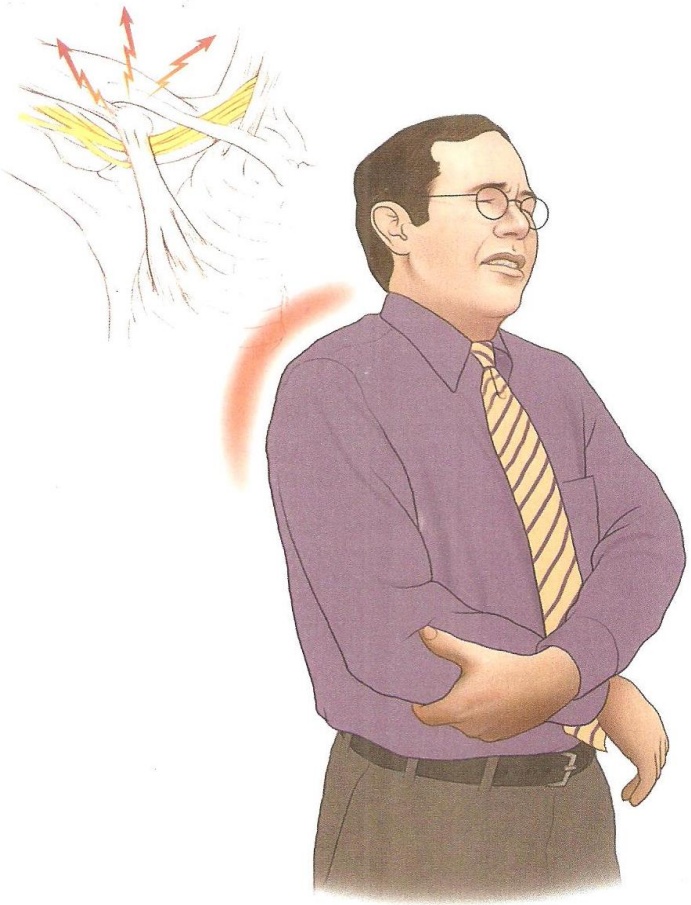




ure 15–1. The pain of brachial plexopathy radiates from the shoulder and supraclavicular region into the aff per extremity.

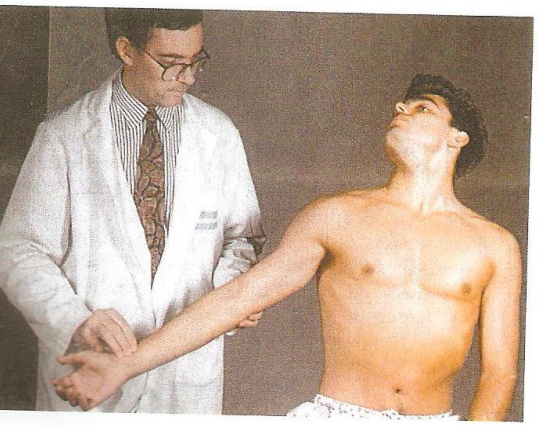


Figure 15–2. The Adson maneuver. The patien hales deeply, extends the neck fully, and turns head to the side being examined. This tests for c pression in the scalene triangle and is positive if t is a diminution in the radial pulse and reproduc of the patient's symptoms. (From Klippel JH, Die PA: Rheumatology, 2nd ed. London, Mosby, 1998.)

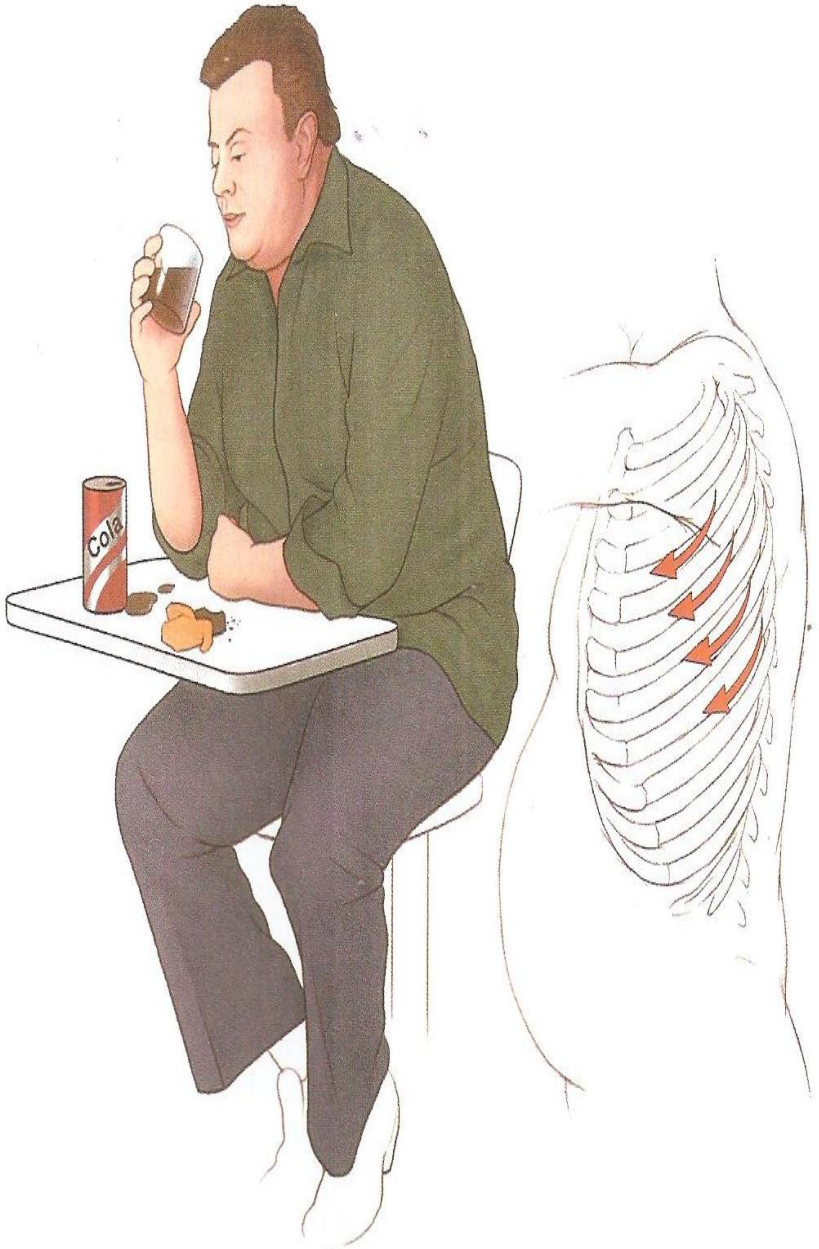
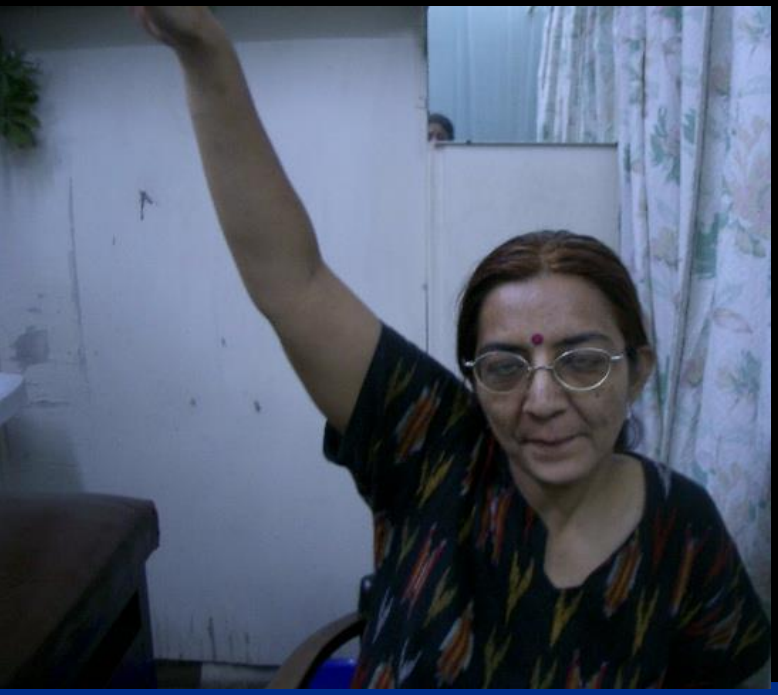
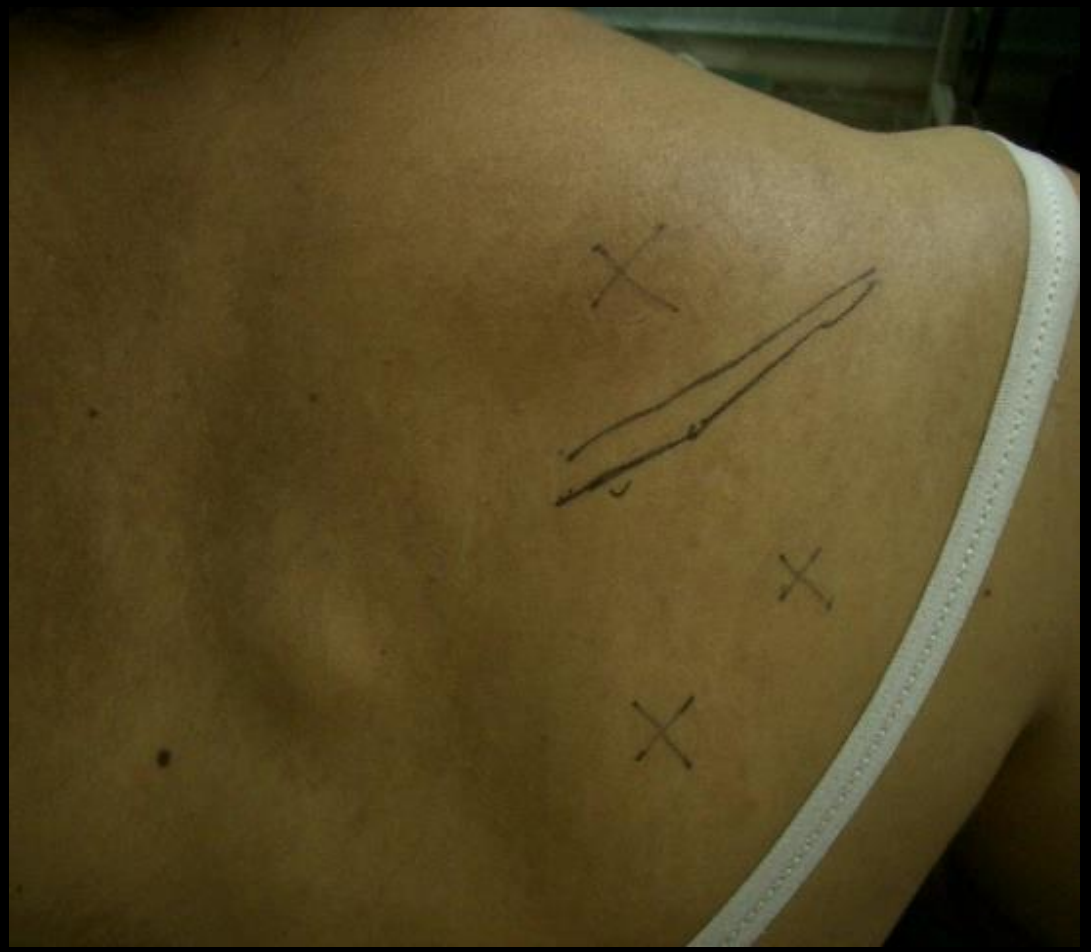
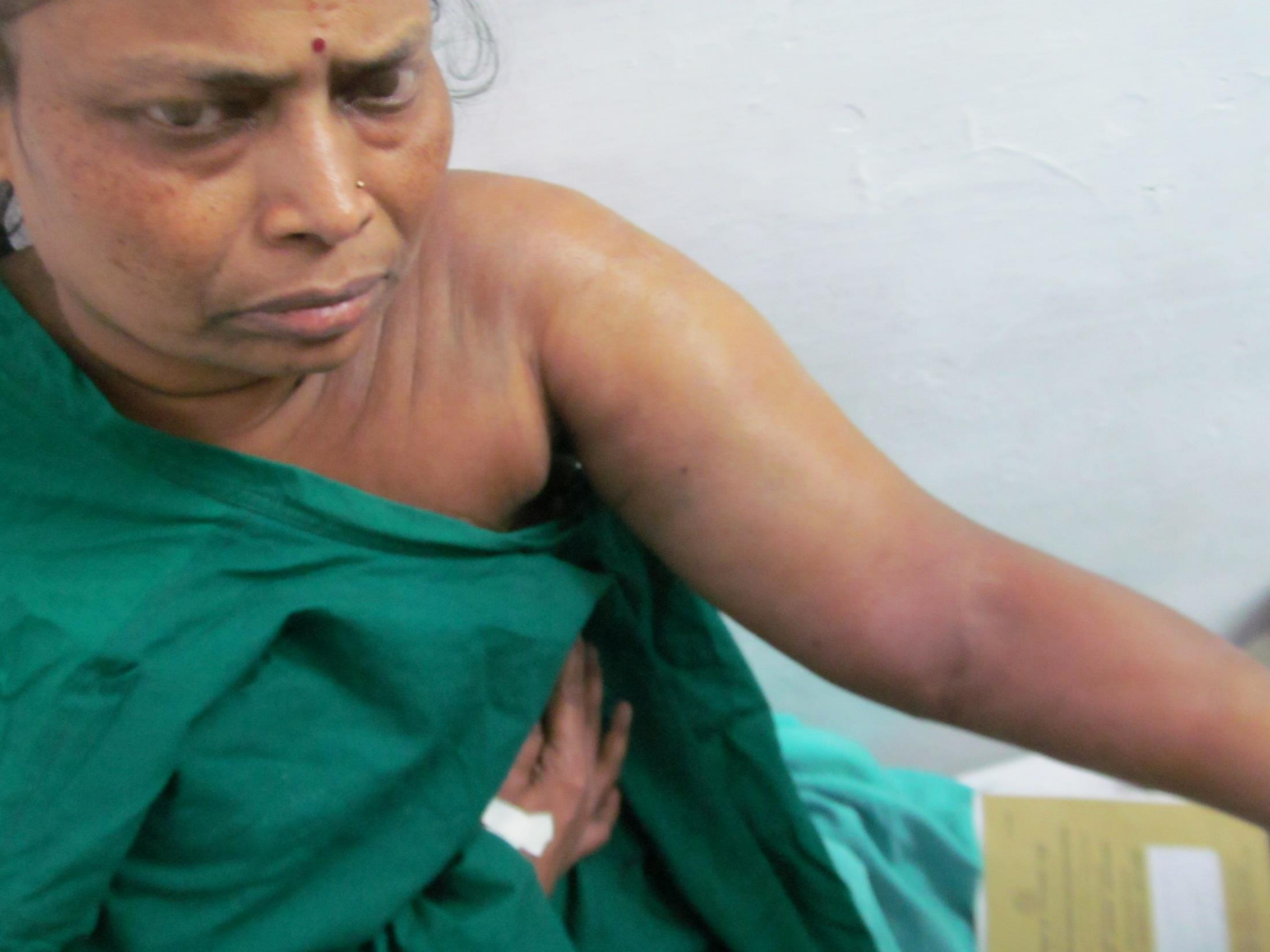


Figure 38-1. The pain of diabetic truncal neuropathy is neuropathic in nature and is often made worse by poorly controlled blood sugar.







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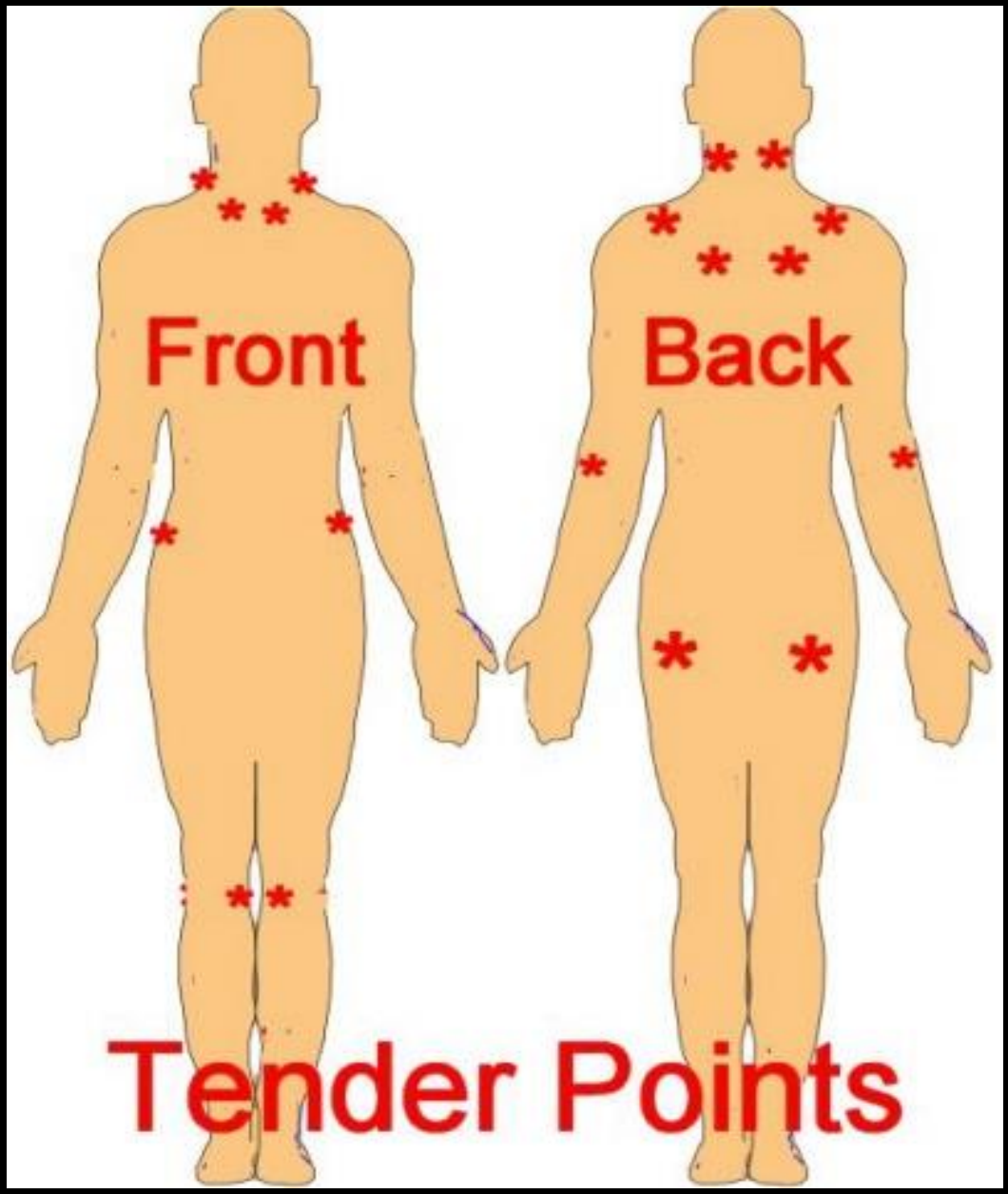
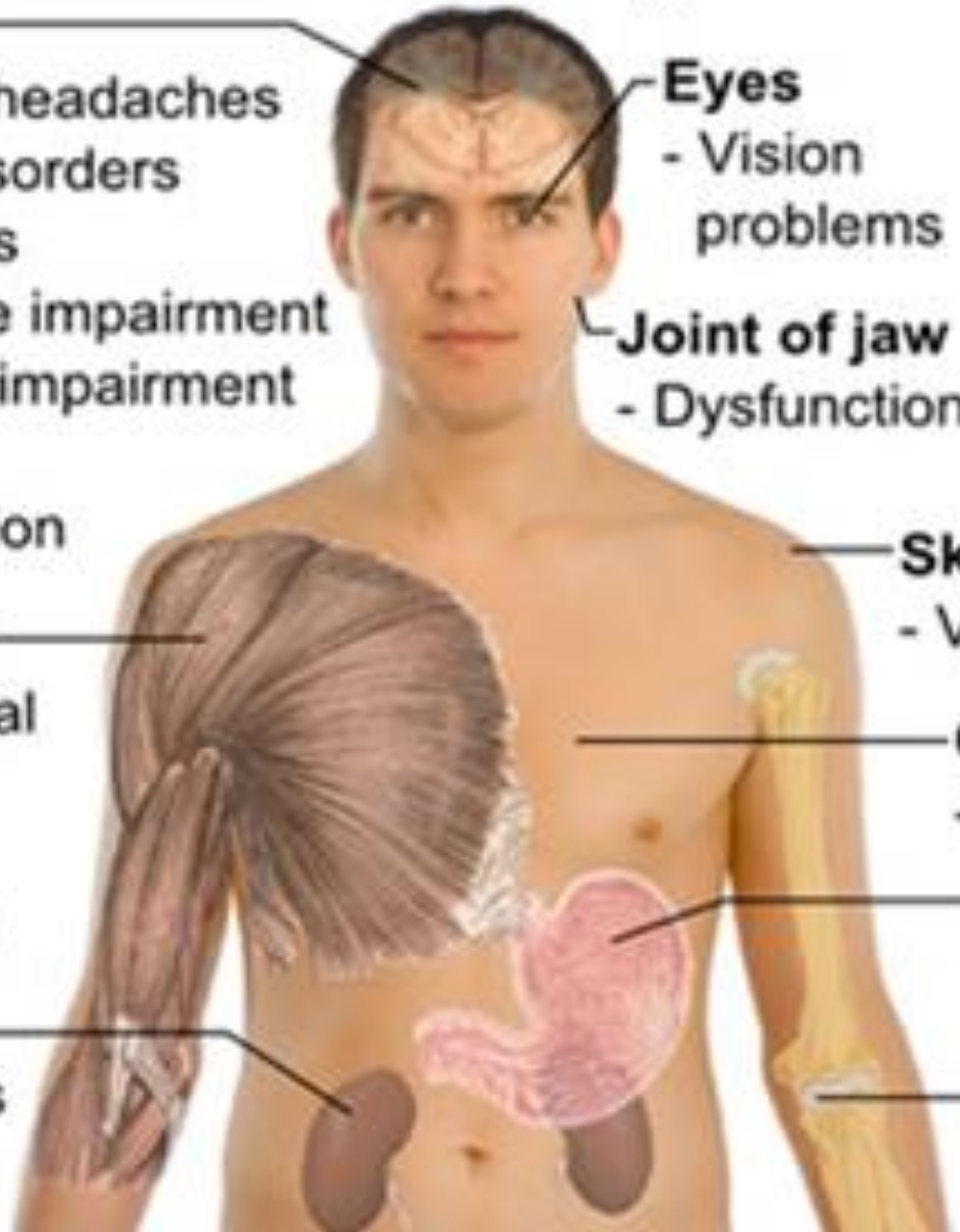
Fibromyalgia/ myofacial pain syndrome



Symptoms of

Fibromyalgia



Central
- Chronic headaches
- Sleep disorders
- Dizziness
- Cognitive impairment
- Memory impairment
- Anxiety
- Depression

Eyes
- Vision problems

Joint of jaw
- Dysfunction

Systemic
- Pain
- Weight gain
- Cold symptoms
- Multiple chemical sensitivity

Skin
- Various complaints

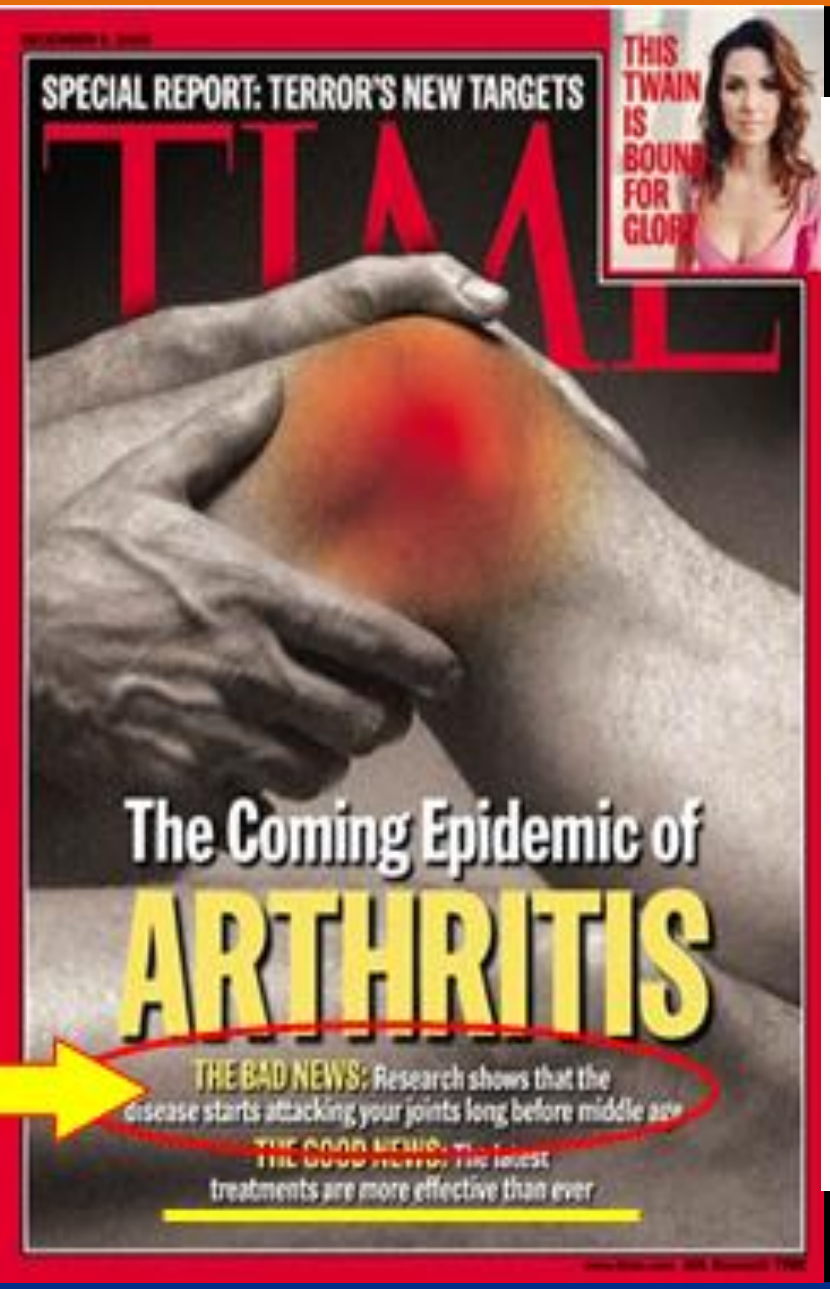
Muscular
- Myofascial pain
- Fatigue
- Twitches

Chest region
- Pain

Stomach
- Nausea

Urinary
- Problems urinating

Joints
- Morning stiffness



Symptoms

Cartilage wears away
Bone ends rub together

Pain may become severe and constant, interferes with normal activities and/or sleep

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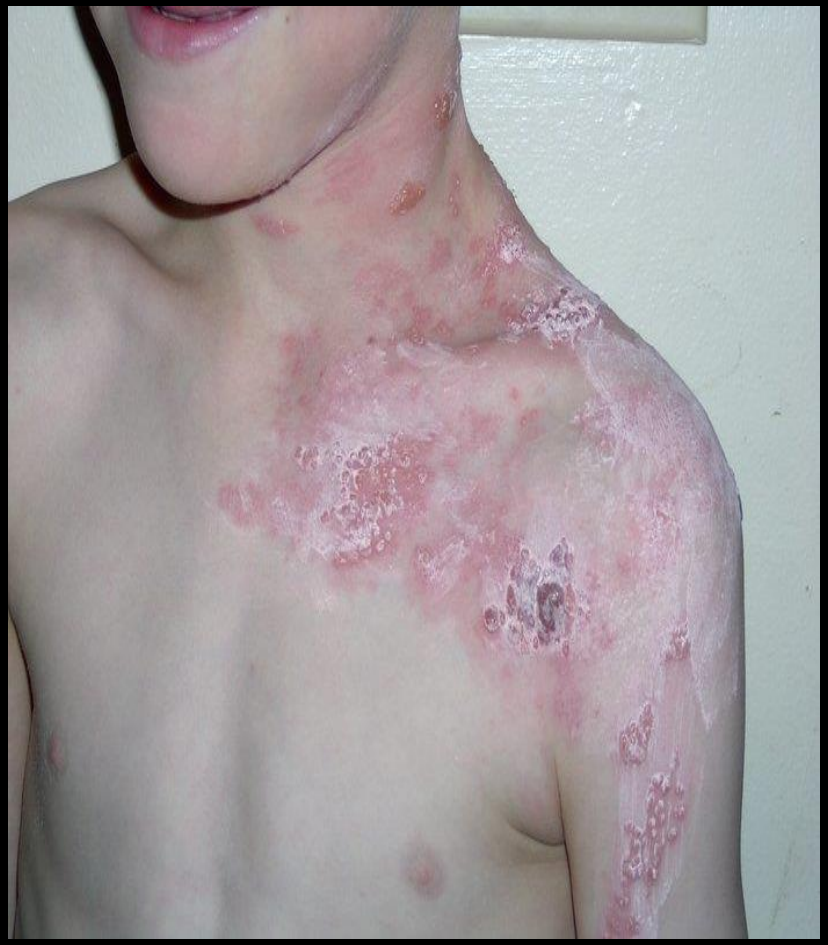
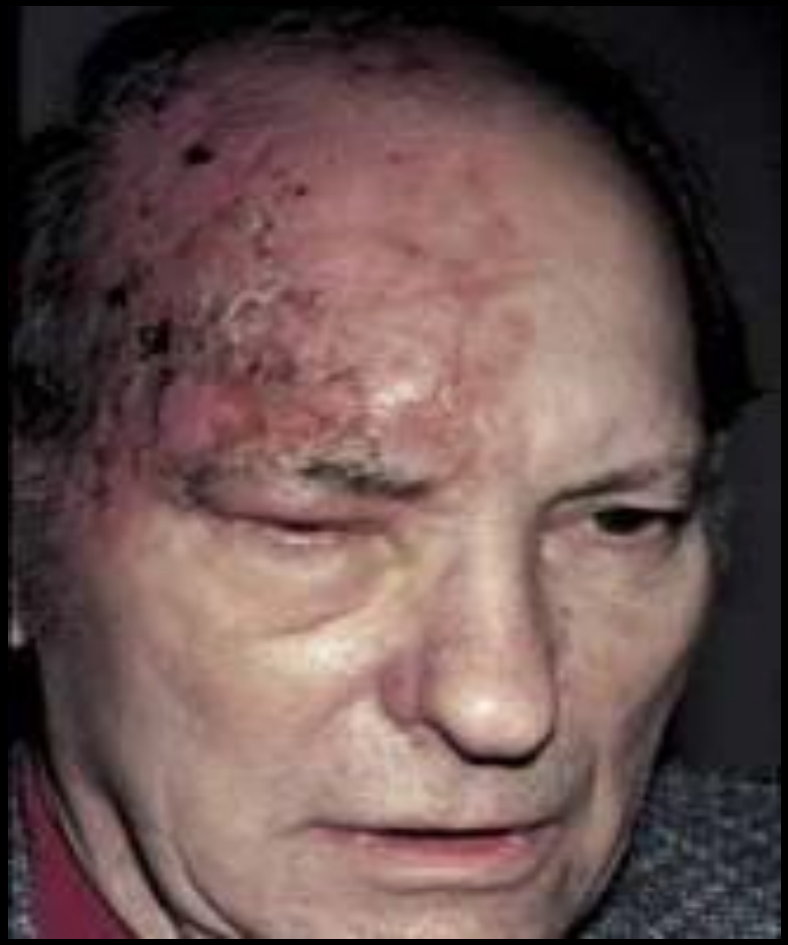
HERPES ZOSTER





RASH MAY APPEAR 2- 10 DAYS AFTER PAIN

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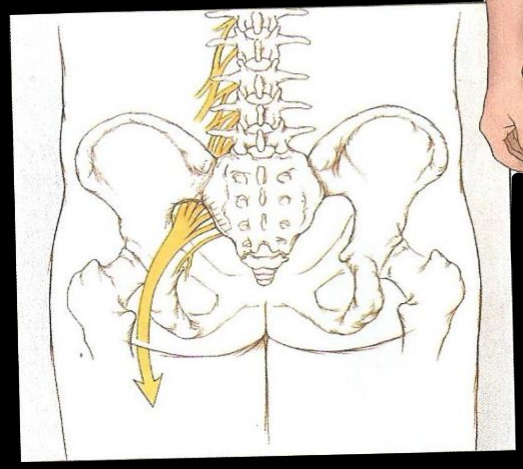
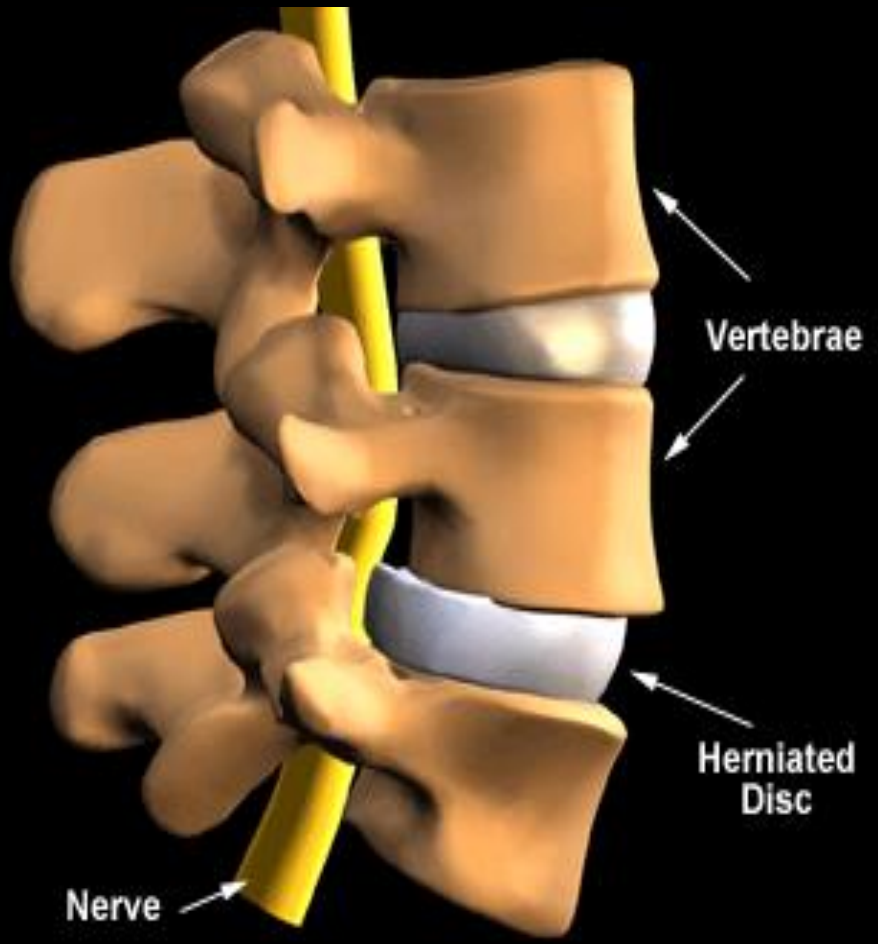
Lumbar radiculopathy- will assume an unnatural posture in na attempt to take pressure off the affected nerve root and relieve pain

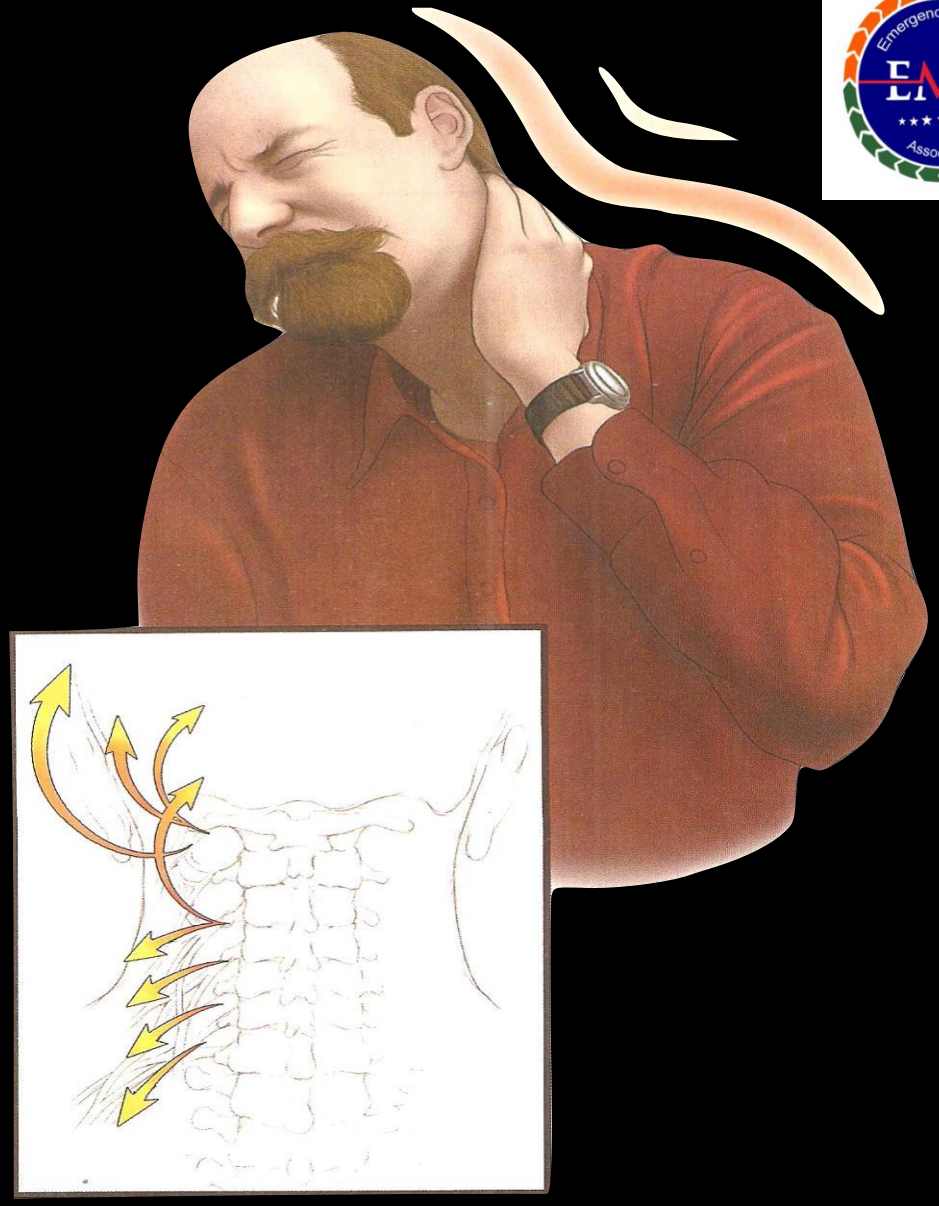


Radiculopathy Model

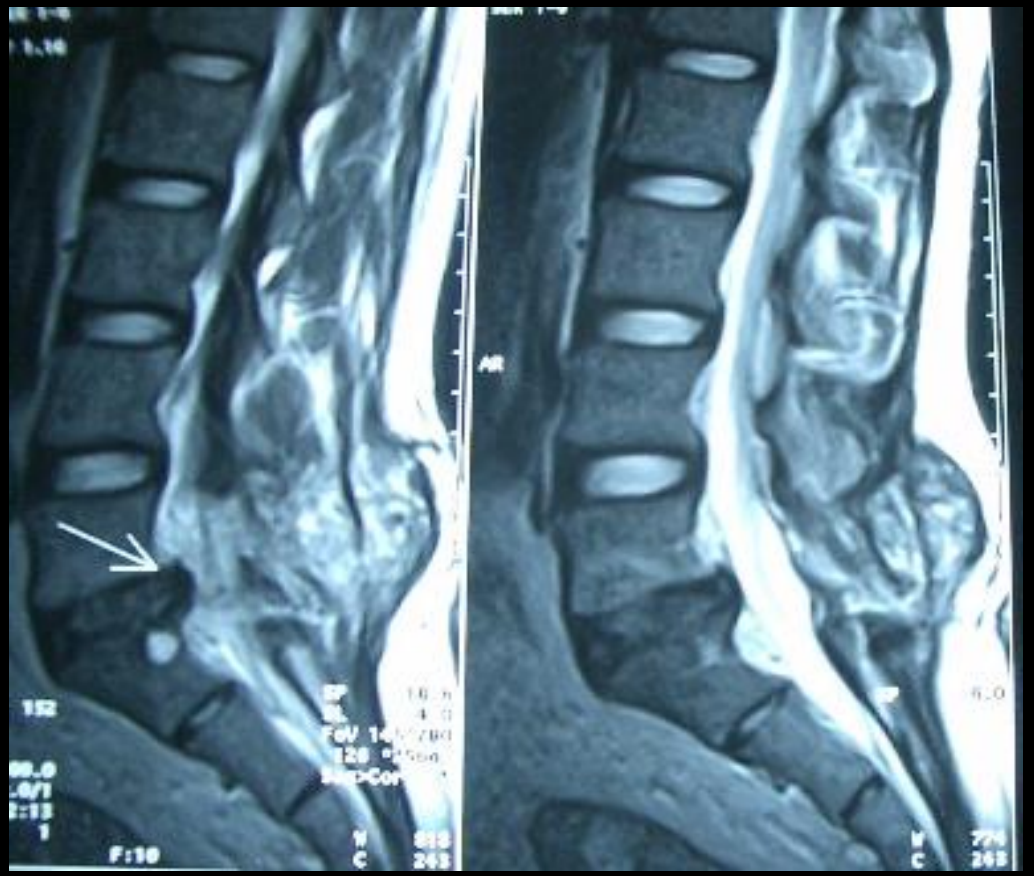
- Spondylosis “ is characterized by degenerative changes in the disc and surrounding structures.
- Victim is the spinal nerve root in the spinal canal or IV foramen.
- Result:attrition of nerve due to pressure, stretch, angulation or friction.



The pain of cervical facet syndrome is made worse by flexion, extension and lateral bending of the cervical spine



- Failed back - Pain persisting even after back surgery
- Aetiology- Adhesions fibrosis around nerves, facet problems, continuing degenerative disease etc



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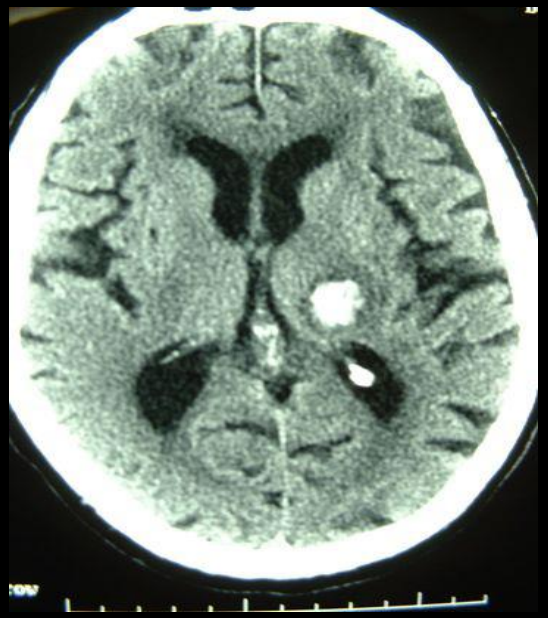
Central post-stroke pain (CPSP)

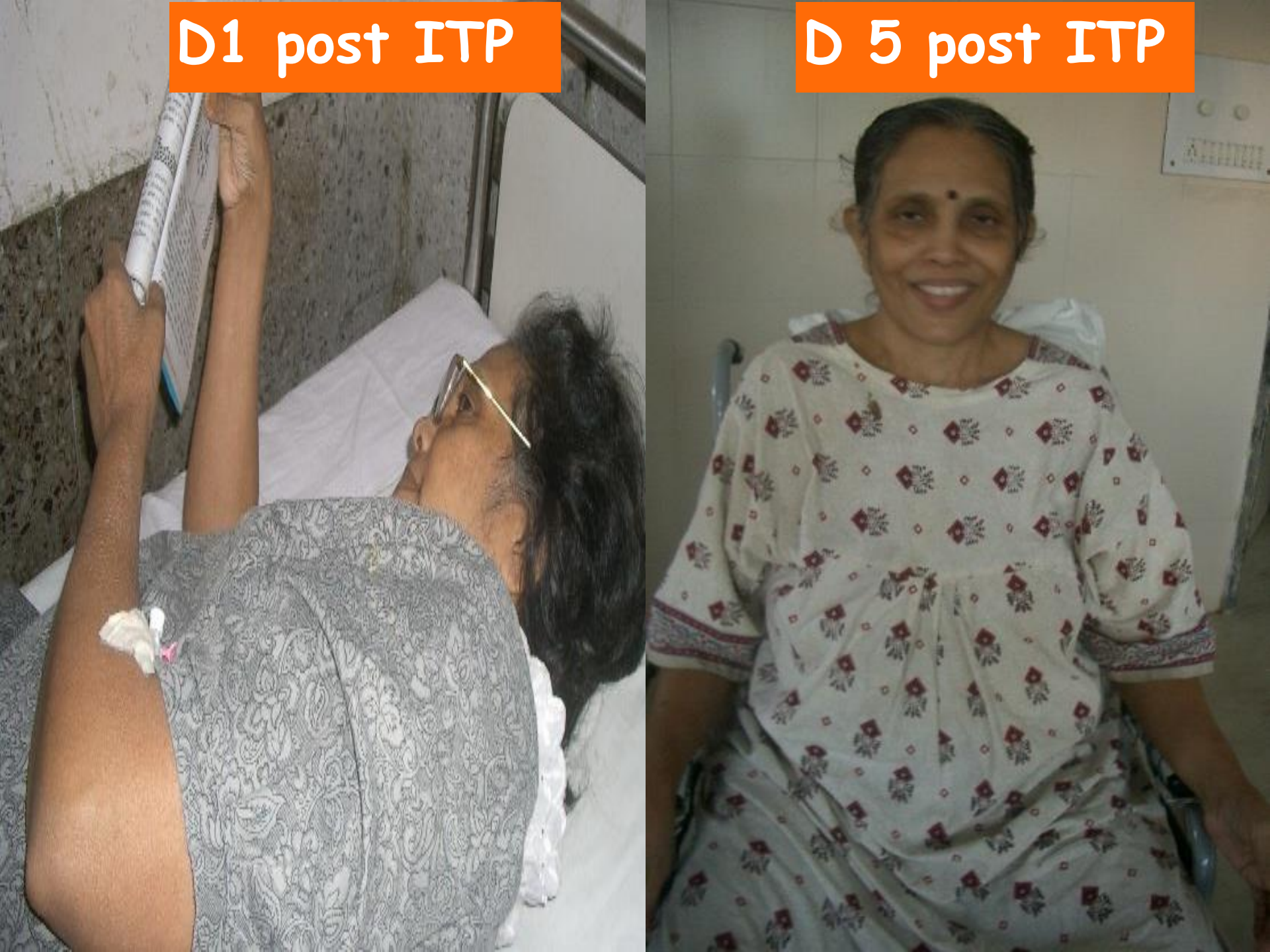
- **Pain occurs in 8% stroke patients**
- **Onset within 6 months**
- **Quality of pain**
  - Lacerating
  - Burning

Thalamic syndrome

- Few days after a thalamic stroke/hemorrhage patient gets new pain or paresthesias
- **Features**
  - Involves UL>LL
  - Burning, tingling, twisting sensation
  - Sensations are less in the area
  - Associated with chorea, dystonia, jerks or tremors
  - Worse with stress, cold weather
  - Difficult to treat

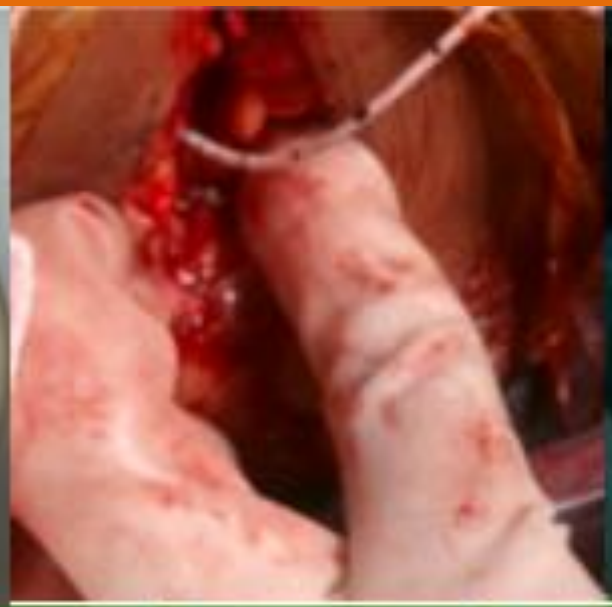



Post Pott' paraplegia: Severe constant buring pain + totally paralyzed, but legs going into flexor spasms every 10-15 m with excruciating pain..
Woman severely demoralized losing weight, exhausted. But cost of ITP unmaageable

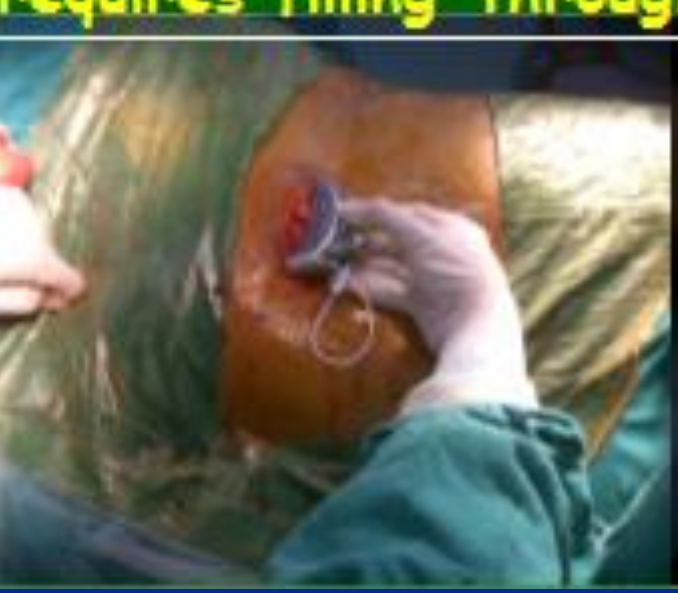

D1 post ITP
D 5 post ITP

Pain is a more terrible lord of mankind than even death itself" Albert Schweizer 1931

49 yr old paediatrician with ovarian cancer with mets. Had 3 surgeries & several cycles of chemo. Constant continuous unrelenting severe pain in abdomen, pelvis radiating to the left leg. No wish to live. RX Immediate IV morphine followed by morphine with infusion pump.

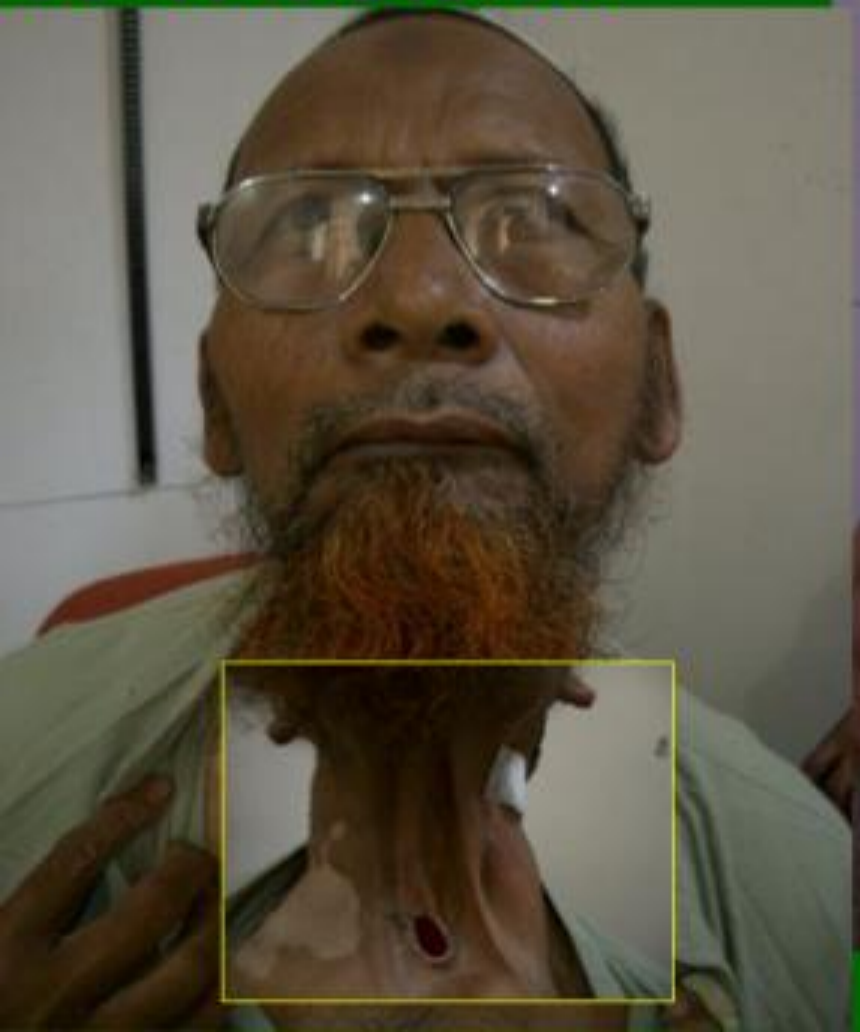


Intrathecal pump implantation for continuous micromg dosing ((0.4mg-4mg/d)of morphine to the spinal cord. Pump requires filling through the skin once in 2-3 m.



Palliative therapy

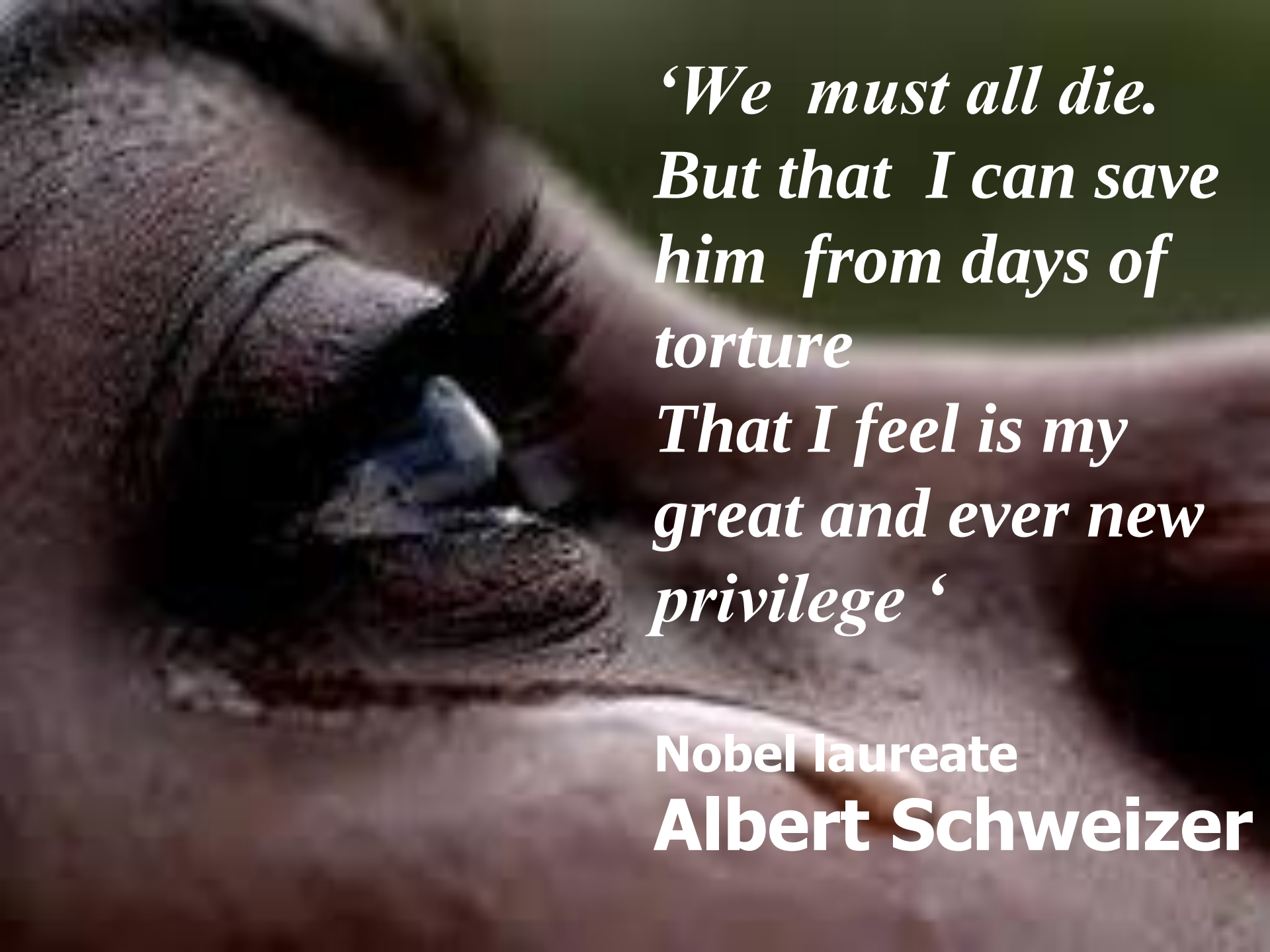
Laryngectomy +RND. Pain In the head neck & chest. Cervical plexus + stellate blk done with LA and Steroid. Still had pain on swallowing. So GPN block.



Immediate post

Patient of mutiple sclerosis
+ Failed back surgery
+ Arachnoiditis
+ Pain from frozen shoulder
+ Ischaemic heart disease
+ Chronic renal failure on biweekly Haemodialysis
+Chronic depression

Millionaire, but bereft of wealth of health
Lonely! Loving but none around to love.


‘We must all die.
But that I can save him from days of torture
That I feel is my great and ever new privilege ‘
Nobel laureate
Albert Schweizer


I CANNOT PREDICT THE FUTURE
I CANNOT CHANGE THE PAST
I HAVE JUST THE PRESENT MOMENT
I MUST TREAT IT AS MY LAST
Thank you

Neurobiology of pain

DR AKKAMAHADEVI. P

Prof & Head, Dept. Of Emergency Medicine

In-charge, pain relief unit

JSS Medical College & Hospital, Mysuru

PAIN

- Derived from Latin word "*peone*" meaning "penalty" or "punishment"
- "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"

-IASP

CLASSIFICATION

BASED ON DURATION:

- **ACUTE**: useful physiologic process
  - Warns the individual about the disease states/ harmful situations
- **CHRONIC:** Pathological with altered anatomy and neural pathways..

  Duration longer than 3 months

  - Expected time to tissue healing

BASED ON PATHOPHYSIOLOGY

NOCICEPTIVE:

Normal nerves transmit information to the central nervous system about trauma to tissues

NEUROPATHIC:

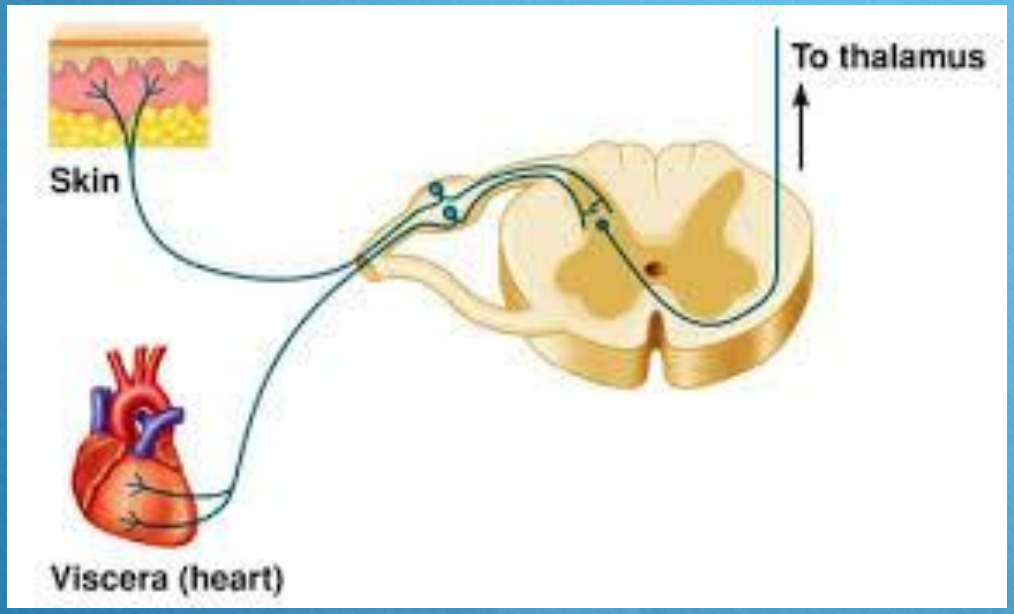
Damage or dysfunction of nerves in the peripheral or central nervous system

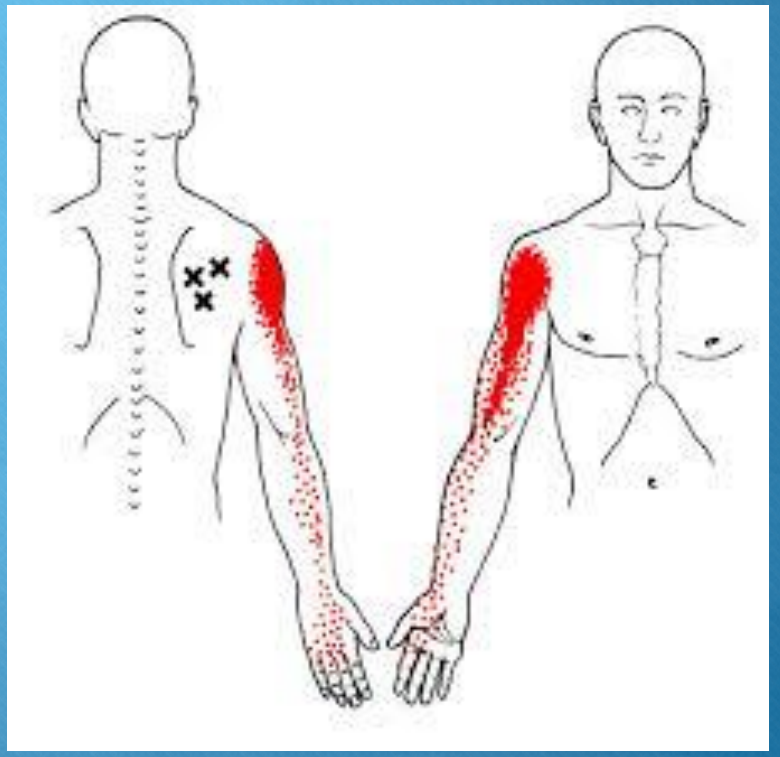
NEURALGIA

Nociceptive pain

- Somatic
- Visceral
  - Ischemia(bradykinin…)
  - Chemical (gastric juice..)
  - Spasm (overdistension)

Referred pain





BASED ON CAUSE

- Cancer
- Non cancer

Transduction- Transmission- Perception- Modulation

PAIN PATHWAY

Transduction

- Pain is produced by the noxious stimuli (nociceptors) which are there at free nerve endings of primary afferent terminals (Aδ and C)fibres.

- Action potentials are generated at nociceptors (transduction), carried to higher cortical centres(transmission).

Transmission

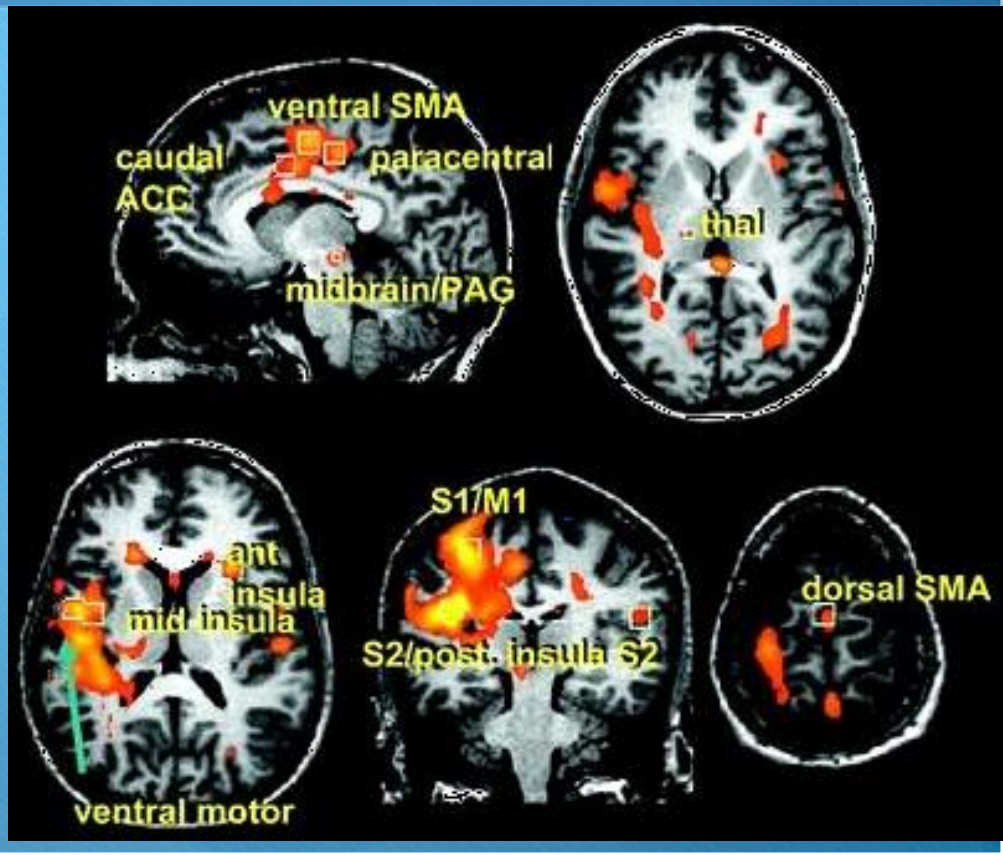
- First order neurons: periphery to the dorsal horn
- Second order neurons: contralateral spinothalamic tract to thalamus.
- Third order neurons: thalamus to somatosensory cortex(postcentral gyrus) →PERCEPTION

Perception

- Post-central gyrus

Areas of brain stimulated in Pain

- Post-central gyrus
- Limbic nuclei
- Reticular network
- Periaqueductal grey

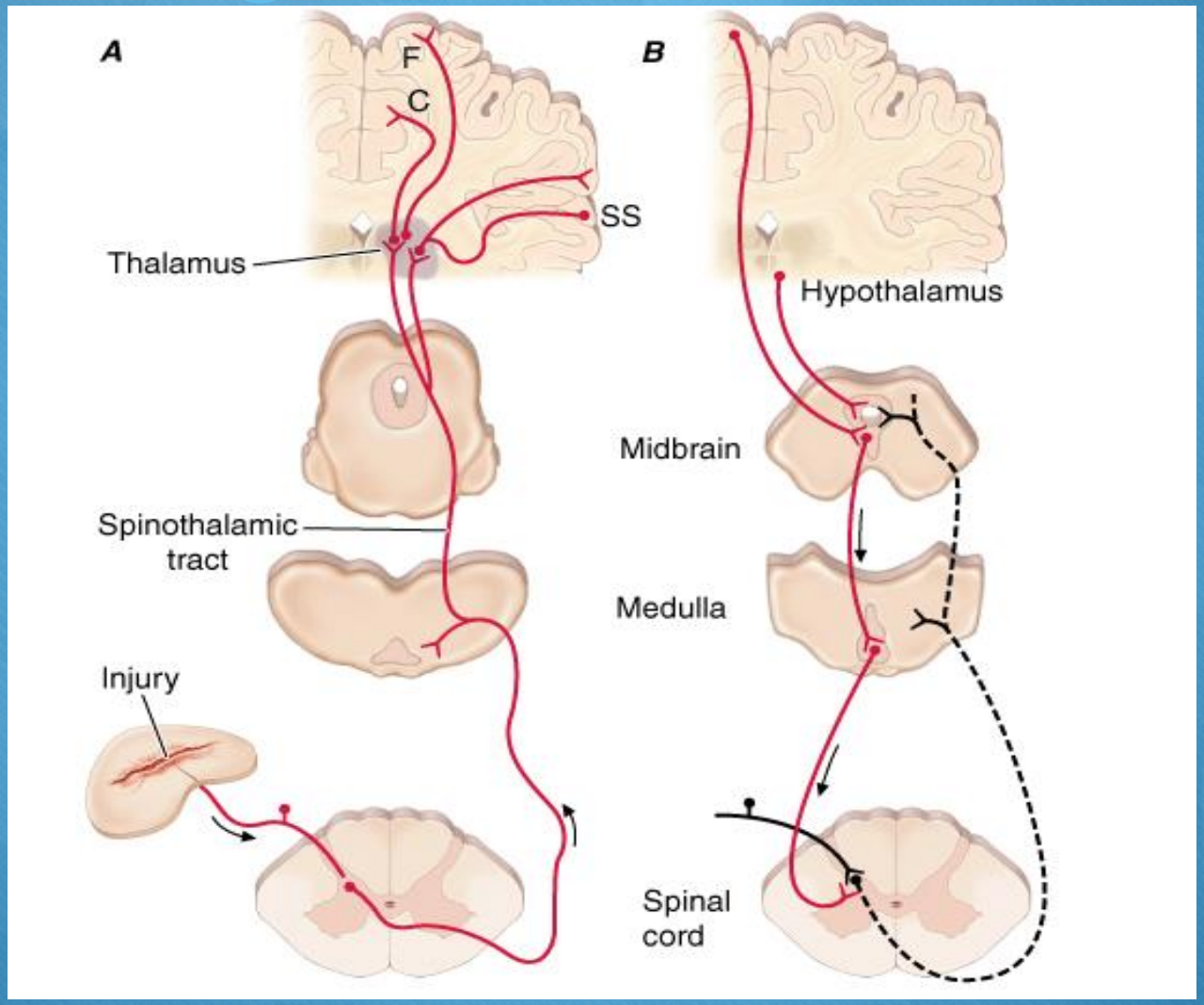


Modulation

- Neural process- reduce the activity in the pain transmission system and reduce the perception of pain in healthy individual.
- Modulation can also increase pain perception in patients suffering from chronic pain.

Modulation

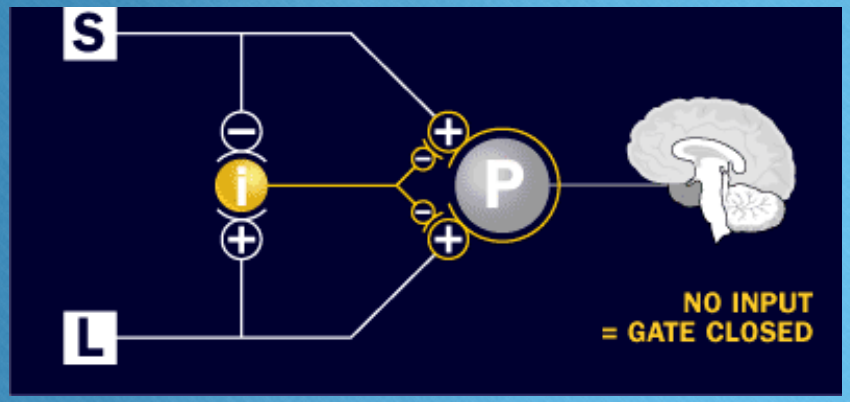
- Descending inhibitory system
- Gate Control therory
- Endogenous pain modulation system: Endogenous opioids (endorphins, enkephalins and dynorphins) acts on the opioid receptors present in the dorsal horn results in presynaptic inhibition.
- Segmental inhibition: By the release of inhibitory neurotransmitter (glycine and GABA)

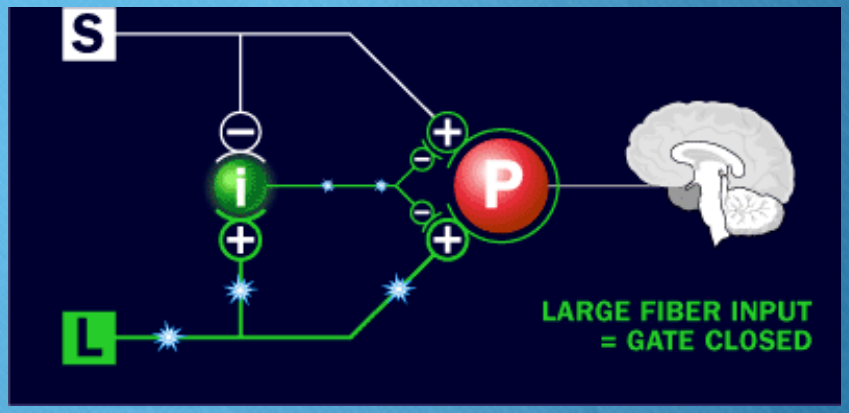


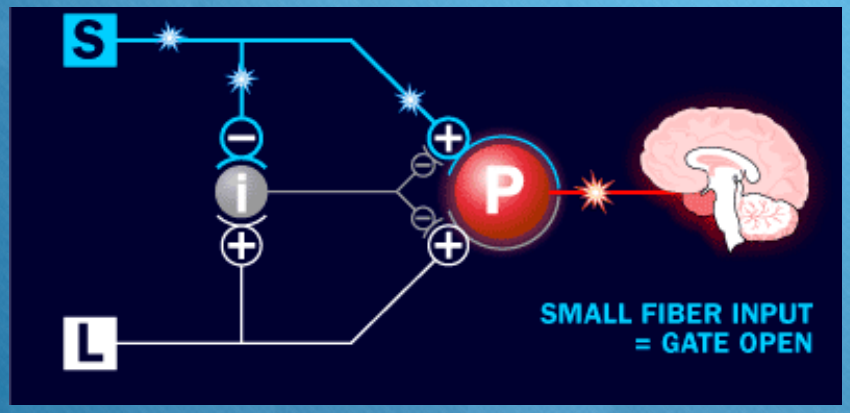
Transmission of nociceptive impulses

Pain modulation network

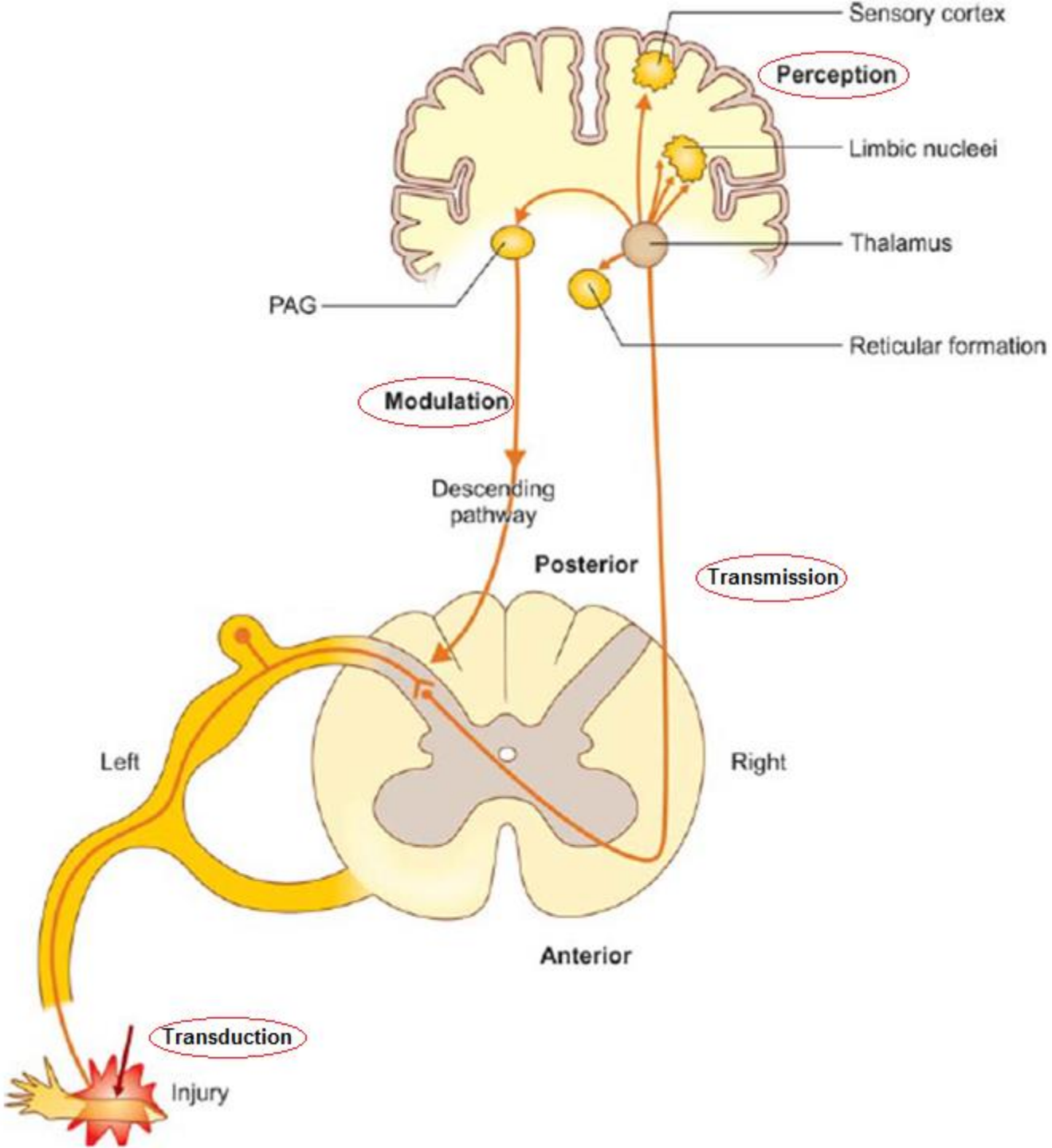
Gate control theory

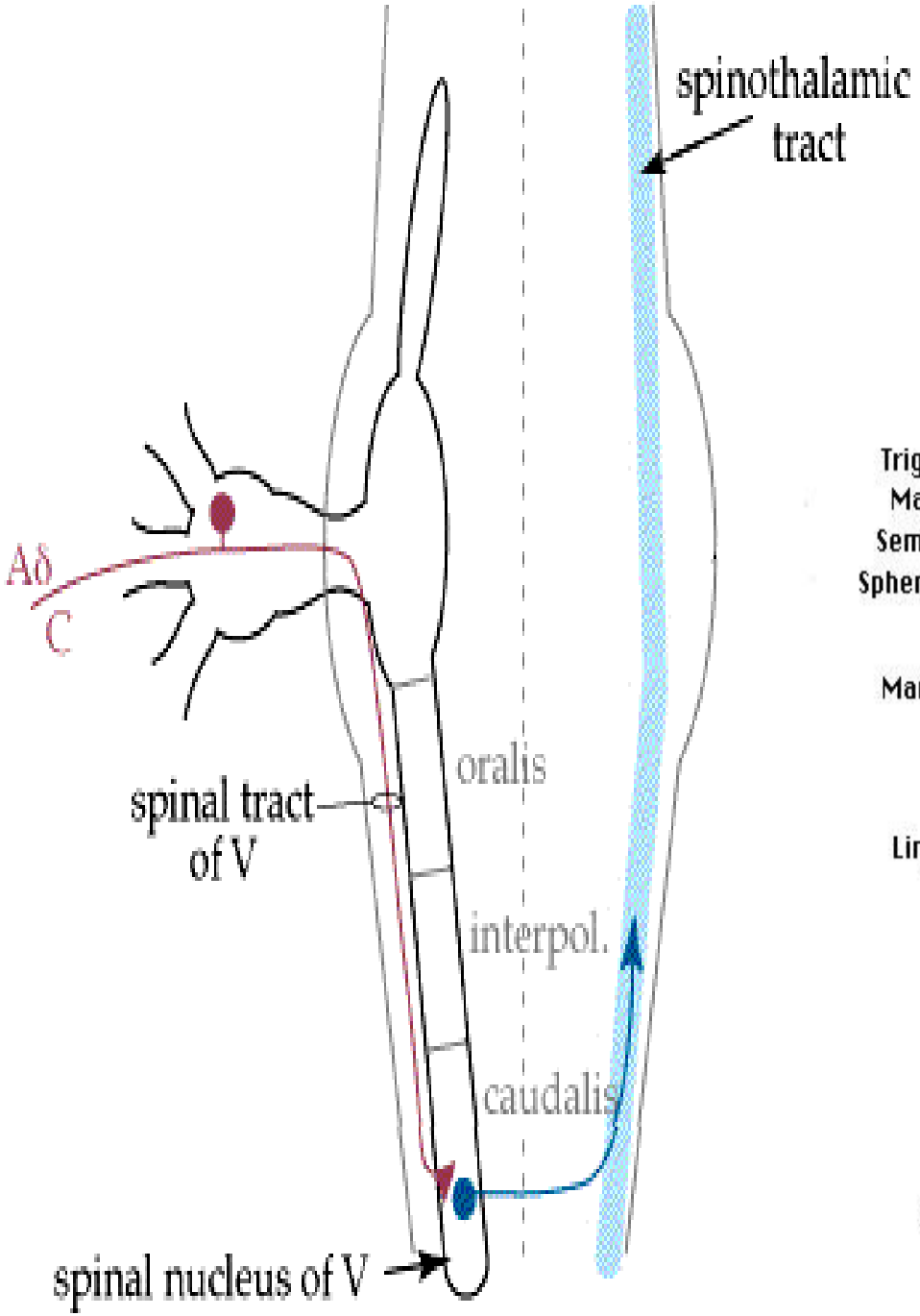


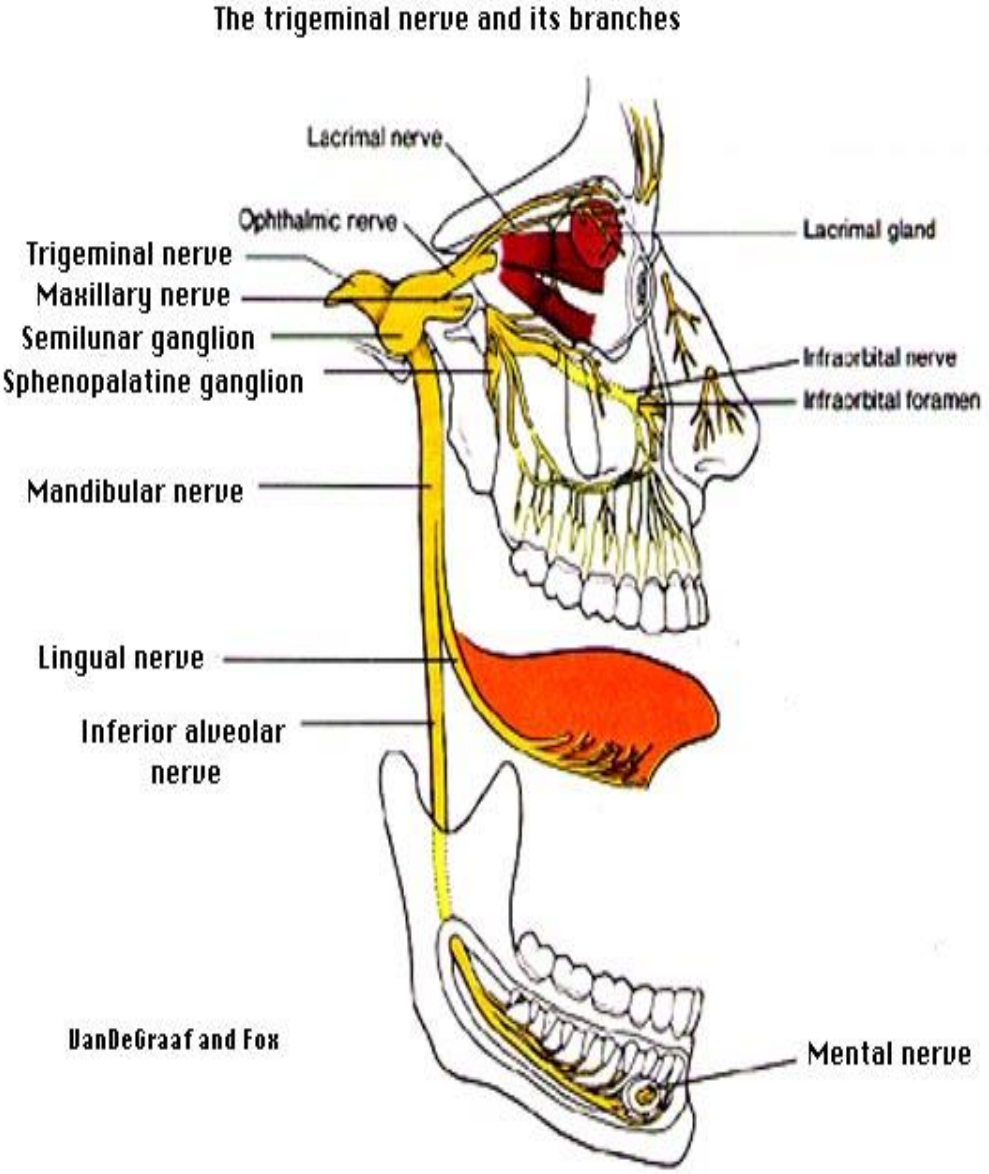




S Small Nerve Fibers
L Large Nerve Fibers
i Inhibitory Neuron
P Projection Cells


Sensory cortex
Perception
Limbic nucleei
Thalamus
PAG
Reticular formation
Modulation
Descending pathway
Posterior
Transmission
Left
Right
Anterior
Transduction
Injury


spinothalamic tract
Aδ
C
spinal tract of V
oralis
interpol.
caudalis
spinal nucleus of V


The trigeminal nerve and its branches
Lacrimal nerve
Ophthalmic nerve
Trigeminal nerve
Maxillary nerve
Semilunar ganglion
Sphenopalatine ganglion
Mandibular nerve
Lingual nerve
Inferior alveolar nerve
Lacrimal gland
Infraorbital nerve
Infraorbital foramen
Mental nerve
VanDeGraaf and Fox

AUTONOMIC NERVOUS SYSTEM

- Maintains homeostasis in the body
- Plays important role in different kinds of pain
  - e.g. Pain from thoracic or abdominal viscera and intervertebral disc & vertebral body are carried by afferent & efferent sympathetic fibres.

AUTONOMIC NERVOUS SYSTEM

SYMPATHETIC SYSTEM

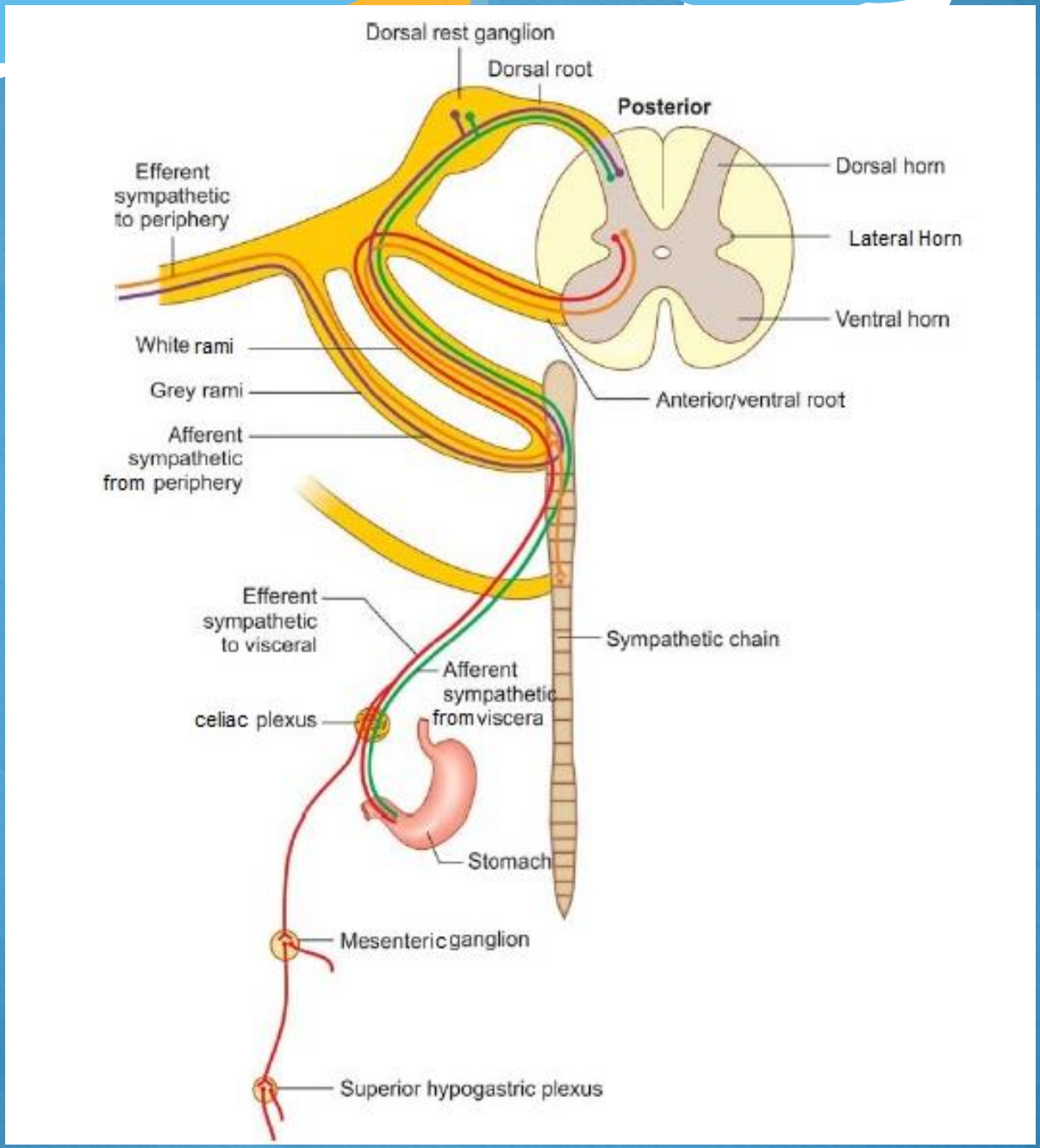
Thoraco - lumbar outflow region of Spinal cord spinal nerve T1-L2

PARASYMPETHETIC SYSTEM

- Cranio-sacral outflow come to periphery through of
- 3^{r}(occulomotor),
- 7th(facial),
- 9th (glossopharyngeal),
- 10th(Vagus) cranial nerves and
- S2-S3 Sacral nerves

SYMPATHETIC NERVOUS SYSTEM

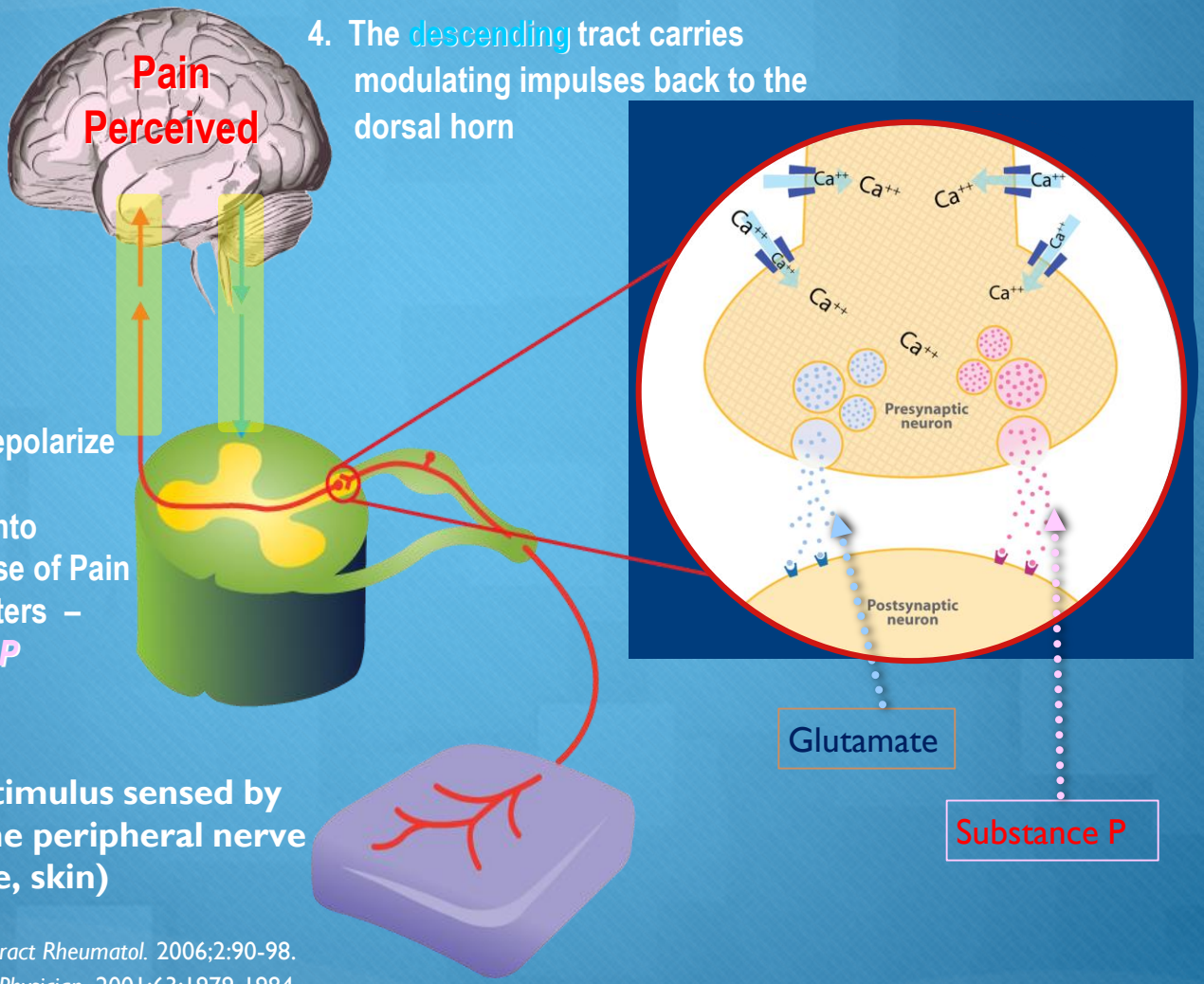
- There are both afferent and efferent sympathetic system and both supply viscera as well as periphery via somatic nerves.
- Efferent sympathetic outflow originates in the lateral horn of the spinal cord from segments T1-L2.
- Sympathetic Chain
  - Situated at the anterolateral border of spine
  - Contains sympathetic ganglions
  - Extends from the base of skull to the coccyx and lie on either side of the vertebral body


Dorsal rest ganglion
Dorsal root
Posterior
Dorsal horn
Lateral Horn
Ventral horn
Efferent sympathetic to periphery
White rami
Grey rami
Afferent sympathetic from periphery
Anterior/ventral root
Efferent sympathetic to visceral
Sympathetic chain
Afferent sympathetic from viscera
celiac plexus
Stomach
Mesenteric ganglion
Superior hypogastric plexus

THE NORMAL PAIN PROCESSING PATHWAY

3. A signal is sent via the ascending tract to the brain, and perceived as pain

4. The descending tract carries modulating impulses back to the dorsal horn

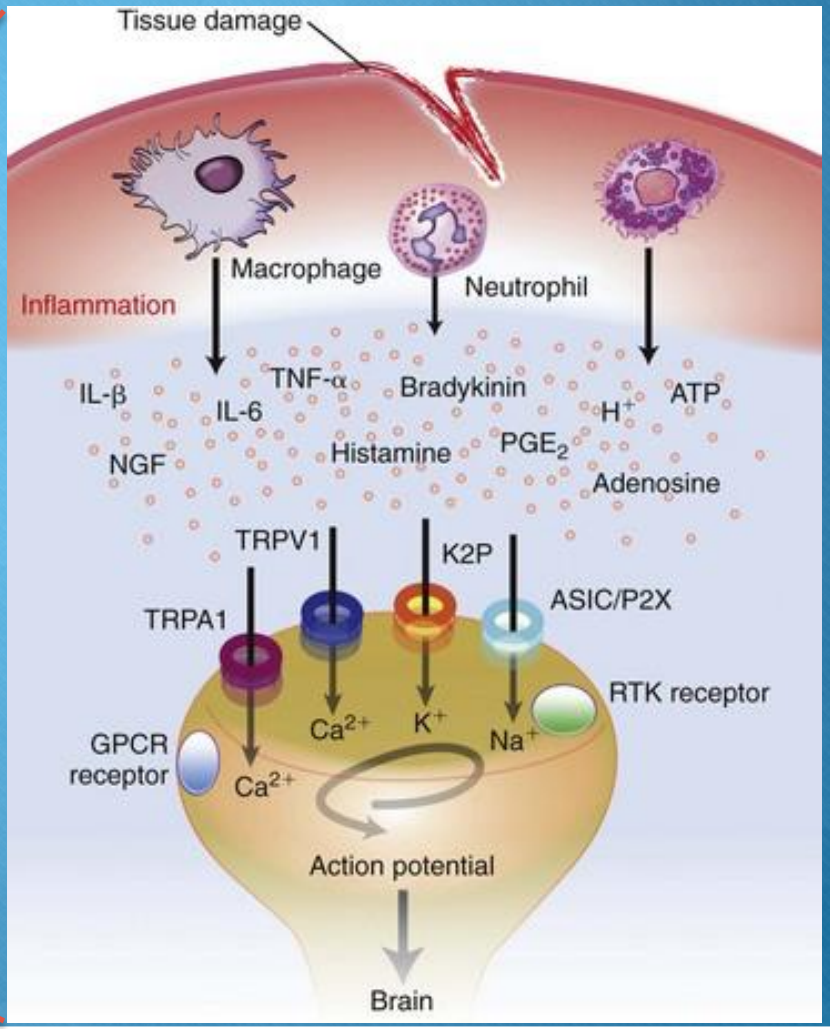


2. Impulses from afferents depolarize dorsal horn neurons, then, extracellular Ca^{2+} diffuse into neurons causing the release of Pain Associated Neurotransmitters – *Glutamate* and *Substance P*

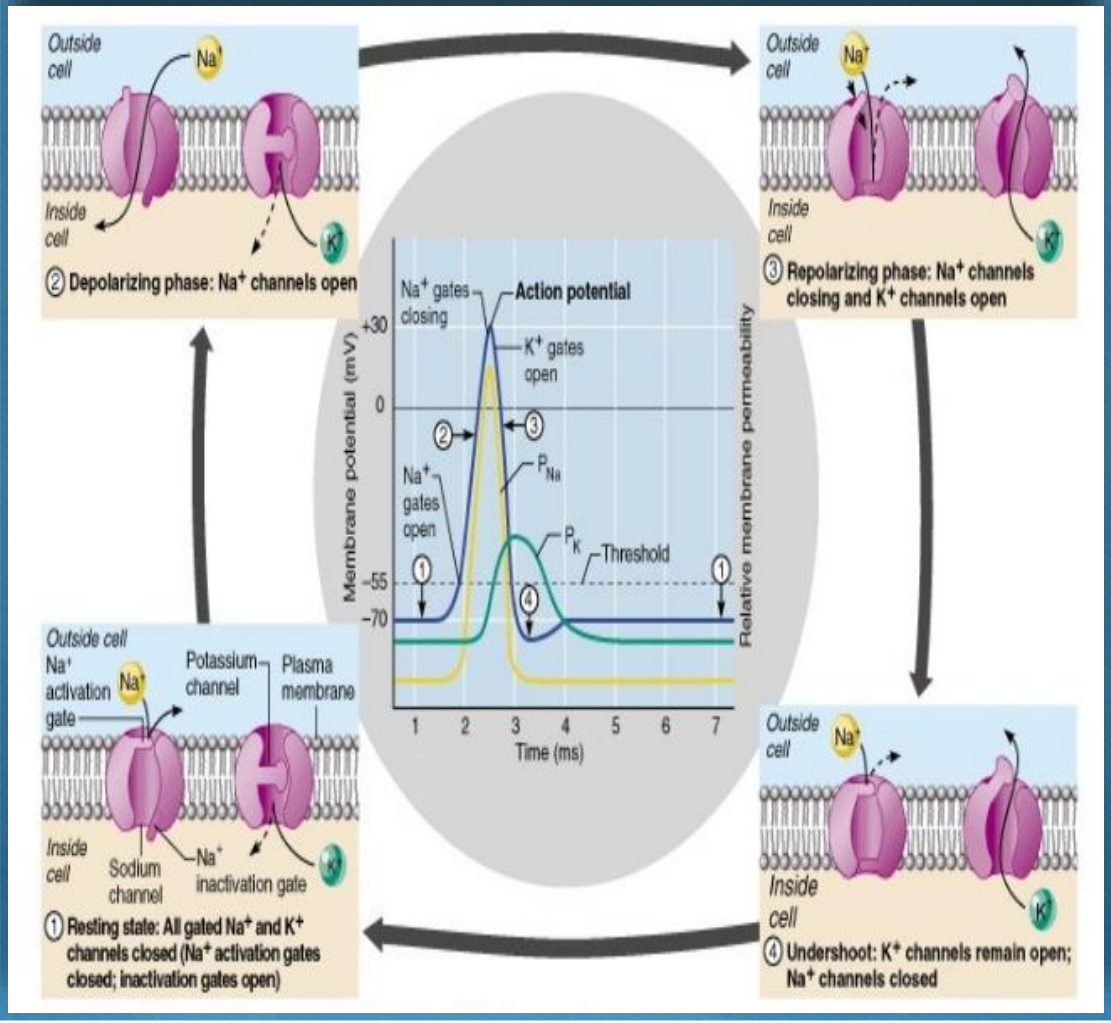
1. Stimulus sensed by the peripheral nerve (ie, skin)

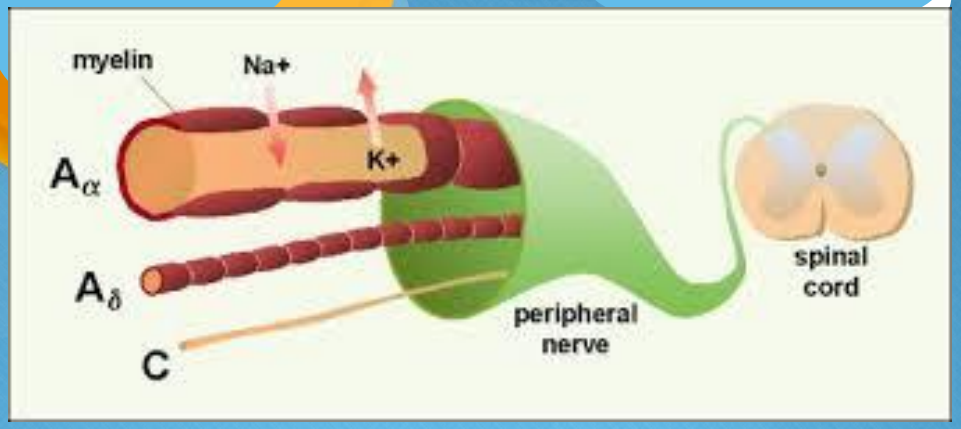
1. Staud R and Rodriguez ME. *Nat Clin Pract Rheumatol.* 2006;2:90-98.
2. Gottschalk A and Smith DS. *Am Fam Physician*. 2001;63:1979-1984.

AT THE PERIPHERAL NERVE LEVEL



GENERATION OF ACTION POTENTIAL



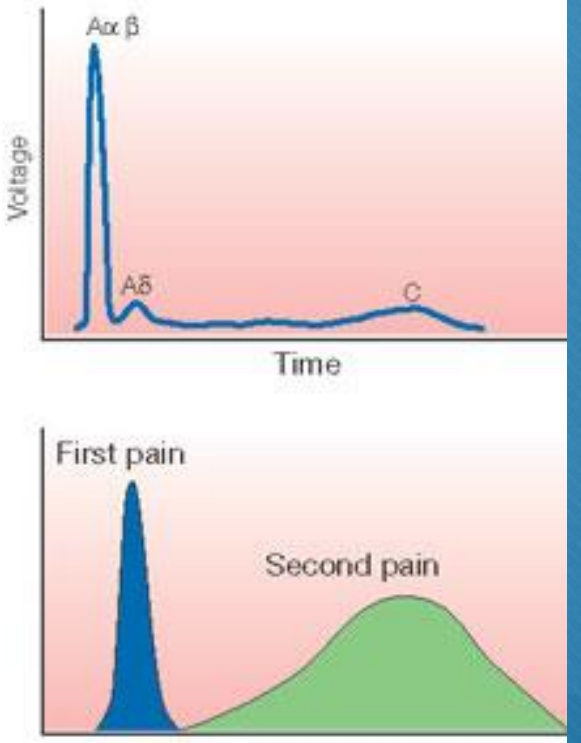


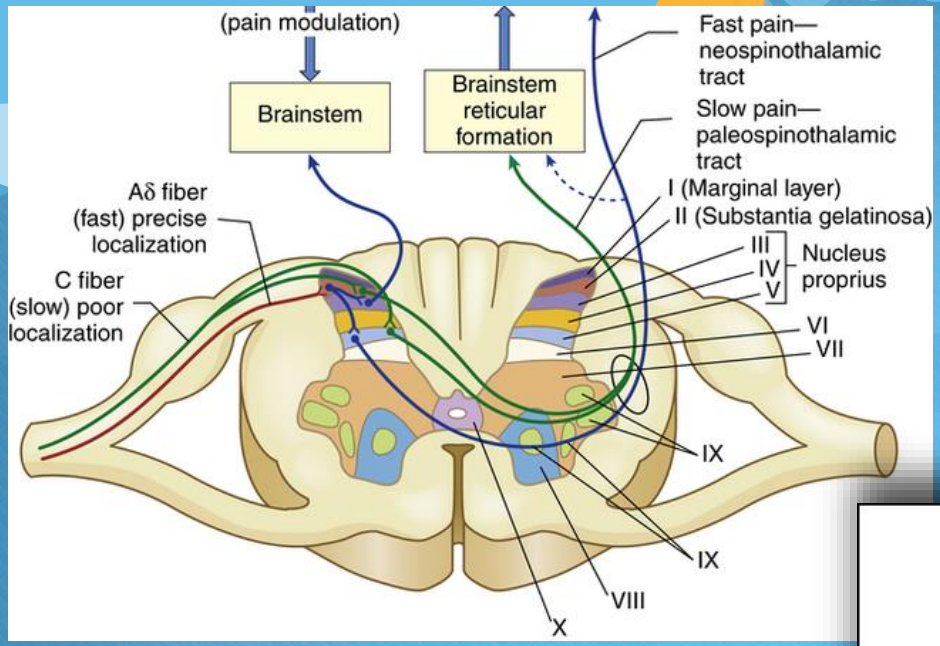
a

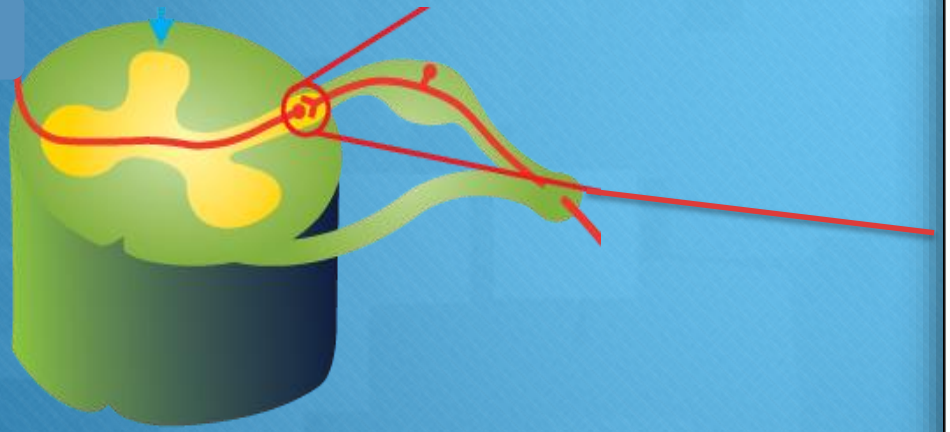
Primary afferent axons

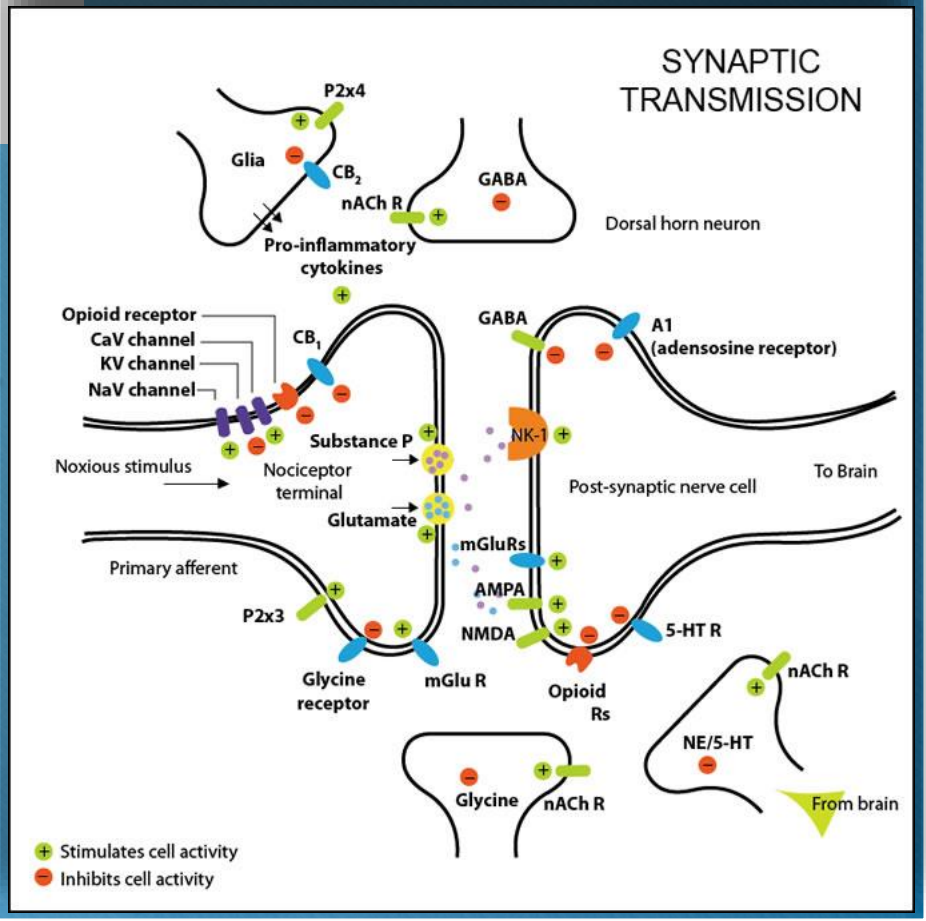
		Thermal threshold
Aα and Aβ fibres	Myelinated Large diameter Proprioception, light touch	None
Aδ Fibre	Lightly myelinated Medium diameter Nociception (mechanical, thermal, chemical)	~ 53 °C Type I ~ 43 °C Type II
C fibre	Unmyelinated Small diameter Innocuous temperature, itch Nociception (mechanical, thermal, chemical)	~ 43 °C

b

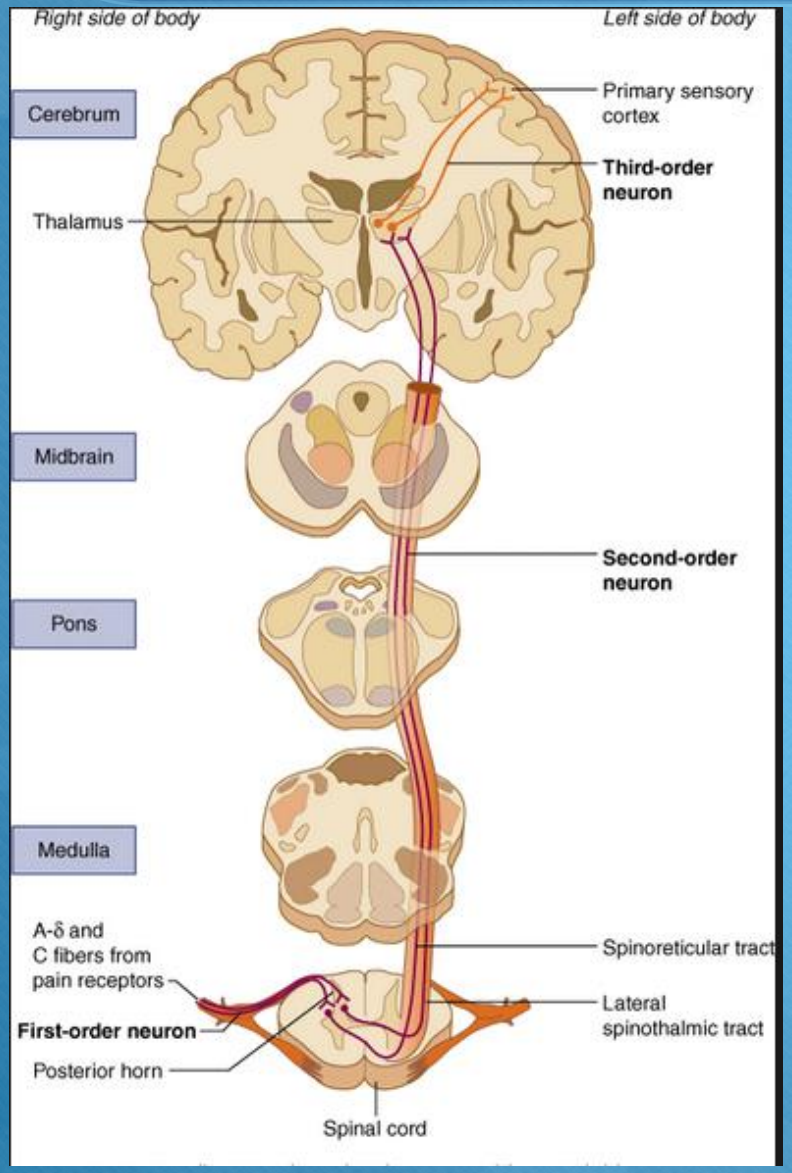


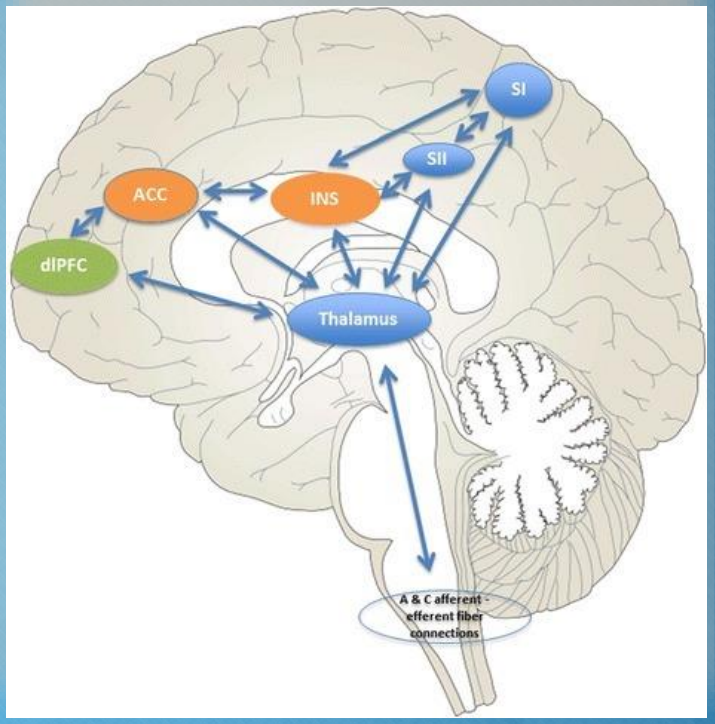

(pain modulation)
Brainstem
Brainstem reticular formation
Fast pain—neospinothalamic tract
Slow pain—paleospinothalamic tract
I (Marginal layer)
II (Substantia gelatinosa)
III
IV
V
Nucleus proprius
VI
VII
IX
IX
VIII
X
Aδ fiber (fast) precise localization
C fiber (slow) poor localization



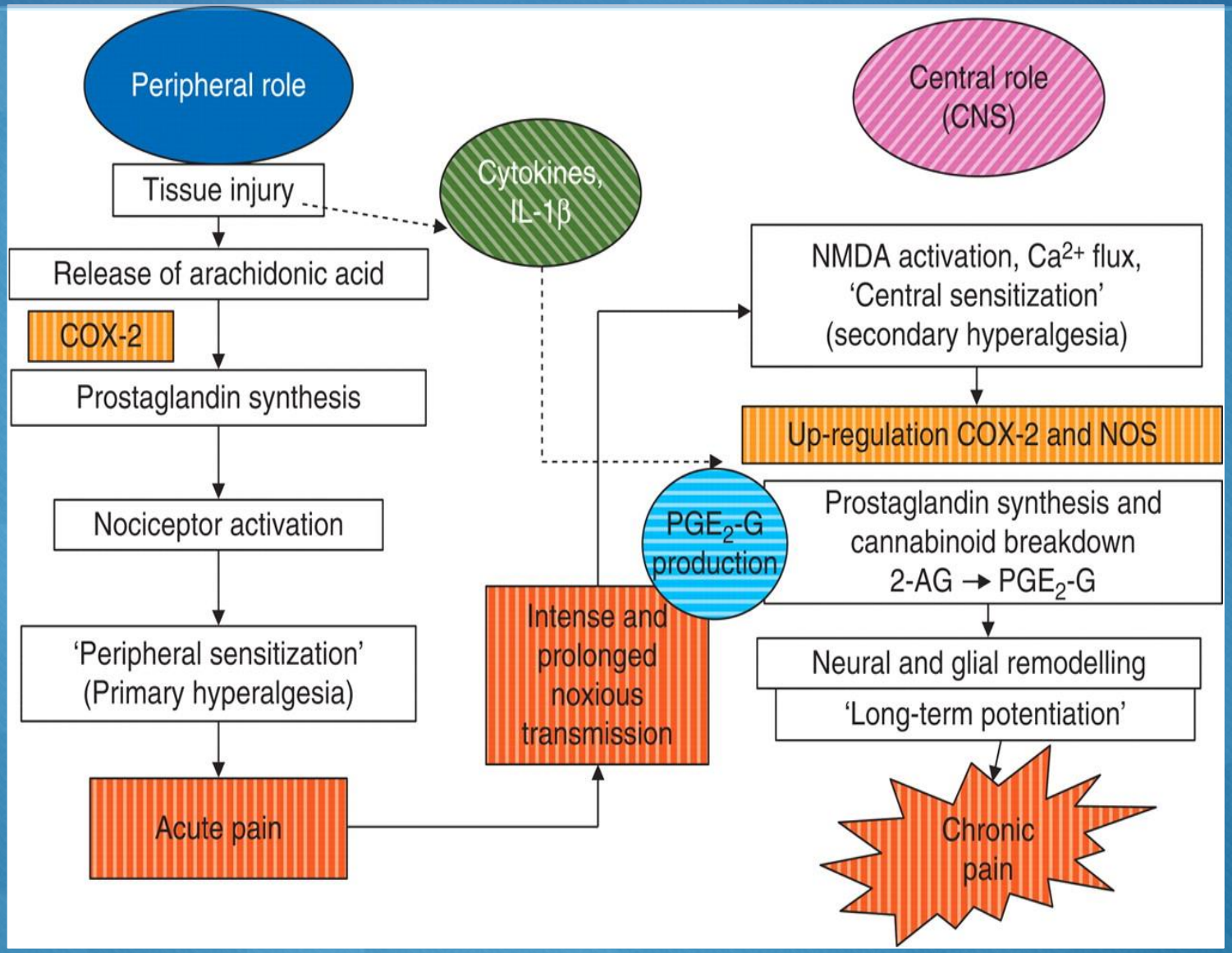

SYNAPTIC TRANSMISSION
P2x4
Glia
CB2
nACh R
GABA
Pro-inflammatory cytokines
Dorsal horn neuron
Opioid receptor
CaV channel
KV channel
NaV channel
CB1
GABA
A1 (adensosine receptor)
Substance P
NK-1
Noxious stimulus
Nociceptor terminal
Post-synaptic nerve cell
To Brain
Glutamate
mGluRs
Primary afferent
AMPA
P2x3
NMDA
5-HT R
Glycine receptor
mGlu R
Opioid Rs
nACh R
NE/5-HT
Glycine
nACh R
From brain
Stimulates cell activity
Inhibits cell activity

Basic pain pathway





Acute to chronic pain



Pathophysiology of Neuropathic Pain

- Sensitization
- IASP define sensitization as “Increased responsiveness of nociceptive neurons to their normal input, and/or recruitment of a response to normally sub threshold inputs.” Sensitization is a key feature of neuropathic pain.

Peripheral Sensitization

IASP defines it as “Increased responsiveness and reduced threshold of nociceptive neurons in the periphery to the stimulation of their receptive fields.”

Factors in peripheral sensitization

- Sensitization of primary afferent terminals.
- Upregulation of active nociceptors
- Damaged axons sprout, forms collaterals.
- Ectopic discharges along nerve axon, terminals & at DRG.
- SNS fibers invade DRG.
- Phenotypic switch in expression of neuropeptides like Sub P, CGRP.

Central Sensitization

IASP defines central sensitization as "Increased responsiveness of nociceptive neurons in the central nervous system to their normal or sub threshold afferent input."

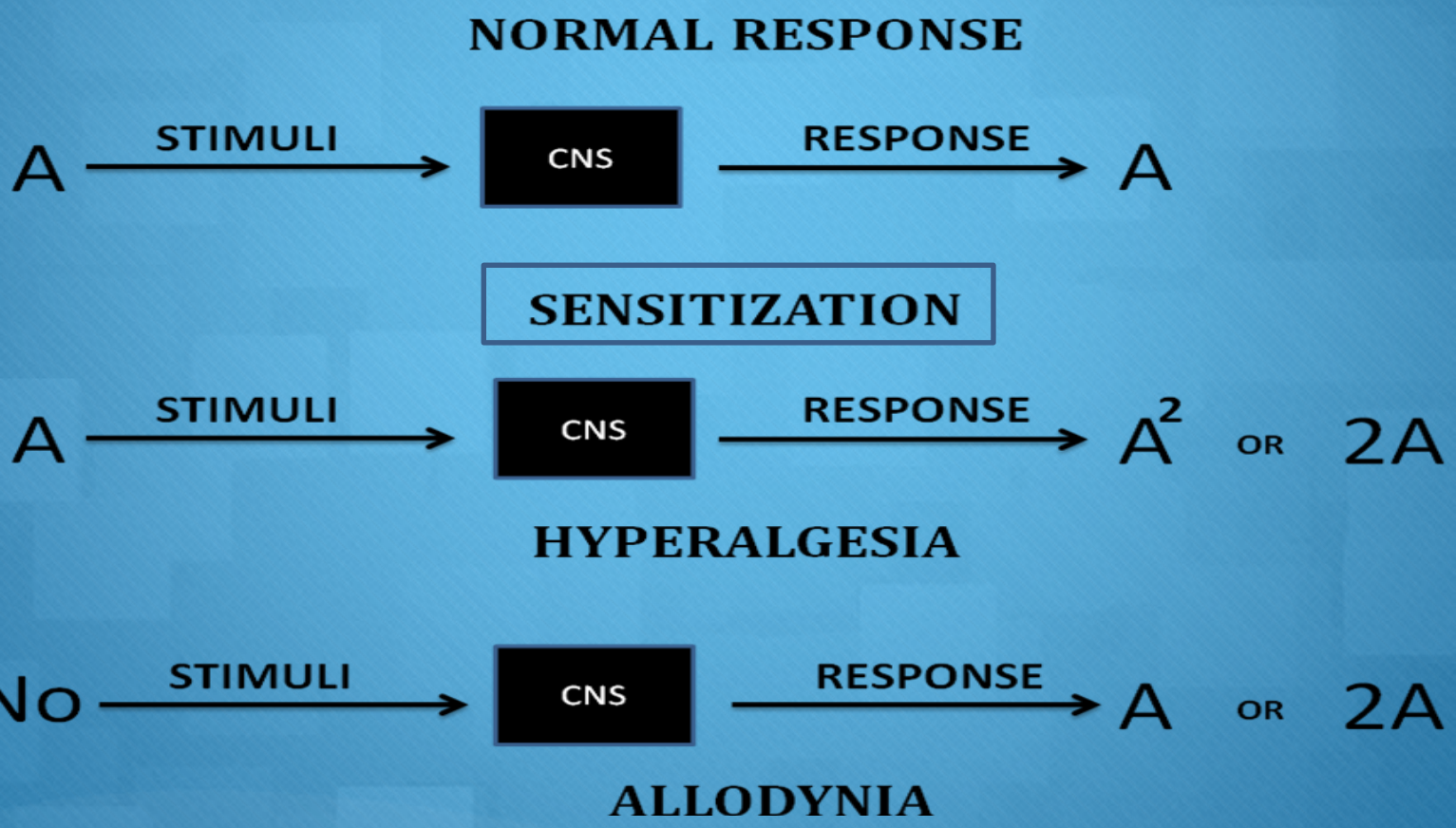
Factors that play a role in central sensitization

- Central Reorganisation.
- Wind up (summation of signals)
- Up-regulation of NMDA receptor
- Ectopic activity
- Depression inhibitory synapses
- Activation of WDR cells.

Results of sensitization

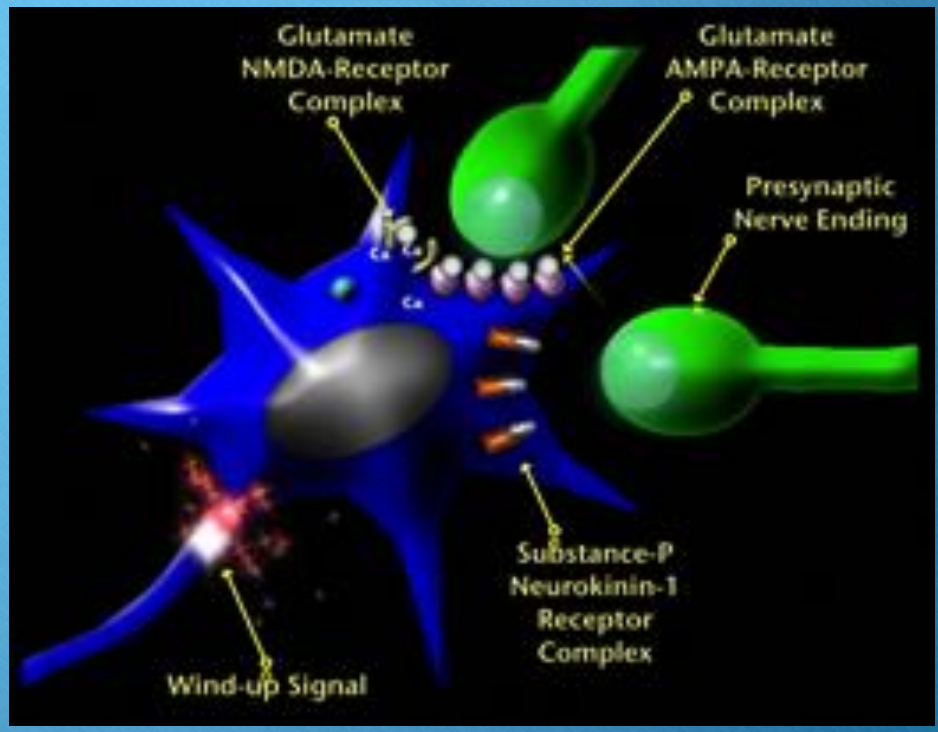
- Increase in the intensity, area and duration of pain
- Decrease in the tolerability of pain
- Development of psychological problems
- Pain becomes unresponsive to conventional analgesics.

Central (Spinalcord)Sensitization: A Theory for Chronic Pain



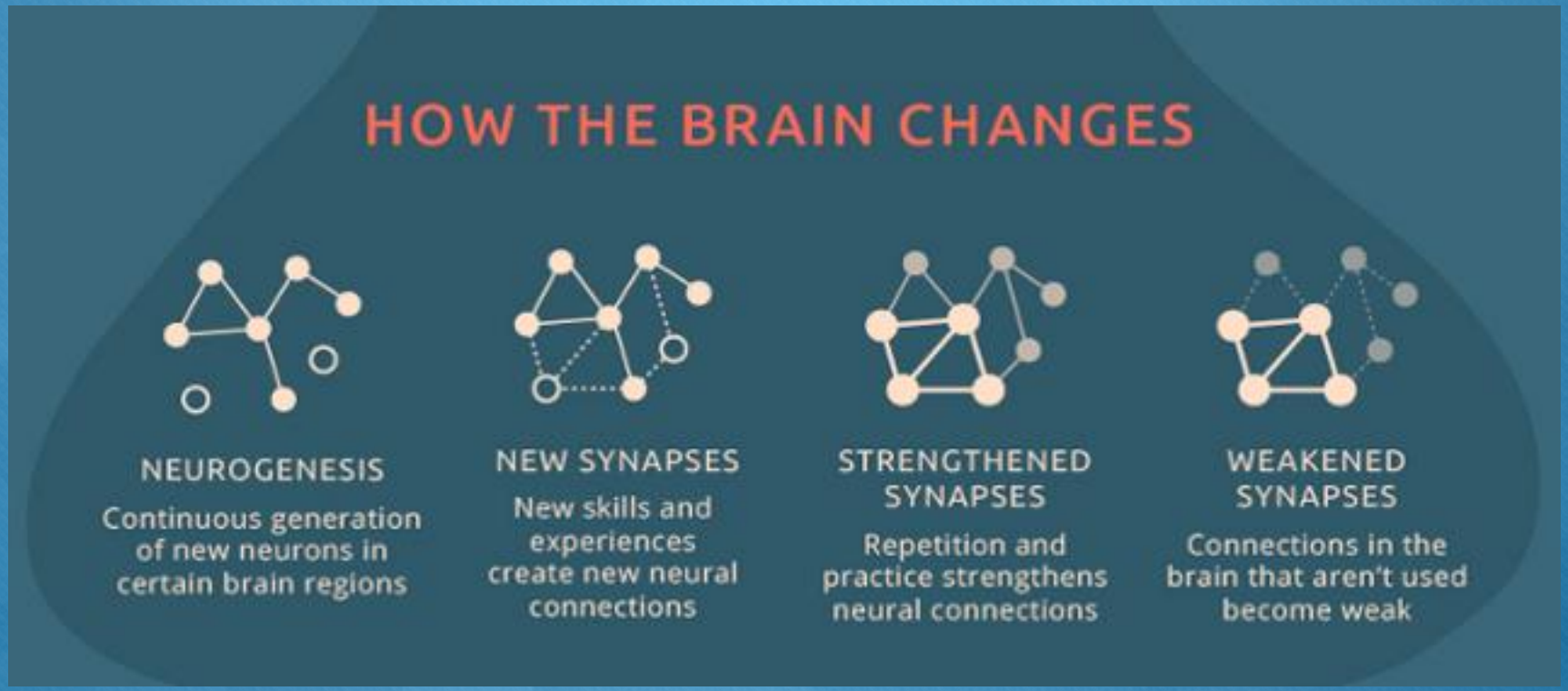
Wind-up phenomenon

- It is perceived as increase in pain intensity over time when a given stimulus is delivered repeatedly above a critical rate.
- Spinal neurons become progressively and increasingly excitable even after the stimulus is removed- central sensitization or wind-up phenomenon

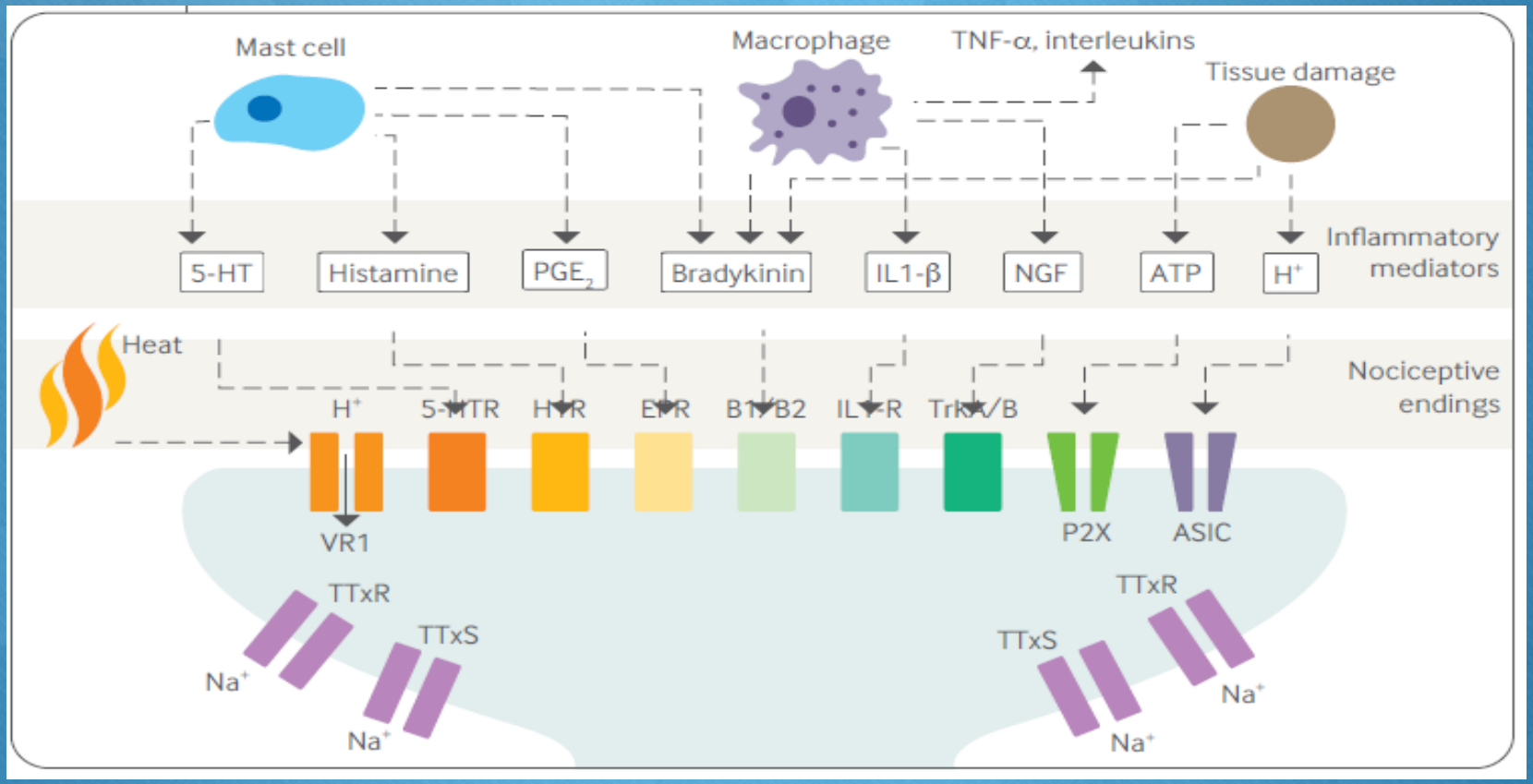


Neuroplasticity

- Capacity to change function, chemical profile and structure

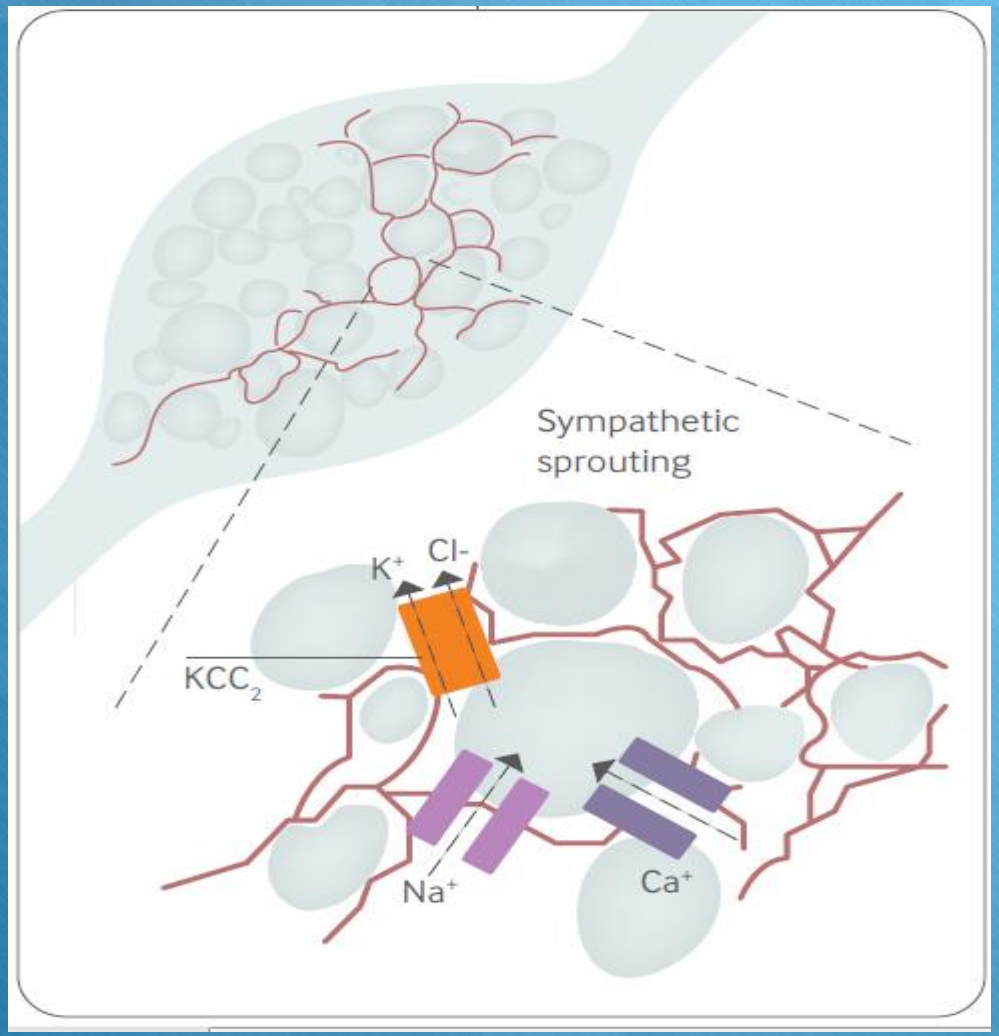


PERIPHERAL NERVE ENDING



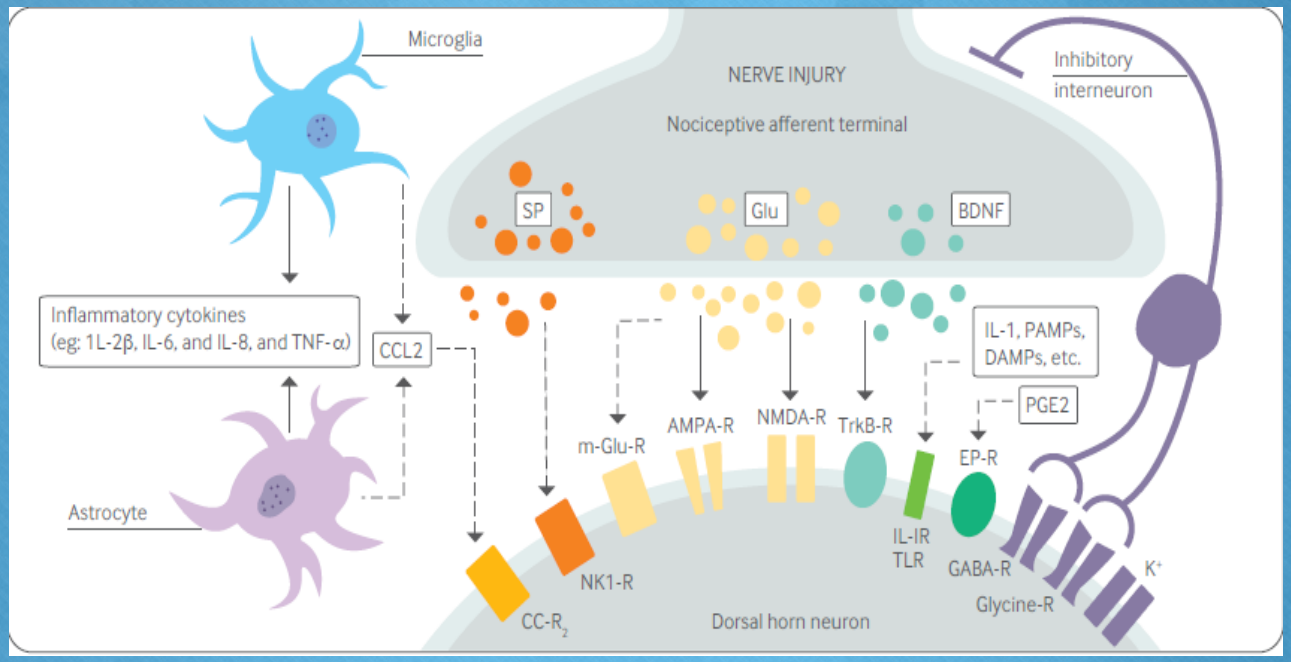
- Inflammatory mediator soup- sensitizes nociceptors- **no single effective drug**
- Unmasking of silent nociceptors
- Phenotypic switch
- Increased expression (proliferation) of sodium channels – **Carbamazepine, TCA, lidocaine.** Not selective to subtypes

DORSAL ROOT GANGLION



- Increased expression of α2-δ calcium channels- **Gabentinoids**
- Reduced activity of K-CL co-transporter
- Increased activity of Na-K-Cl co-transporter
- Decreased expression of μ opioid receptor – **High dose of opioids** required
- Sympathetic sprouting-
  - IV infusion phentolamine
  - Sympathetic block

SYNAPTIC JUNCTION- DORSAL HORN OF SPINAL CORD



- Synaptic plasticity- Summation, expansion of receptive fields
- Wind up – Increased glutamate activity – enhanced NMDA and AMPA activity- **NMDA receptor antagonist, Botolinium Toxin A**
- Glial activation – pro inflammatory cytokines – No clinical effect of cytokine inhibitors (Minocycline, etc)
- Disinhibition – Decreased activity of Norepinephrine, serotonin, dopamine, endogenous opiates- **TCA, SNRI, SSRI**


THANK
YOU

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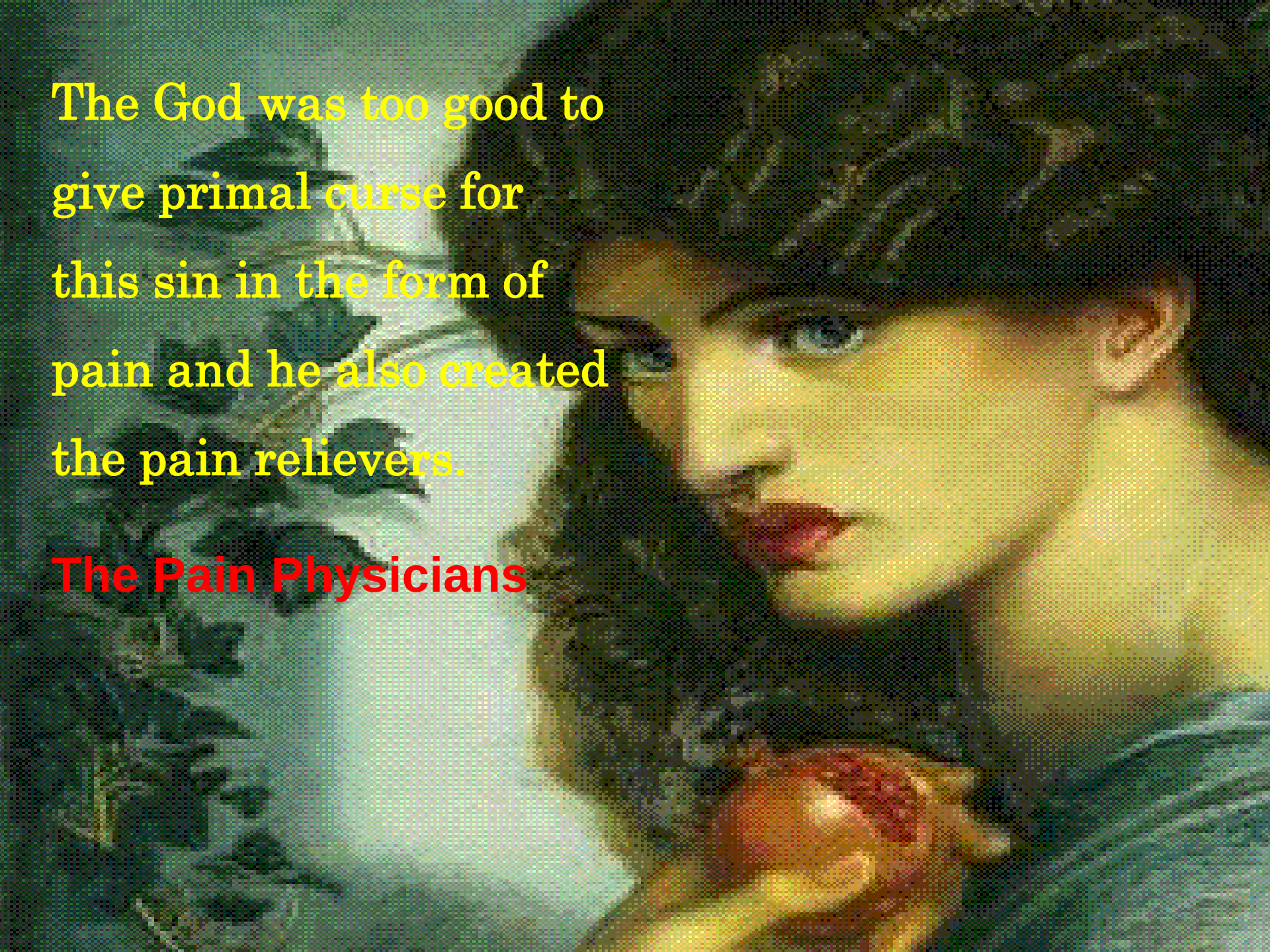
DR AKKAMAHADEVI. P

Prof & Head,
Dept. Of Emergency Medicine
Head, Pain and Palliative care unit
JSS Medical College & Hospital, Mysuru

God Relieved Adam from Pain, a pain of loneliness


The God was too good to
give primal curse for
this sin in the form of
pain and he also created
the pain relievers.
The Pain Physicians

- 40-year-old man walking on the side walk , had a sudden twist of ankle and presented to ED with a sharp pain on his left ankle

- 55-year-old woman with metastatic breast cancer , has severe chest wall and low back pain and is expected to die within a few weeks.

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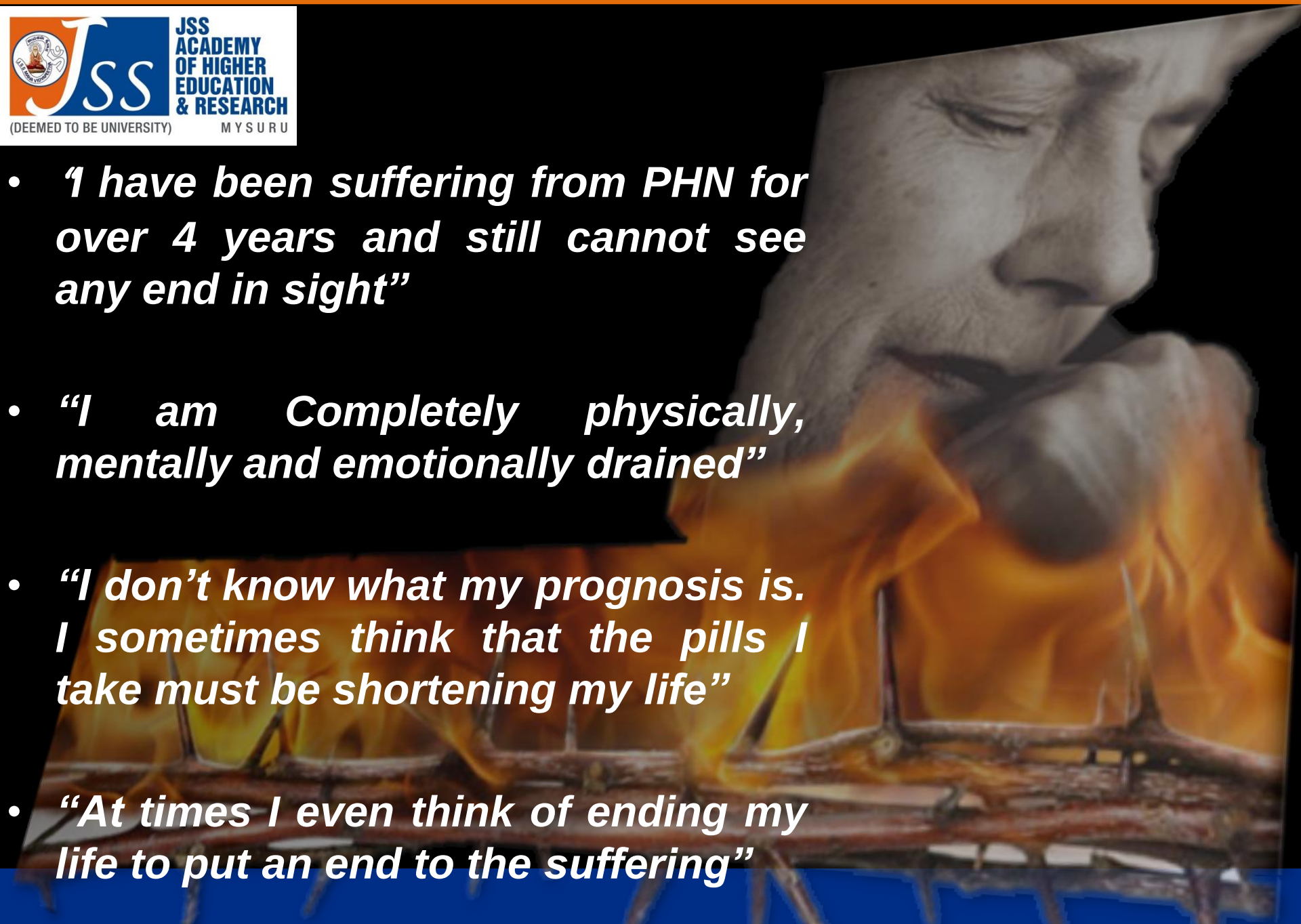

- *"I have been suffering from PHN for over 4 years and still cannot see any end in sight"*
- *"I am Completely physically, mentally and emotionally drained"*
- *"I don't know what my prognosis is. I sometimes think that the pills I take must be shortening my life"*
- *"At times I even think of ending my life to put an end to the suffering"*

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(Adopted by the American Board for Hospital Accreditation)

Lynch ME et al. Pain Res Manage Vol 11 No 1 Spring 2006

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PHARMACOLOGY OF PAIN

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Why a physiotherapist ?

"Eyes do not see what the mind does not know"

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Objectives

- Definition
- Classification
- Pain pathway
- Assessment
- Pharmacology

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PAIN

- Derived from Latin word "*peone*" meaning "penalty" or "punishment"

- "Pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage"

-IASP

CLASSIFICATION

BASED ON DURATION:

– ACUTE: useful, physiologic process

- warns the individual about the disease states/ harmful situations

– CHRONIC: pathological with altered anatomy and neural pathways.

- Duration longer than 3 months

Expected time to tissue healing

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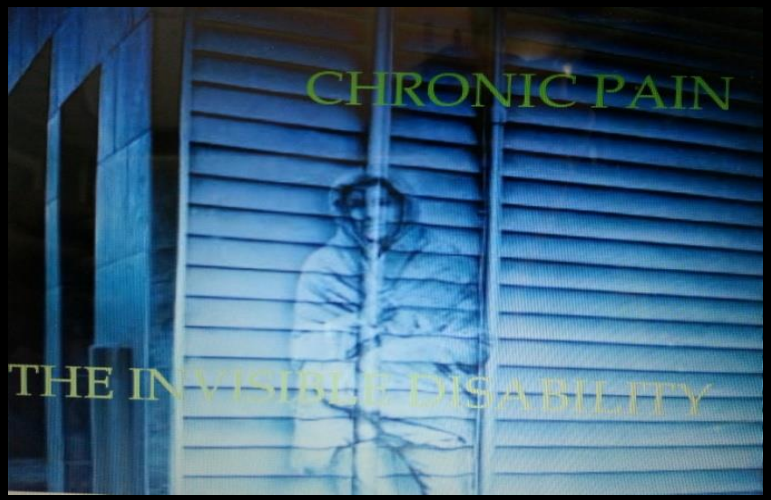
ACUTE

- Sudden onset
- Useful / protective
- Diagnosed and treated easily
- Adaptive

CHRONIC

- Insidious onset
- Useless/destructive
- Remodelling of brain and PNS
- Maladaptive



Based on pathophysiology

NOCICEPTIVE:

Normal nerves transmit information to the central nervous system about trauma to tissues

NEUROPATHIC:

Damage or dysfunction of nerves in the peripheral or central nervous system

Neuralgia

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BASED ON CAUSE

- Cancer
- Non cancer

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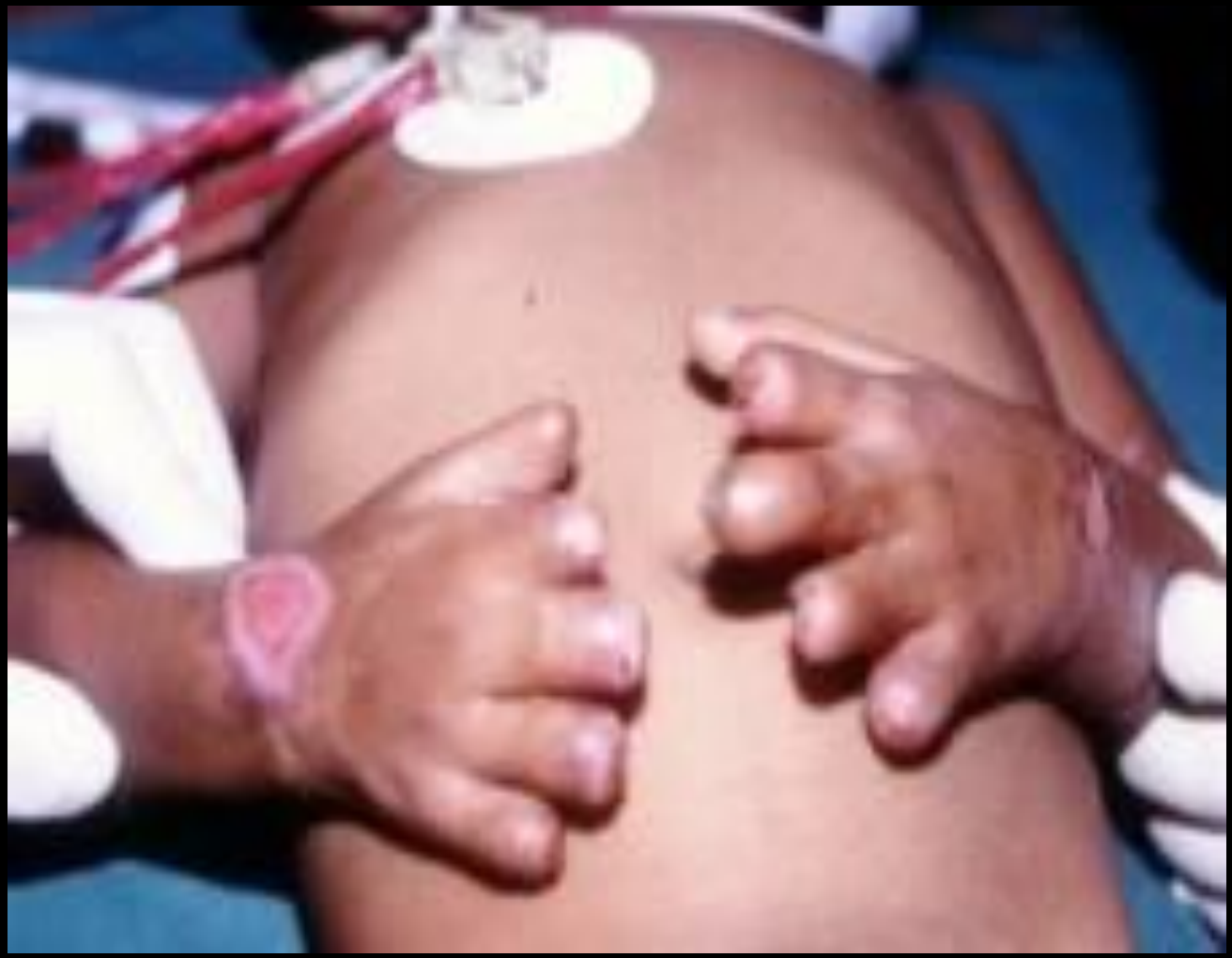
CONGENITAL ABSENCE OF PAIN



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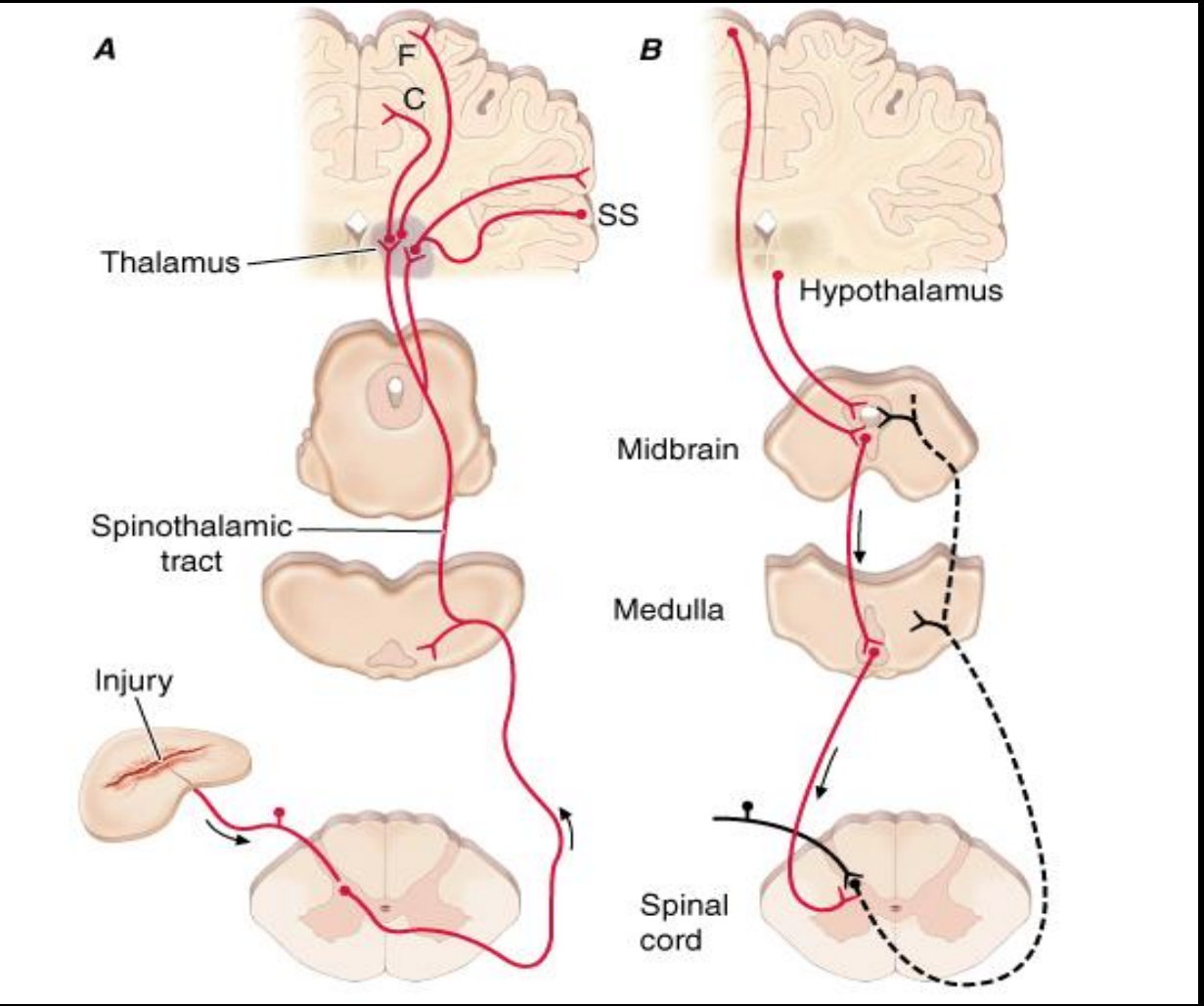
PAIN PATHWAYS



Nociceptive impulses

Pain modulation

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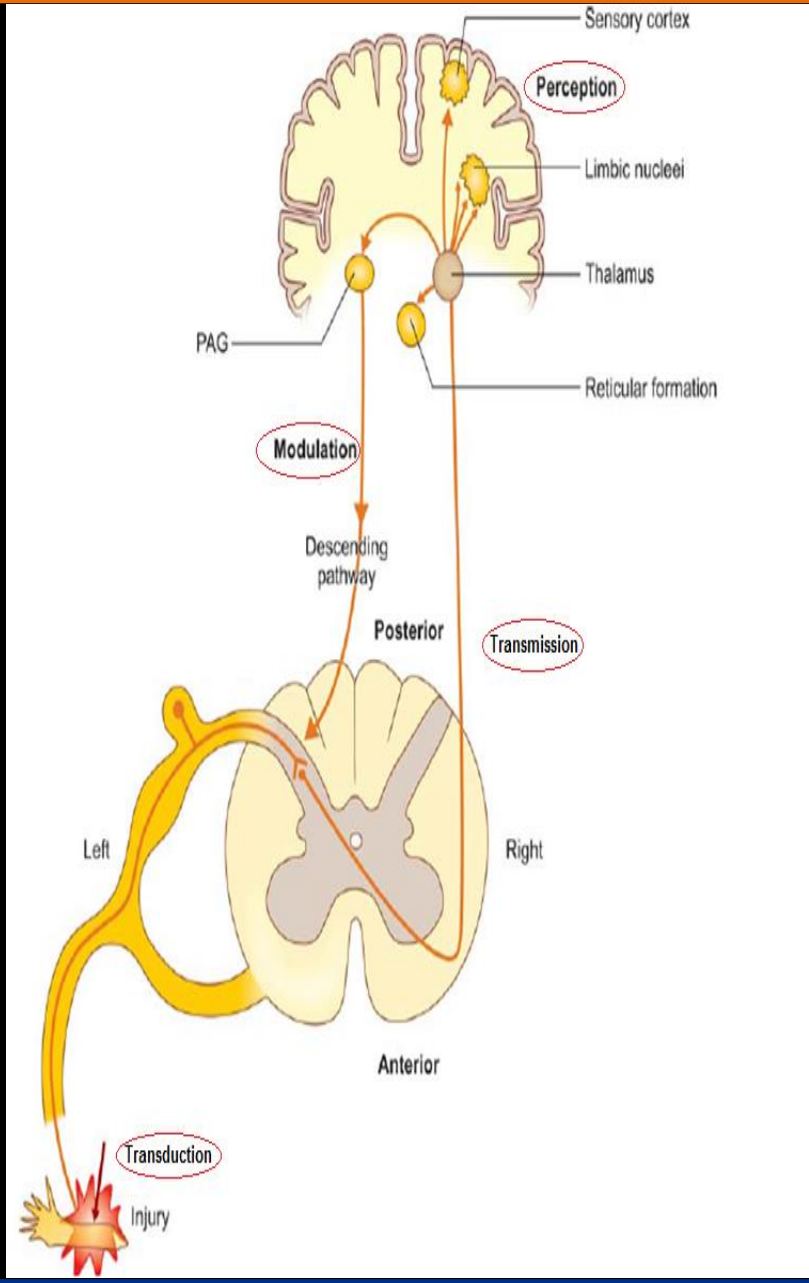
EVENTS INVOLVED

- **TRANSDUCTION**: conversion of one form of energy to another
- **TRANSMISSION**: electrical event transmitted along neuronal pathways
- **MODULATION:** adjustment of events, by up- or downregulation.
- **PERCEPTION**: awareness or understanding the sensory information



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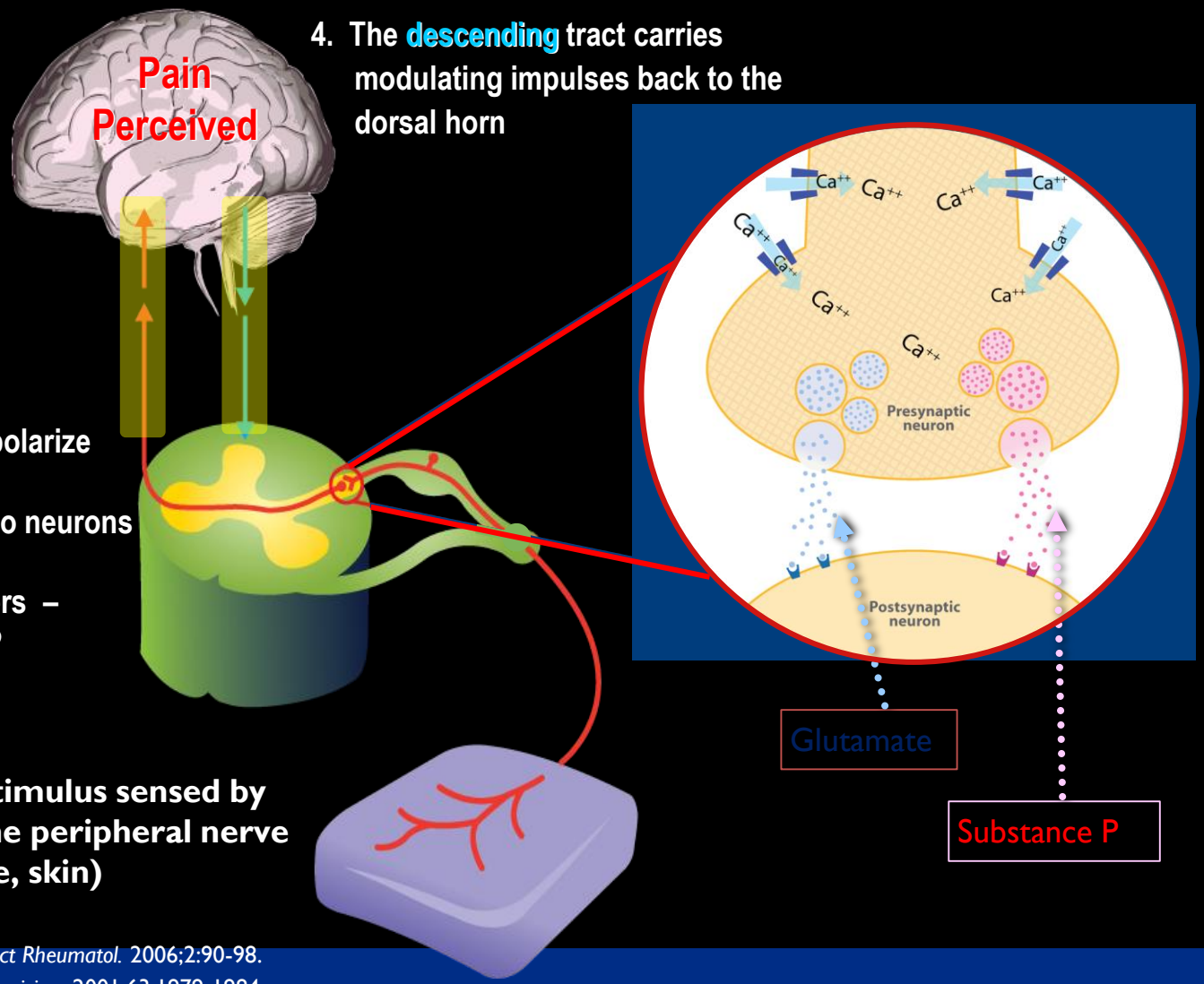
THE NORMAL PAIN PROCESSING PATHWAY

3. A signal is sent via the ascending tract to the brain, and perceived as pain

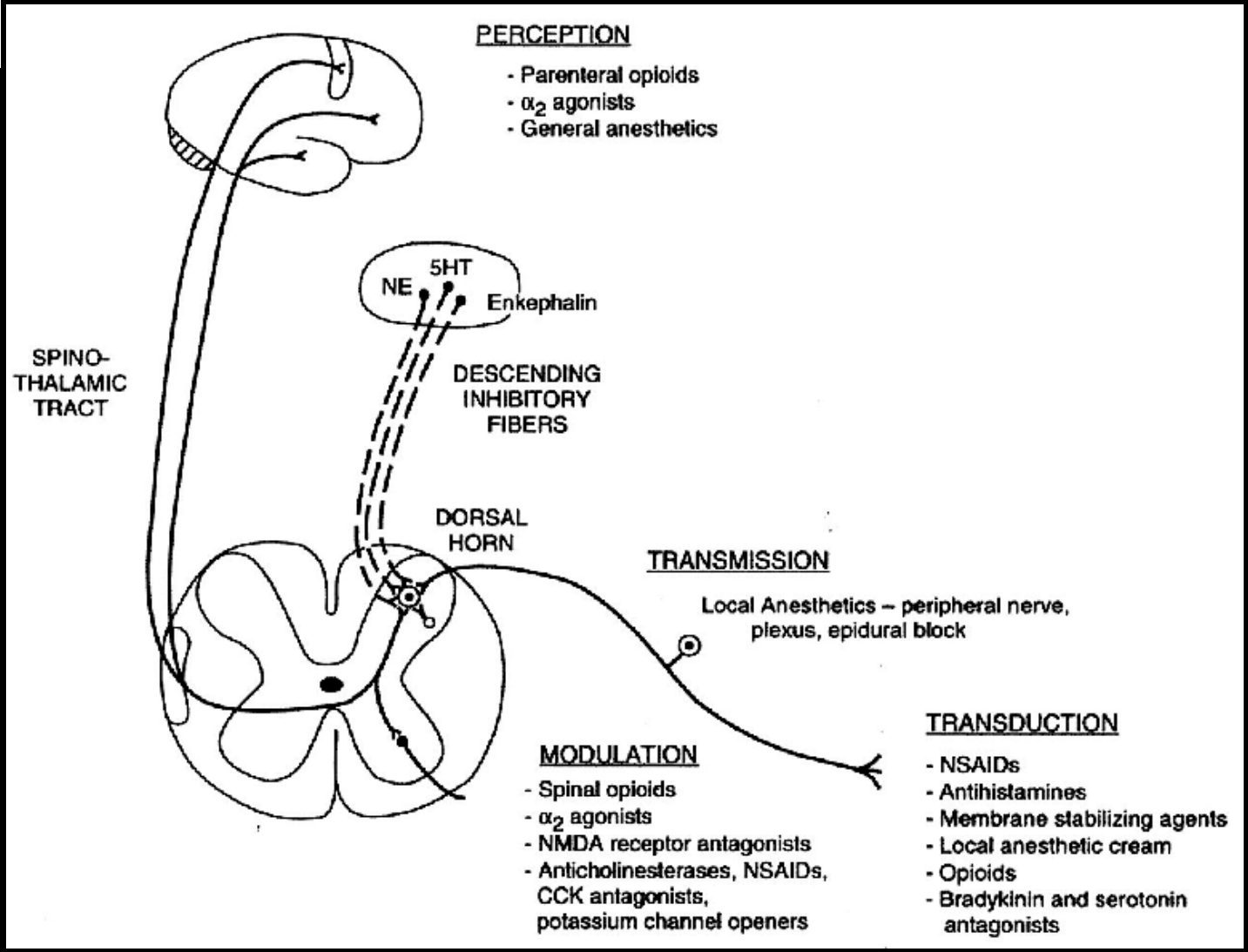
4. The descending tract carries modulating impulses back to the dorsal horn

2. Impulses from afferents depolarize dorsal horn neurons, then, extracellular Ca^{2+} diffuse into neurons causing the release of Pain Associated Neurotransmitters – *Glutamate* and *Substance P*

1. Stimulus sensed by the peripheral nerve (ie, skin)



1. Staud R and Rodriguez ME. *Nat Clin Pract Rheumatol.* 2006;2:90-98.
2. Gottschalk A and Smith DS. *Am Fam Physician*. 2001;63:1979-1984.


PERCEPTION
- Parenteral opioids
- α_2 agonists
- General anesthetics
5HT
NE
Enkephalin
SPINO-THALAMIC TRACT
DESCENDING INHIBITORY FIBERS
DORSAL HORN
TRANSMISSION
Local Anesthetics – peripheral nerve, plexus, epidural block
TRANSDUCTION
- NSAIDs
- Antihistamines
- Membrane stabilizing agents
- Local anesthetic cream
- Opioids
- Bradykinin and serotonin antagonists
MODULATION
- Spinal opioids
- α_2 agonists
- NMDA receptor antagonists
- Anticholinesterases, NSAIDs, CCK antagonists, potassium channel openers

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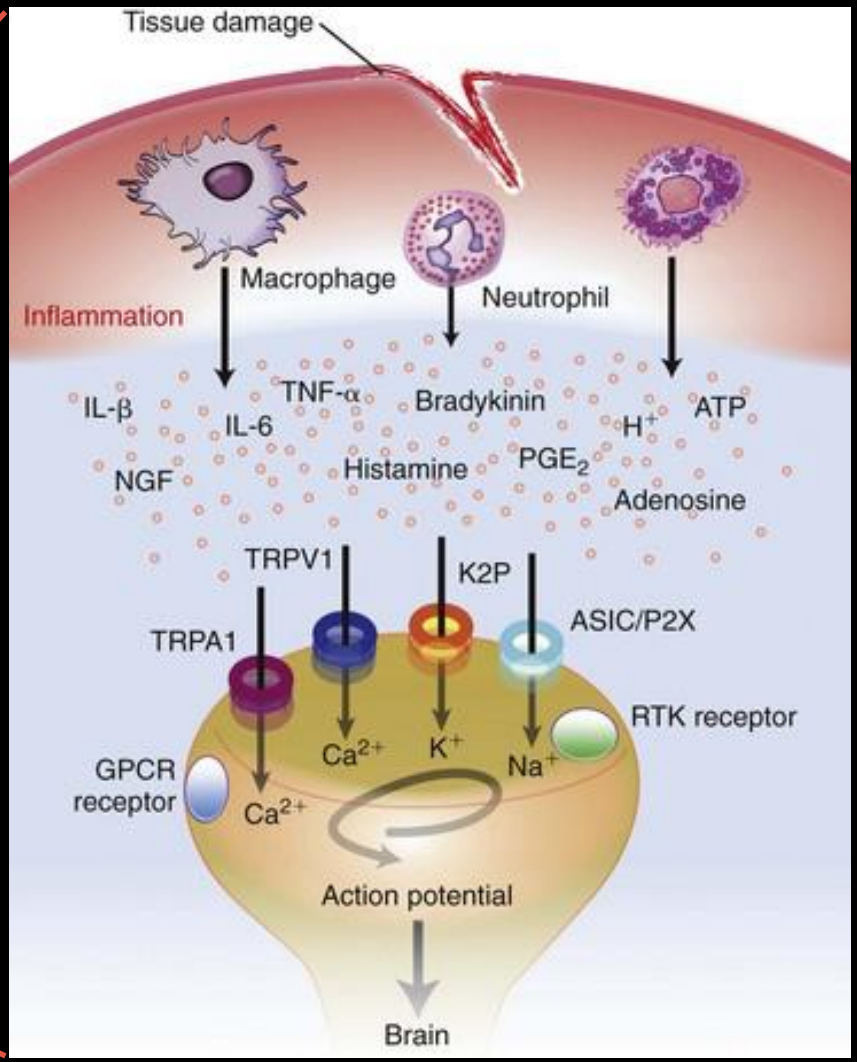
AT THE PERIPHERAL NERVE LEVEL



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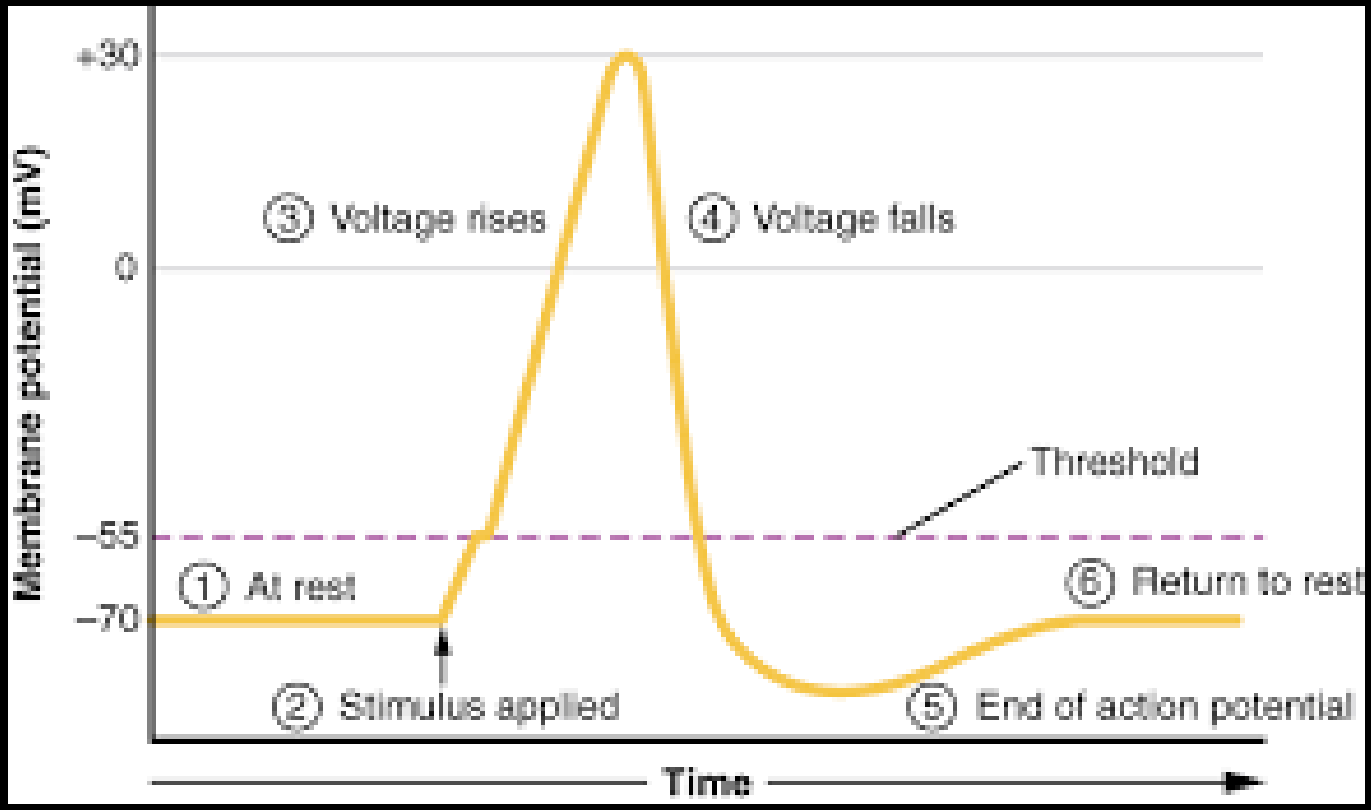
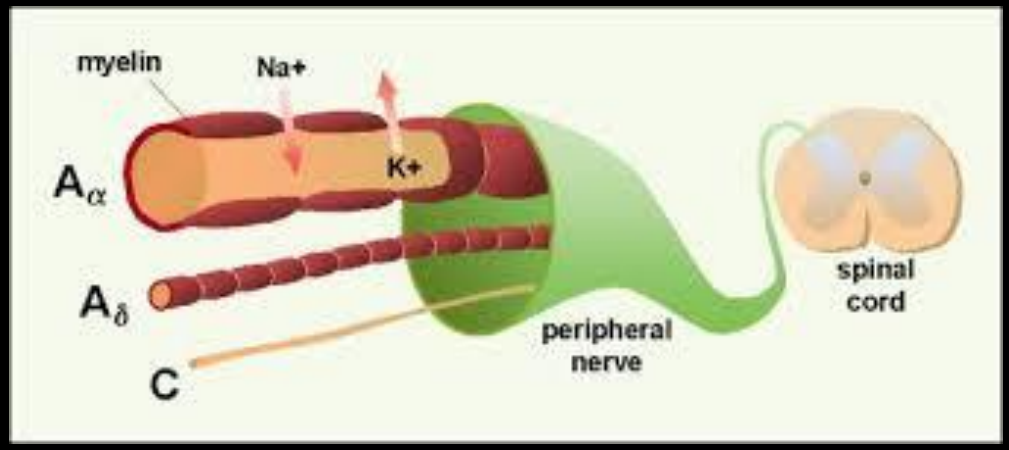
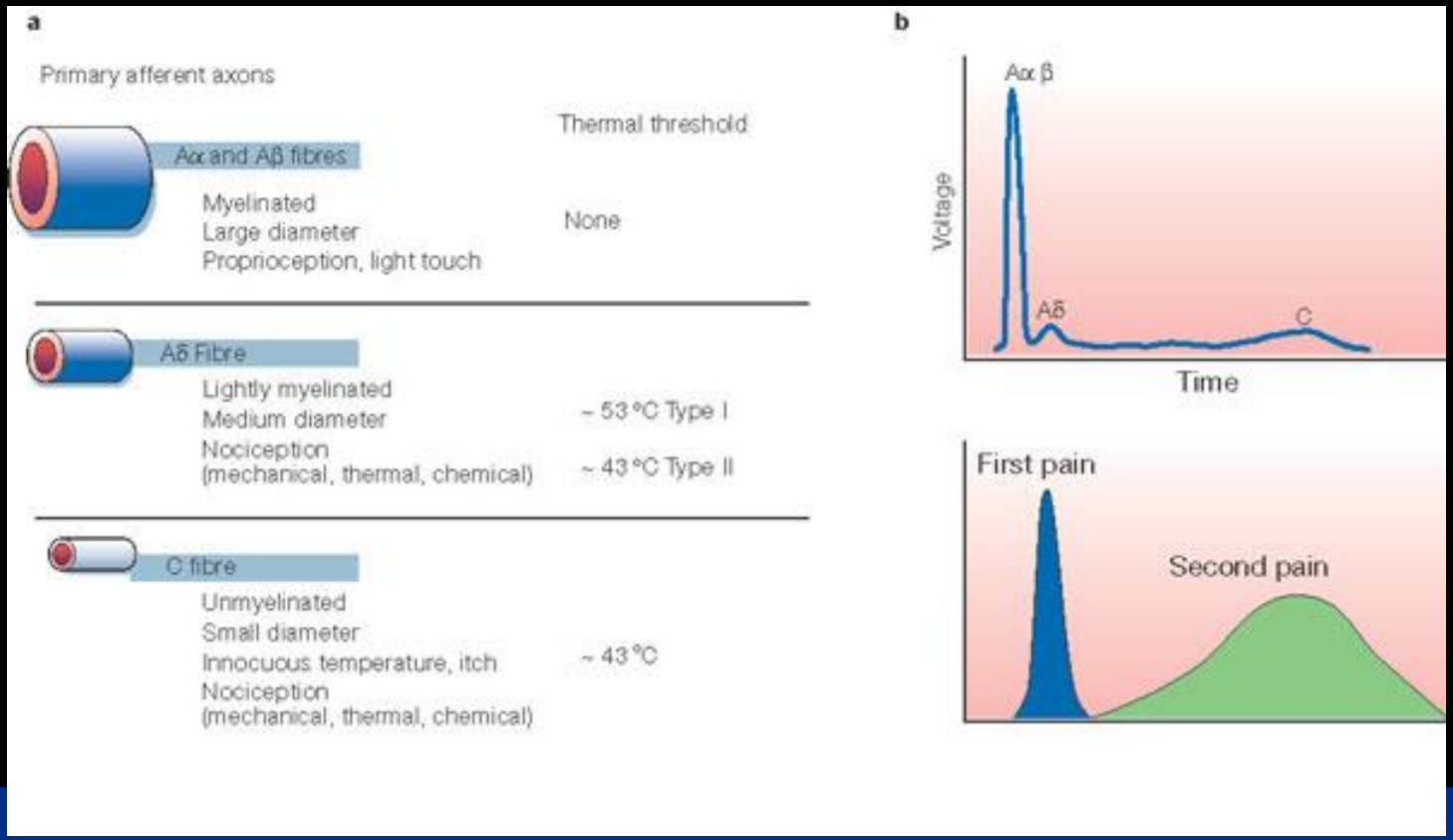


GENERATION OF ACTION POTENTIAL


myelin
Na+
K+
A_α
A_δ
C
peripheral nerve
spinal cord


a
Primary afferent axons
Thermal threshold
Aα and Aβ fibres
Myelinated
Large diameter
Proprioception, light touch
None
Aδ Fibre
Lightly myelinated
Medium diameter
Nociception
(mechanical, thermal, chemical)
~ 53 °C Type I
~ 43 °C Type II
C fibre
Unmyelinated
Small diameter
Innocuous temperature, itch
Nociception
(mechanical, thermal, chemical)
~ 43 °C
b
Aα β
Aδ
C
Voltage
Time
First pain
Second pain

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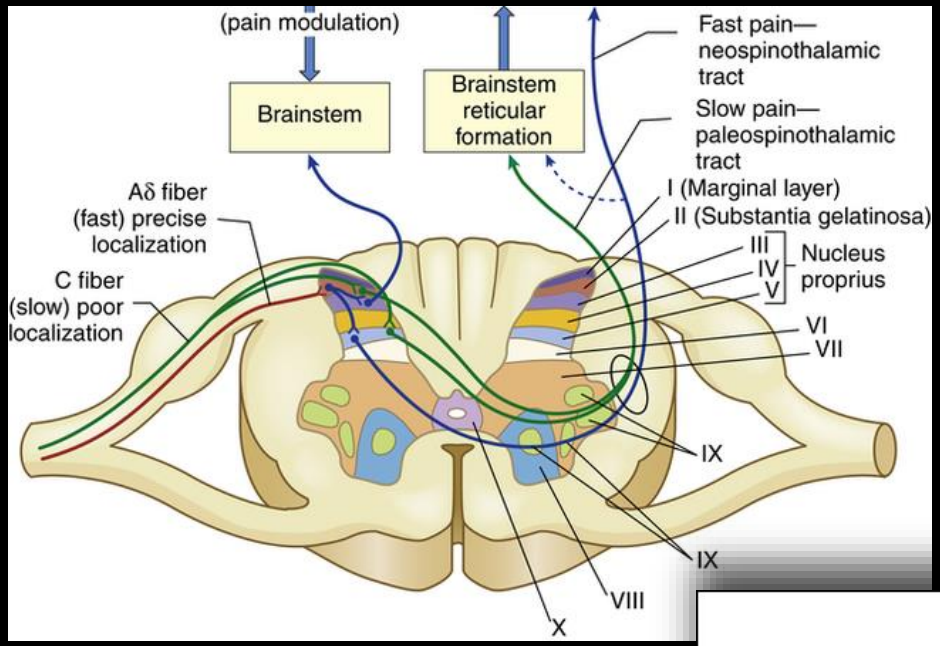

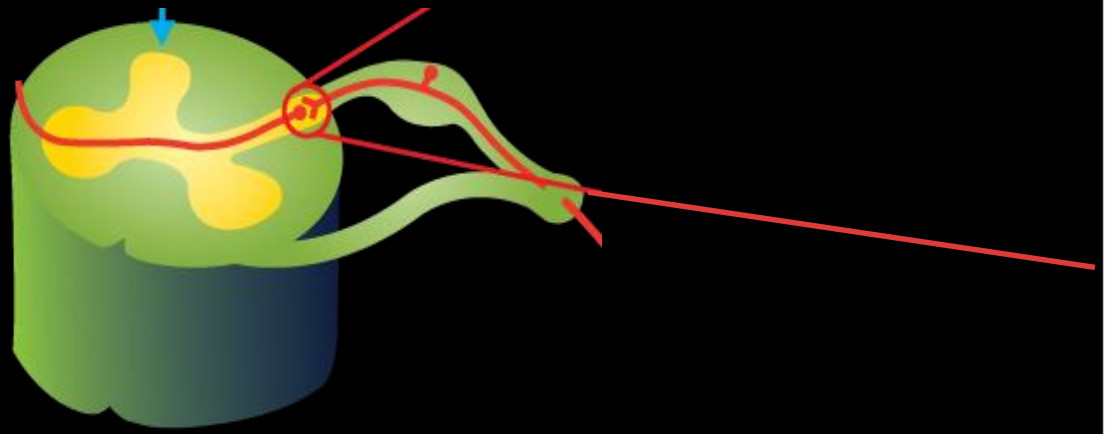

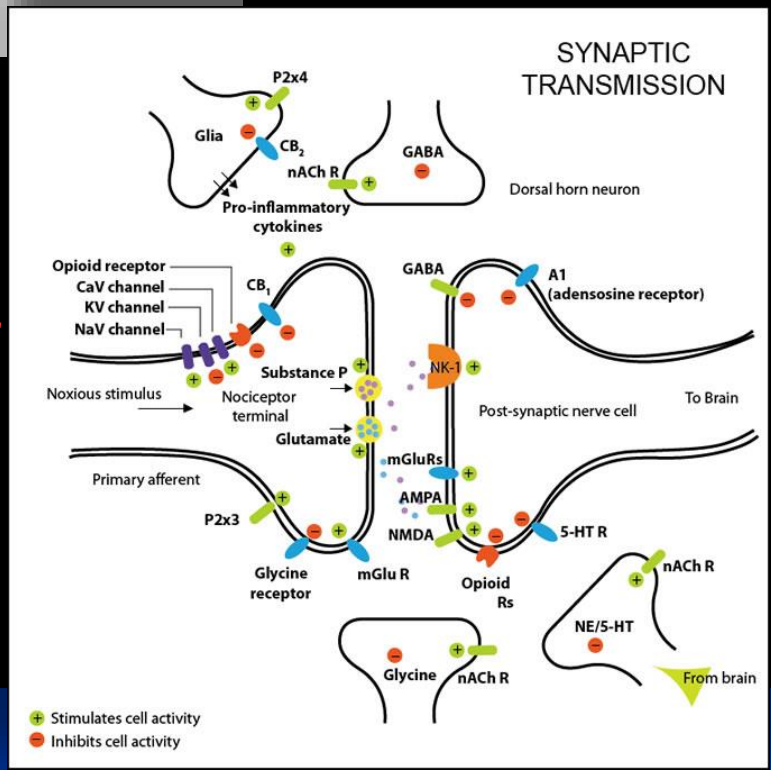

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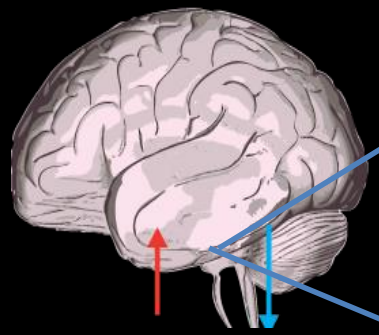

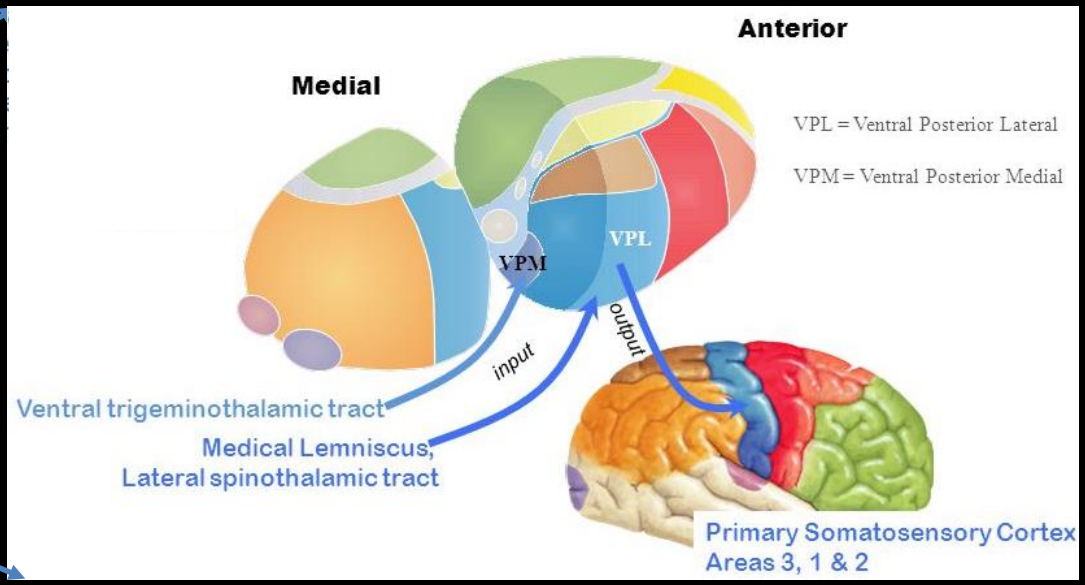

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Acute to chronic

PATHOPHYSIOLOGY OF CHRONIC PAIN

Peripheral nervous system

Sensitisation of nociceptors

- Unmasking of silent nociceptors
- Increased activity of damaged axons and their sprouts
- Abnormal firing of dorsal root ganglion cells
- Invasion of DRG by sympathetic post-ganglionic fibres

Central nervous system

- Hyperexcitability of central nervous(central sensitisation)
- Reorganisation of synaptic connectivity in spinal cord.

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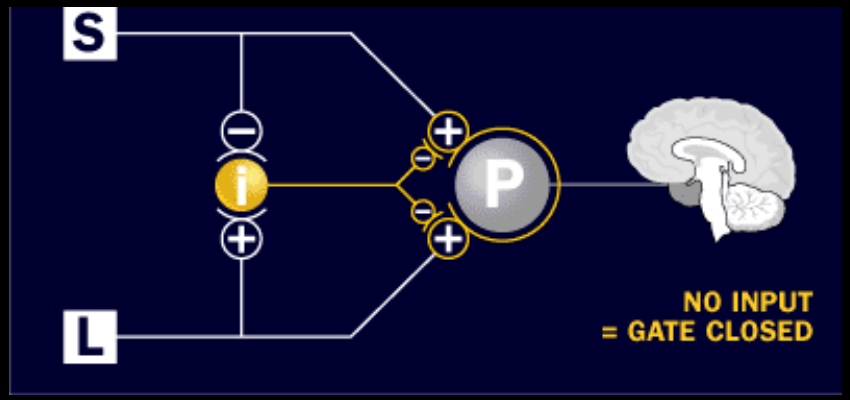
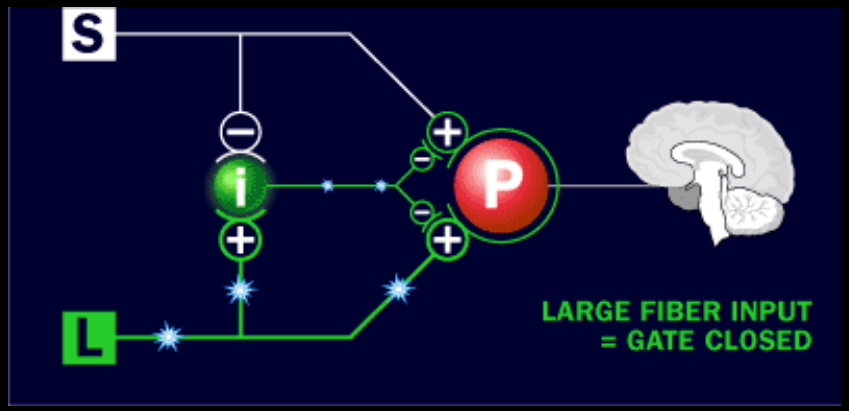
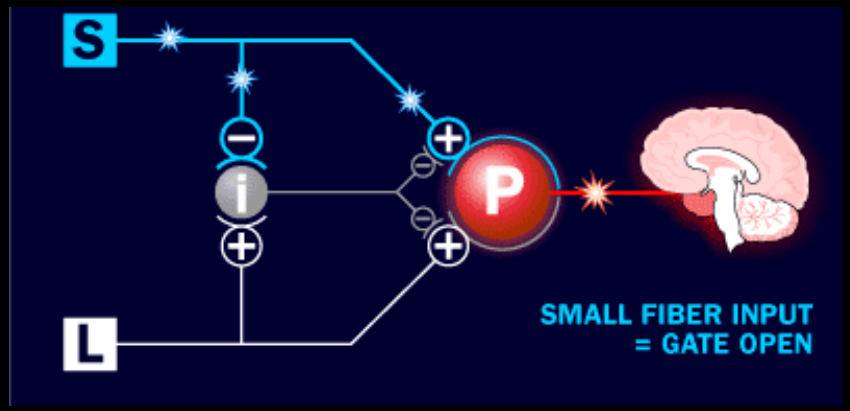
Gate control theory







S Small Nerve Fibers
L Large Nerve Fibers
i Inhibitory Neuron
P Projection Cells

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RAT APPROACH

- **R**ecognize
- **A**ssess
- **T**reat

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Approach to Pain

- **Recognize**
  - Does the patient have pain?
  - Do other people know the patient has pain?

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- **Assess**
  - How severe is the pain?
  - What type of pain is it?
  - Are there other factors?

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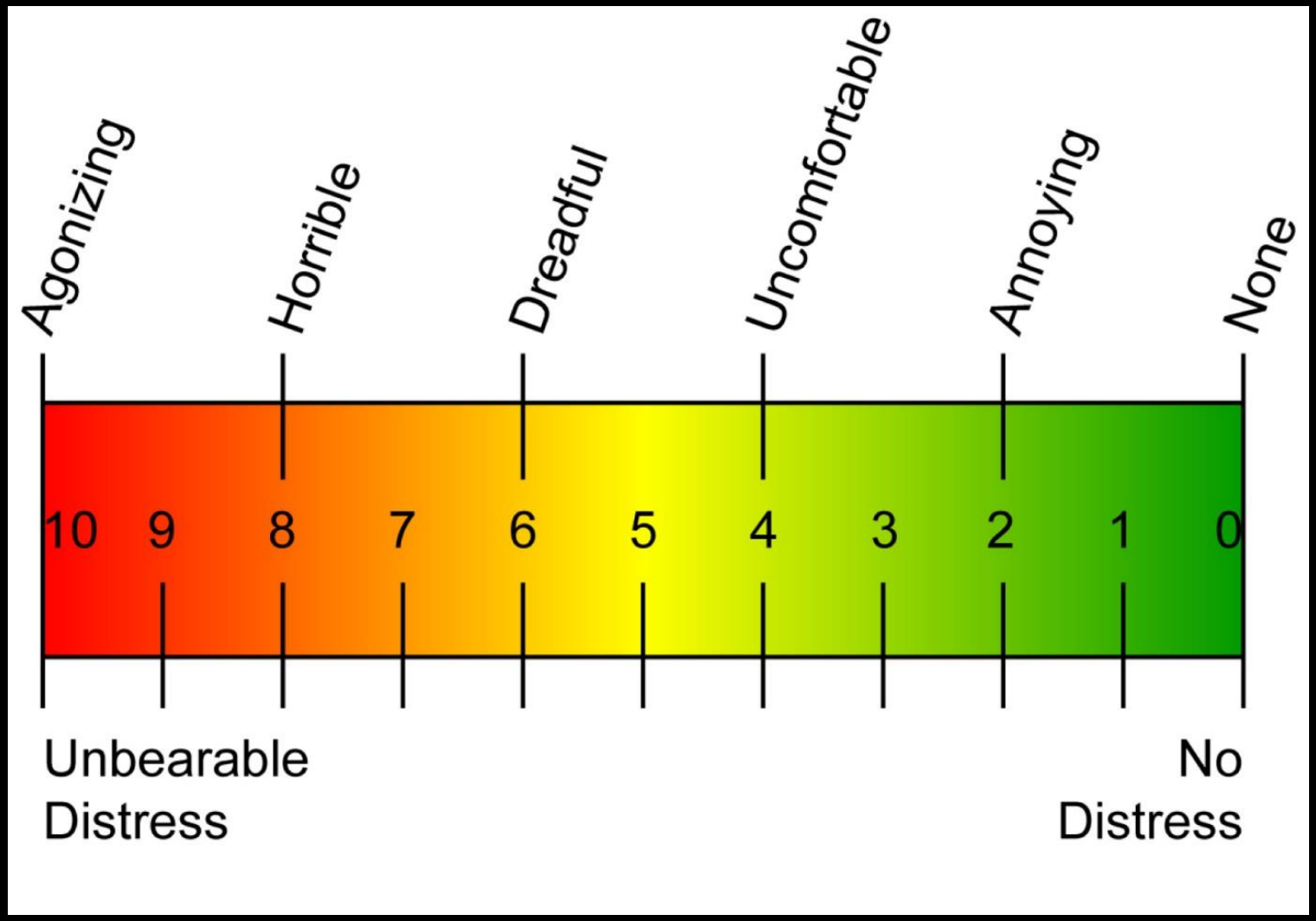
Visual Analog Scale (VAS)



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Numerical Rating Scale

No Pain										Worst Possible
0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain!!

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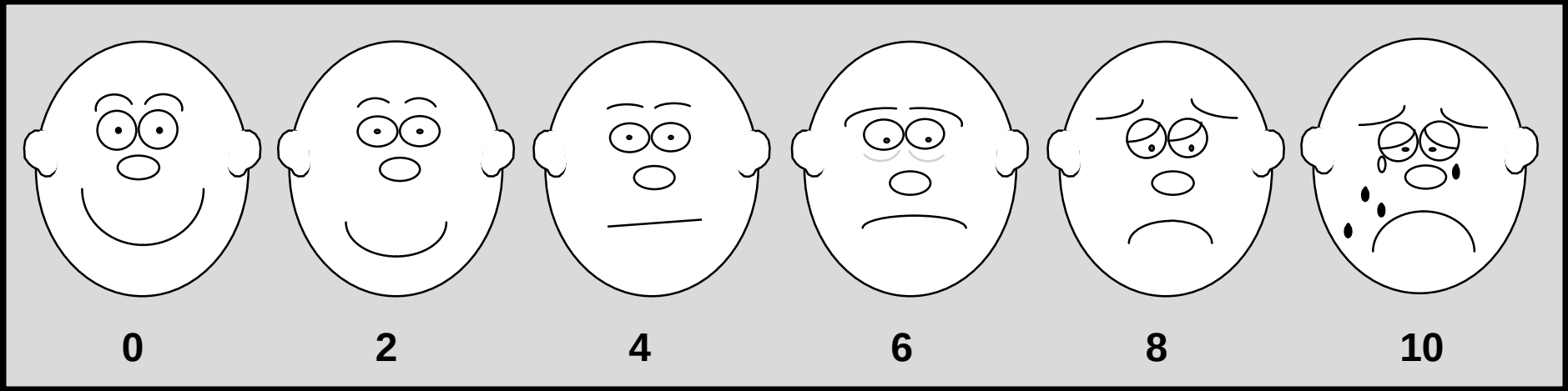
FACES Rating Scale



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Treat

Why?

- To relieve the patient from suffering
- To decrease the stressors on other systems
- To hamper the progression into chronic pain
- For the upliftment of mood
- Improve the quality of life

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Non-Drug Treatments

- **Physical**
  - Rest, ice, compression, elevation
  - Surgery
  - Acupuncture, massage, physiotherapy
- **Psychological**
  - Explanation
  - Reassurance
  - Counselling

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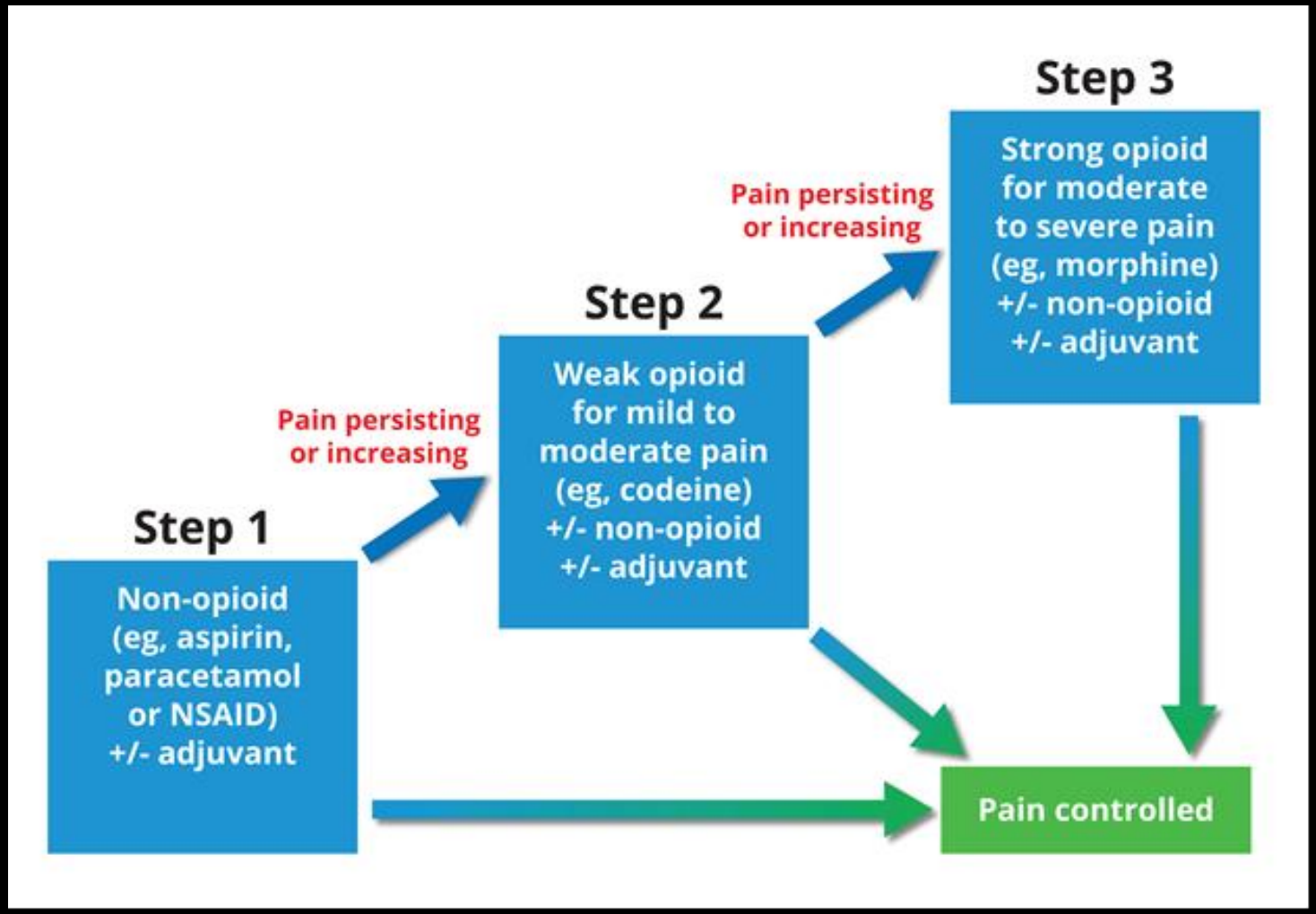
WORLD HEALTH ORGANISATION (WHO) ANALGESIC LADDER STEP



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Drugs

- **Simple analgesics**
  - **Paracetamol (acetaminophen)**
  - **Anti-inflammatory medicines**
    - **NSAIDs**
- **Opioids**
  - **Mild- Codeine**
  - **Strong- Morphine, pethidine, oxycodone**
- **Muscle relaxants**
  - diazepam, chlorzoxazone, thiocolchicoside, baclofen, hyoscine

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Drugs

- **Antidepressants**
  - Tricyclic
  - SSNRI
- **Anticonvulsants**
  - Gabapentin
  - Pregabalin
  - Carbamazepin

- **Lidocaine**
- **Capsaicin**
- **Botulinum toxin A**
- **Ketamine**
- **Miscellaneous**

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A 65 year old female with history of type 2 diabetes mellitus on regular treatment, came to the orthopaedic OPD with complains of bilateral knee pain. She has restriction of movement and swelling in both her knees.

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NSAIDs

- Analgesics, anti-inflammatory and antipyretics
- For mild to moderate pain
- As adjuvants in bone and neuropathic pain

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Classification

Nonselective COX inhibitors (traditional NSAIDs)

1. Salicylates: Aspirin.
2. Propionic acid derivatives: Ibuprofen, Naproxen, Ketoprofen, Flurbiprofen.
3. Anthranilic acid derivative: Mephenamic acid.
4. Enolic acid derivatives: Piroxicam, Tenoxicam.
5. Acetic acid derivative: Ketorolac.
6. Pyrazolone derivatives: Phenylbutazone, Oxyphenbutazone.

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Preferential COX-2 inhibitors

Nimesulide, Diclofenac, Aceclofenac, Meloxicam

Selective COX-2 inhibitors

Celecoxib, Etoricoxib, Parecoxib.

Analgesic- antipyretics with poor antiinflammatory action

1 Paraaminophenol derivatives: Paracetamol (Acetaminophen).

2 Pyrazolon derivatives : Metamizol (Dipyrone), Propiphenazone

3. Benzoxazocine derivative: Nefopam.

Drugs

Phospholipids

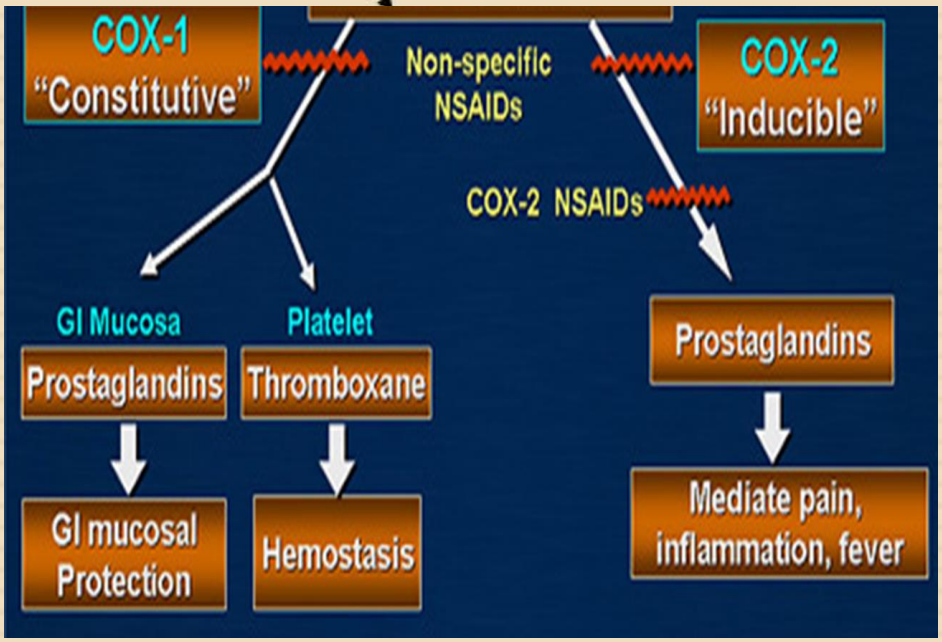
Corticosteroids → **Phospholipase A_2**

Arachidonic Acid

Zileuton → **Lipoxygenase**

Leukotrienes

NSAIDs → **Cyclooxygenase**



Action	COX-1/ COX-2 inhibitors	COX – 2 inhibitors
1. Analgesic	+	+
2. Antipyretic	+	+
3. Antiinflammatory	+	+
4. Antiplatelet aggregatory	+	-
5. Gastric mucosal damage	+	-
6. Renal salt/ water retention	+	+
7. Delay/ prolongation of labour	+	+
8. Ductus arteriosus closure	+	?
9. Aspirin sensitive asthma precipitation	+	-

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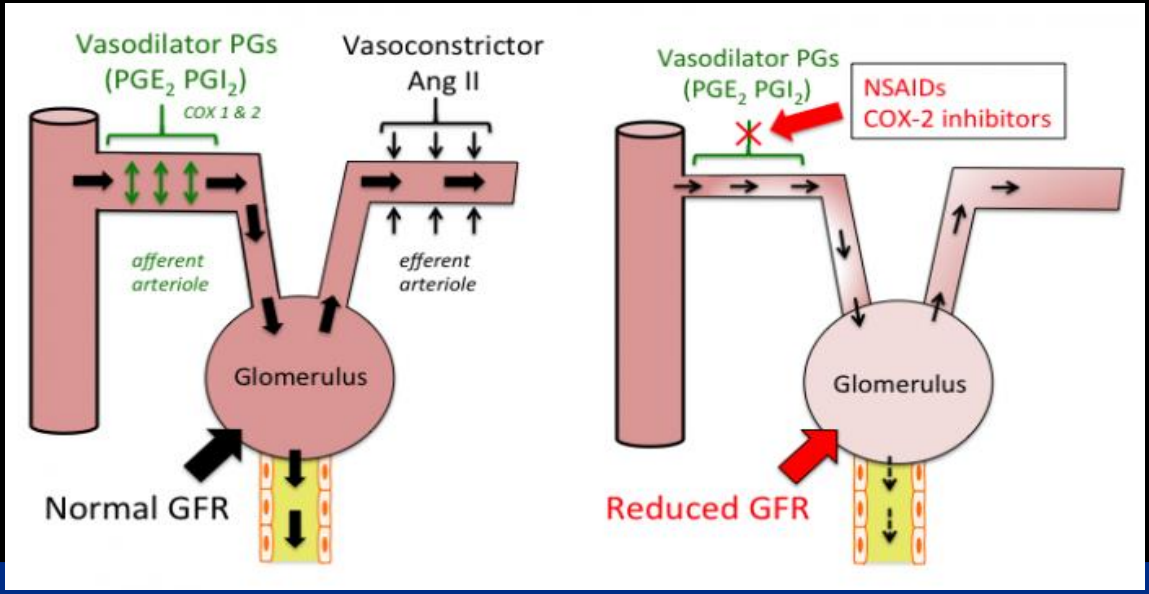
RENAL EFFECTS

1. COX inhibition- vasoconstriction- ↓ renal blood flow - ↓ GFR → worsen renal insufficiency.
2. Juxtaglomerular COX-2 (probably COX-1 also) dependent Na+ and water retention.
3. Papillary necrosis on habitual intake.



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Hippocrates – 5th century

ASPIRIN

?

(Antiinflammatory and antiplatelet activity)

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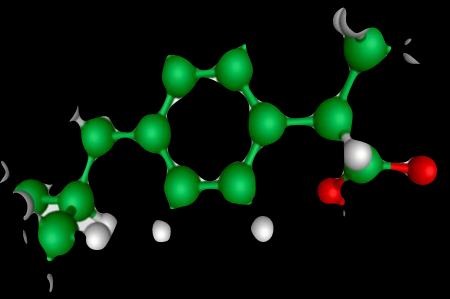
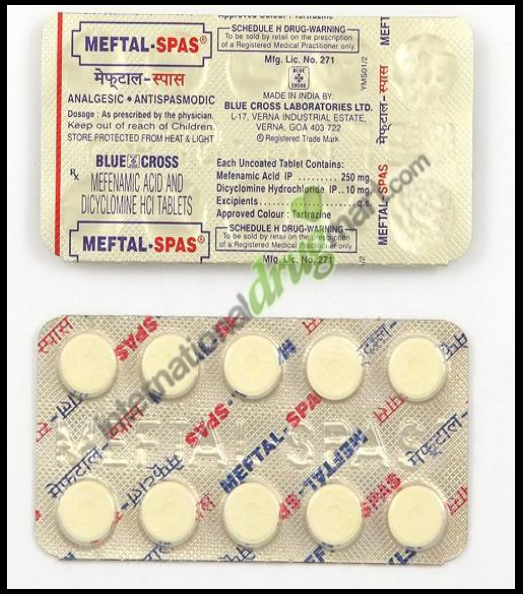
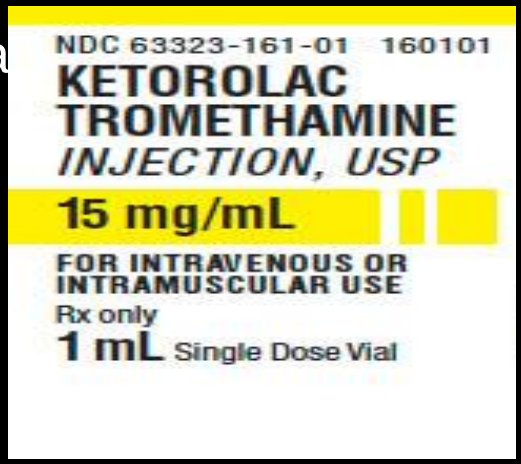


PROPIONIC ACID DERIVATIVES

Drug	Plasma t ½ (hours)	Dose	Indications / Remarks
Ibuprofen	2 – 4	400-600 mg (5-10 mg/kg) t.i.d	Rheumatoid arthritis, osteoarthritis, musculoskeletal disorders
Naproxen	12 – 16	250 mg b.i.d or t.i.d	Acute gout, Rheumatoid arthritis, ankylosing spondylitis, migraine
Ketoprofen	2 – 3	50 – 100 mg b.i.d or t.i.d	More side effects
Flurbiprofen	4- 6	50 mg b.i.d or q.i.d	Ocular inflammations

- **Mephenamic acid** – dysmenorrhea
  - t1/2-2-4hr
  - 250 mg-500 mg t.i.d
- **Piroxicam** -RA, OA, ankylosing spondylitis
  - t1/2-50hr
  - PO 20 mg b.i.d for 2 days, followed by 20mg OD
- **Ketorolac** -
- post operative pain, dental, musculoskeletal pain, rena colic, paediatric**migraine and pain due to**
- **bony metastasis**
  - t1/2-2hr
  - PO 10 mg q6H; IV/IM : 30 mg q6H





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Diclofenac sodium

- **Preferential COX-2 inhibitor**
- **Short lasting antiplatelet action**

USE

- RA, OA, bursitis, ankylosing spondylitis, dysmenorrhoea,
- post-traumatic and postoperative – quick relief of pain and edema.
- t1/2-2hr
- 50 mg b.i.d/ t.i.d
- IV, transdermal, rectal
- Risk of MI , stroke

COX- 2 INHIBITORS

- Celecoxib and etoricoxib - commonly used.
- Etoricoxib – t ½ 24 hours , OD dosing
- No gastric irritation, platelet aggregation
- ↓ PG I2 production by vascular endothelium- prothrombotic influence- ↑ cardiovascular risk

SUCCESS-1, CLASS trial

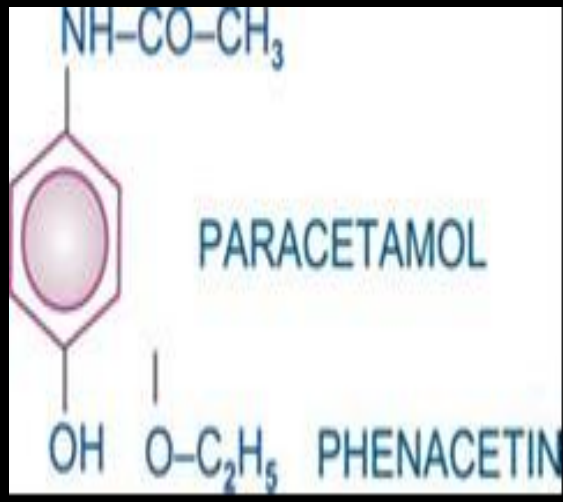
SELECTIVE COX-2 INHIBITORS AND CARDIOVASCULAR RISK

- **VIGOR study:** 4-fold higher incidence of MI in rofecoxib than naproxen.
- **APPROVE trial:** rofecoxib withdrawn 2004 (MI and stroke)
- **Metaanalysis (18 trials)**: rofecoxib for musculoskeletal disorders - ↑ MI.
- **Valdecoxib** : ↑ MI in patients undergoing CABG. Withdrawn : 2005.

- No clear evidence that etoricoxib increases CV risk.
- Warning labelling : CV risk.
- Therefore, selective COX-2 inhibitors
  - only in patients at high risk of peptic ulcer disease, perforation, GI bleeds
  - Lowest dose for the shortest time
  - Avoid : history of IHD, HTN, HF, CVA

PARACETAMOL

- Mild – moderate pain, fever
- Deethylated active metabolite of phenacetin.
- Weak anti-inflammatory action
- Site of action: ? COX-1, COX-3
- Pharmacokinetics:
  - Well absorbed PO
  - Plasma t½ is 2–3 hours
  - Action after oral dose last for 3–5 hours.



- **Metabolism:** conjugation with glucuronic acid and sulfate (P450 enzyme)

- **Dosage:** Adults/ children> 12 years
  - PO 500mg to 1g q 4-6 hrly (max 4 g/24 hrs)
  - IV 5 mg/kg; Rectal 40-60 mg/kg

- **Adverse effects:**
  - *Analgesic nephropathy*
  - Acute paracetamol poisoning - liver failure (centrilobular hepatic necrosis) : overdose of > 10g or > 200mg/kg

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Mrs. Uma, 62y/f came with complaints of severe upper abdominal pain since a few months. She was recently diagnosed with primary liver cancer, for which she is on palliative care. But her pain is increasingly severe, she even has crying spells at night. She says " I want a drug or treatment that won't make me feel any pain at all".

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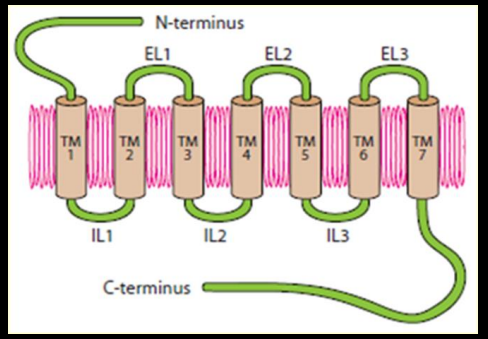
OPIOIDS

Papaver somniferum

OPIOID RECEPTORS

- Brain, spinal cord and peripheral nervous system
  - Mu (μ_1 and μ_2): central analgesia, euphoria, dependance, miosis, respiratory depression
  - Kappa (k1 & k3): analgesia, sedation
  - Sigma - dysphoria, hallucination
  - Delta (δ): Euphoria



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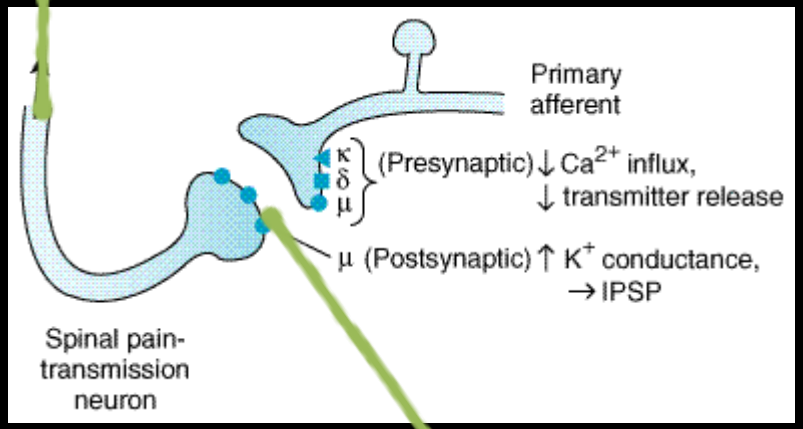
SPINAL SITES OF OPIOID ACTION

Hyperpolarize
second-order pain transmission neurons by increasing K+ conductance, evoking an inhibitory postsynaptic potential



reduce transmitter release
from presynaptic terminals of nociceptive primary afferents

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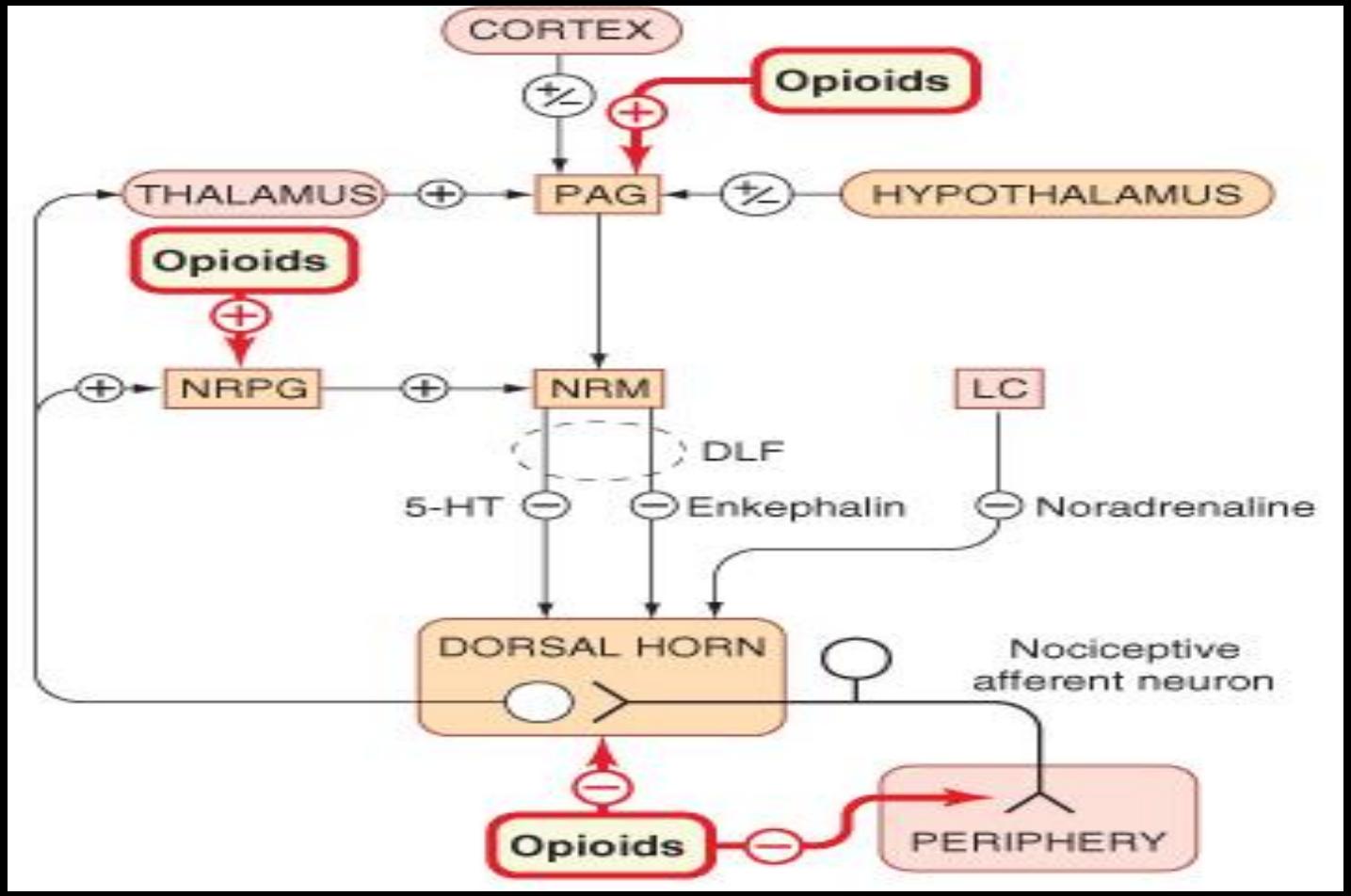

THE DESCENDING CONTROL SYSTEM, SHOWING THE MAIN SITES OF ACTION

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MORPHINE

- Strong analgesic- severe pain
- Degree of analgesia increasing with dose.
- Dull, poorly localized visceral pain
- Nociceptive > neuropathic
- Cancer pain
- Non cancer pain (short term)

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Mood and subjective effects

In patients
Pain relief
No addiction

In normal persons
Dependence and
Addiction

Tolerance

- Upregulation of cAMP
- Downregulation of μ receptors

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EFFECTS

- Reduces gastrointestinal motility
- Depresses respiratory centre
- Depresses vasomotor centre
- Bronchoconstriction
- Retention of urine

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PHARMACOKINETICS

- Metabolized: glucuronide conjugation
- Morphine-6-glucuronide: active metabolite
- Crosses placenta
- t ½ : 2-3 hours. Effect : 4-6 hours
- Oral, rectal, IV and SC

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ORAL MORPHINE

1. **By mouth**
2. **By the clock**
3. **By the ladder**
4. **For the individual**

   correct dose = dose that relieves pain
5. **With attention to detail –treat side**

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"ANYONE WHO SAID 'OUCH' IS ENTITLED TO RECEIVE OPIOIDS IN WHATEVER DOSE THEY SEEM TO NEED."

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FENTANYL

- Pethidine congener
- 80-100 times potent than morphine in analgesia and resp. depression
- Cardiostable
- High lipid solubility
- Peak effect: 5 min, Action 30-40 min

Transdermal patch

- 25-75 µg /hr, acts for 72 hours
- Latency of action- 10-12hr
- Acts for 24hr after removal
- Erratic absorption in summer
- More absorption if febrile

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Fentanyl Oral Transmucosal Lozenges
Par Pharmaceutical

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BUPRENORPHINE

- High-efficacy partial agonist of μ receptor
- Antagonist of K-receptor.
- Less dependence and respiratory depression
- Duration of action = 6-8 hrs
- Dose: 0.3-0.6 mg IM, SC, 0.2 -0.4 mg S/L
- Use: cancer, MI, Post Operative, morphine dependence

Tramadol

- A weak mu receptor agonist
- Inhibits reuptake of serotonin and norepinephrine
- NNT = 4.8
- Painful polyneuropathies
- 50 mg OD/ BD, increase by 50- 100 mg every 3- 7 days (max: 400mg)
- Extended-release available
- Side effects: Sedation, dizziness, nausea
- Serotonin syndrome
- Avoid in seizures

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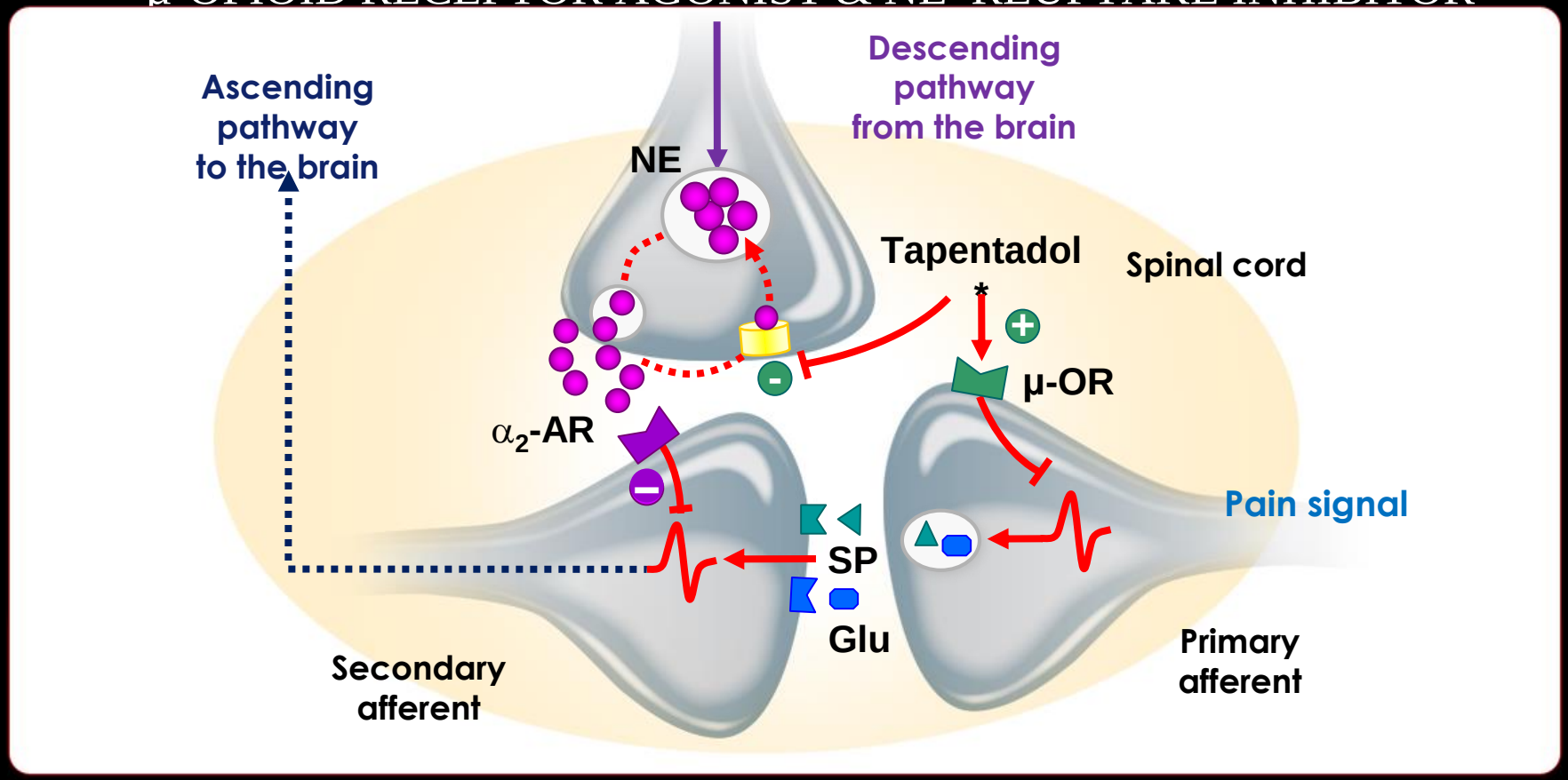
TAPENTADOL

μ-OPIOID RECEPTOR AGONIST & NE REUPTAKE INHIBITOR



Simplified schematic for mechanism of action.

Dose : 50mg, 75mg or 100mg in every 4 to 6 hours (maximum dose up to 600mg / day)

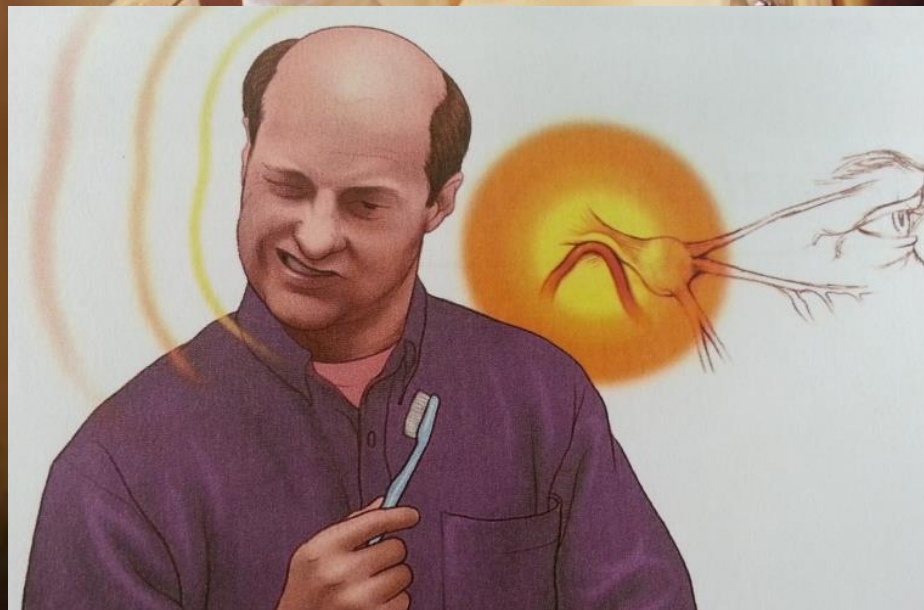
Muscle relaxants

- Painful reflex muscular hypertonicity
- Muscle spasm, strains and sprains
- **Diazepam -**
  - Tranqulizing (limbic system)
  - Depress polysynaptic reflexes (at spinal cord and reticular formation)
  - 2-5mg TID

))

- **Chlorzoxazone:** Centrally acting
- **Thiocolchicoside-** GABA and glycine receptor antagonist
- **Tizanidine-** alpha2 agonist
- **Baclofen-** analogue of GABA
    - MS, post spinal injury, TGN
- **Hyoscine-** smooth muscle relaxant

Countess of Northemberland – sharpest most uncomfortable pain , deprived her of sleep rarely allowed her only 5-6 mins of peace per hour unable to eat , drink , cough , spit , or wipe her face.



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Chronic pain (neuropathic)

Recommendations for the Pharmacological Management of Neuropathic Pain: An Overview and Literature Update

Robert H. Dworkin, PhD; Alec B. O'Connor, MD; Joseph Audette, MD; Ralf Baron, Dr Med; Geoffrey K. Gourlay, PhD; Maija L. Haanpää, MD, PhD; Joel L. Kent, MD; Elliot J. Krane, MD; Alyssa A. LeBel, MD; Robert M. Levy, MD, PhD; Sean C. Mackey, MD, PhD; John Mayer, DC, PhD; Christine Miaskowski, RN, PhD; Srinivasa N. Raja, MD; Andrew S. C. Rice, MB, MD, FRCA; Kenneth E. Schmader, MD; Brett Stacey, MD; Steven Stanos, DO; Rolf-Detlef Treede, Dr Med; Dennis C. Turk, PhD; Gary A. Walco, PhD; and Christopher D. Wells, MB

The Neuropathic Pain Special Interest Group (NeuPSIG) of the International Association for the Study of Pain

GMMMG Greater Manchester Medicines Management Group

Neuropathic Pain Guideline

GUIDELINES

Australian Government Department of Veterans' Affairs

Veterans'MATES

Therapeutic Brief 35

www.veteransmates.net.au

Topic 35: Managing neuropathic pain: a stepwise approach

NHS

European Journal of Neurology 2010, 17: 1113–1123 doi:10.1111/j.1468-1331.2010.02999.x

EFNS GUIDELINES

EFNS guidelines on the pharmacological treatment of neuropathic pain: 2010 revision

N. Attal[a,b], G. Cruccu[a,c], R. Baron[a,d], M. Haanpää[a,e], P. Hansson[a,f], T. S. Jensen[a,g] and T. Nurmikko[a,h]

Pharmacological management of chronic neuropathic pain – Consensus statement and guidelines from the Canadian Pain Society

DE Moulin MD[1], AJ Clark MD[2], I Gilron MD MSc[3], MA Ware MD[4], CPN Watson MD[5], BJ Sessle MDS PhD[5], T Coderre PhD[4], PK Morley-Forster MD[1], J Stinson RN PhD[6], A Boulanger MD[7], P Peng MBBS[5,8], GA Finley MD[9,10], P Taenzer PhD[2], P Squire MD[11], D Dion MD MSc[7], A Cholkan CA[12], A Gilani MD[13], A Gordon MD[5,12], J Henry PhD[13], R Jovey MD[5], M Lynch MD[9], A Mailis-Gagnon MD MSc[5], A Panju MB ChB[13], GB Rollman PhD[1], A Velly DDS PhD[14]

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NeuPSIG guidelines recommend

- **First line treatment =** Efficacy in NP has been established in multiple RCTs (grade A recommendation)
- **Second line treatment =** Efficacy in NP has been established in multiple RCTs but there were reservations about the use of medications relative to first line medications
- **Third line treatment =** only one RCT has shown efficacy in NP or if results of 2 or more RCTs were inconsistent (Grade B recommendation)

First Line Treatment

- **Antidepressents**
  - TCA
  - SNRI
- **Calcium Channel α2-δ Ligands**
  - Gabapentin P
  - Pregabalin

(revised NeuPSIG recomm 2015 using GRADE)

- **Second Line Treatment**
  - Lidocaine patch
  - Capsaicin patch
  - Tramadol
- **Third line treatment**
  - Strong opioids
  - Botulinum A toxin

(revised NeuPSIG recomm 2015 using GRADE)

Tricyclic Antidepressants

- **1st observed to treat NP in depressed patients – 1960 – imipramine**
- **Tertiary amines**
  - Amitriptyline
  - Imipramine
- **Secondary amines**
  - Nortriptyline
  - Desipramine

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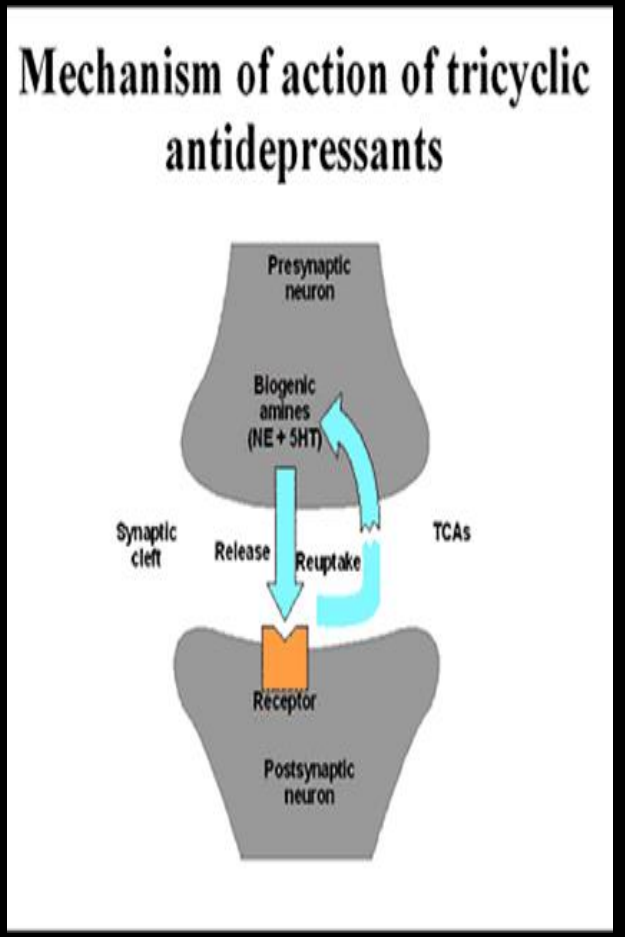
Tricyclic Antidepressants

Mechanisms of action

- re-uptake inhibition of NE and 5HT-activation of DIP in the midbrain and spinal cord.
- Histamine , cholinergic and NMDA receptors blocker
- Direct blockade of membrane ion channels (reducing neuronal influx of Ca+ and Na+)



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CONTD..

- DPN, PHN (EFNS Level A evidence)
- Central pain (Spinal cord injury, CPSP), post-traumatic/ post surgical NP, cancer NP, multi-aetiology NP (EFNS Level B evidence)

- NNT = 3.6
- NNH = 6

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CONTD..

- Lower dose than for depression
- Side effects like postural hypotension, dry mouth, and sedation, cardiac toxicity (ECG)
- Start low, go slow

  (EX: Tab Amitriptyline 10 mg at night)
- Cost effective
- Contraindictions- Cardiac patients, glaucoma, dysuria

SSNRI

- Painful polyneuropathy, DPN (Attal et al, 2010)- Level A EFNS
- NNT = 6.4 (Finnerup, et al, 2015)
- NNH= 11.8 (Finnerup, et al, 2015)

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Duloxetine

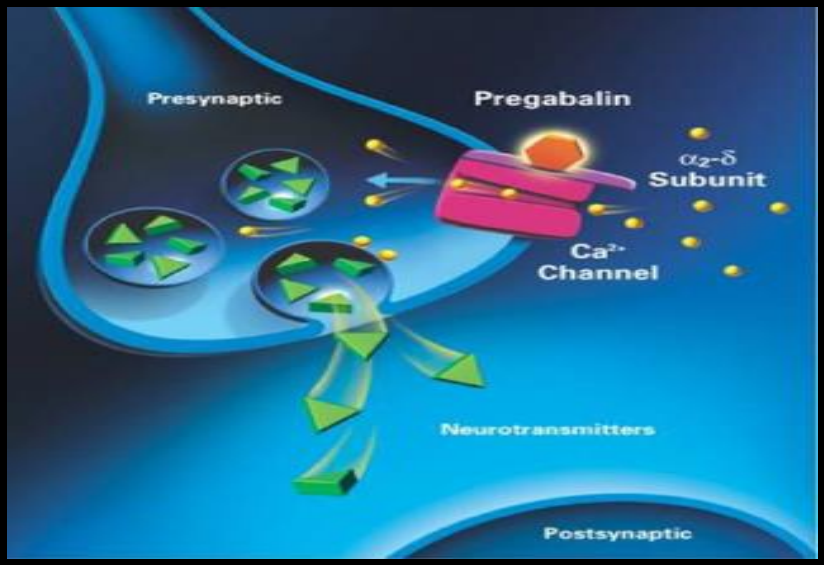
- Nausea
- 30 mg OD , increase to 60 mg OD after 1 week
- CI: Renal and Hepatic impairment

Venlafaxine

- Nausea
- 37.5 mg OD, increase to 75 mg after 1 week
- CI : Cardiac disease, with tramadol
- Abrupt discontinuation- Withdrawal syndrome

CALCIUM CHANNEL A2-Δ LIGANDS

- Structural analogues of GABA
- α2-δ subunit of calcium channels
- DPN, PHN (Level A EFNS)
- Phantom limb pain, Mixed NP, HIV Neuropathy (EFNS Level A/B)
- Side effects- Sedation, dizziness and peripheral edema, risk of substance misuse



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Gabapentin

- NNT = 7.2, NNH = 25.6
- Non-linear pharmacokinetics
- Improvements in sleep, mood, and quality of life
- 100-300 mg bedtime followed by tid
- Increase weekly by 100-300 mg tid upto 3600mg

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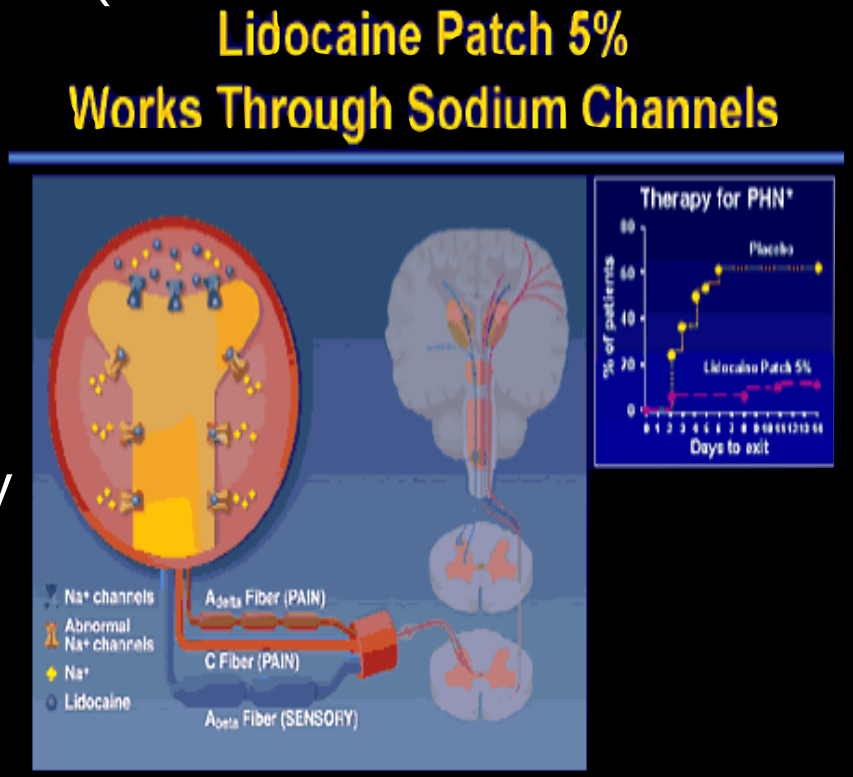
Pregabalin

- NNT = 7.7, NNH = 13.9
- Linear pharmacokinetics
- DPN, PHN, Spinal cord injury
- 150 mg/d in 2 or 3 divided doses,
  titrated up to 300 mg/d after 1 or 2 weeks
- Quicker analgesia than gabapentin

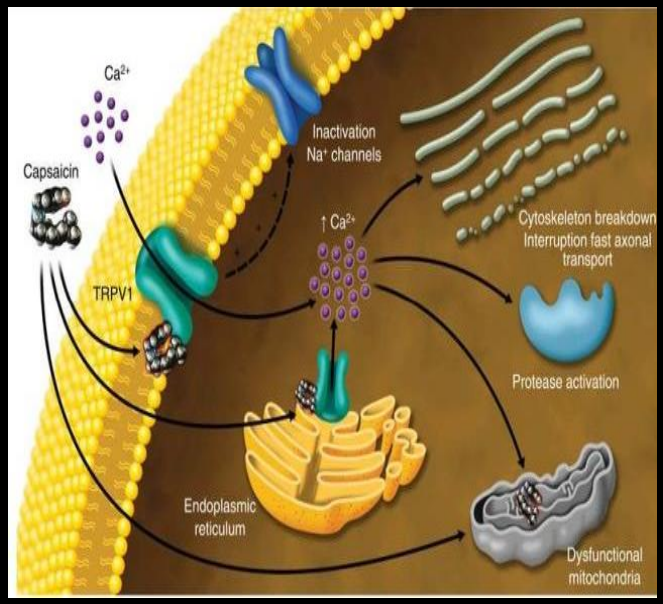
Lidocaine

- 5% (700 mg) patch and gel form (less expensive)
- Acts on sodium channels
- Efficacious in allodynia
- Excellent safety and tolerability profile (even 3 concurrent patches) , elderly
- Left for 12-18hrs
- 1st line for localized NP, PHN



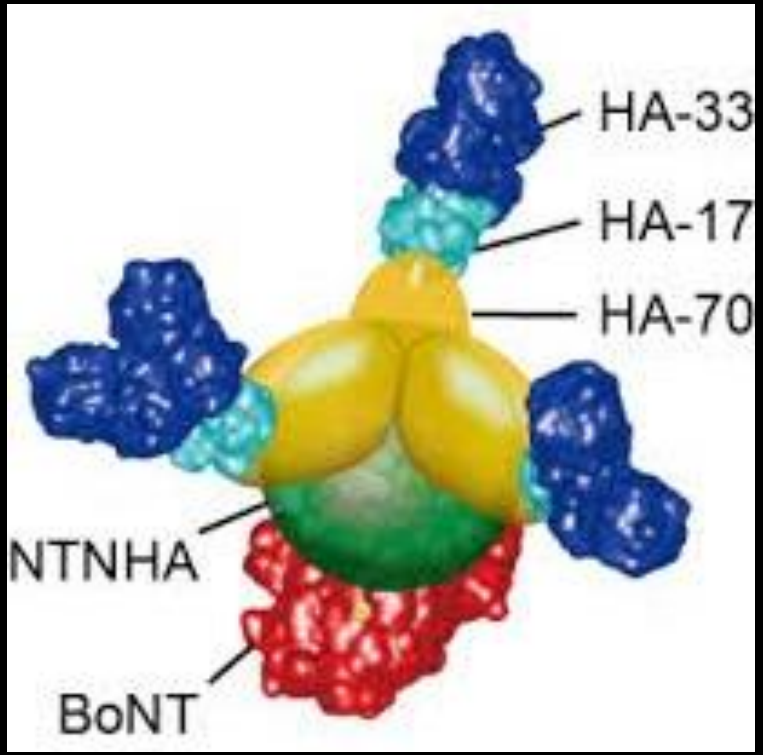
Capsaicin 8% patch

- Extract of hot chili peppers
- Agonist of the vanilloid receptor TRPV1.
- NNT 10.6
- PHN, HIV neuropathy
- Topical LA cream 30 minutes prior
- Left for 1 hr- 12 weeks of relief
- Rare ADR- Increased BP



BOTULINUM TOXIN A

- Clostridium botulinum
- Inhibits release
  - Glutamate, Substance P, CGRP
  - Presynaptic Ach
- PHN, Post traumatic, Post Op pain



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MISCALLANEOUS

- Antiepileptic medications - carbamazepine, lamotrigine, oxcarbazepine, topiramate, and valproic acid
- Ketamine (NMDA receptor antagonist)-low dose
- Systemic lignocaine* - painful DPN, PHN, Peripheral nerve injury
- Cannabinoids- Multiple sclerosis, plexus avulsion, mixed NP

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Ketamine

- NMDA antagonist
- Spinal sensitisation and wind up
- Refractory cancer, CRPS
- Oral, buccal, nasal, IM, IV, SC, rectal
- Peak conc.- IV-1m, IM-5-15m, oral-30m
- Emergence delirium

Corticosteroids

- Acute nerve compression
- Bone pain
- Visceral pain (capsular disruption)

Dexamethasone 2mg= prednisalone 15mg = hydrocortisone60mg= methyl prednisalone 12mg

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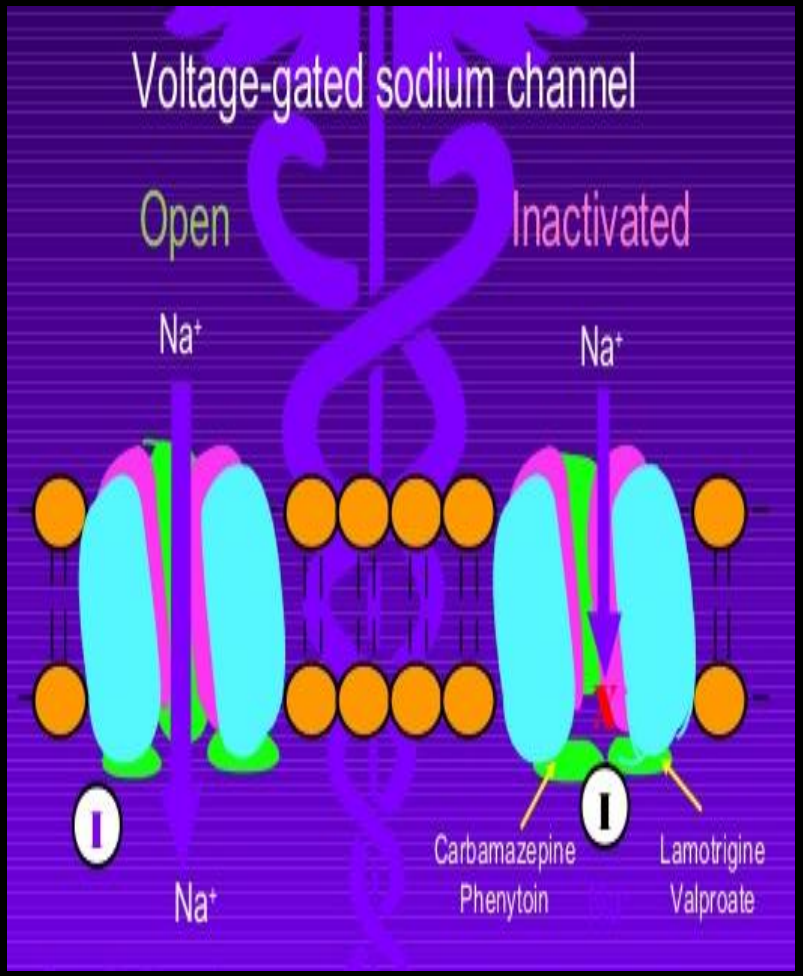
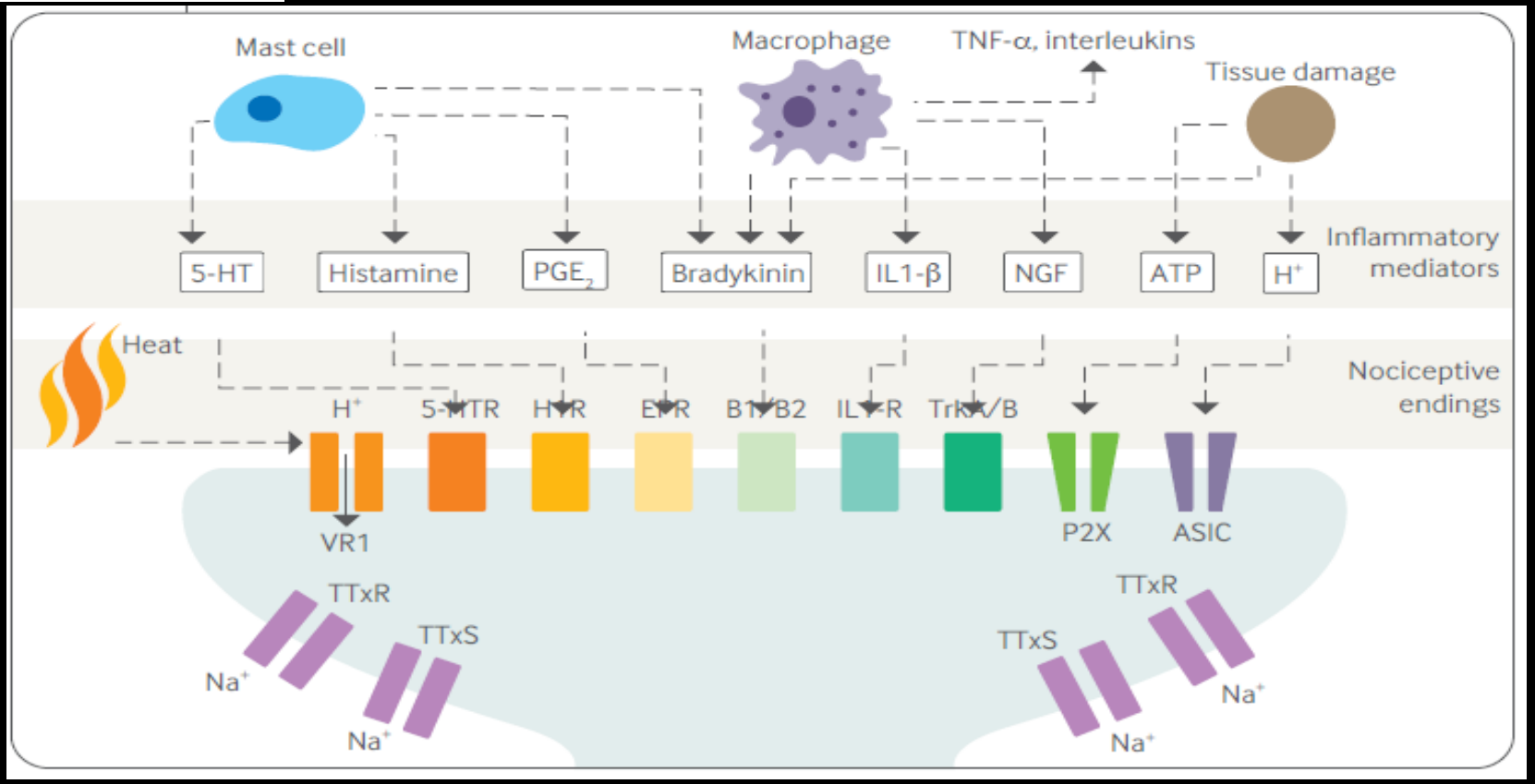
CARBAMAZEPINE

- Sodium channel blocker
- Drug of choice- Trigeminal neuralgia
- Daily requirement : 200mg – 1000 mg
- Side effects- Nausea, drowsiness, dizziness, bone marrow depression, thrombocytopenia



	Acute noci mild	Acute noci severe	Acute Neuro	Chronic non cancer	Chronic cancer
Paracetamol	+++	++	+	+	+
NSAIDs	++	++	+	+/-	+/-
Morphine		+++	++		+++
TCA	-	-	++	++	++
Anticonvulsants	-	-	++	++	+

PERIPHERAL NERVE ENDING



- Inflammatory mediator soup- sensitizes nociceptors- **no single effective drug**
- Unmasking of silent nociceptors
- Phenotypic switch
- Increased expression (proliferation) of sodium channels – **Carbamazepine, TCA, lidocaine.** Not selective to subtypes

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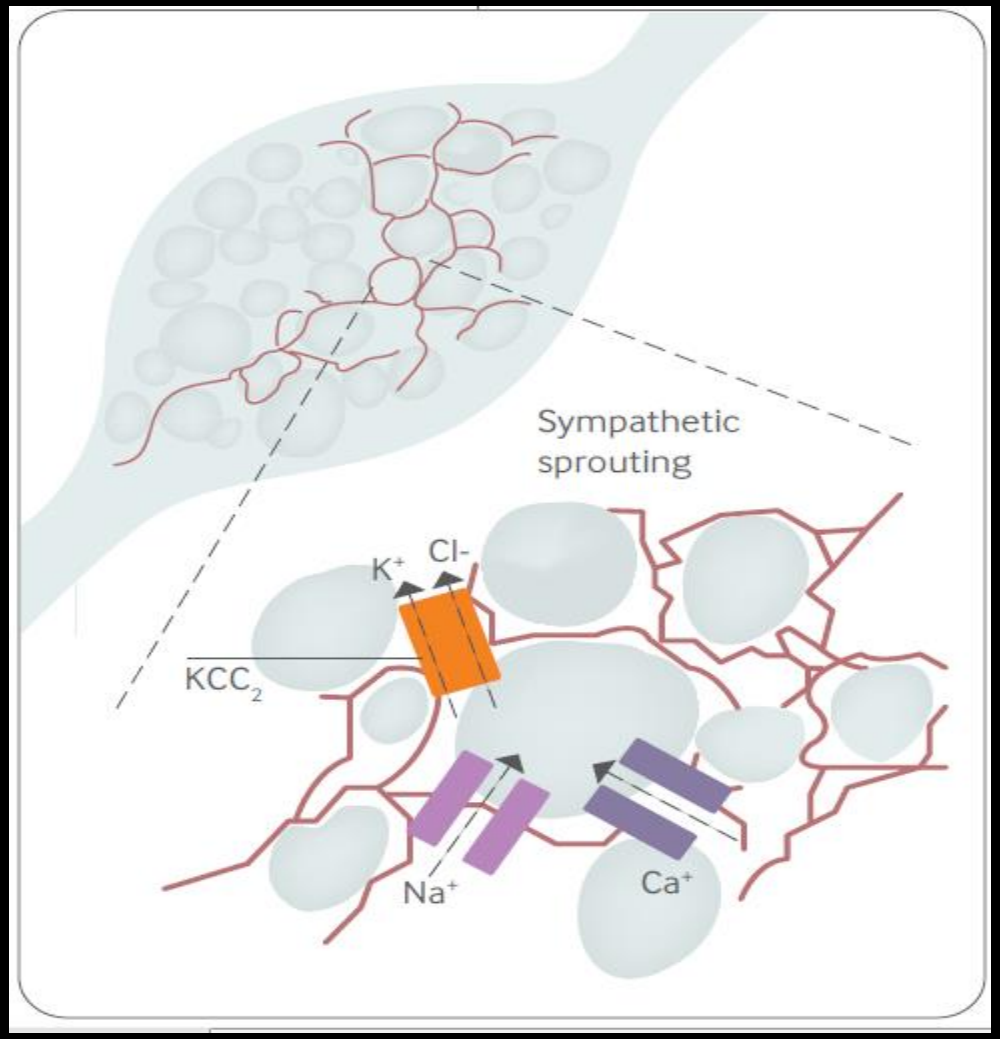
DORSAL ROOT GANGLION



- Increased expression of α2-δ calcium channels- **Gabentinoids**
- Reduced activity of K-CL co-transporter
- Increased activity of Na-K-Cl co-transporter
- Decreased expression of μ opioid receptor – **High dose of opioids** required
- Sympathetic sprouting-
  - IV infusion phentolamine
  - Sympathetic block

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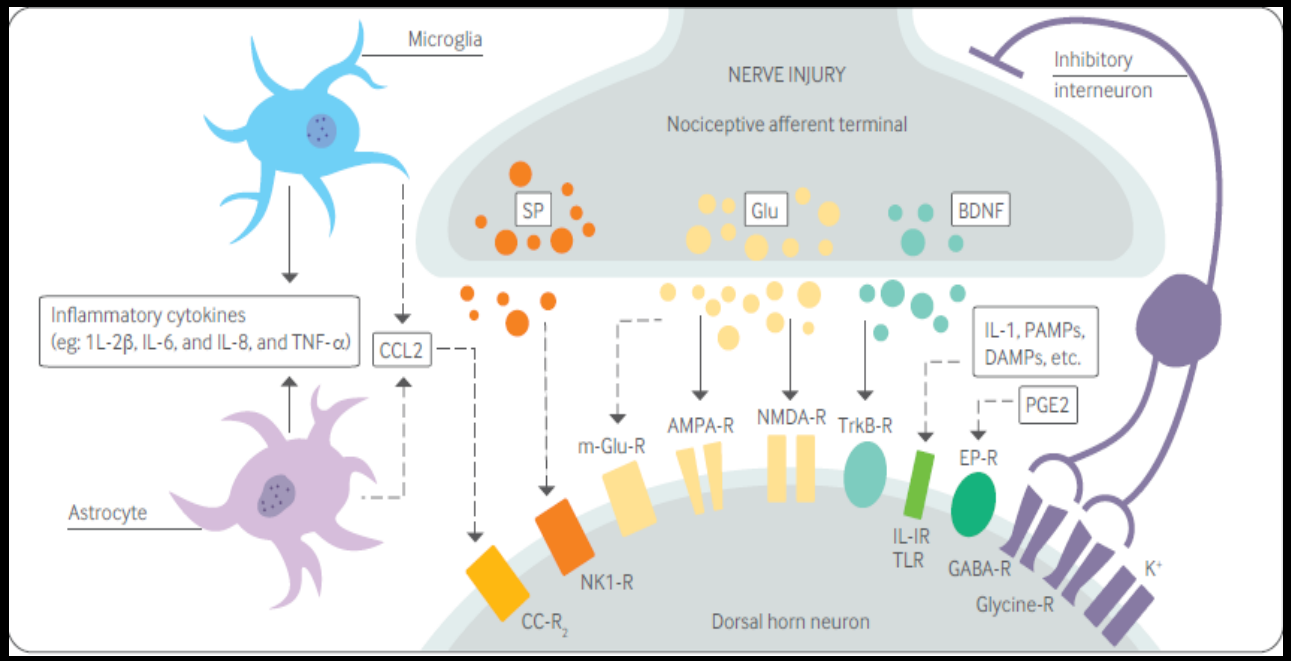
SYNAPTIC JUNCTION- DORSAL HORN OF SPINAL CORD



- Synaptic plasticity- Summation, expansion of receptive fields
- Wind up – Increased glutamate activity – enhanced NMDA and AMPA activity- **NMDA receptor antagonist, Botolinium Toxin A**
- Glial activation – pro inflammatory cytokines – No clinical effect of cytokine inhibitors (Minocycline, etc)
- Disinhibition – Decreased activity of Norepinephrine, serotonin, dopamine, endogenous opiates- **TCA, SNRI, SSRI**

Treatment depending on signs and symptoms

- **Stimulus independent pain**
  - Paroxysmal, shooting, stabbing pain
    - Carbamazepine, oxcarbazepine (TGN)
    - Lamotrigine
    - TCA
    - Gabapentin (Burning and paroxysmal pain)

Paul M Scholten, Norman Harden. Assessing and Treating patients with neuropathic pain. PM R. 2015; 7: S257-S269.

Treatment depending on signs and symptoms

Stimulus dependent pain

Hyperalgesia

- Lidocaine patch
- Lidocaine infusion
- Lidocaine gel
- Capsaicin

Allodynia

- Local aesthetics
- TCA
- Anticonvulsants
- Opioids
- GABA agonists
- NMDA antagonists

Paul M Scholten, Norman Harden. Assessing and Treating patients with neuropathic pain. PM R. 2015; 7: S257-S269.

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Case Scenario

65 years old male with Herpes zoster of left C3,C4 and C5 roots.After 3 months

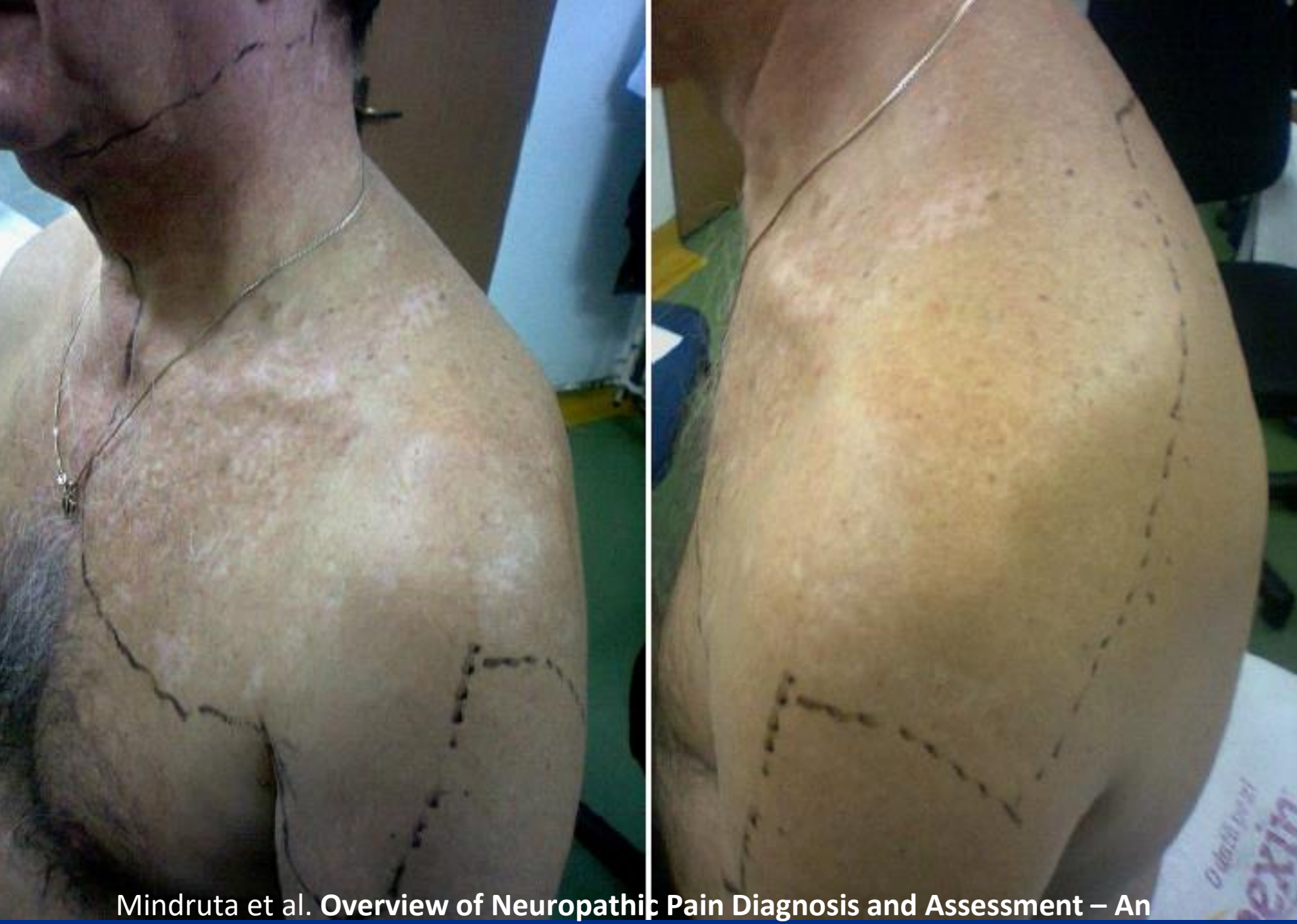
c/o

- Superficial burning
- Hot wire , shooting
- Episodic
- Itching
- Sensation of numbness
- NRS = 10

- Pain on light touch, slight pressure and warm water

Neurological examination

- Static and mechanical allodynia
- Heat allodynia
- Temporal summation



Mindruta et al. **Overview of Neuropathic Pain Diagnosis and Assessment – An Approach Based on Mechanisms. Book: *Neuropathic pain*. 2012**

- Spontaneous activity in C and Aδ fibres , C -nociceptors
- Peripheral & central sensitisation
- Choice of pharmacotherapy
    - Capsaicin patch
    - Sodium channel blocker (Carbamazepine)
    - TCA
    - Opiates
    - Calcium channel blocker (Gabapentinoids)

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Steps for successful therapy

- Medication/ medical history
- Look for drug related fears and misconception
- Thorough knowledge about the drug
- Define realistic goals (primary and secondary)
- Choice of drug should depend on the type and severity of pain
- Give adequate therapeutic trial/ dose

- **Combination therapy- 2 or more drugs with complimentary action**
  - Avoid drugs belonging to same group
  - Be aware of possible interactions
- Beware of addictions
- Taper and discontinue drug

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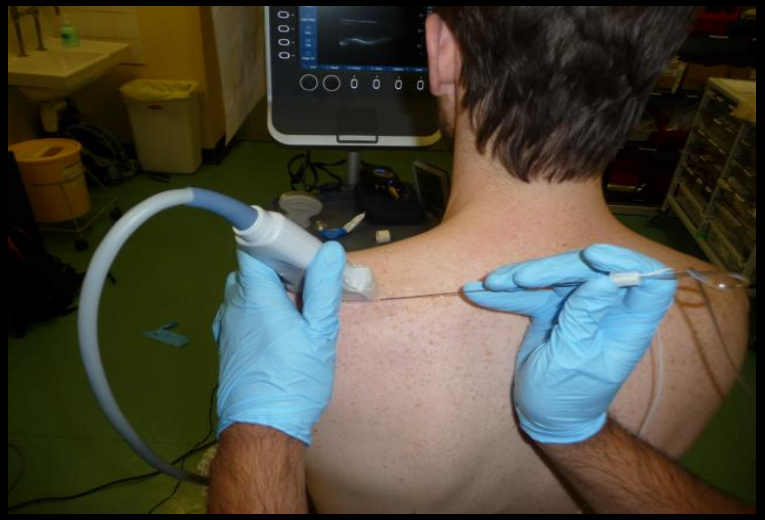
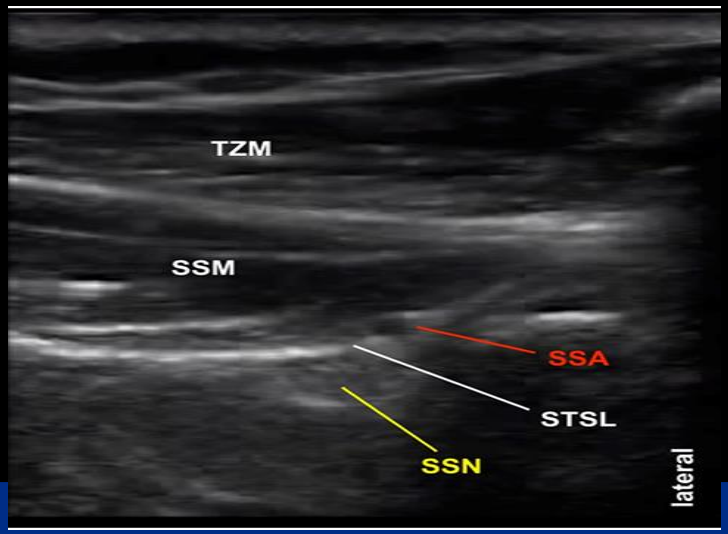
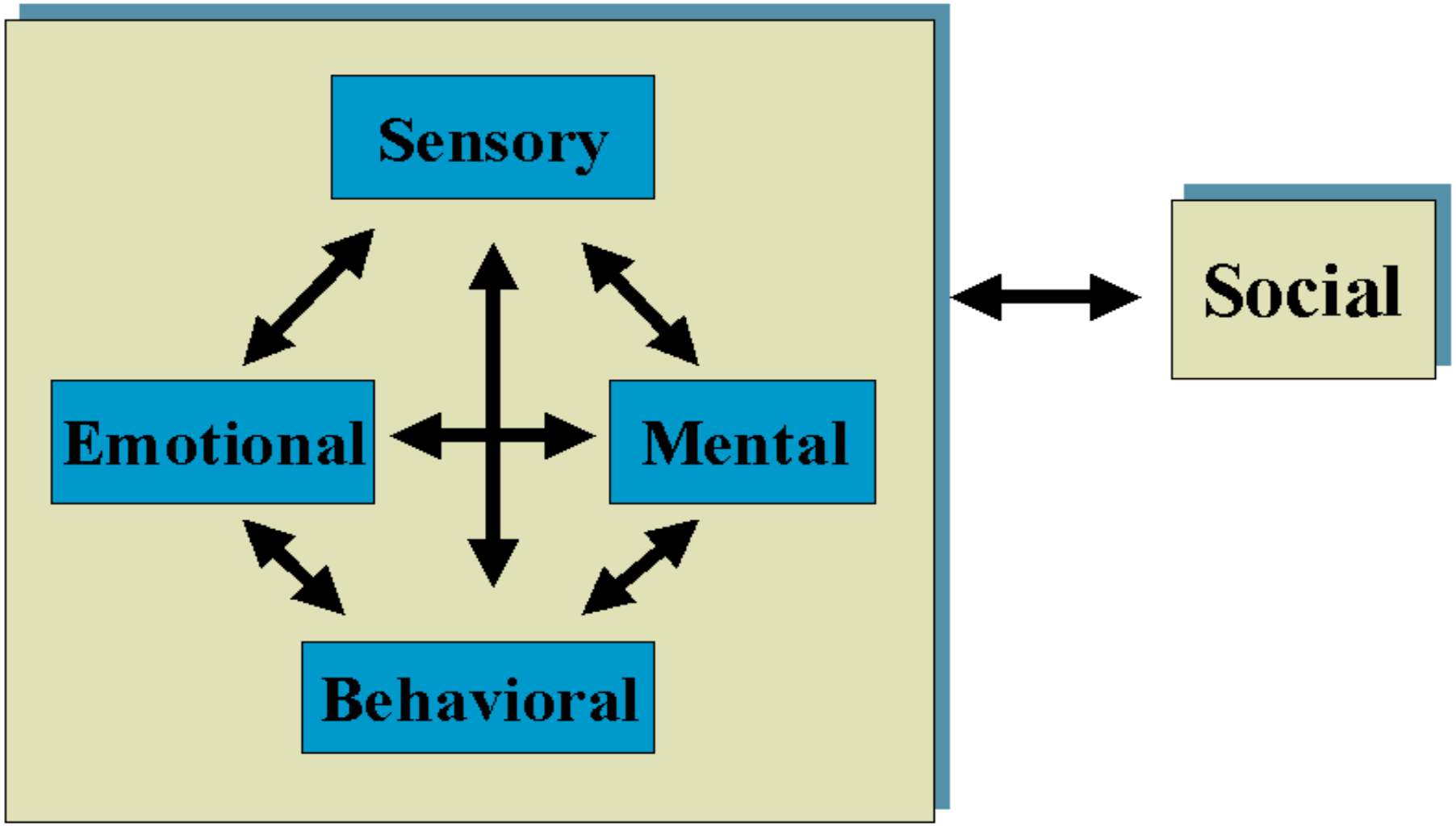
Interventions





Biopsychosocial Interactions



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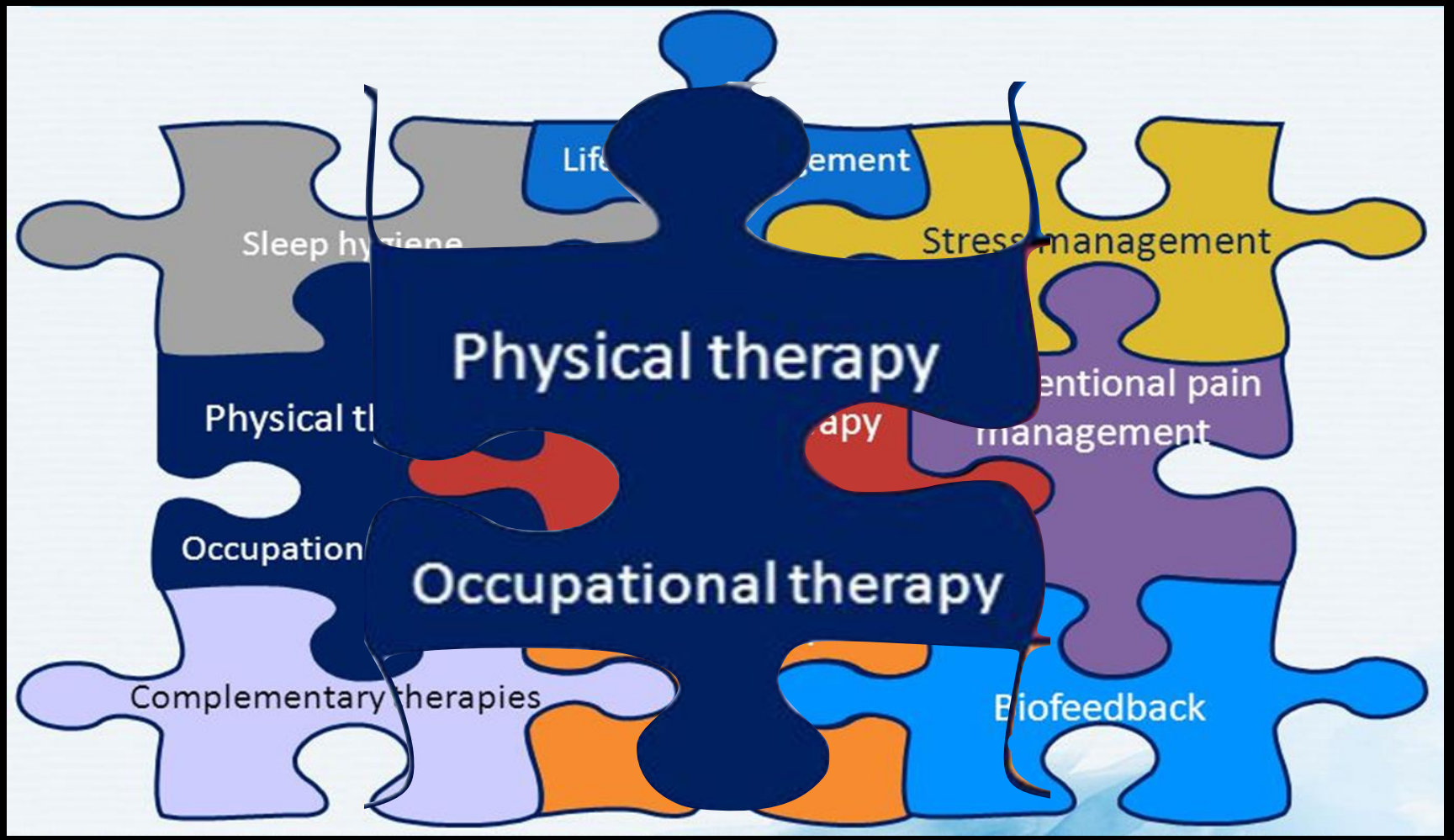
Combination therapy and multimodal approach IDEAL



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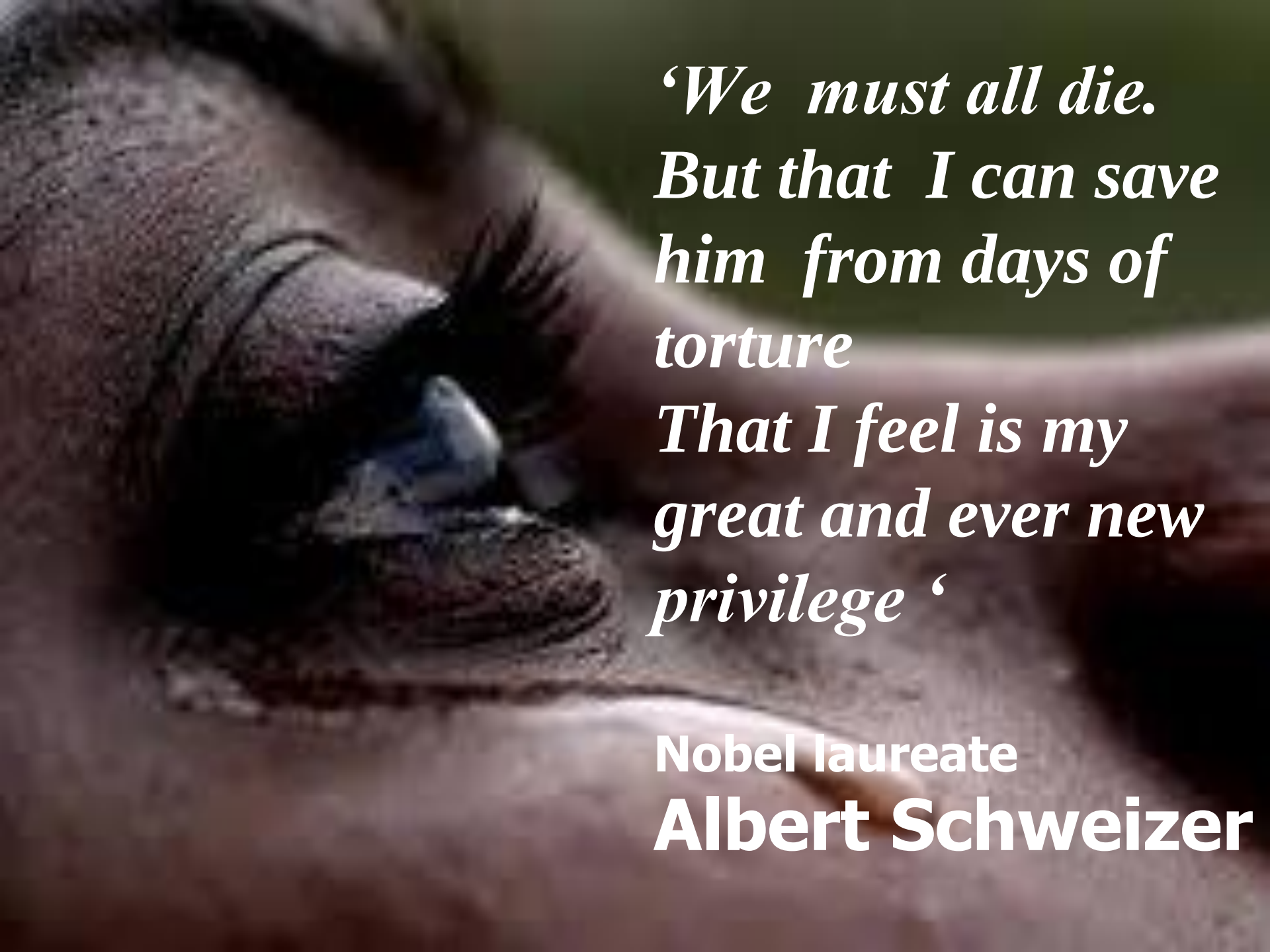
Goals

- Reduction of pain intensity
- Improvement of quality of life
- Improvement of psychological functioning
- Reduction of healthcare utilization
- Promotion of return to work/school class and/or role within the family/society

Views on pain depend on whether the doctor is supine or standing !


‘We must all die.
But that I can save him from days of torture
That I feel is my great and ever new privilege ‘
Nobel laureate
Albert Schweizer


I CANNOT PREDICT THE FUTURE
I CANNOT CHANGE THE PAST
I HAVE JUST THE PRESENT MOMENT
I MUST TREAT IT AS MY LAST
Thank you

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JSS HOSPITAL

DR AKKAMAHADEVI. P
PROF & HEAD, DEPT. OF EMERGENCY MEDICINE
JSS MEDICAL COLLEGE, MYSURU

Mr Aradhya, 70yr M.

K/C/O Ca prostate , bony metastases

C/o Severe pain - Lower abd &back .

Generalise pain , Fatiguability, lowerlimb weakness.

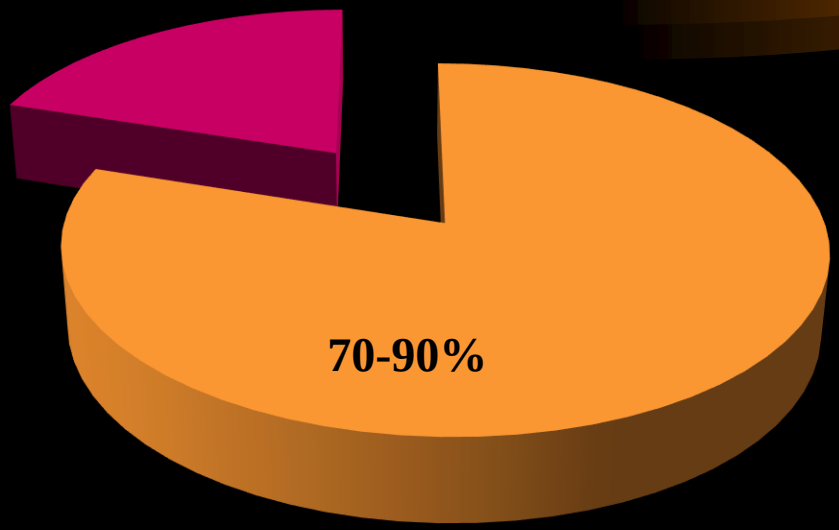
Oral opioids Morphine CR 90mg BD

Gabapen 2700 mg

No relief , sedation on increasing dose.

Emotionally disturbed

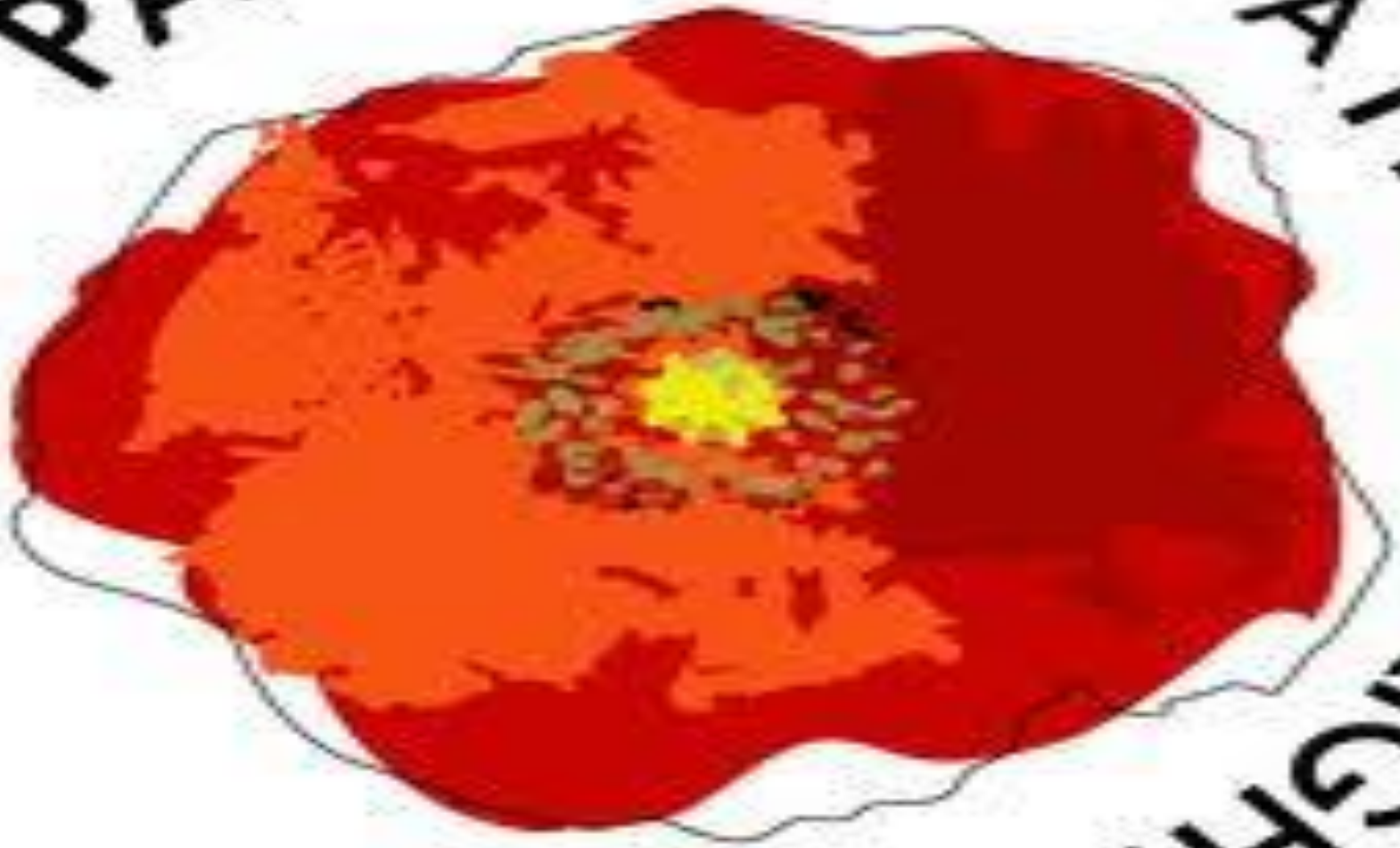
- >10 million people - Cancer



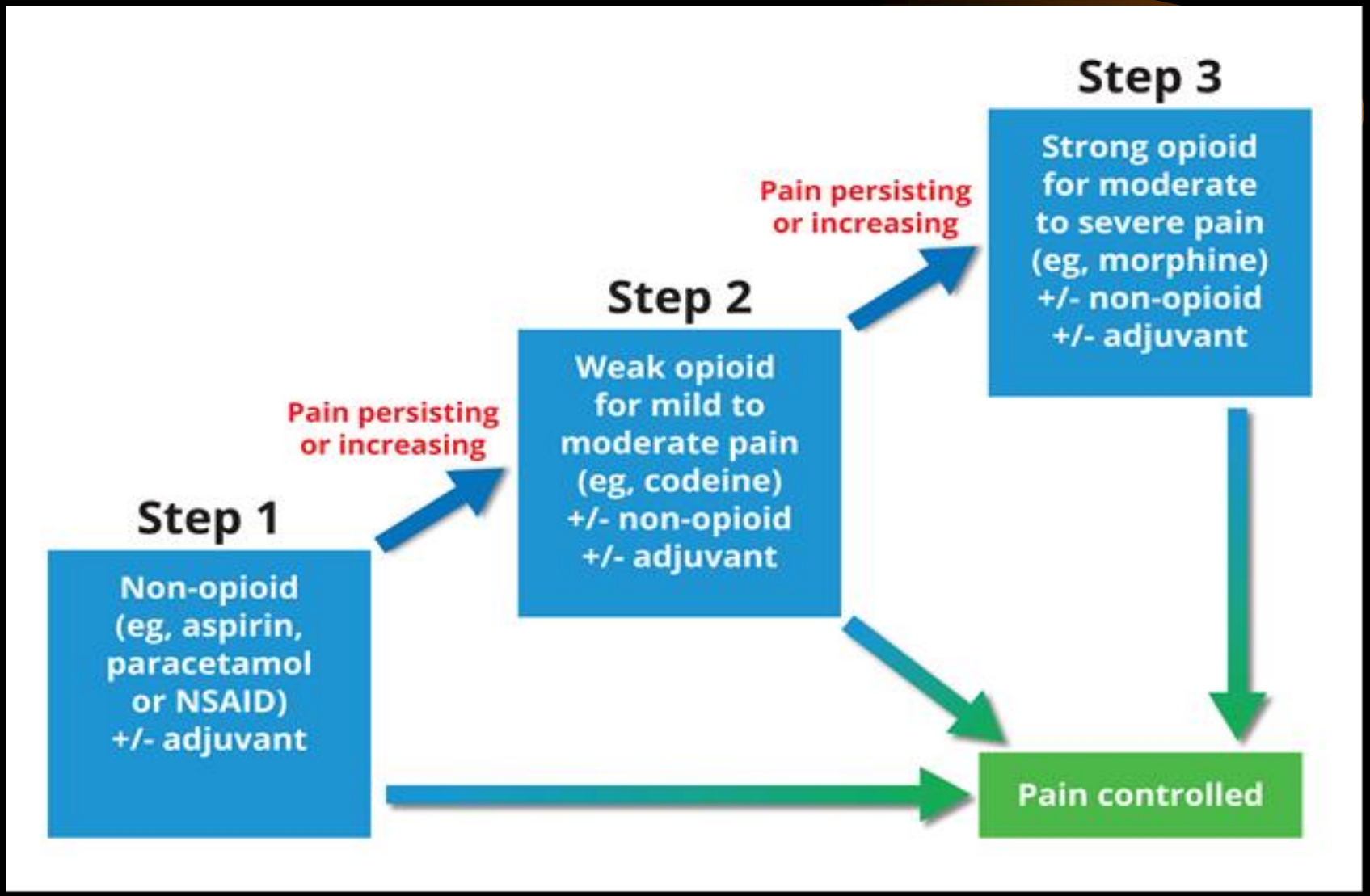
75% at advanced stage have pain

25 – 30% have severe pain - Bonica ,1990

PAIN RELIEF IS A HUMAN RIGHT

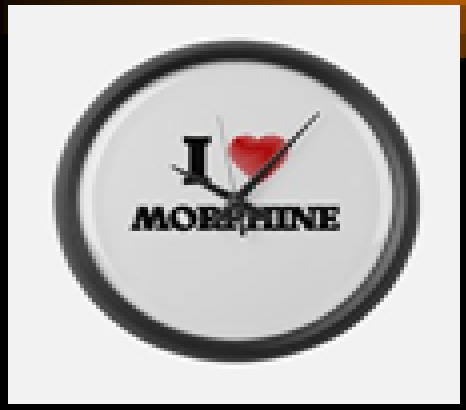


World Health Organisation (WHO) Analgesic ladder- 75-90% pain relief



WHO cancer pain relief Albany 1986

Oral morphine



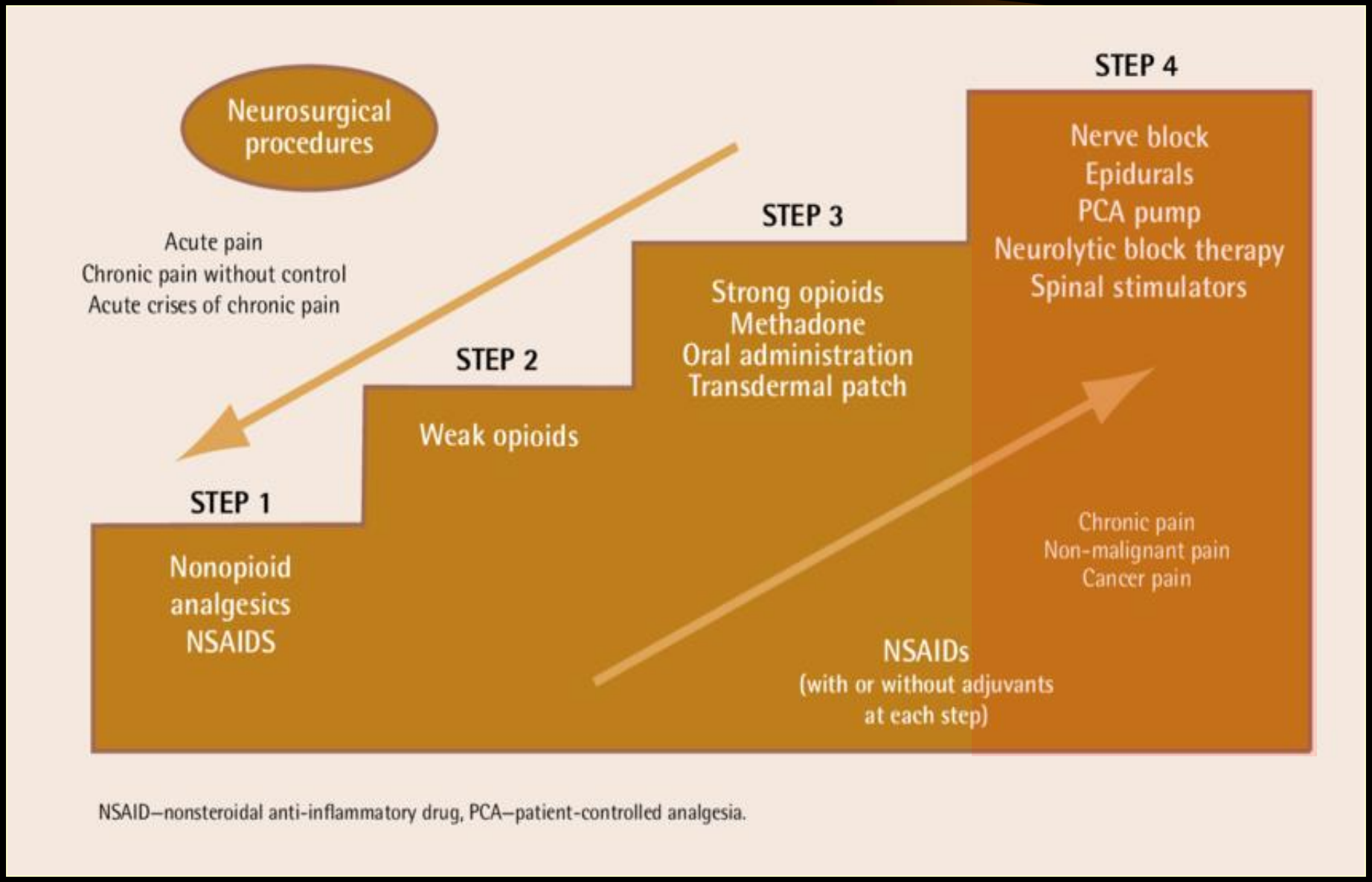
1. By mouth
2. By the clock
3. By the ladder
4. For the individual

   correct dose = dose that relieves pain
5. With attention to detail —treat side

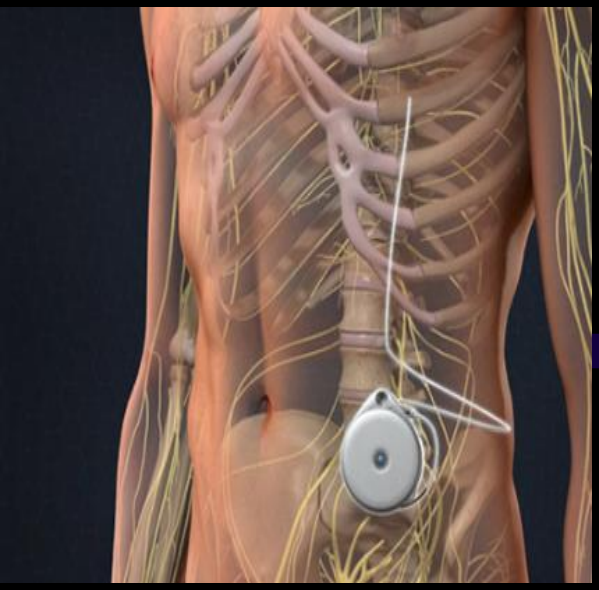
10-15% resistant!

- 2007 systematic review – suggested additional modalities

Modified WHO ladder



NSAID—nonsteroidal anti-inflammatory drug, PCA—patient-controlled analgesia.



INTERVENTIONAL PROCEDURES FOR CANCER PAIN MANAGEMENT

Causes of cancer pain

- Tumor invasion (local and systemic)
- Response to therapy (Surgery, chemo, radiotherapy and Biopsy)
- Non-Cancer related (IVDP, diabetic neuropathy)

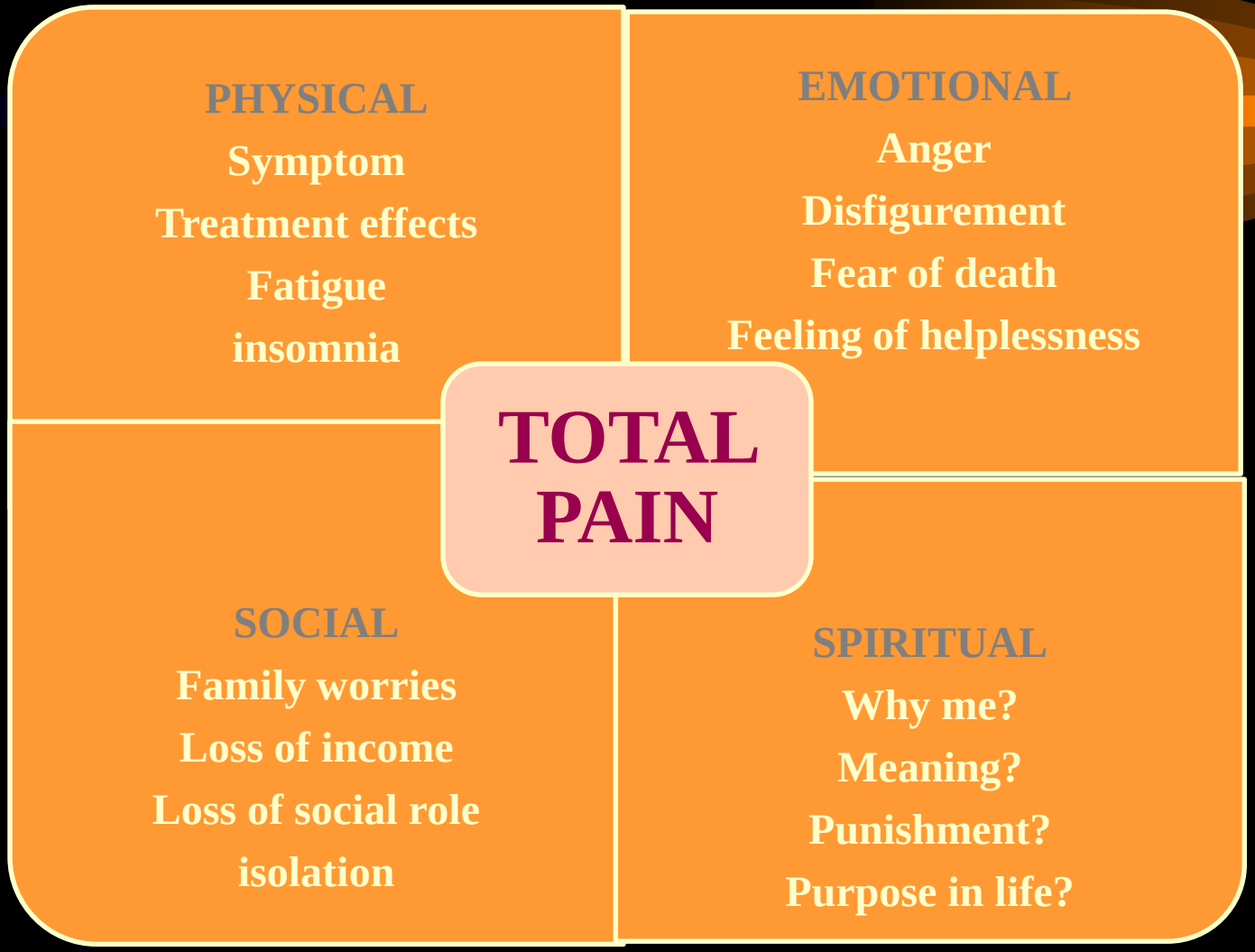
Pathophysiology

- Visceral – poorly localized, diffuse pressure type
- Somatic – localized, sharp squeezing
- Neuropathic – Burning, tingling, lancinating
  ? RESISTANT
- Mixed

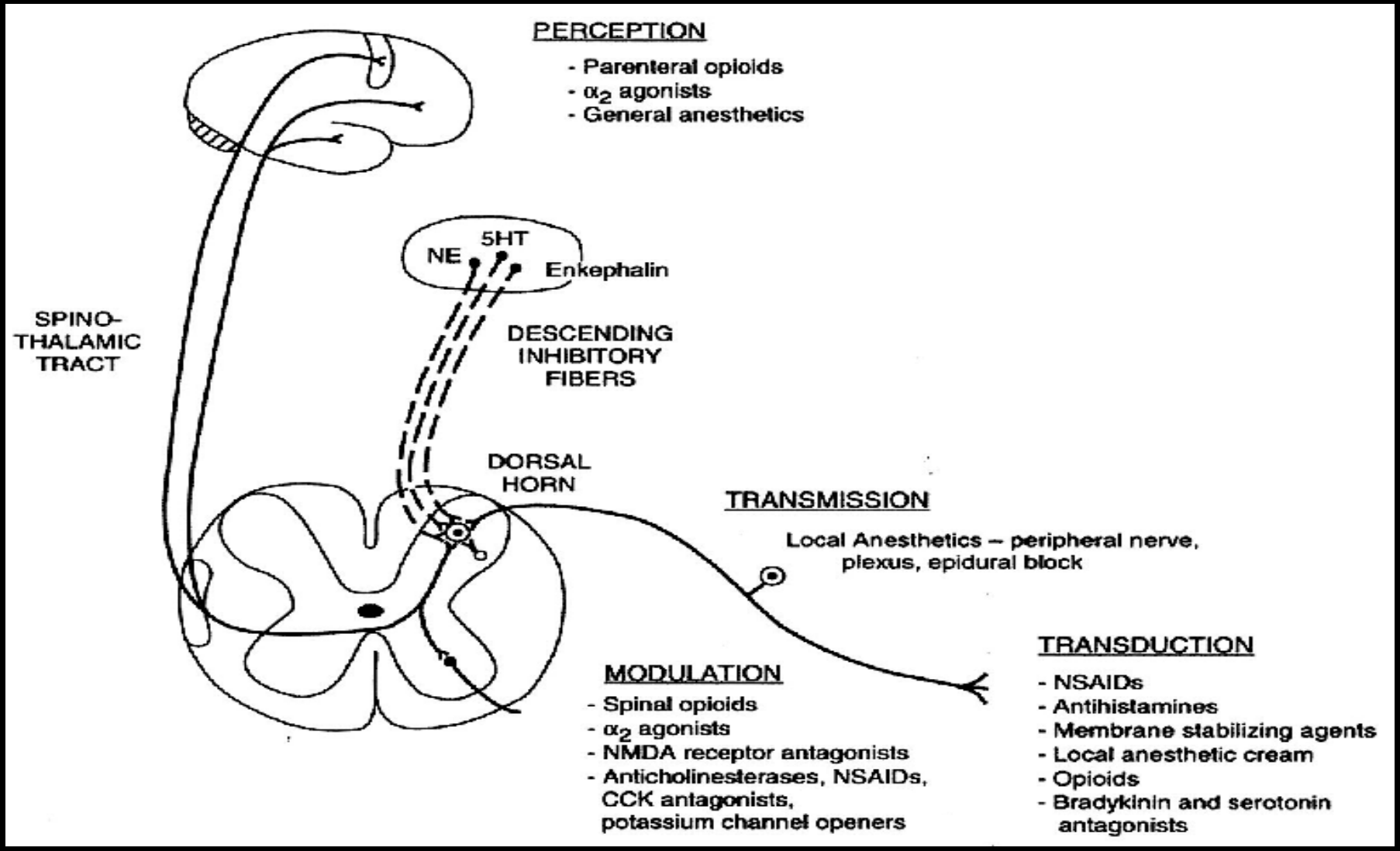

cancer
mouth
Oral
may
spread
neck
therapy
include
Oral
problems
Surgery
tongue
use
swallowing
area
health
radiation
cancers
treatment
ulcer
people
often
difficulty
alcohol
group
hygiene
Tongue
commonly
lymph
nodes
diagnosis
occur
provider
increases
risk
lip
sore
cell
tobacco
Complications
dentist
tumor
done
care
Mouth
lump
speech
biopsy
dental
factors
support
half
also
used
doctor
metastasis
Taking
However
including
deep
quickly
Swallowing
burning
enough
early
Cheek
Causes
prognosis
usually
throat
chewing
See
Head
X-rays
persons
appointment
dark
survival
Expectations
Weight
examine
avoid
Heavy
common
discovered
determine
increase
sensation
Approximately
Pain
advanced
Limit
Roof
Cancer
older
CT
papilloma
delayed
Treatment
face
discolored
system
Poor
exam
Disfigurement
Calling
joining
involves
Squamous
Call
smoking
good
weaken
movement
Practice
particularly
get
Gum
Last
men
scans
Avoid
pale
dry
surgery
Chronic
crack
hard-edged
leukoplakia
dentures
palate
Speech
routine
corrected
infection
tend
confirm
Floor
cleaning
treatments
detected
Usually
painless
cure
tissue
Human
sores
white
stress
go

MIXED > 40%

Concept of 'Total Pain'



INTERVENTIONAL PROCEDURES



"Intervention on appropriate nerves may provide further pain relief if the drugs are not wholly effective "

-World Health Organization. WHO's pain relief ladder. http://www.who.int/cancer/palliative/painladder/en/.

INTERVENTIONAL TECHNIQUES

Reversible Techniques:

- Nerve block with or without infusion
  PN block (Intercostal nerve block, femoral nerve block)
- Plexus block (lumbar, brachial)
- Epidural and intrathecal - spinal cord and nerve roots

Destructive techniques:

Ablative neurolytic (chemical, RF)

- Peripheral nerve
- Epidural
- Intrathecal
- Sympathetic nerve blocks
- Percutaneous cordotomy

Stimulation Techniques:

- TENS
- Acupuncture
- Peripheral nerve stimulator
- Spinal cord stimulation
- Deep brain stimulation

Neurological techniques:

- Surgical cordotomy
- Midline myelotomy


NEURO-ABLATORY
(DESTRUCTIVE)
REVERSIBLE
(NON-DESTRUCTIVE)

failing to prepare = prepare to fail

Evaluation

- Pain evaluation
- History
- Examination – Neurological
- Investigations – PT/INR, others

Selection of patients

- Inability to achieve – with 3rd step
- Severe side effects
- Patients choice - to be tailored.

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A palliative care intervention for pain refractory to a percutaneous cordotomy

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The University of Texas MD Anderson Cancer Center, Houston, Texas

(RECEIVED November 7, 2013; ACCEPTED January 14, 2014)

ABSTRACT

Background: Intrathecal analgesia and radiofrequency techniques for tumor ablation are employed for palliation of symptoms. These interventions are efficacious in a select number of patients for controlling pain and improving quality of life. Careful selection of an appropriate candidate must be performed to prevent needless, invasive, and costly interventions, as interventional pain management alone will not treat total pain in cancer patients. We describe here a patient who experienced intractable pain and unsuccessfully underwent cordotomy but responded to the interdisciplinary (IDT) palliative care approach in an acute palliative care unit (APCU).

Preparation

- Theatre type of environment – Asepsis
- Monitoring
- Imaging- USG, Fluroscopy, CT
- IV line
- Resuscitation and post-procedure
- Trained assistance.


Rx 20ml
BUPIVACAINE
HYDROCHLORIDE
INJECTION I.P.
ANAWIN® 0.25%
LOCAL ANAESTHETIC
PRESERVATIVE NOT ADDED
एनाविन
0.25%
NEON
LOX® 2%
30ml
NEON
Dexalab


EXPERTISE
ABILITY
EXPERIENCE
KNOWHOW

Evidence

Level of evidence	Description
1A	Systematic review of randomized controlled trials (RCTs)
1B	RCTs with narrow confidence intervals
1C	All or none case series
2A	Systematic review cohort studies
2B	Cohort study/low-quality RCT
2C	Outcomes research
3A	Systematic review of case-controlled studies
3B	Case-controlled study
4	Case series, poor cohort case-controlled study
5	Expert opinion

Evidence to practice and practice to evidence redefines **EBM as a circular integration of its 3 components**

Neurolytic agents

Countess of Northemberland

– sharpest most uncomfortable pain , deprived her of sleep rarely allowed her only 5-6 mins of peace per hour unable to eat , drink , cough , spit , or wipe her face.

- Neurolytic agents - alcohol and phenol
- Thermal neurolysis - radio-frequency ablation

- **Alcohol -** 50 -100%
- dehydration of axons - axonal damage
- intense pain on injection
- mixed with local anaesthetic to mitigate
- hypobaric when injected intra-thecally

- **Phenol -** 7 -12%
- protein precipitation and axonal damage.
- more viscous
- local anaesthetic effect
- Toxicity - more than 1gm for a single procedure.
- hyperbaric when injected intra-thecally

Radio-frequency –

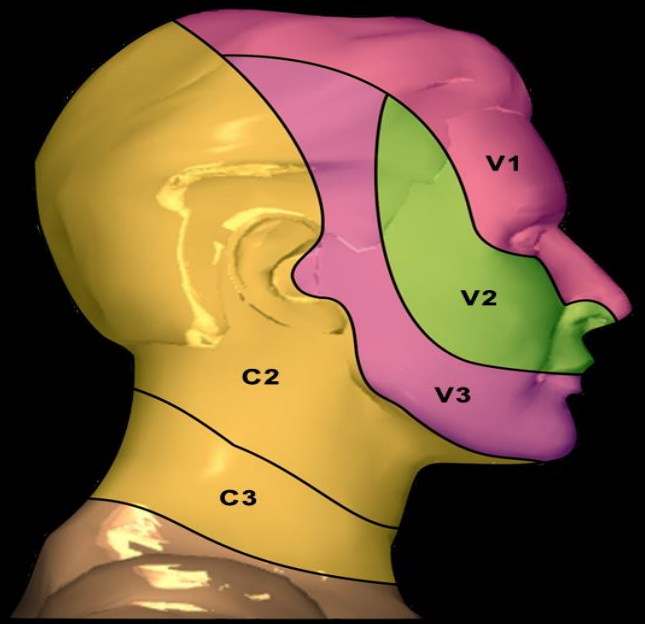
- alternating current of 50-500 KHz - heating effect - ablate peripheral and central sensory pathways.

- **Conventional RF** needle tip is heated to 80-90^0 C for 60-90 seconds.

- **Pulsed RF -** temperature is kept below 43^{0}C by the use of 2Hz, 20ms pulses of alternating current of 3-5 minutes.
  - less effective than continuous RF
  - less tissue damage (Deafferentation pain)

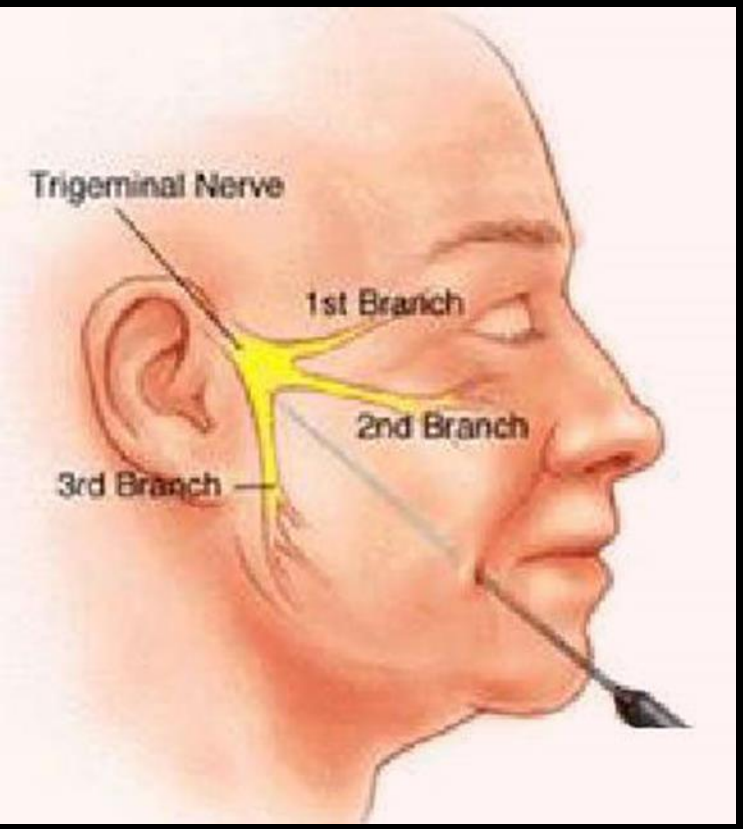
Head and neck

- Prevalence 85%
- 93% mixed pain (nociceptive and neuropathic)
- Pain of varying severity



Trigeminal Ganglion

- Mixed nerve – primarily sensory.

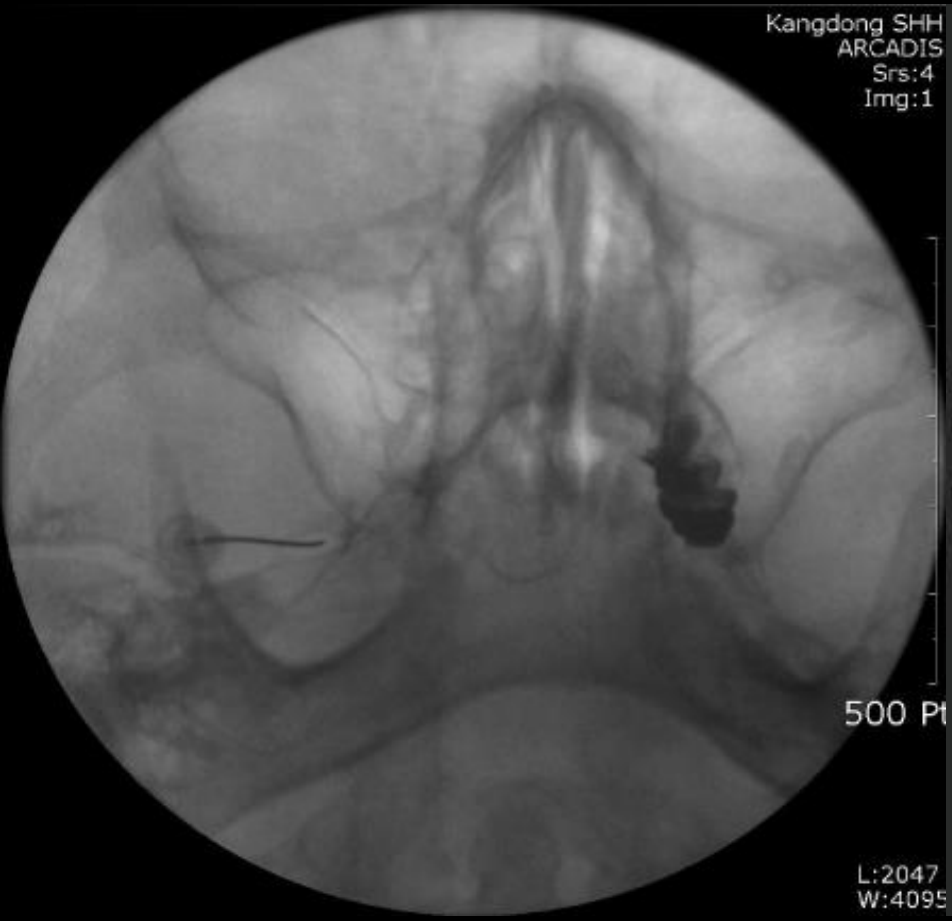


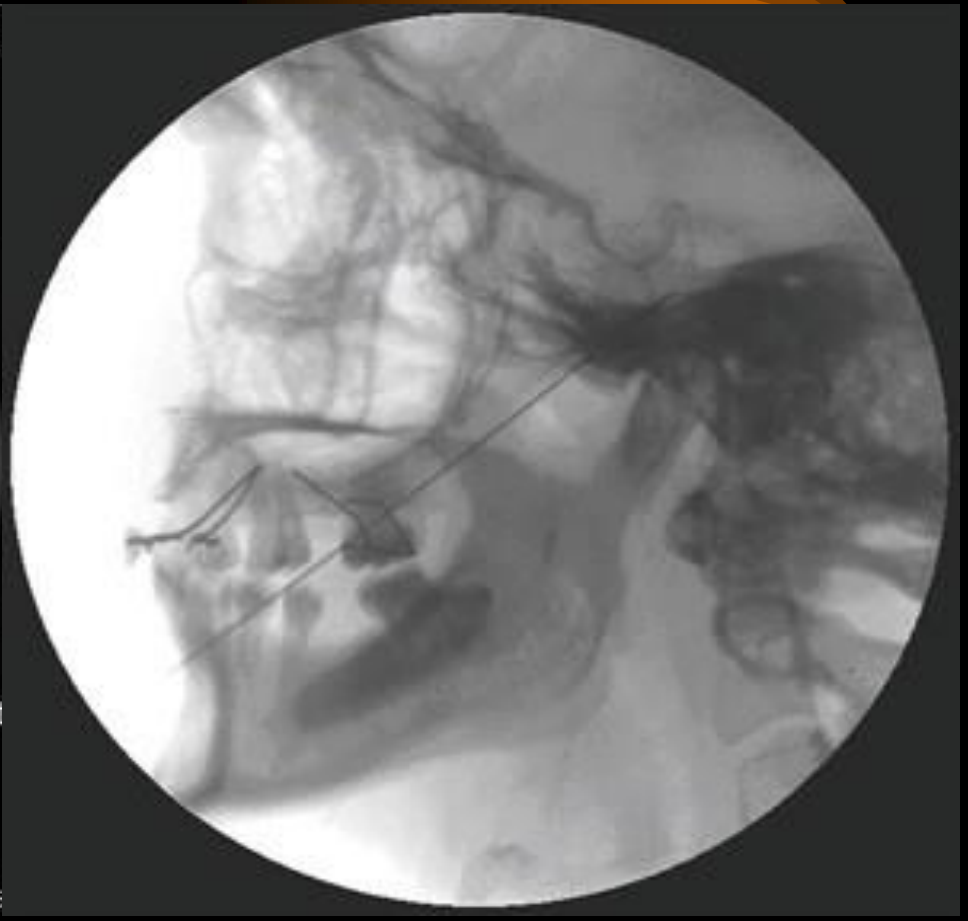
RF- not for Ophthalmic.

Balloon decompression

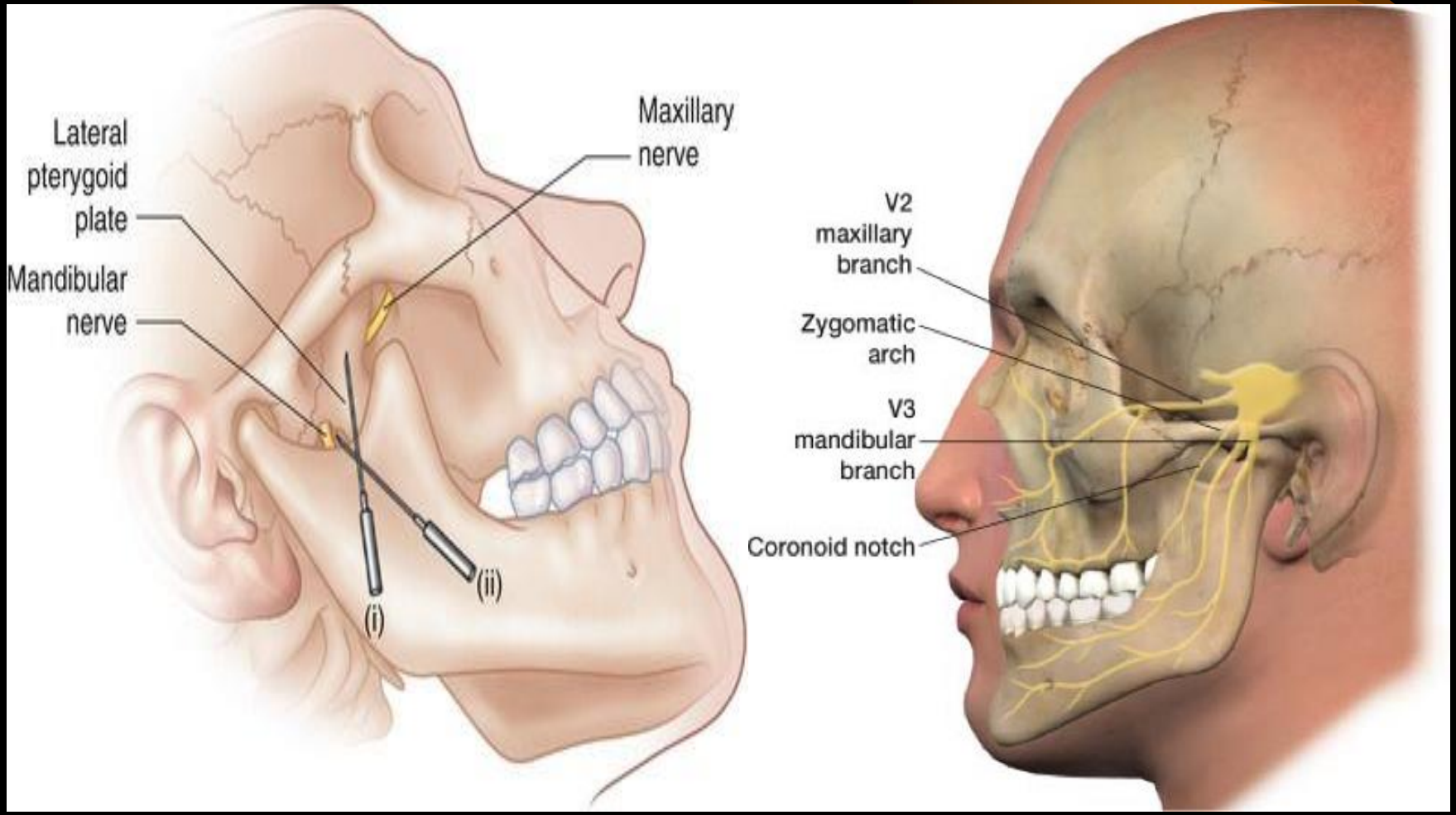
Glycerol-0.2-0.6 cc

Gasserian ganglion block



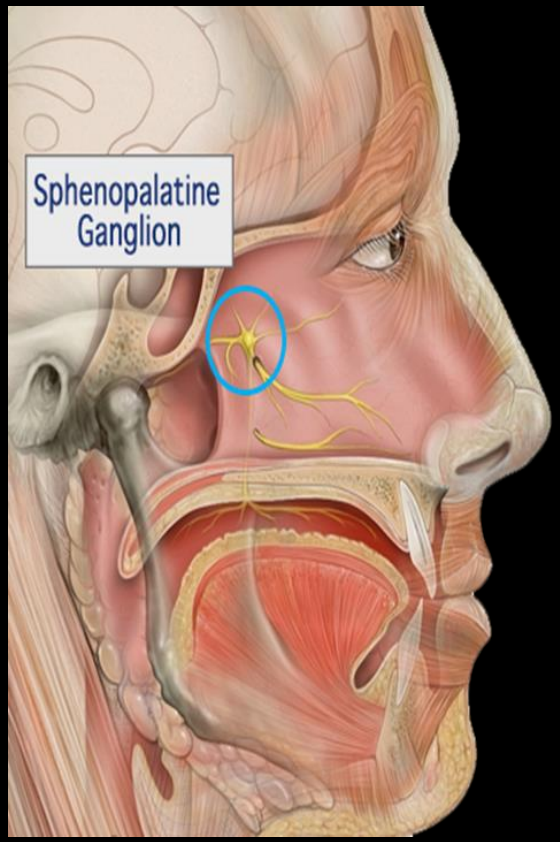


Mandibular/Maxillary



Sphenopalatine ganglion block *2B+*

Important facial ganglion



Indications

- Cancer of

  Palate

  Base of tongue

  Pharynx

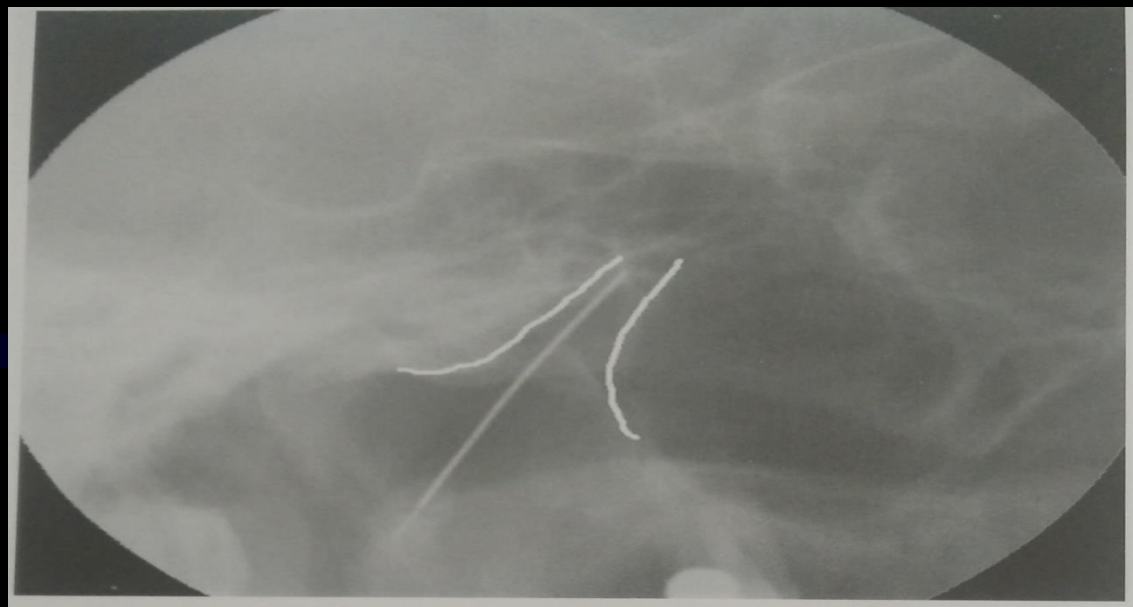
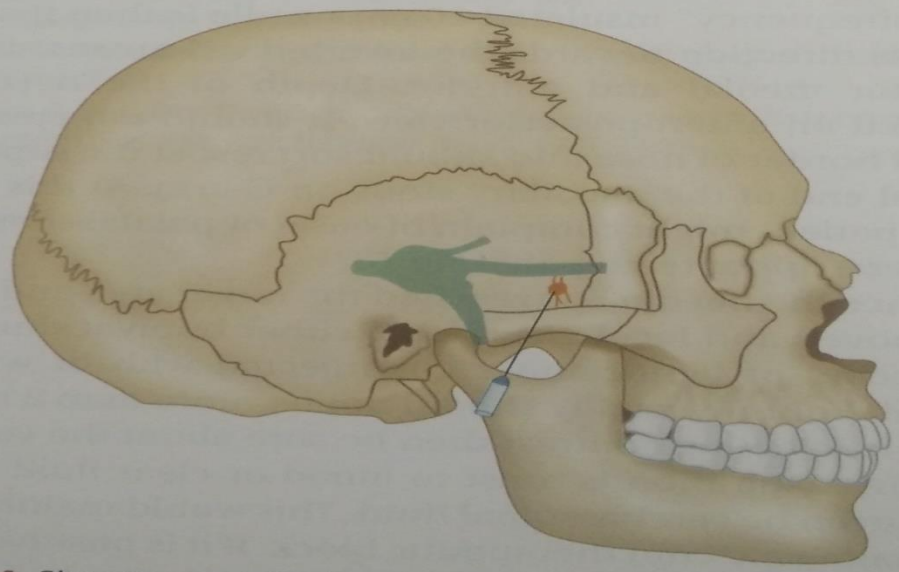
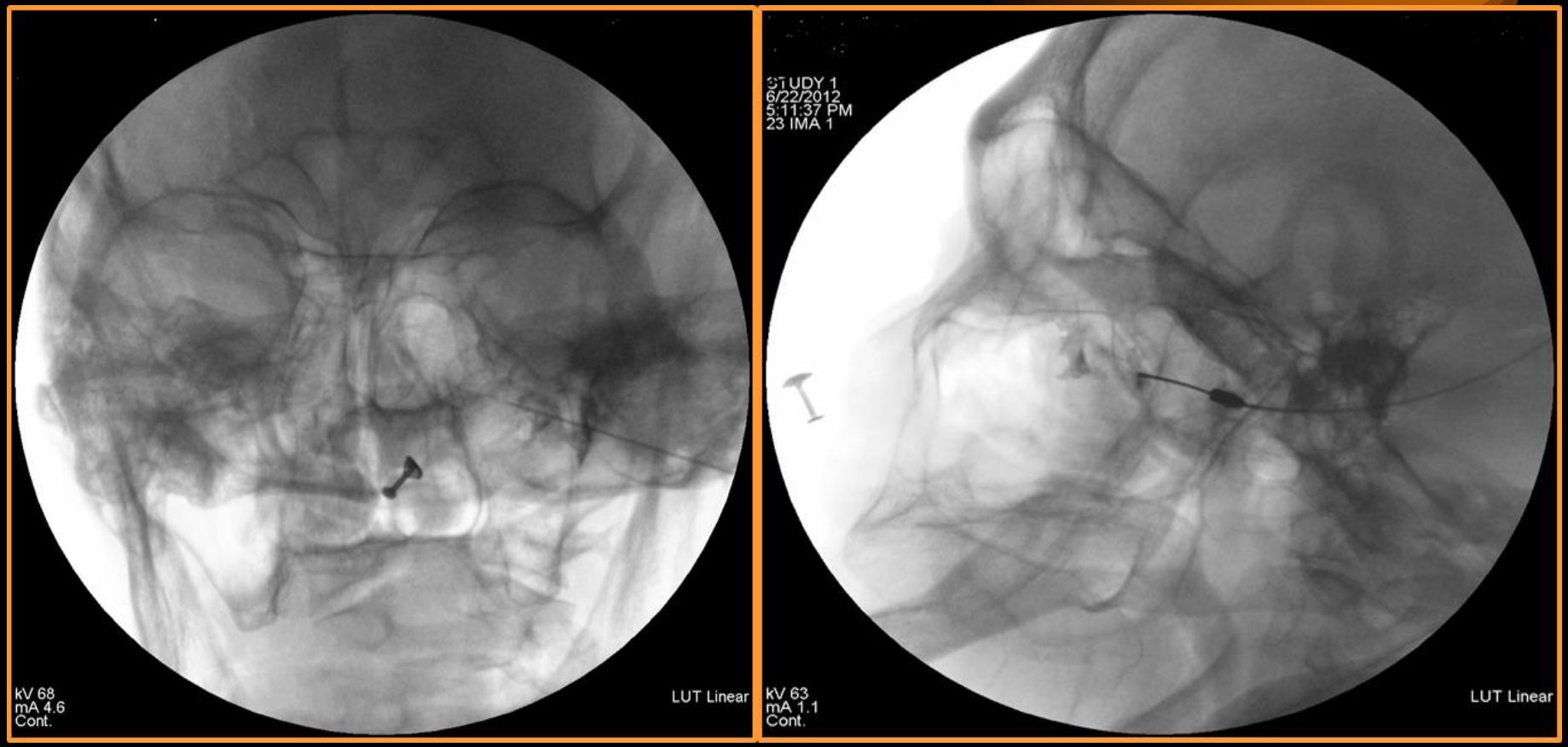


Figure 3 Showing needle in the "inverted vas" under C-arm which is pterigopalatine fossa



igure 4 Showing needle through the center of the coronoid notch, lthough in diagram it looks as if it is over zygomatic arch but in reality goes underneath the zygomatic arch

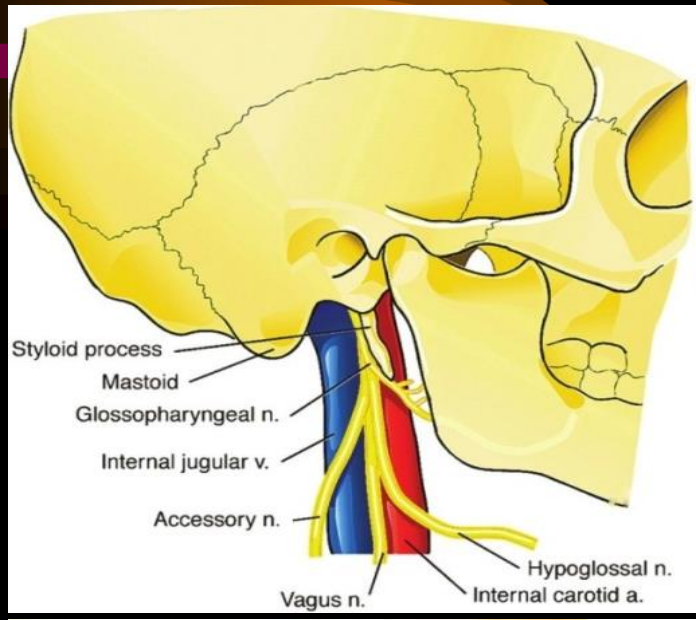


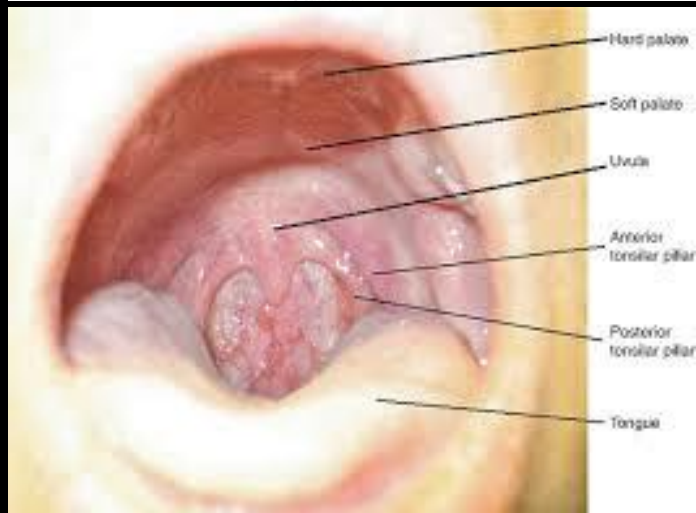
Bupivacaine .5% , Lignocaine 2% 2ml, RF ablation

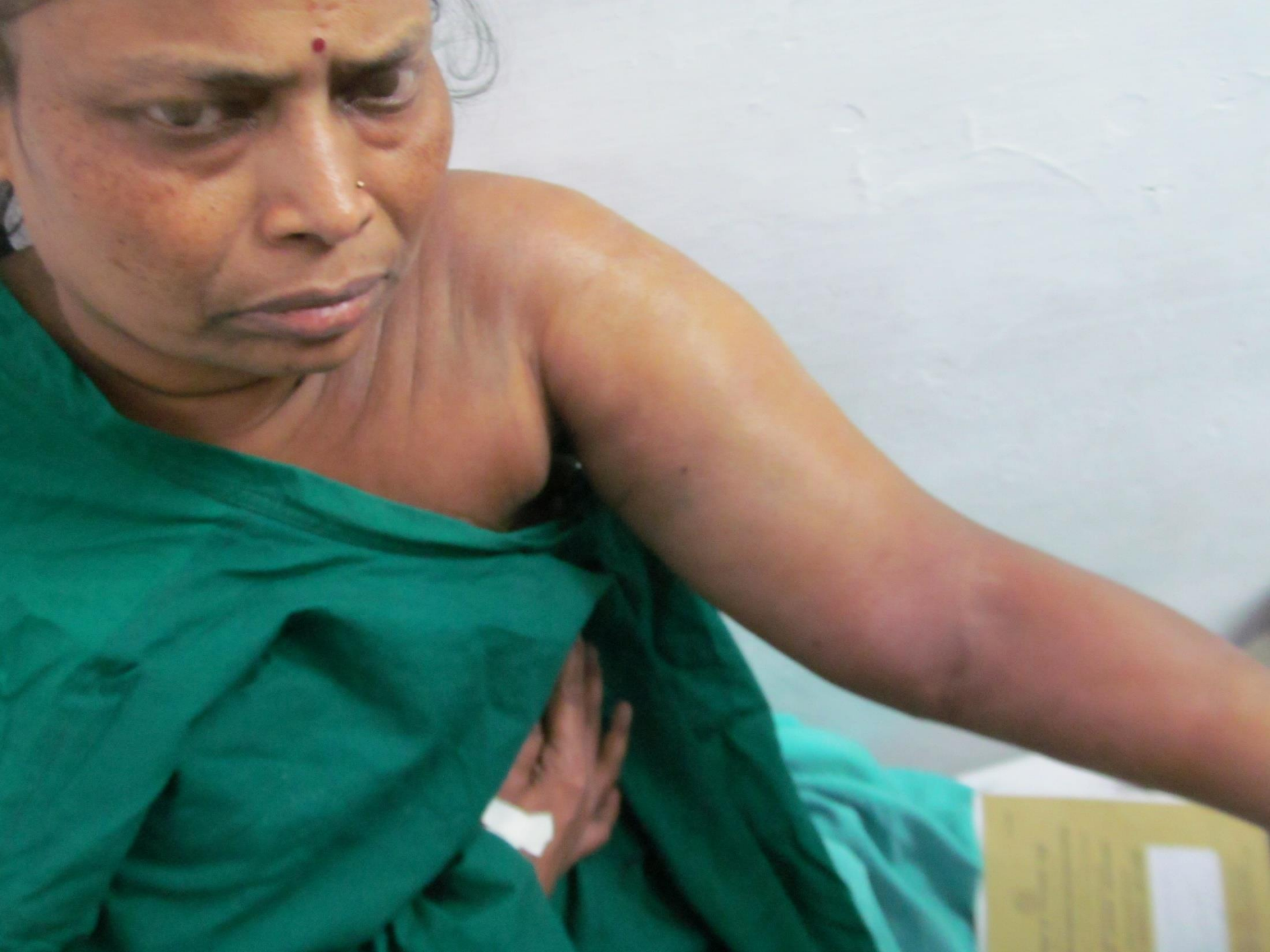
Glossopharyngeal nerve block

- Mixed nerve.
- Ca -Ear,
  - Pharynx
  -Tonsils, Epiglottis
  - Post 1/3 tongue.

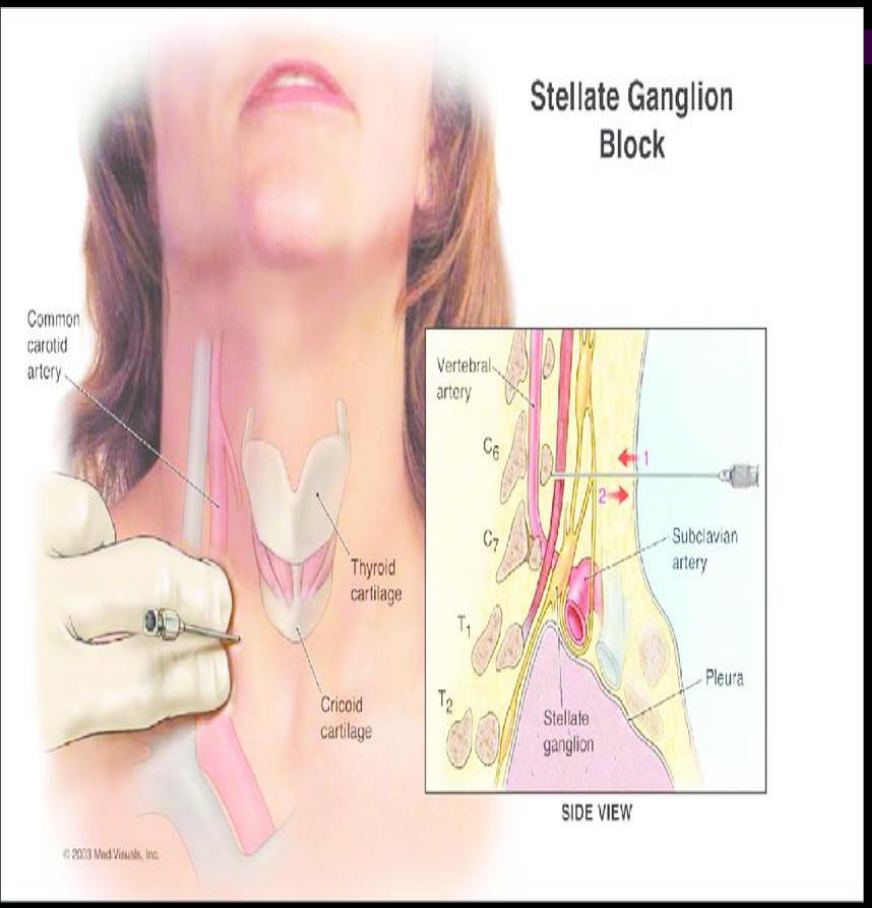
Extra & intra oral approach







Stellate ganglion block



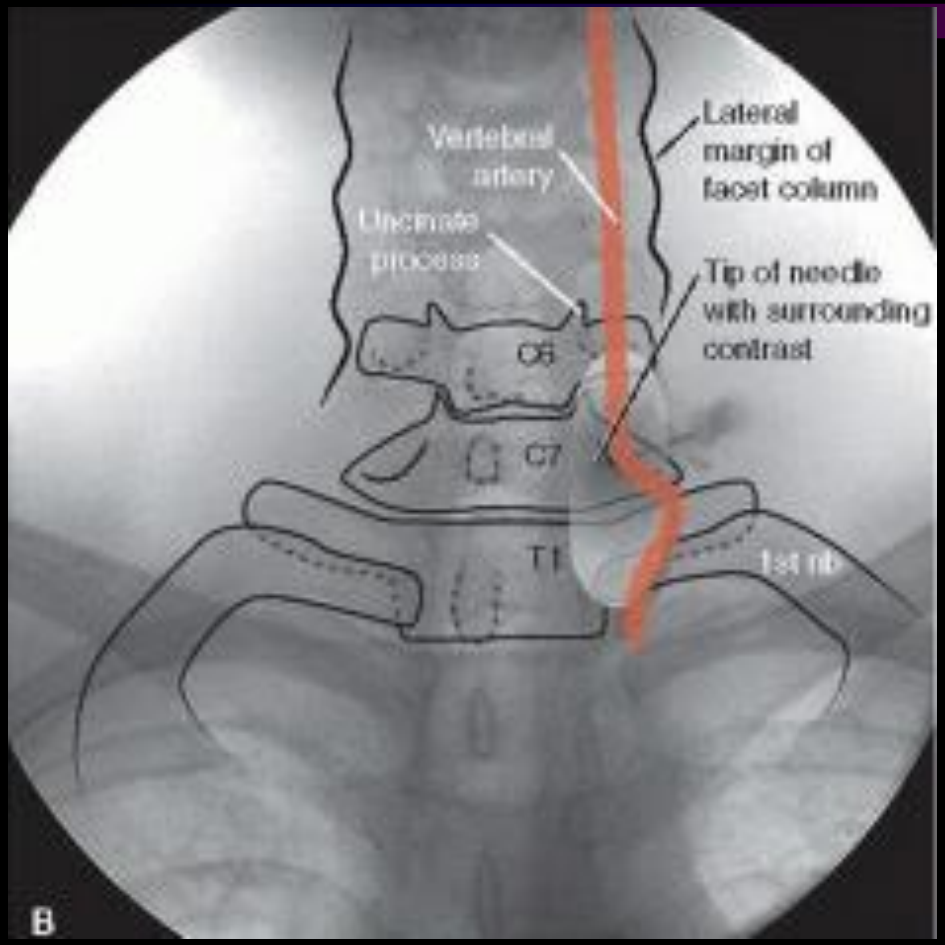
- Stellate – star shaped
- Inferior cervical fused with first thoracic – 70-80%
- 2.5cm x 1cm

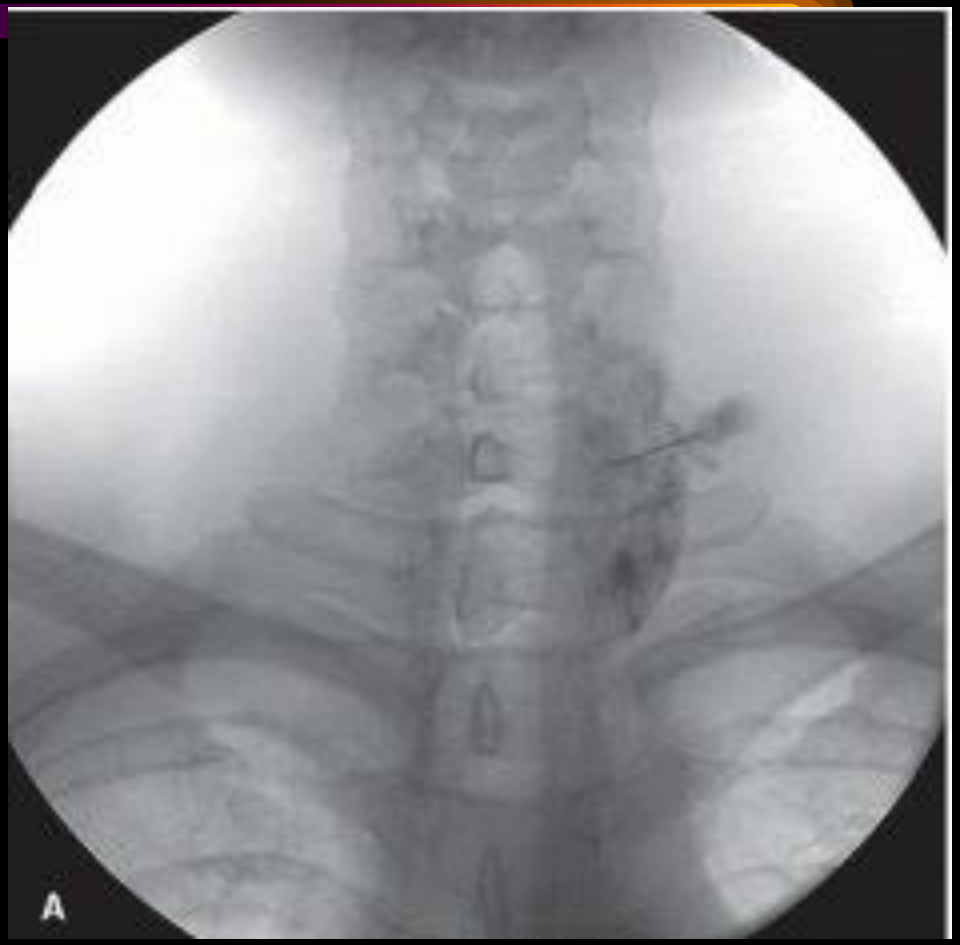
Indications-

Brachial plexus encroachment

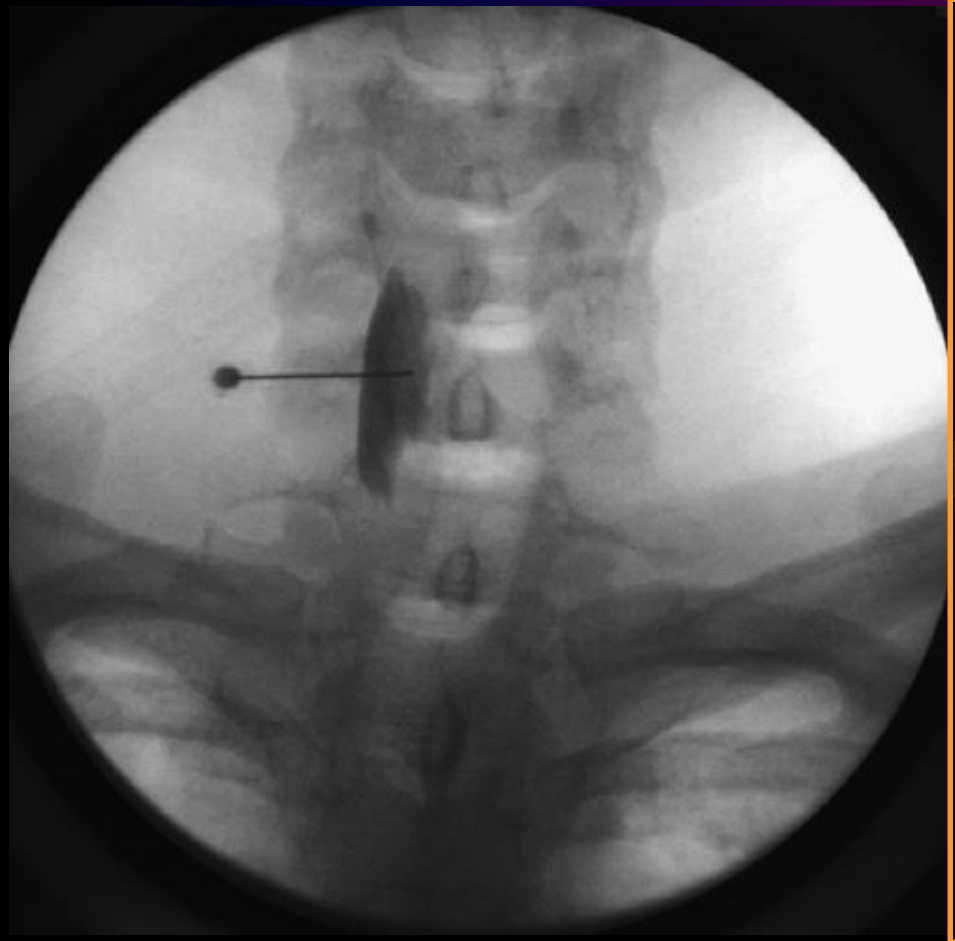
Lymphedema

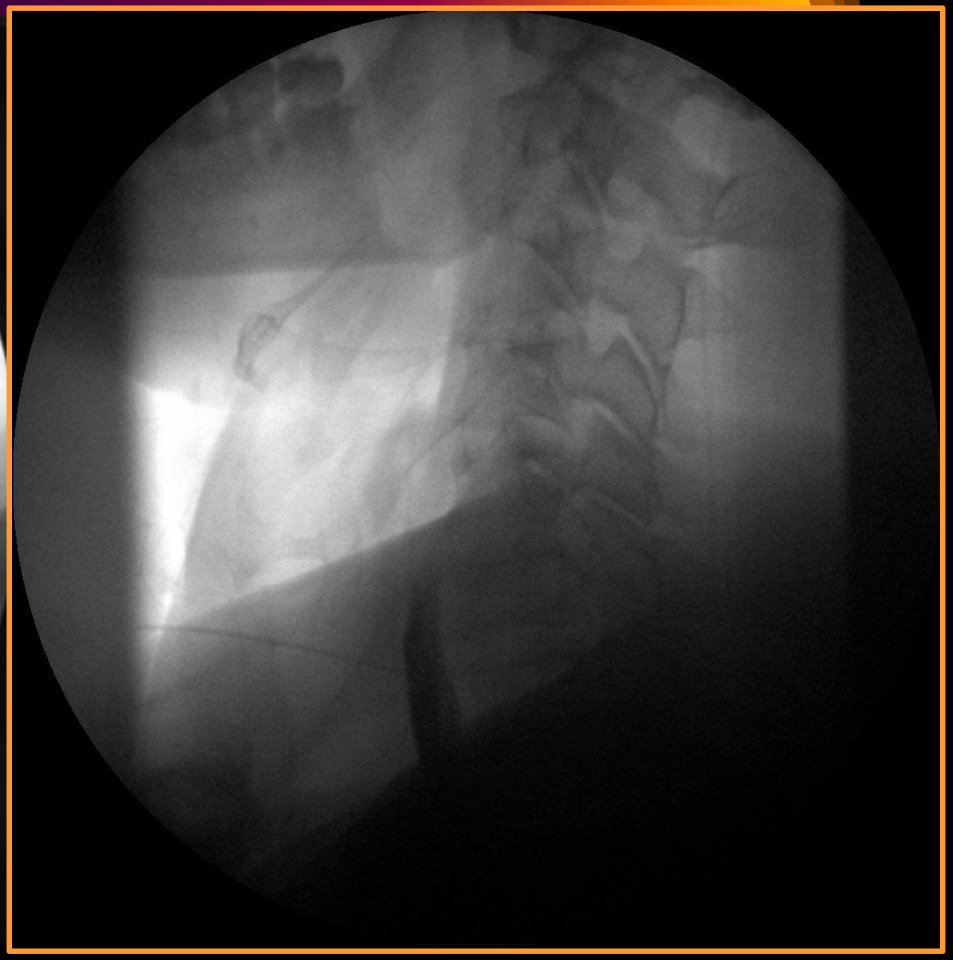
Stellate ganglion block



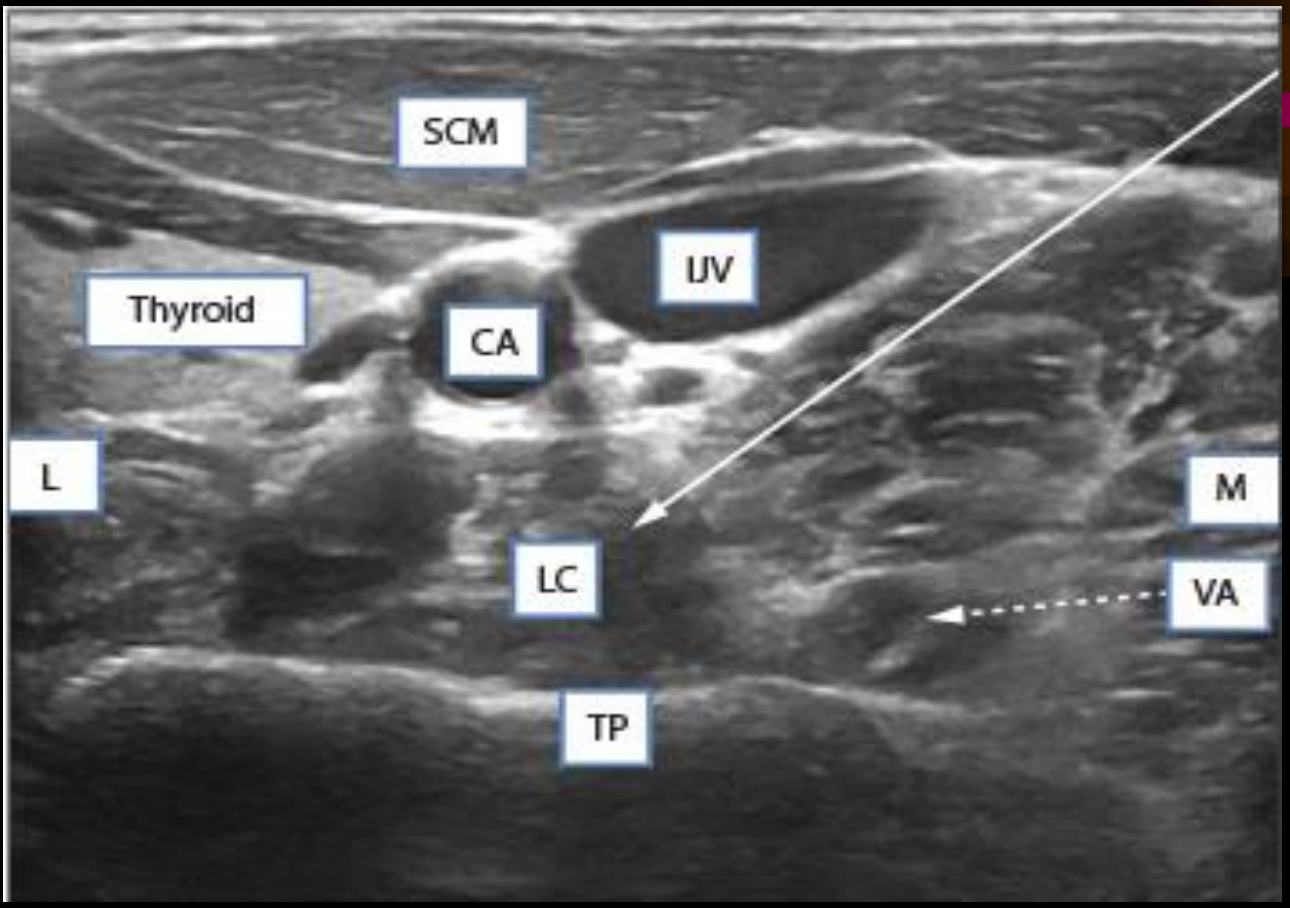


Stellate ganglion block





Stellate ganglion block- ultrasonography



LA+ Steroid

RF ablation

Indicators of success

- Horner's Syndrome in 5 mins
- 1-3degree temp increase
- Increase in blood flow by 50%

Case Report

Somatic blockade of contralateral roots of brachial plexus after a stellate ganglion block

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Department of Anesthesiology, [1]Junior Resident, JSS Medical College, Mysore, Karnataka, India

ABSTRACT

The stellate ganglion block is a common procedure performed for management of the Complex Regional Pain Syndrome (CRPS) of the upper limb. Somatic anesthesia of the ipsilateral brachial plexus is a known complication of the stellate ganglion block. We report a case of CRPS of the left upper limb developing somatic blockade of the contralateral brachial plexus following a stellate ganglion block. This case report emphasizes the importance of vigilant monitoring during every procedure, as unusual complications can occur.

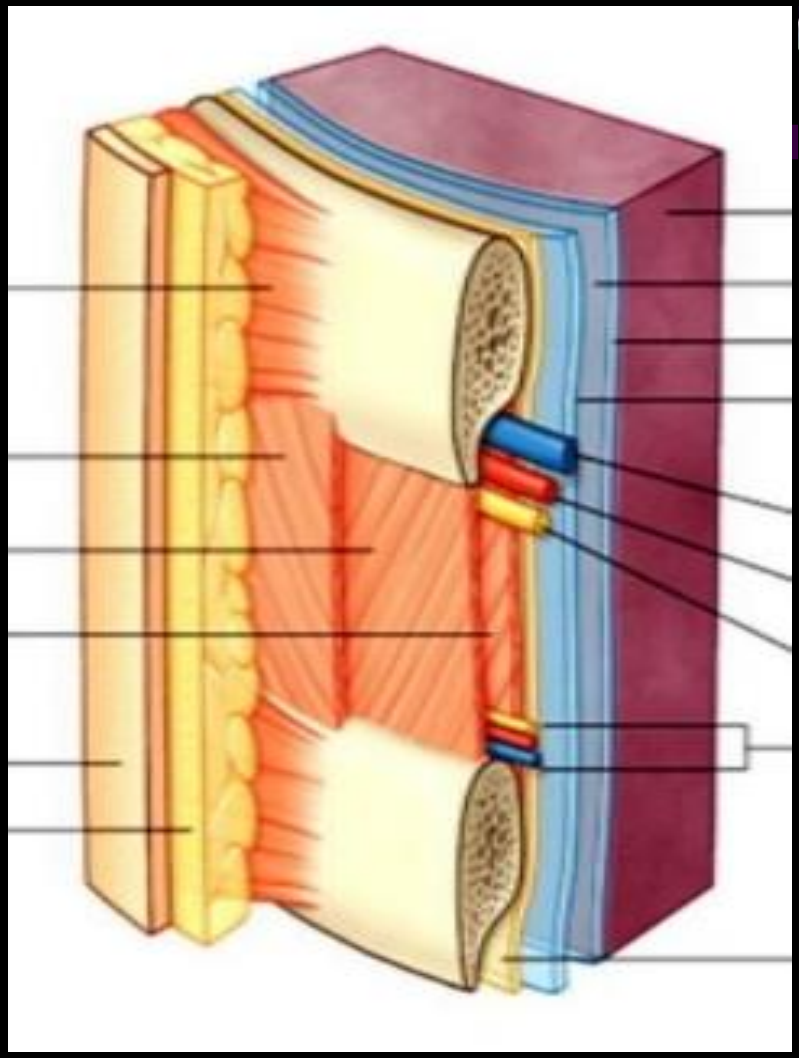
Key words: Complex regional pain syndrome, contralateral brachial plexus block, stellate ganglion block

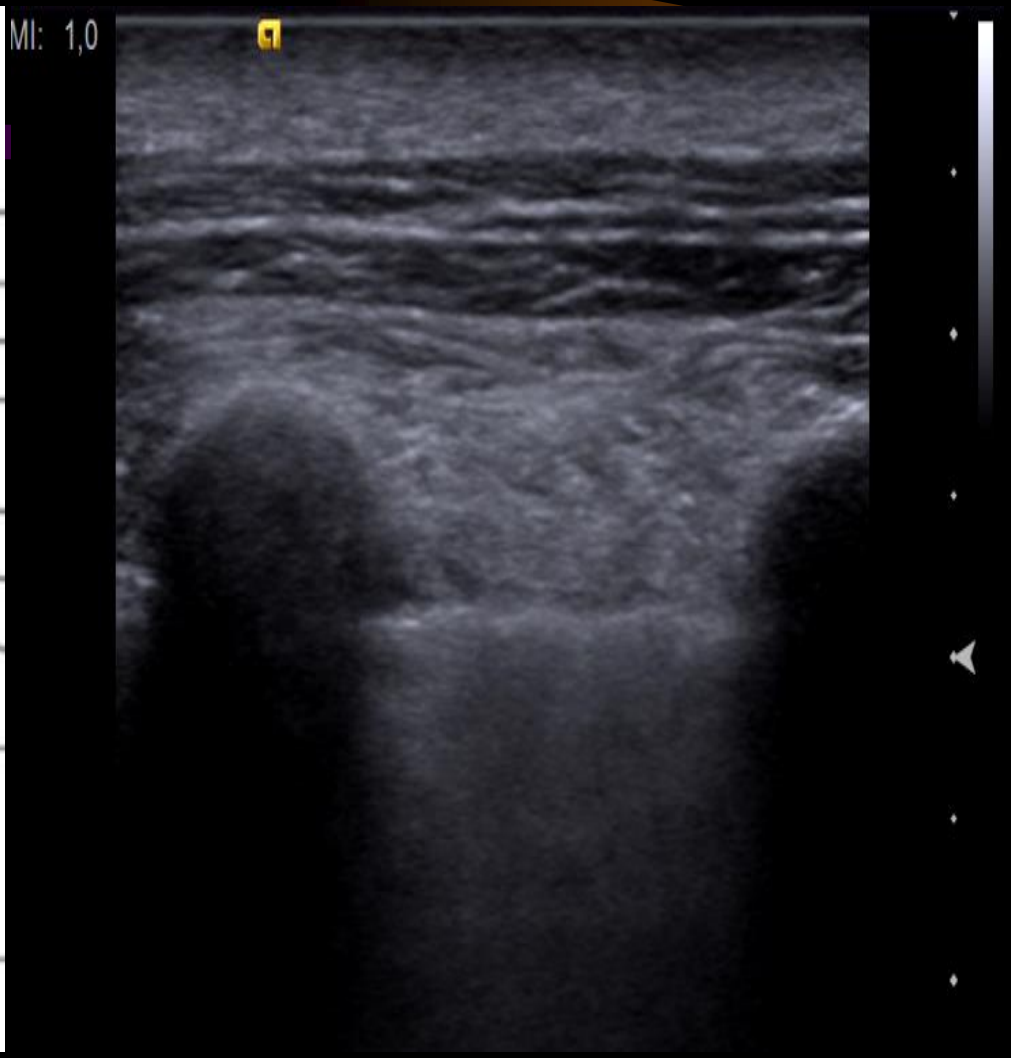
- Mr. Rangappa, 50y
- Enjoyed his cigarettes
- Developed lung cancer – advanced
- Sudden localized pain at mid-thoracic level
- 7/10, increased by coughing, breathing
- Palpation – multiple rib fractures (confirmed by chest x-ray)

- Inter-costal nerve block
- Inter-pleural block
- Paravertebral nerve block
- Erector-spinae plane block

  - Relieves pain
  - Improves pulmonary function
  - Facilitates physiotherapy

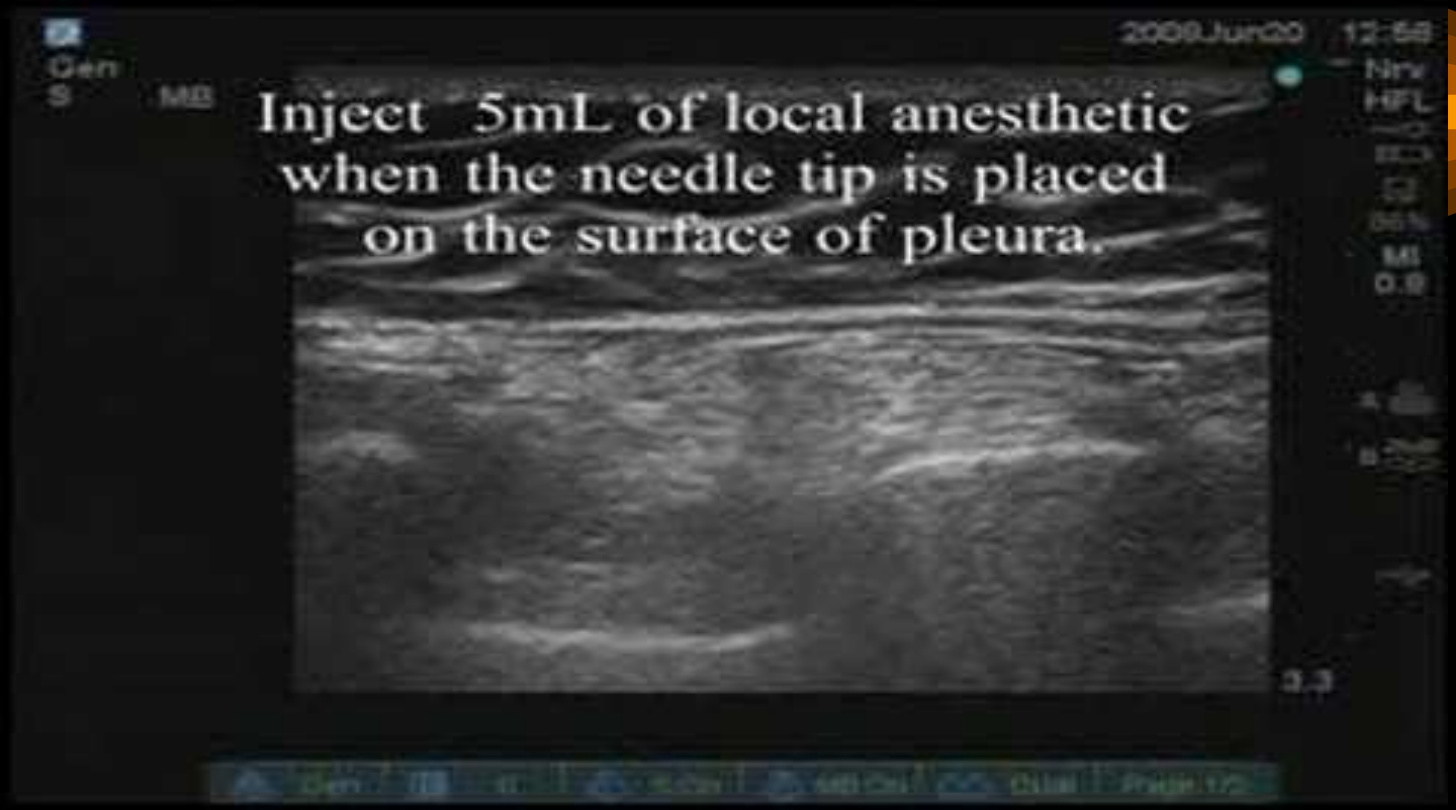
Intercostal Nerve





1-2ml LA , RF

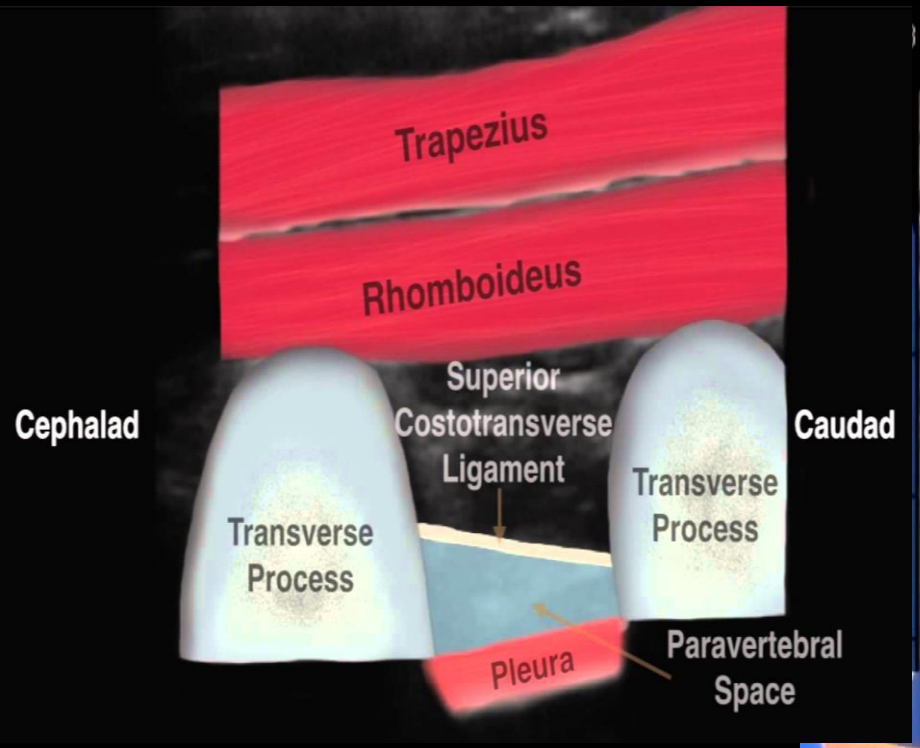
Intra-pleural block

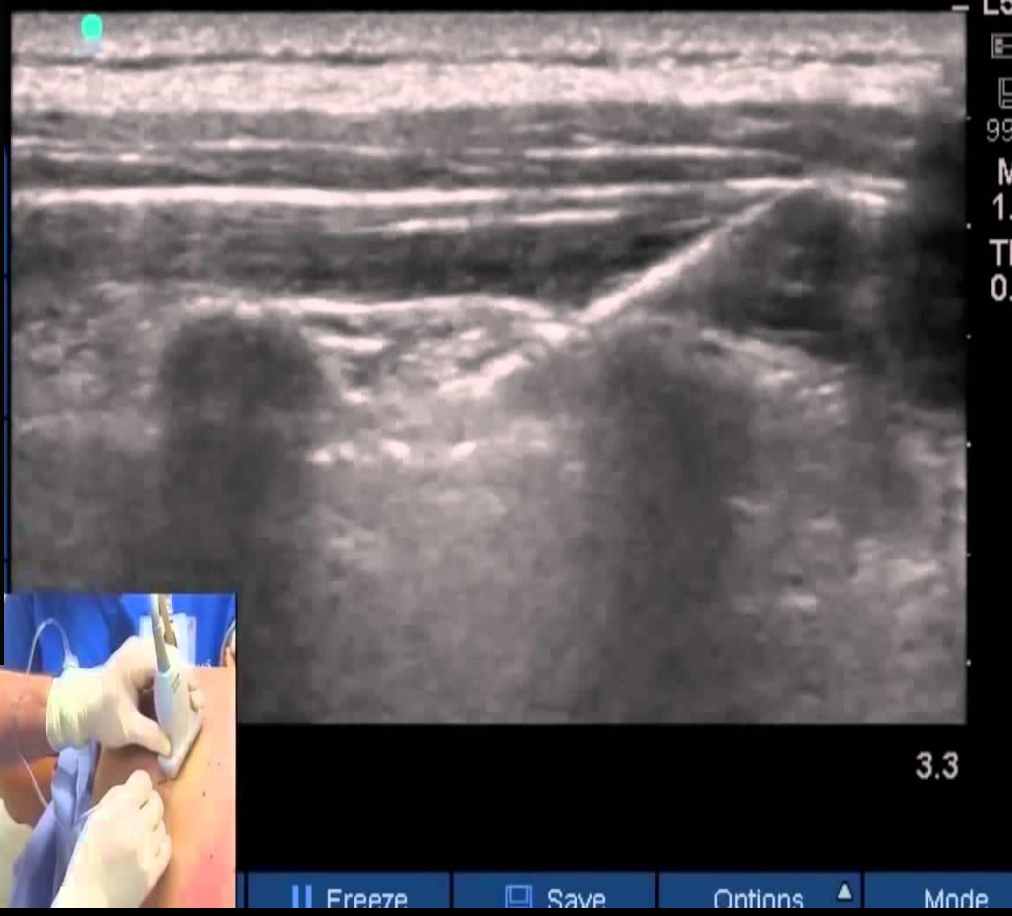


6ml/hr infusion

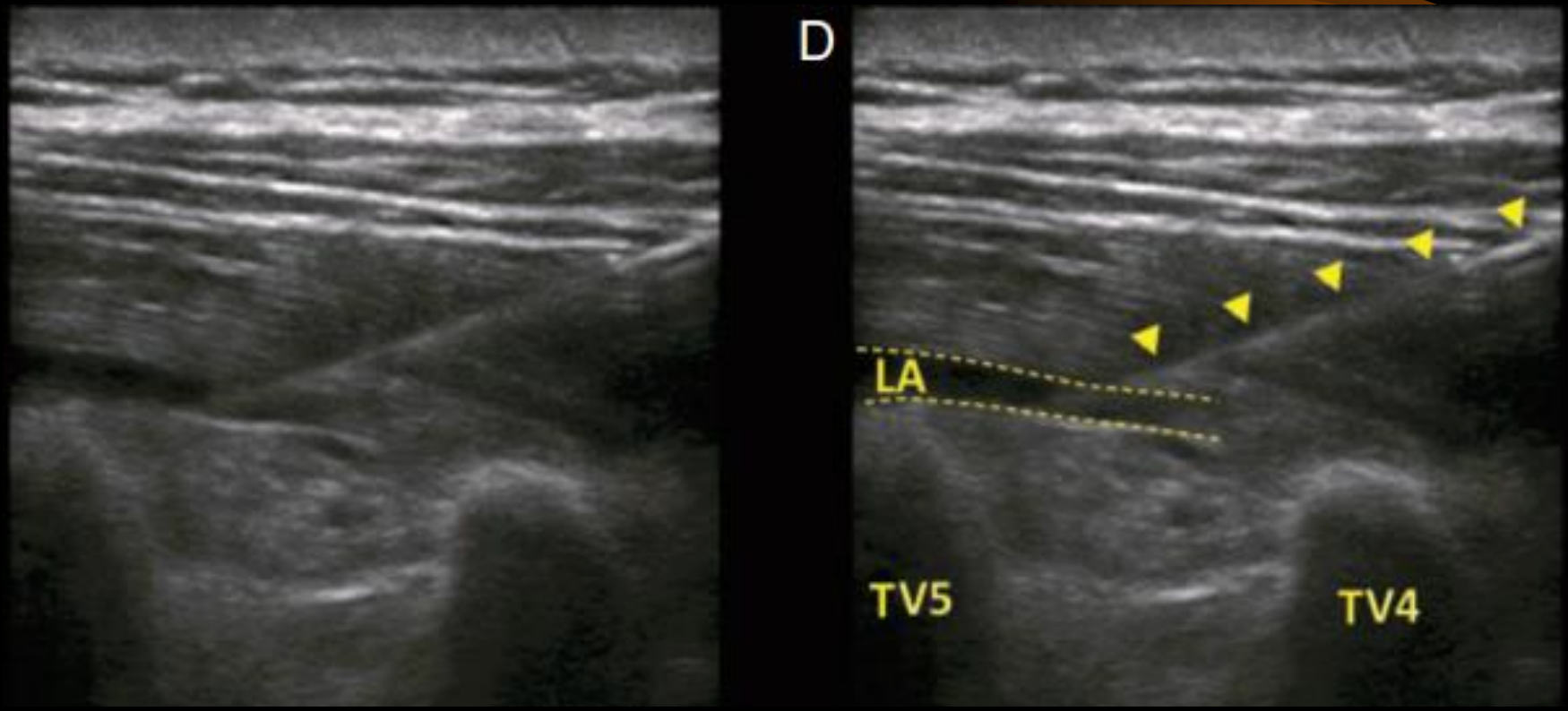
Contraindication – chest-wall pathology, pleurodesis

Paravertebral block





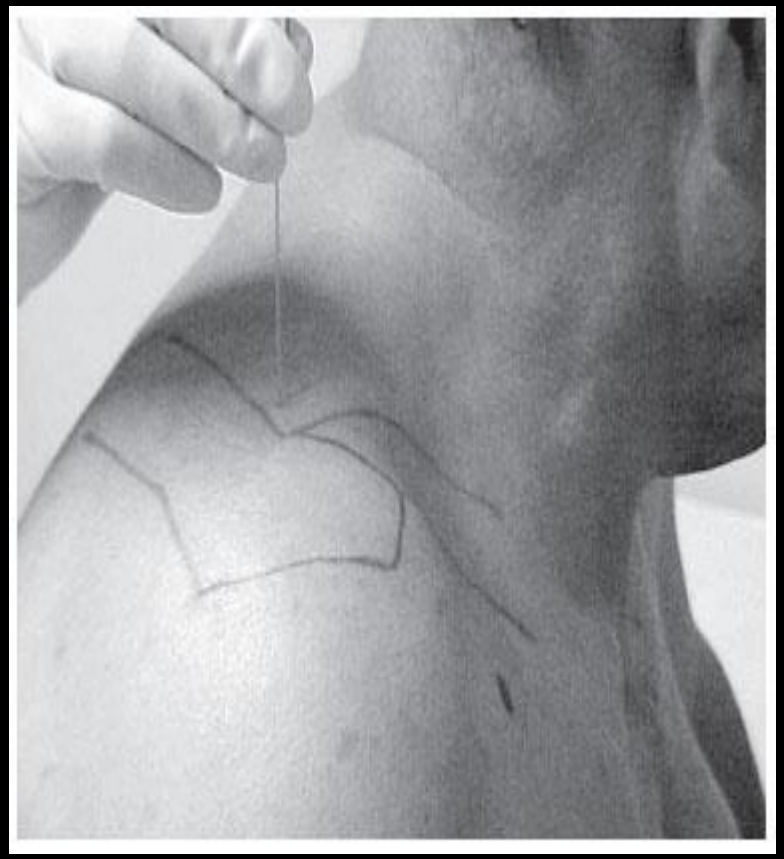
Erector spinae plane block

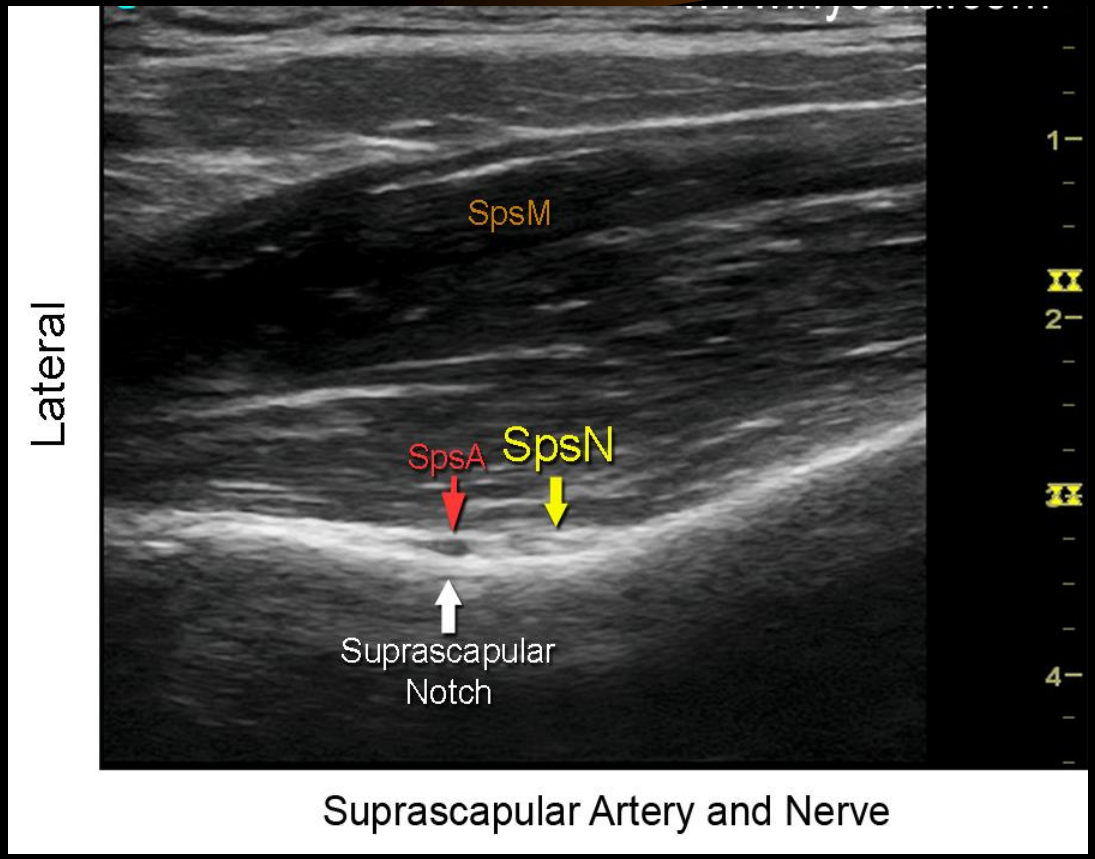


- Ca Lung
- Chest wall tumour
- Post Thoracotomy pain

Supra-scapular block

- For tumors in the shoulder





Suprascapular Artery and Nerve

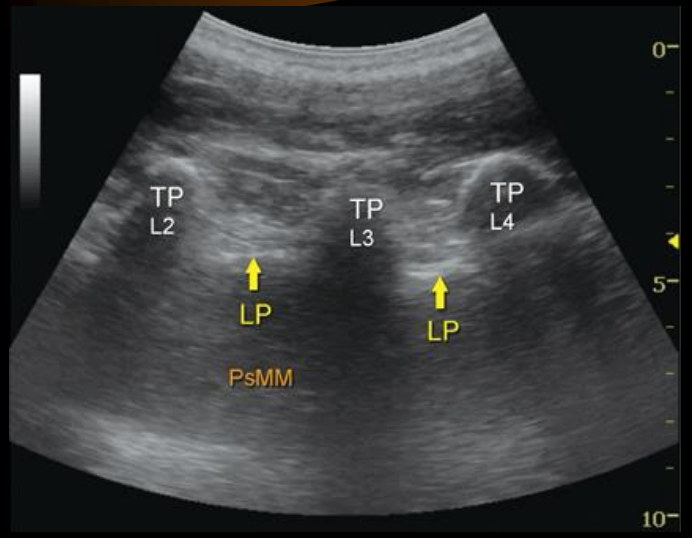
- Brachial plexus – Encroachment

- Lumbar plexus – cancer patients with low back, pelvic and lower limb pain

  - Malignant psoas syndrome
  - Acetabular secondaries
  - D/D - IVDP

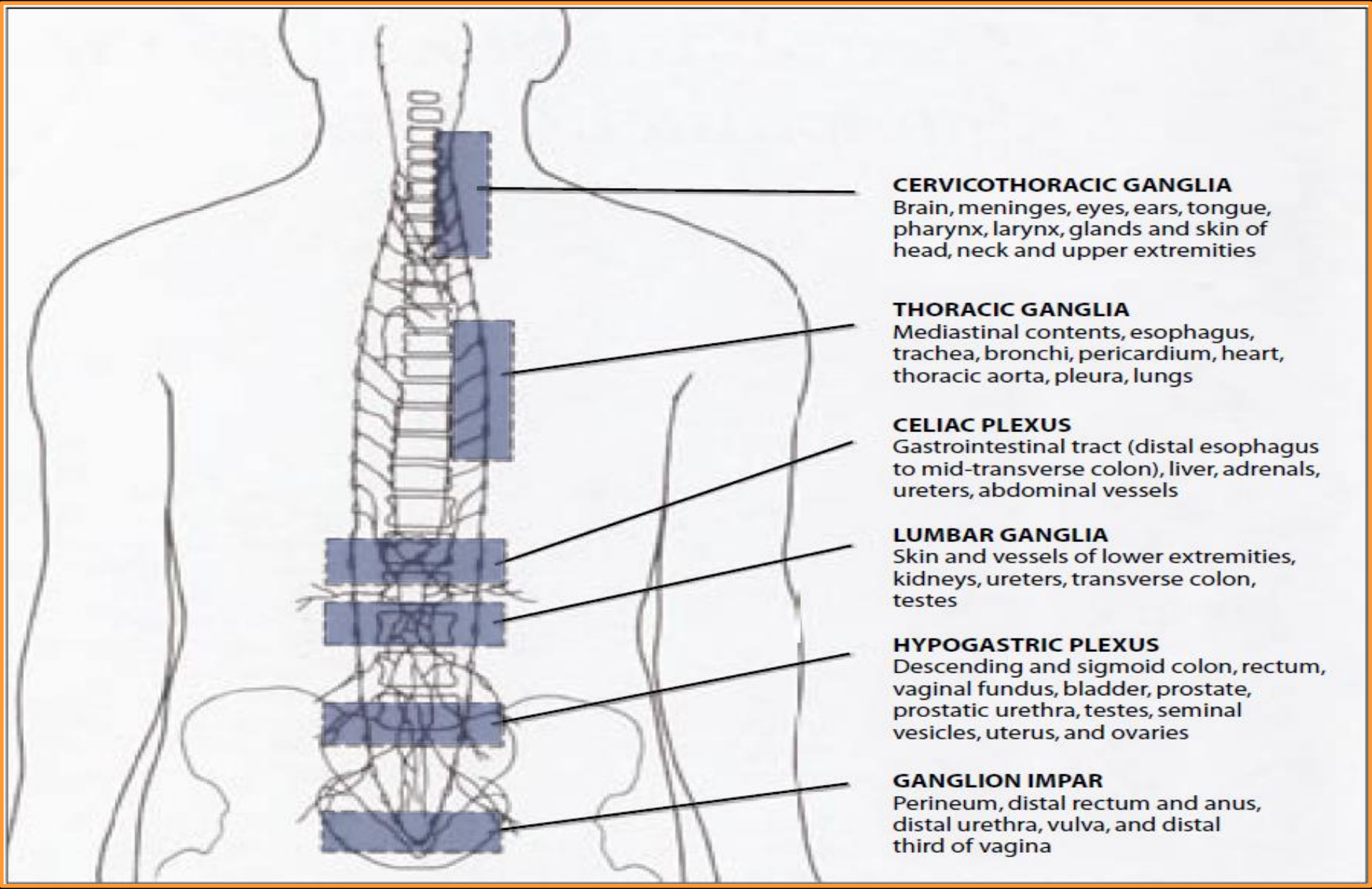
Lumbar plexus block V/S Neuraxial

- Unilateral
- Preserves motor and autonomic functions of contralateral limb

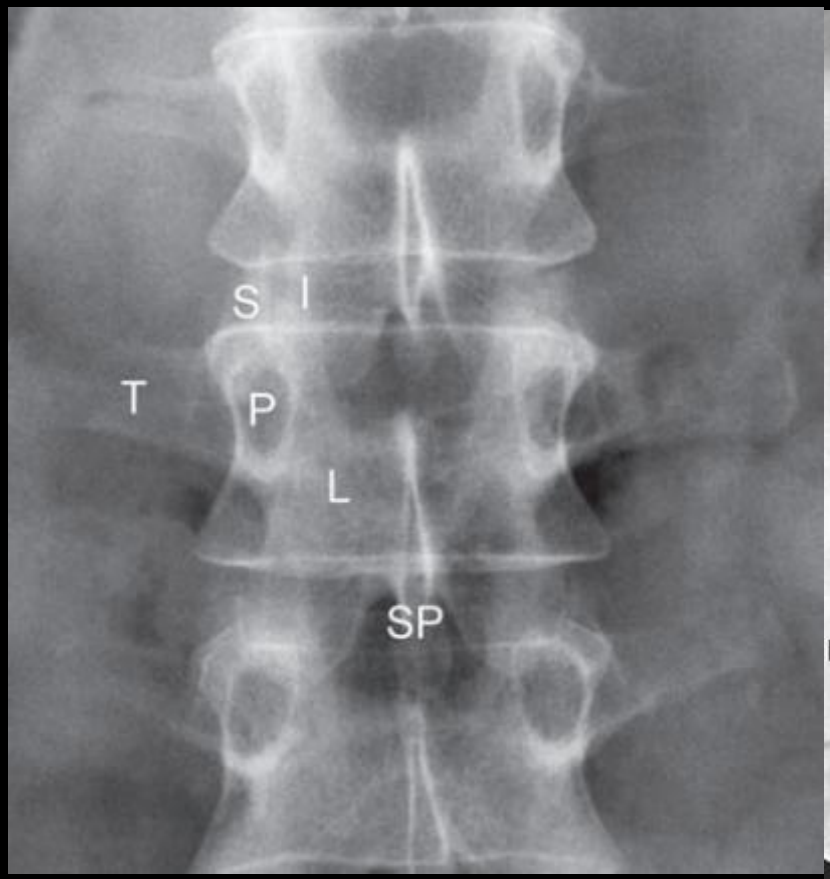


- Tunneled catheter attached to external pump

Symphathetic ganglia



Fluroscopy


S
I
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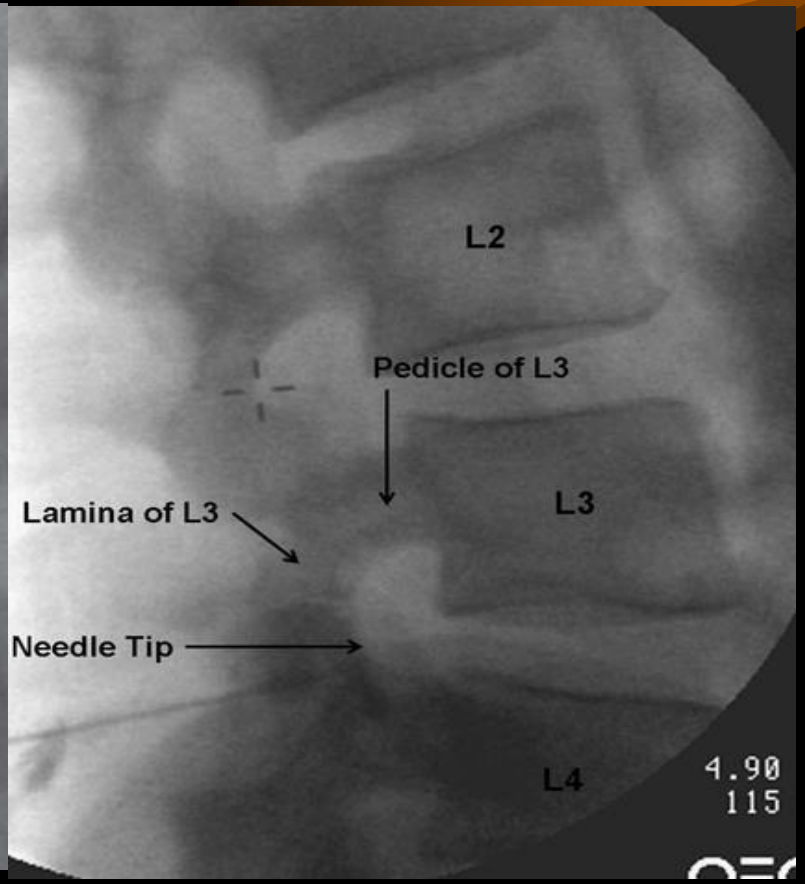
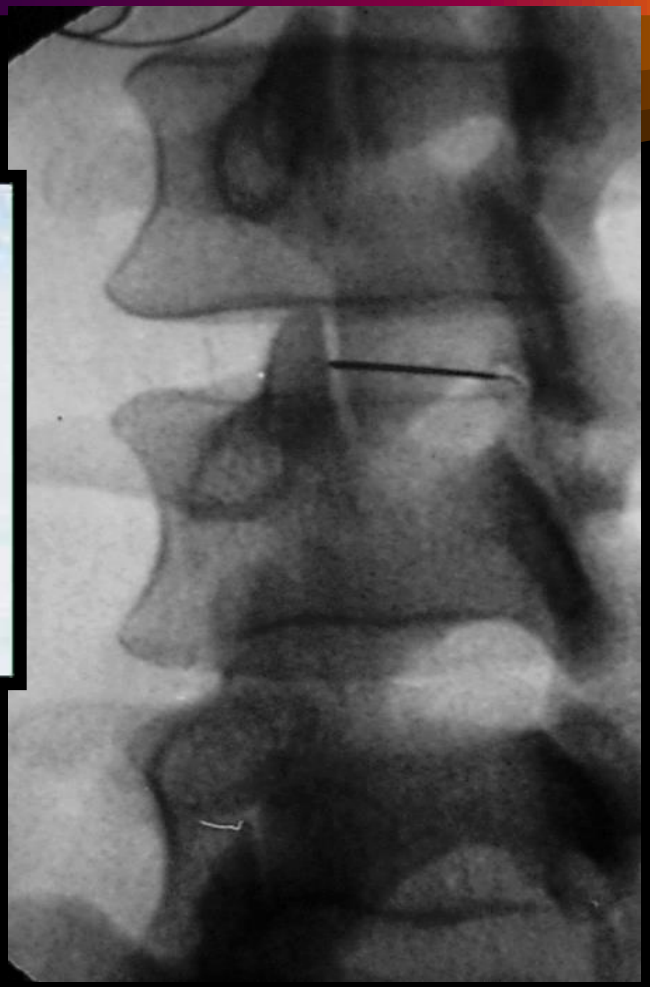
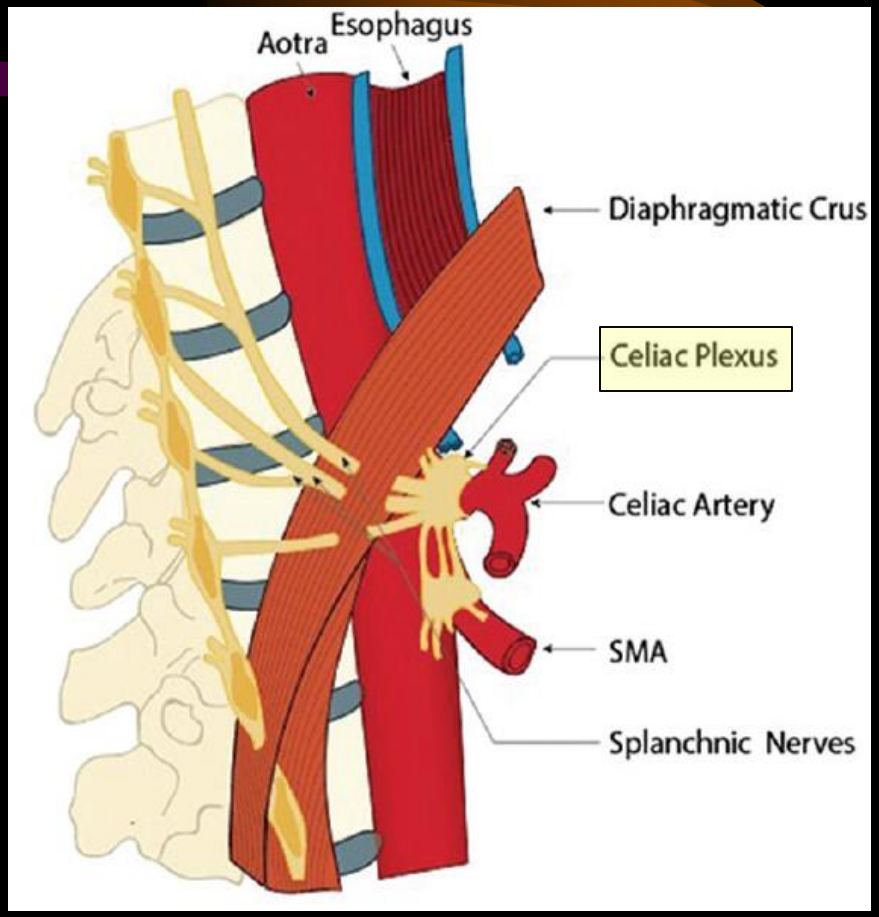
P
L
SP


L2
Pedicle of L3
L3
Lamina of L3
Needle Tip
L4
4.90
115



Celiac Plexus Block

- Preganglionic Greater, lesser & least splanchnic nerves – retroperitoneal
- Celiac plexus – anterior to the crura-T12,L1

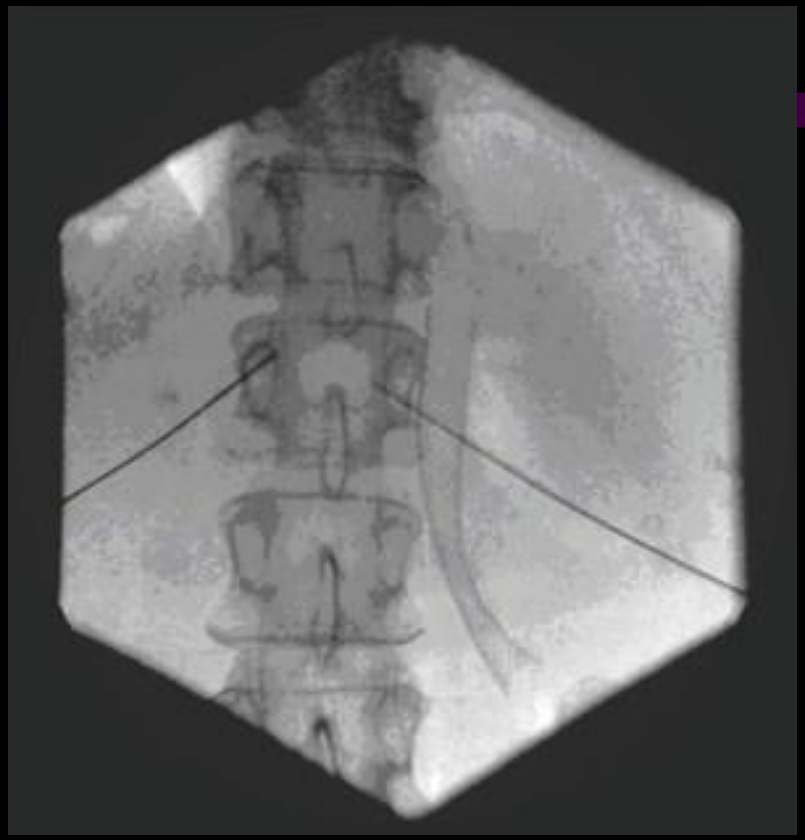


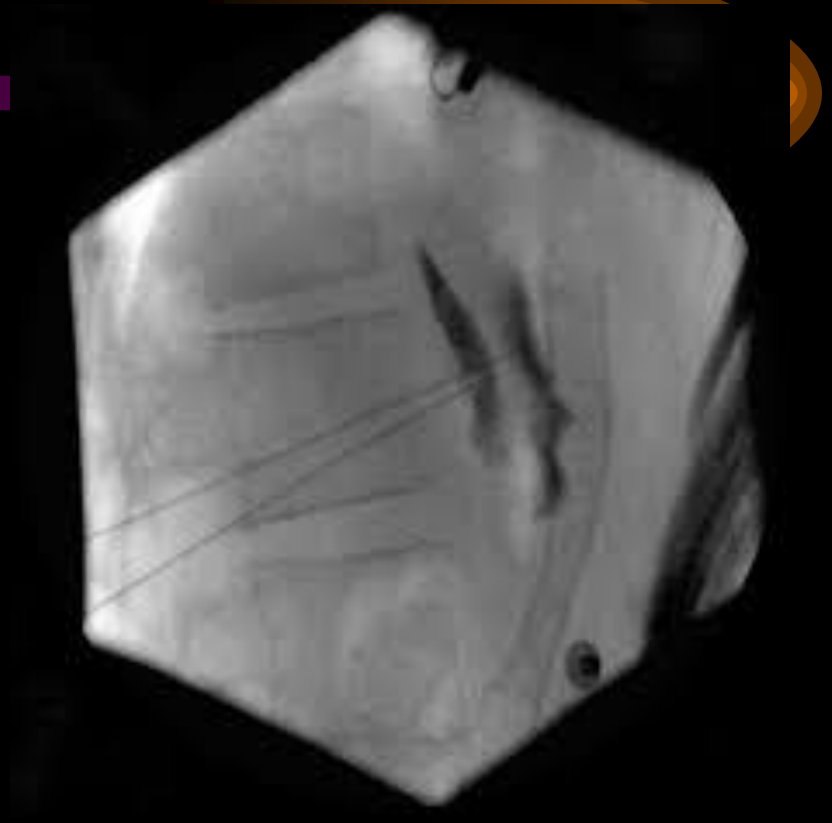
Celiac Plexus Block

- 5 RCTs support efficacy of celiac plexus block for abdominal pain secondary to pancreatic or other cancers
- Metaanalysis & Cochrane review- lower VAS compared to Medical management.
- 2A+

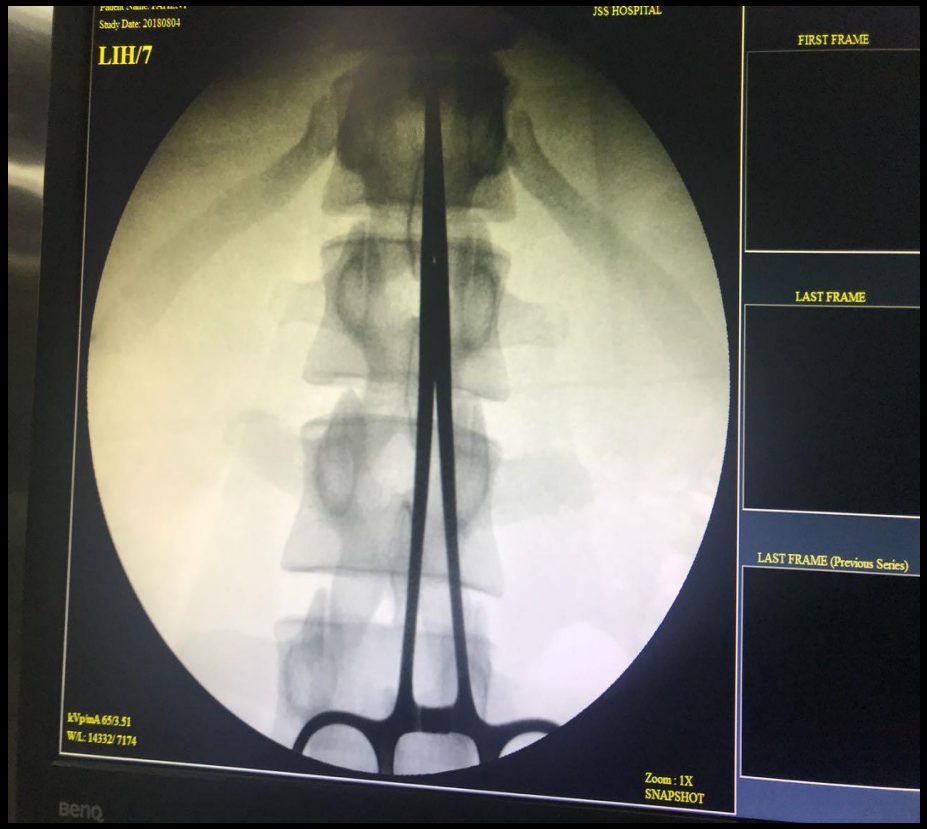
- Posterior approach
  - Classic retrocrural -1-2cm beyond anterior margin of L1
  - Anterocrural – anterior and caudal to diaphragm
  - Trans-aortic approach
  - Trans-discal – between T12 and L1
- Anterior approach – needle through epigastrium
- Endoscopic ultrasound guided

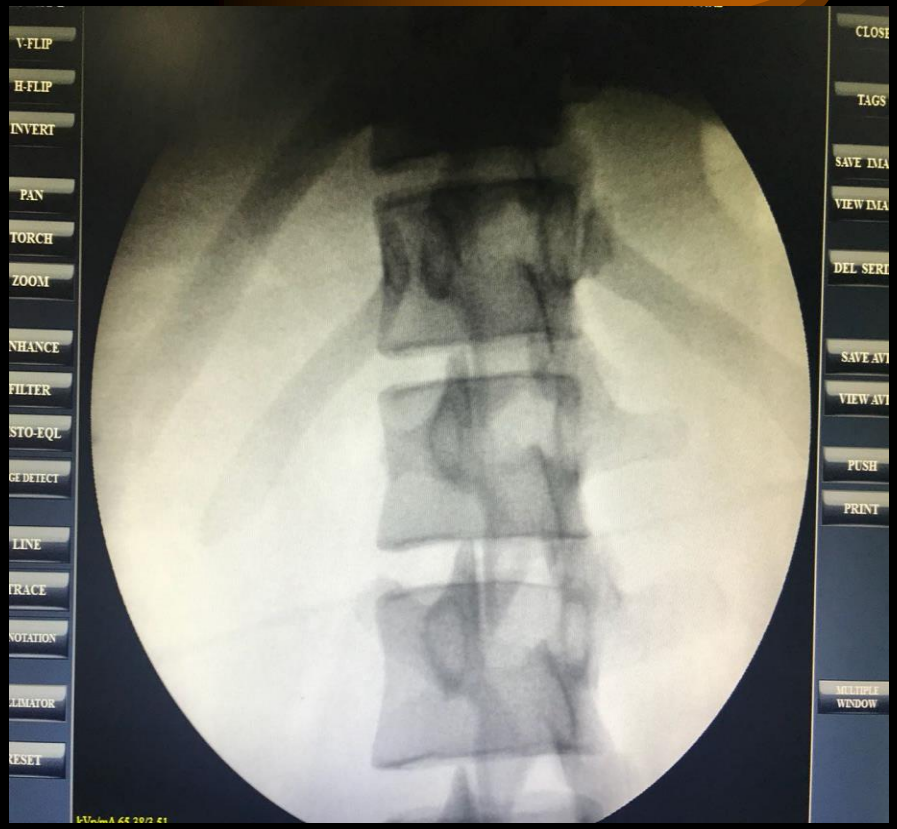
- Splanchnic nerve block appears more efficacious – T12 level





- 20/22 g spinal needle
- 25 ml of 50% alcohol bilaterally after confirmation by diagnostic block.


Study Date: 20180804
JSS HOSPITAL
LIH/7
FIRST FRAME
LAST FRAME
LAST FRAME (Previous Series)
kVp/mA 65/3.51
W/L: 14332/ 7174
Zoom : 1X
SNAPSHOT
BenQ


V-FLIP
H-FLIP
INVERT
PAN
TORCH
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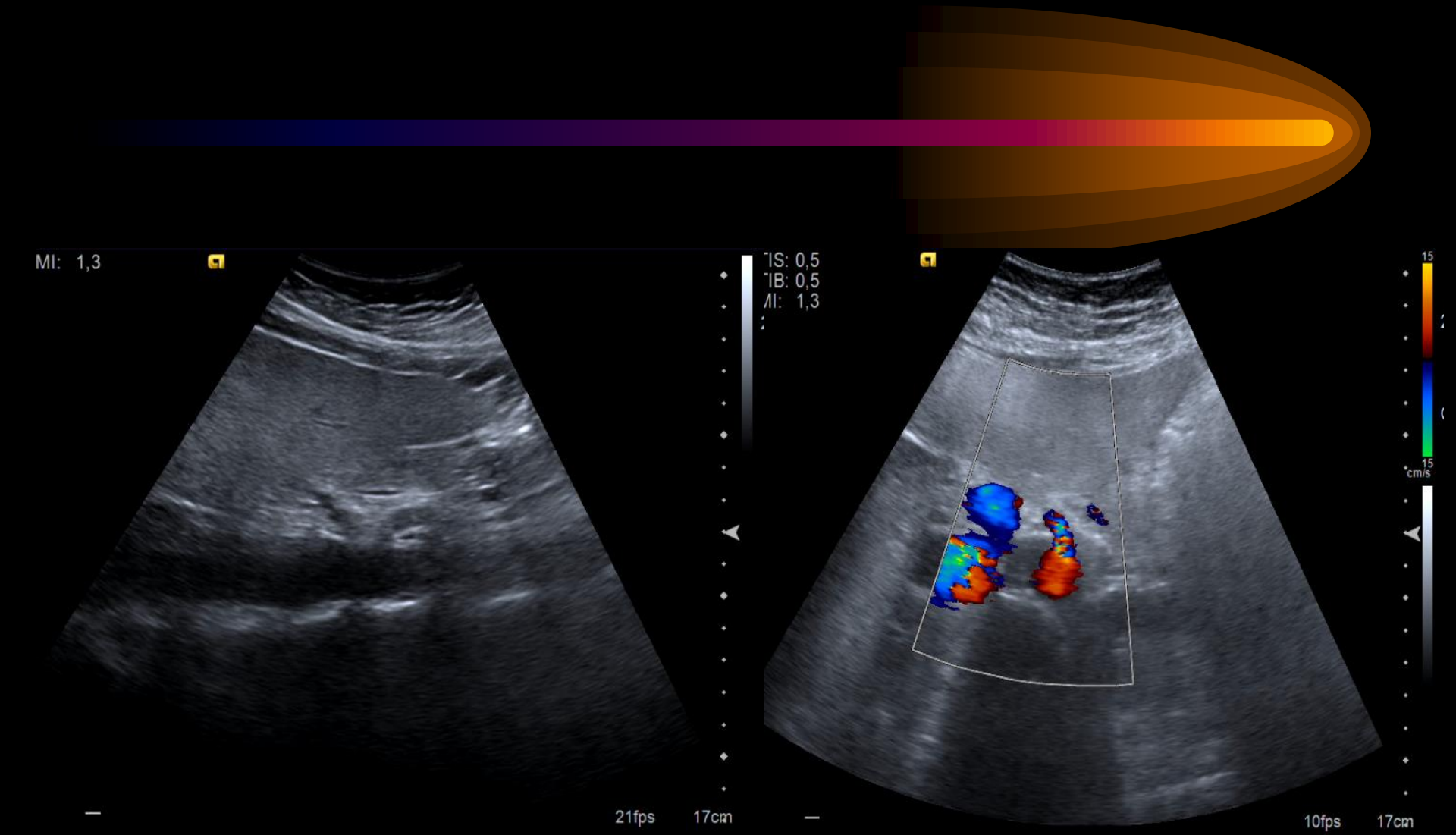
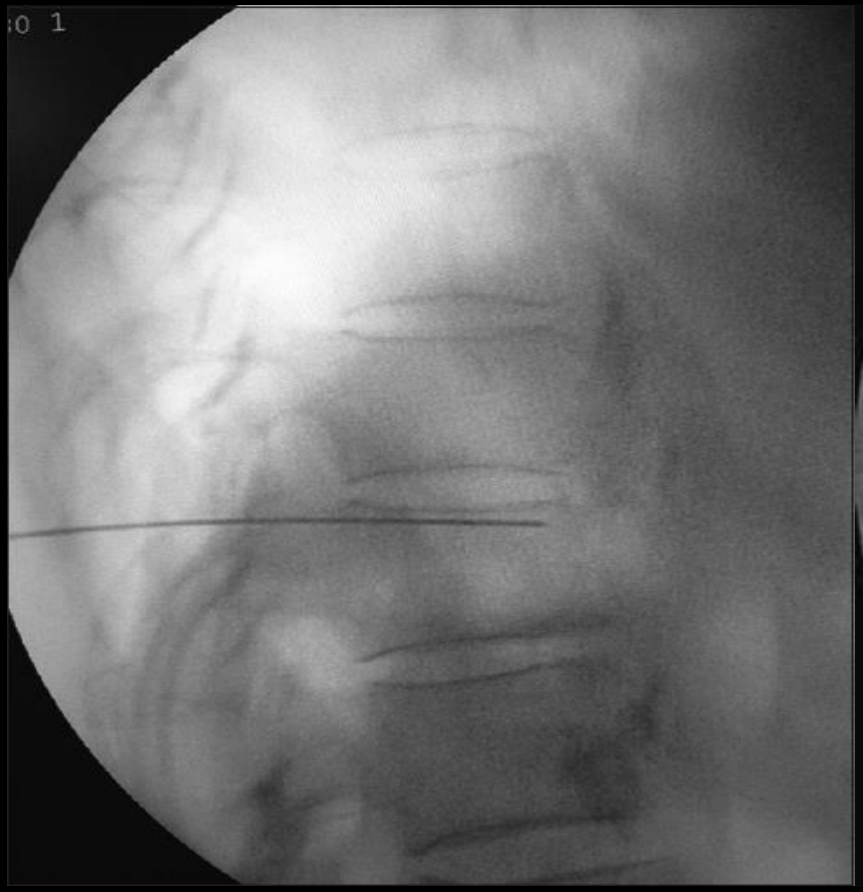
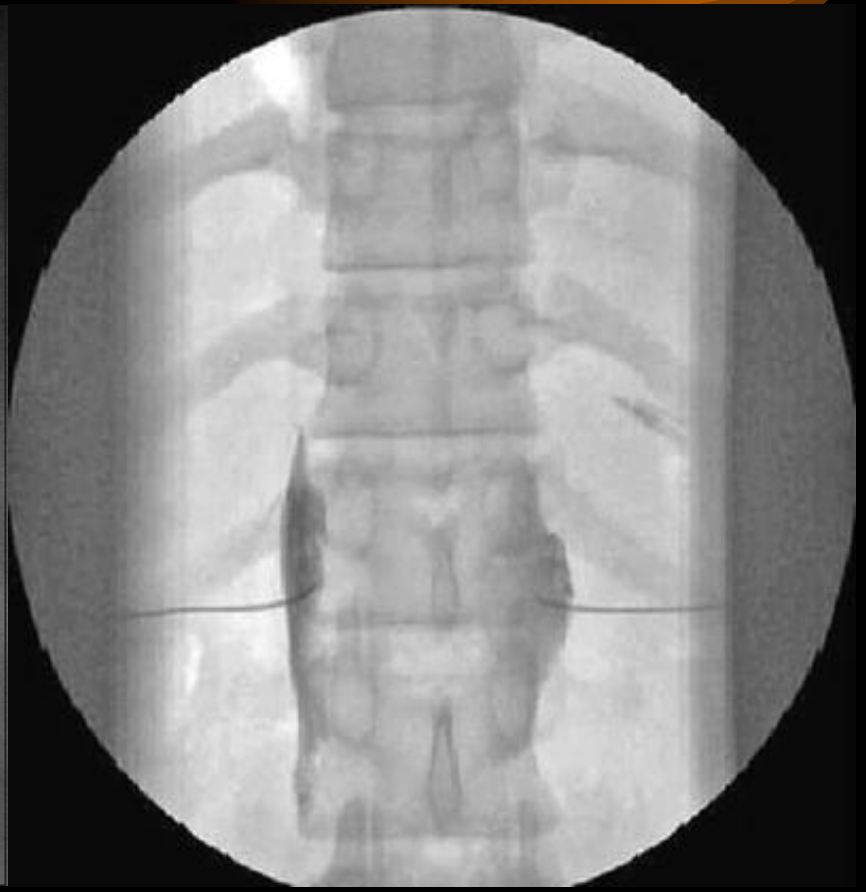
FILTER
PUSH
PRINT
MULTIPLE WINDOW


MI: 1,3
TIS: 0,5
TIB: 0,5
MI: 1,3
21fps
17cm
15
15
cm/s
10fps
17cm

Splanchnic plexus block





Complications

MECHANICAL

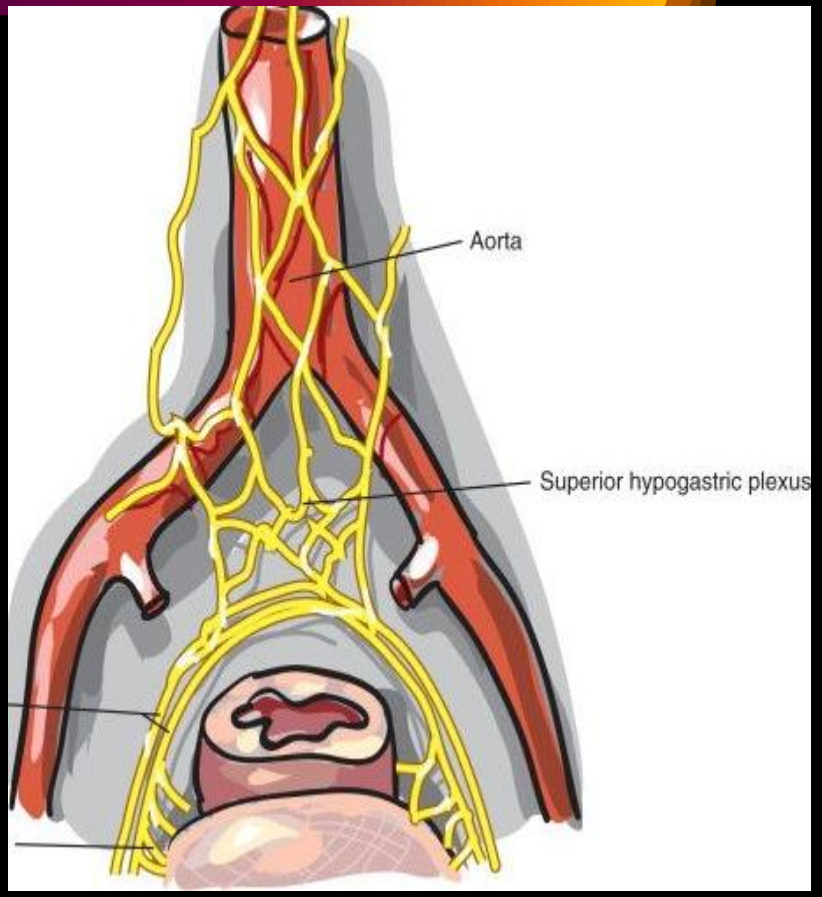
- Injury to adjacent structures (kidney,ureter .lung ,pleura)
- Paraplegia due to intrathecal/intravascular injection ; trauma to spinal arteries.

PHARMACOLOGIC

- Hypotension
- Intravascular injection (seizures)
- Neuropathic pain

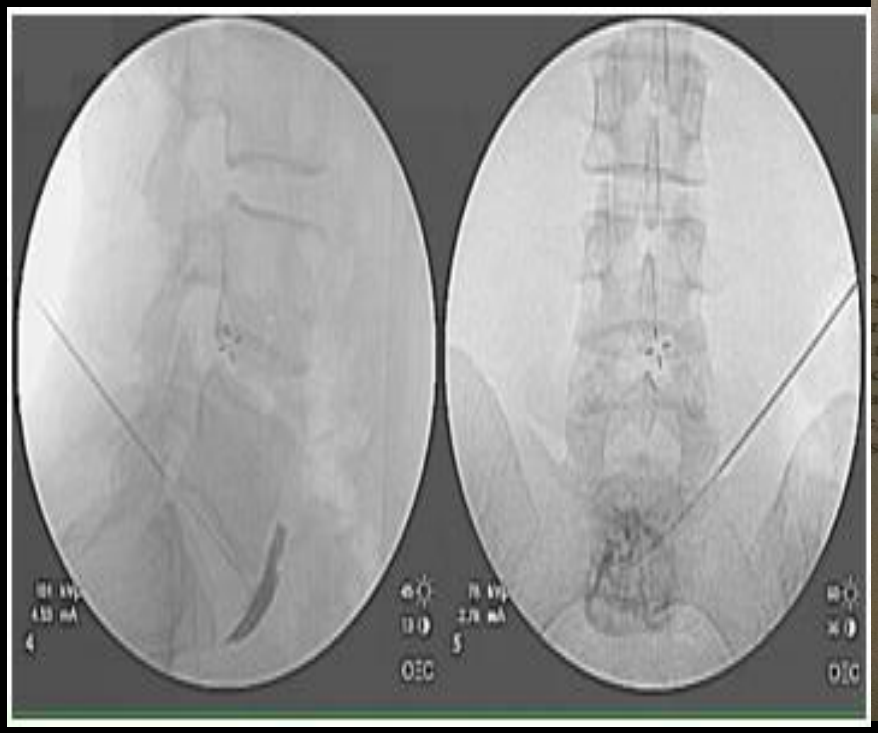
Superior hypogastric plexus block

- plexus - anterior to the bifurcation of the abdominal aorta at L5-S1
- carried into the pelvis as two main trunks



- <u>Indicated in</u>
  - Pelvic malignancy
  - Endometriosis
  - Pid

2C+



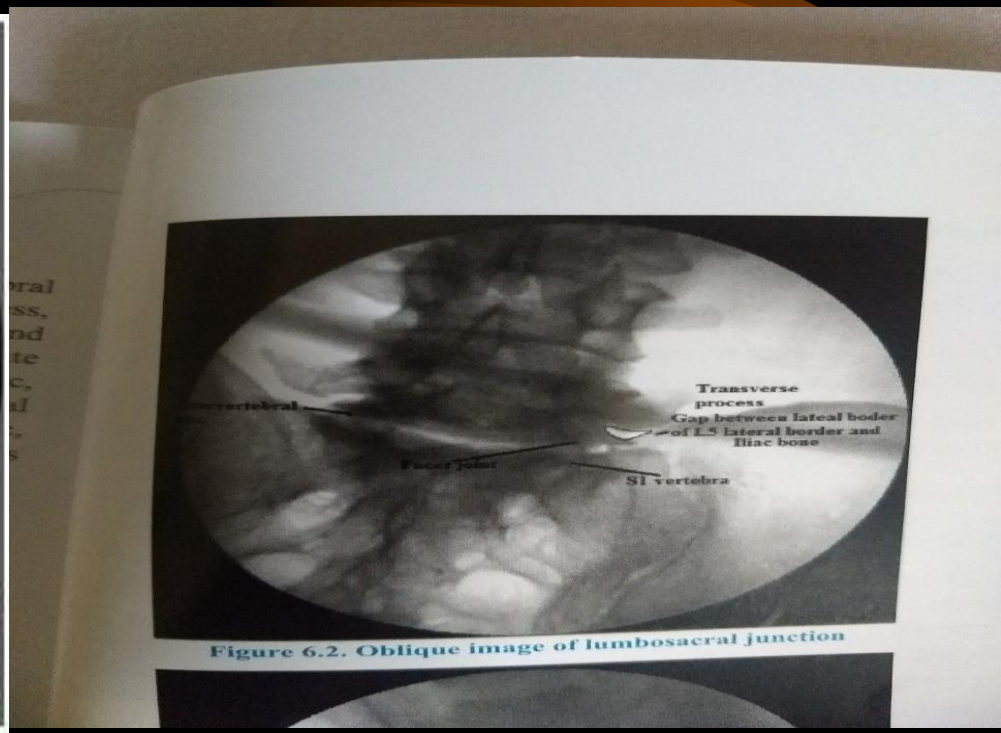


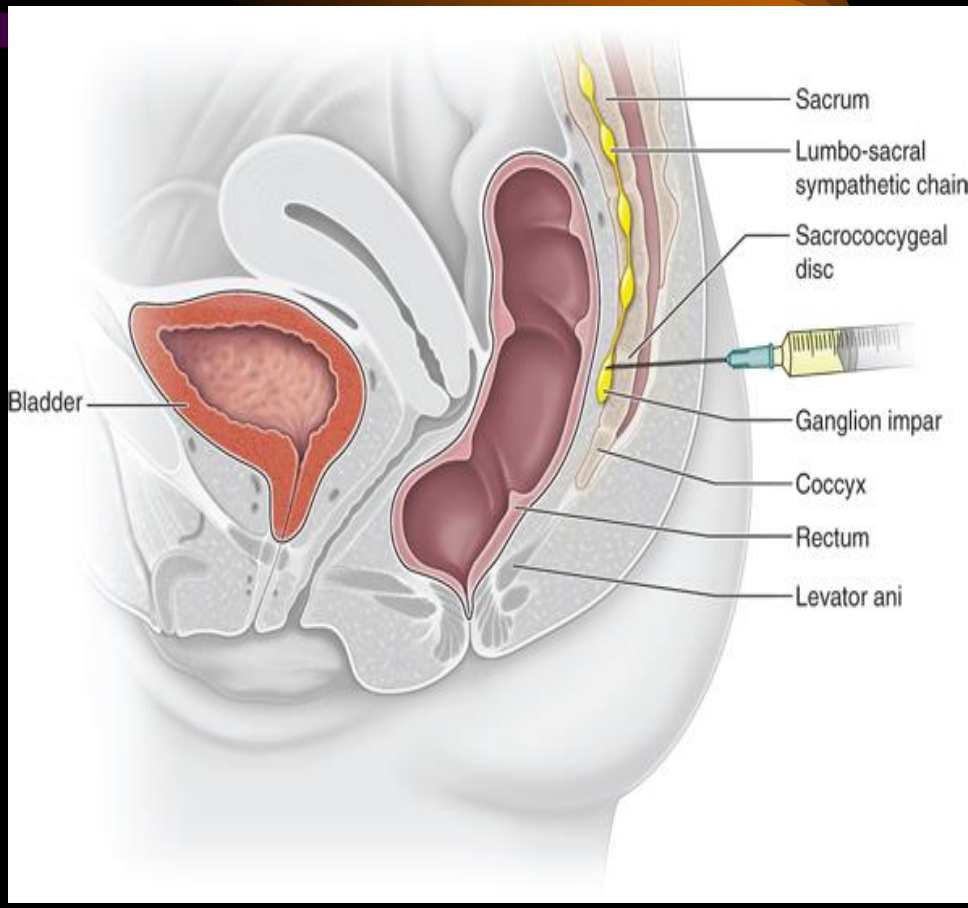
Figure 6.2. Oblique image of lumbosacral junction

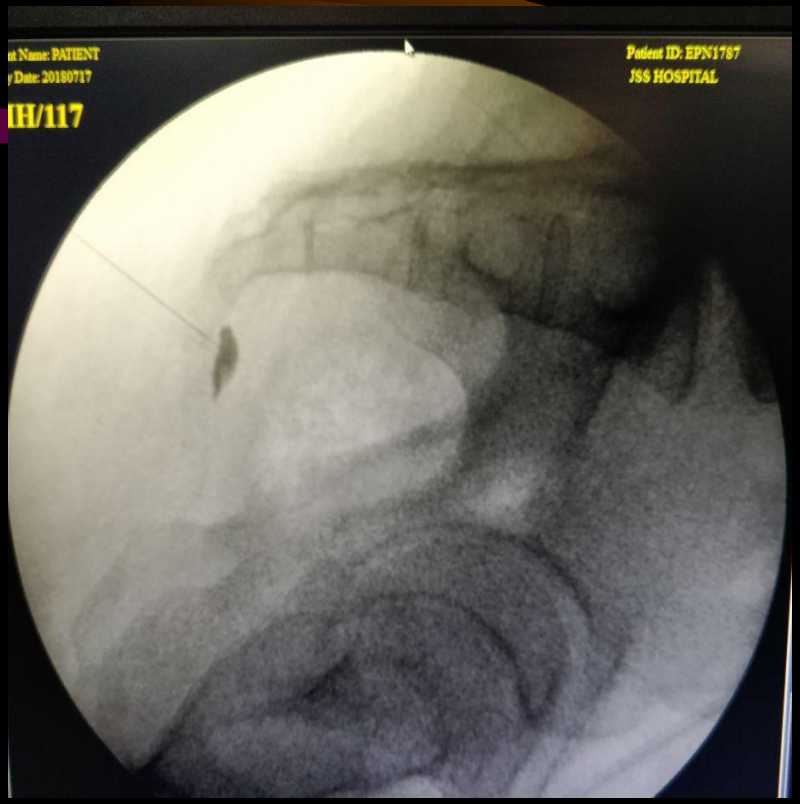
20/22 G ; 12/15 cm needle

8-10 ml of 50% alcohol on both sides after successful diagnostic block

Ganglion impar Block

- fused terminus of the sympathetic chain.
- retroperitoneal, anterior to the sacrococcygeal junction
- innervates the perineum, distal rectum, distal vagina, distal urethra, and anus.





3.5-6.0 cm needle

2-4 ml of 50%-70% alcohol/6% Phenol

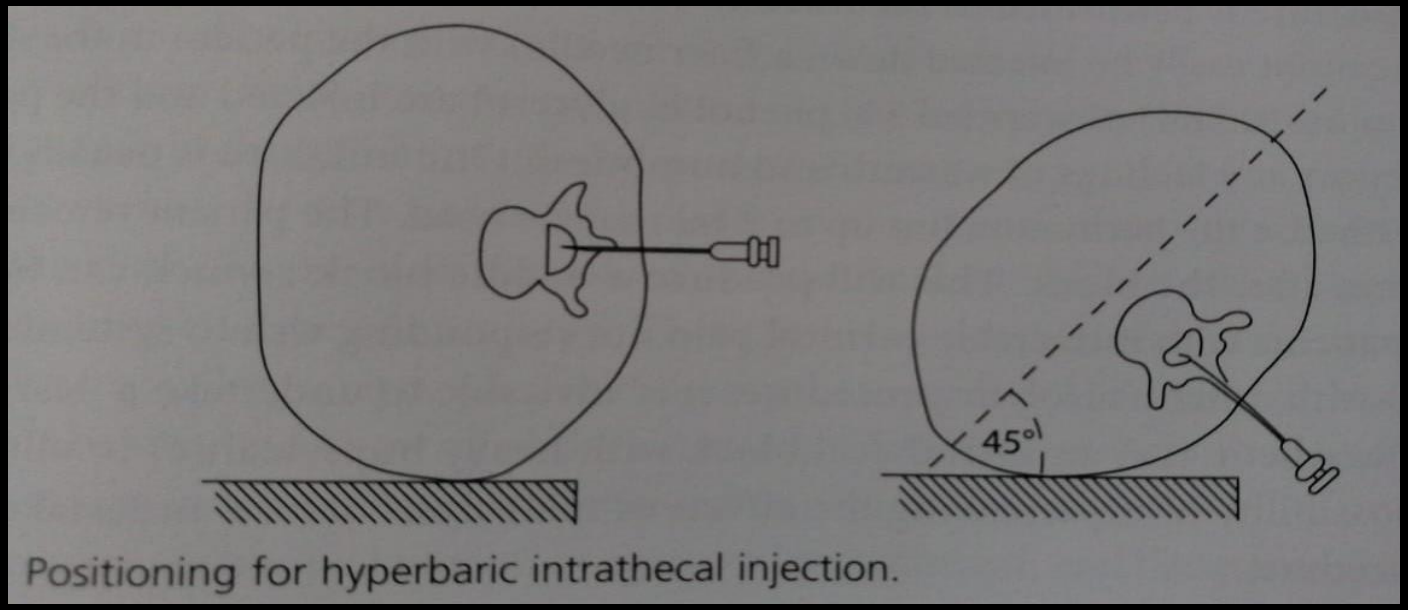
Rectal injury, Nerve injury

- Mrs. Fathima, 50y
- Ca rectum, colostomy
- Pain in the perineal region
- Urinary and fecal incontinence
- Refuses pills
- Wants pain relief, pain relief, pain relief!

Has a red hot poker up the bottom

Intra-thecal neurolysis

- Last resort
- Intractable cancer pain in terminal phase
- Between L5-S1
- Sitting up position and tilted to 45 degrees



Positioning for hyperbaric intrathecal injection.

- Phenol in increments of 0.1-0.3ml upto 3ml

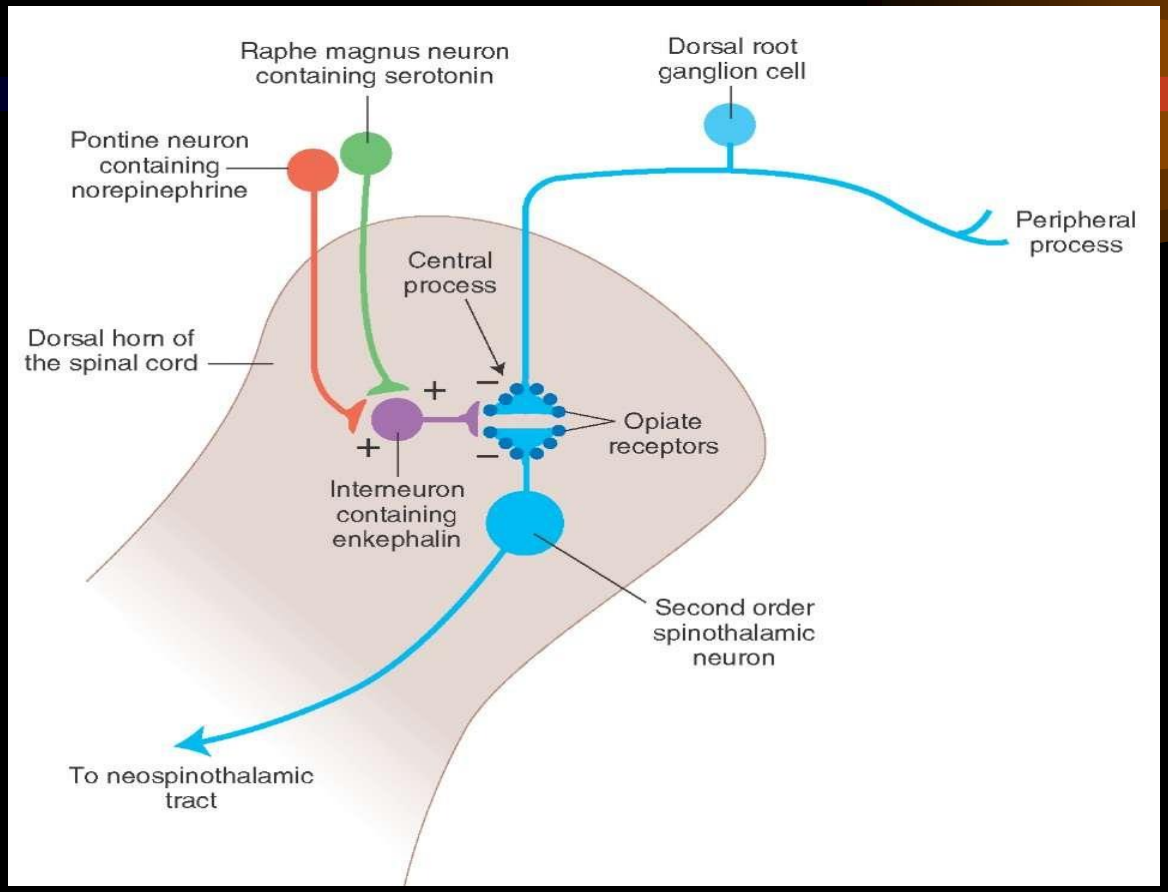
- Mr. Raju, 50y
- Primary hepatoma
- Celiac plexus block 6 months back
- Presents with lower thoracic back pain radiating to upper abdomen
- Generalized heavy dull ache
- Altered sensation at L1
- Image – Tumor spread to posterior abdominal wall
- Refused oral analgesics for nasty hallucinations and sedation

Choice ?

- Celiac ✗
- Thoracic Epidural/Spinal ✓

  – Currently most popular interventional procedure for cancer pain

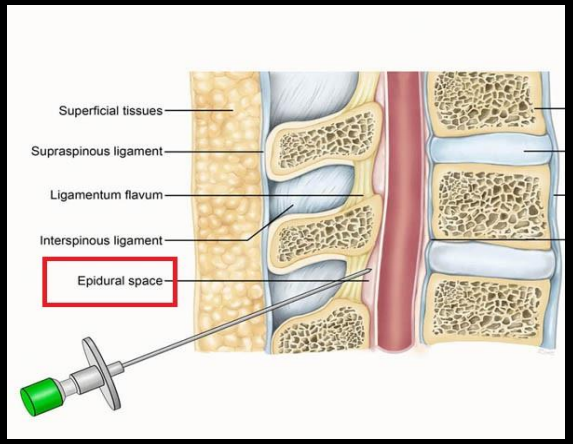
Spinal analgesia



Wang and colleagues in 1979 – deposited morphine in subarachnoid space

Epidural 2C+

- For localized pain
- Short life expectancy



Spinal 2B+

- For diffuse pain
- For long term home care
- Less dose (0.5-4ml/hr)
- Improve analgesia
- Lower failure rate

Cockrane review shows that all routes are effective (including cerebroventricular)

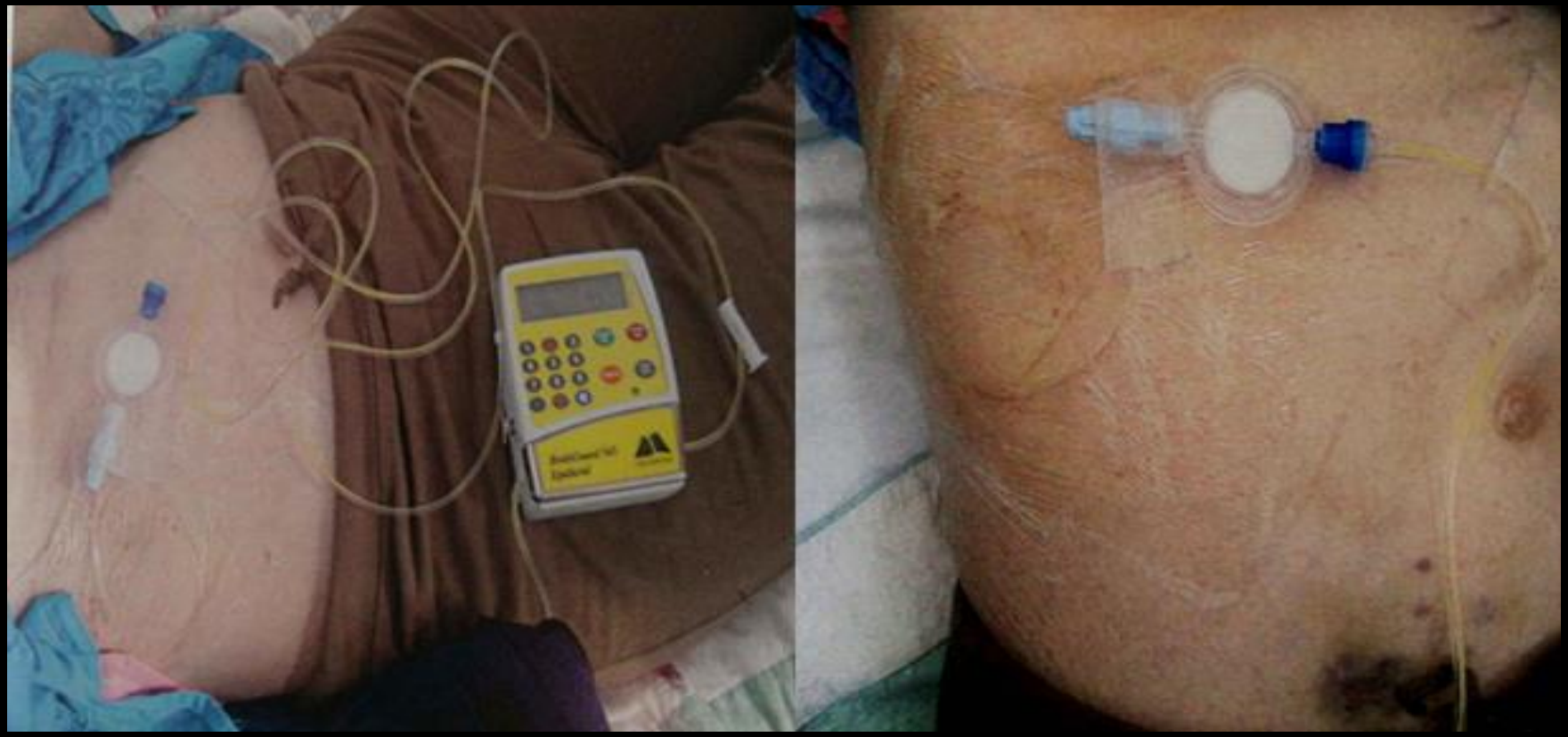
- **Epidural**
- Epidural hematoma
- Infection
- Fibrosis
- Obstruction &displacement of catheter

- **Spinal**
- Spinal headache
- Meningitis
- Supression of HPA
- Intraspinal granuloma

Visceral and Somatic Pain	
Opiods	Morphine
	Hydromorphine
	Fentanyl
	Sufentanyl
Local anaesthetics	Lidocaine
	Bupivacaine
	Tetracaine
Neuropathic pain	
Local anesthetics	Lidocaine
	Bupivacaine
	Tetracaine
Alpha-2 agonists	Clonidine
	Dexmedetomidine
Antispasmodics	Baclofen
NMDA receptor antagonist **Calcium channel blocker**	Ketamine Ziconotide

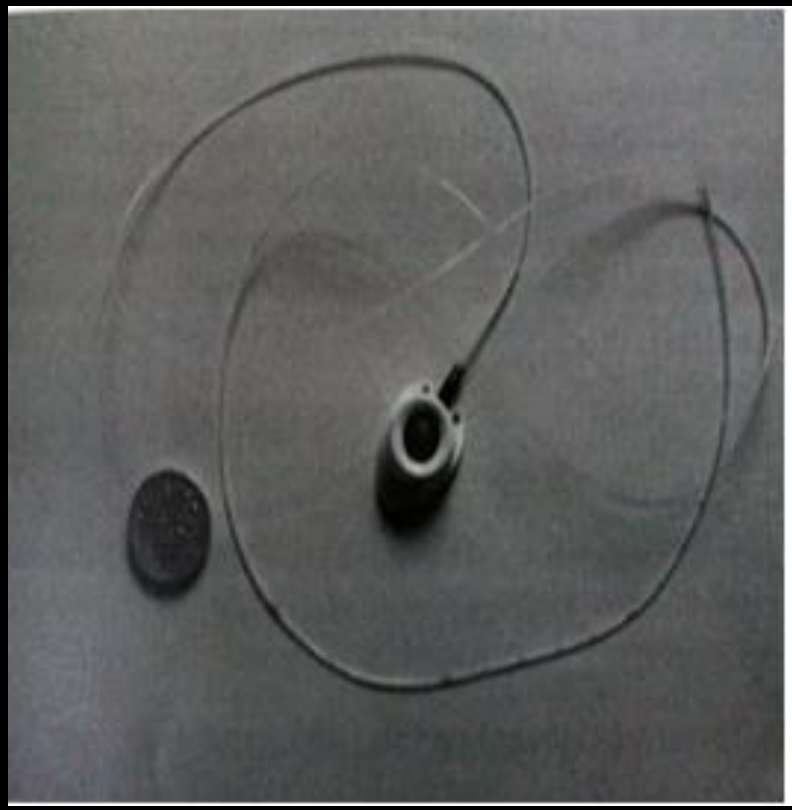
Drug Delivery Systems

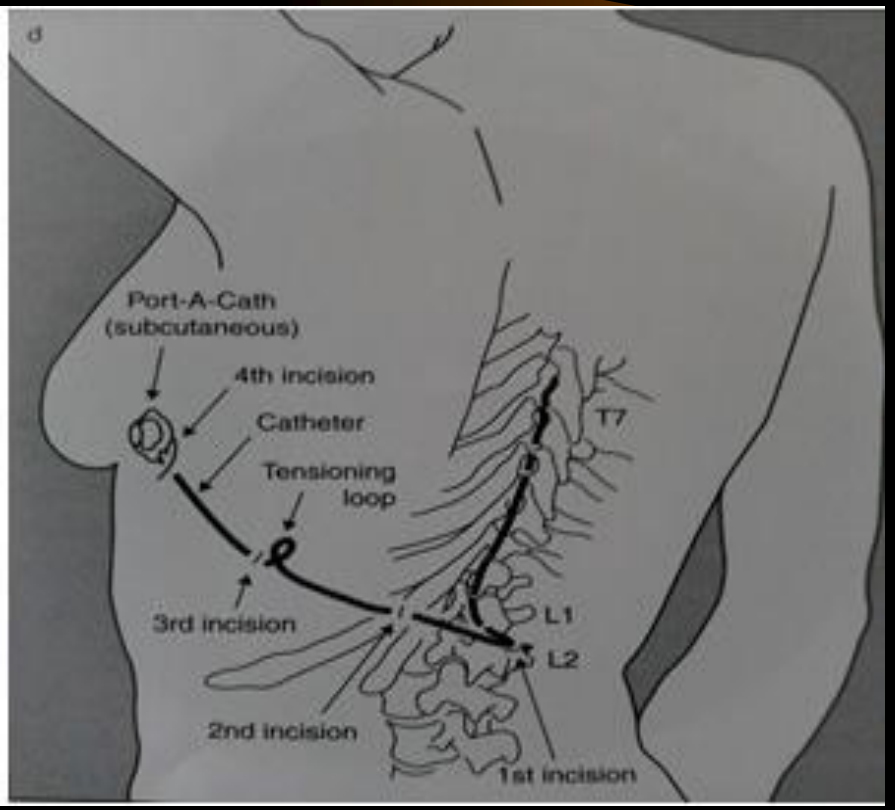
- Percutaneous short term catheters (externalized)
- Totally implanted catheter with s.c injection port
- Totally implanted catheter and pump



- Used for short term (days to weeks)
- Catheter tunneled for 8-10cms
- Intermittent or continuous infusion

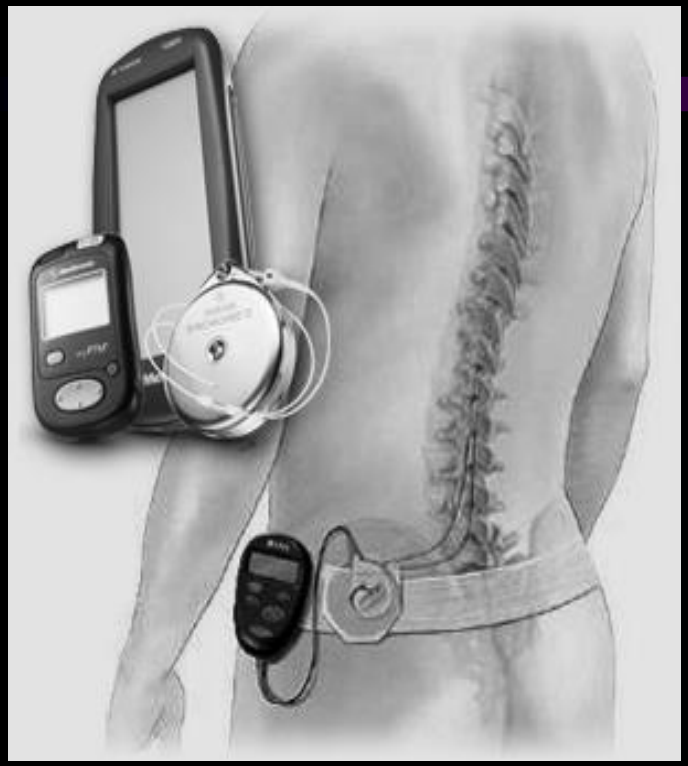
Totally implanted catheter with s.c injection port





- Injection port in the s.c tissue
- For medium length stay
- Catheter tunneled till the port

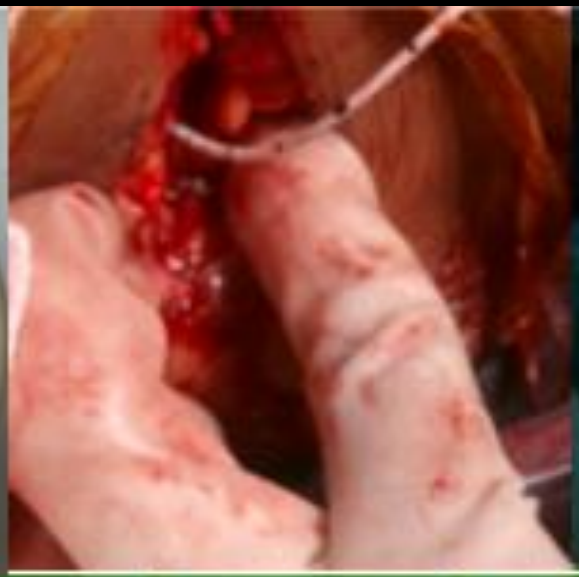
Totally implanted catheter and pump(intrathecal)

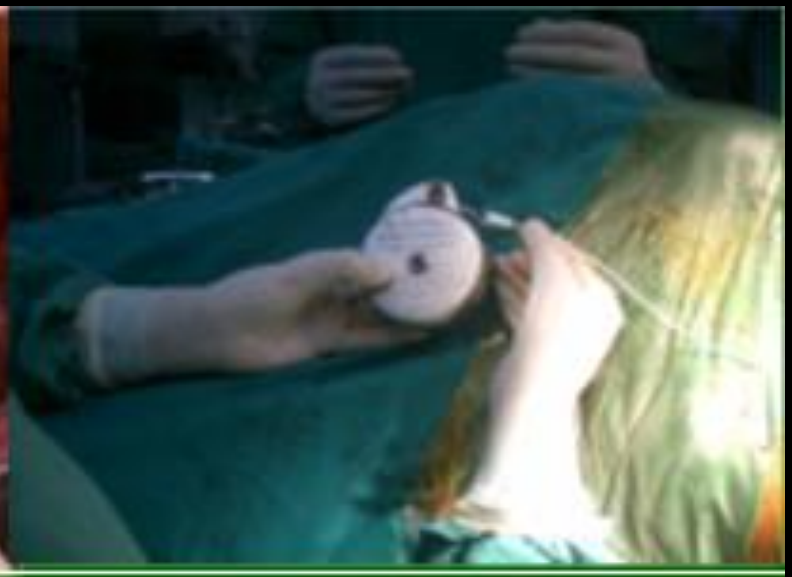


Patient therapy manager

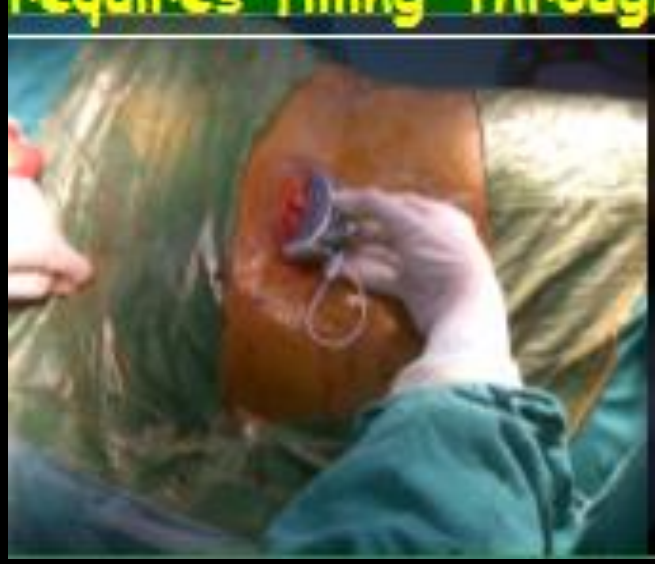
- Battery powered pump
- 20-40ml reservoir
- Filling port, side port

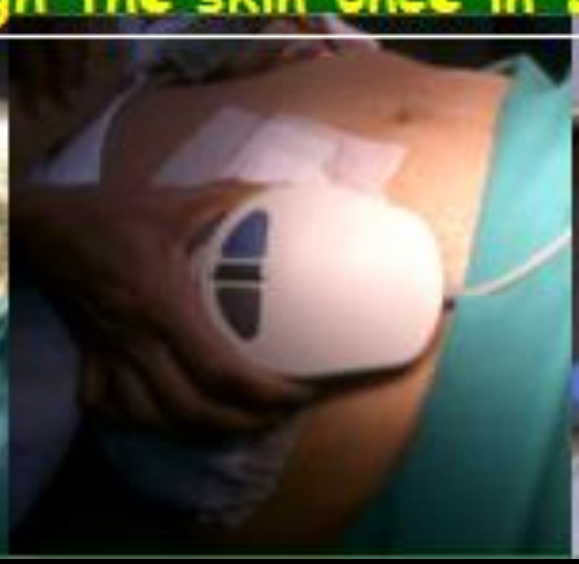
- Triggers delivery of the drug
- Gives alarm

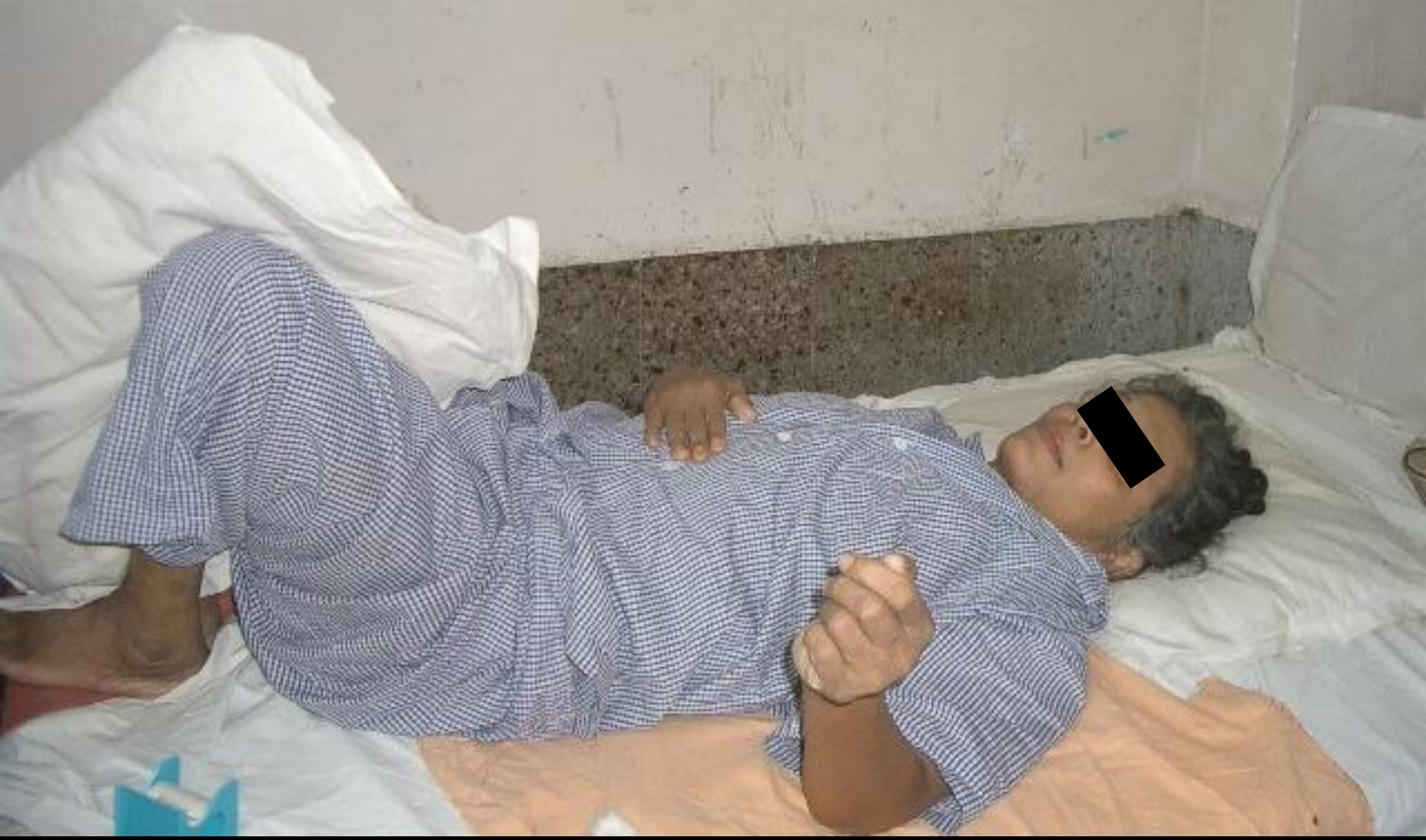




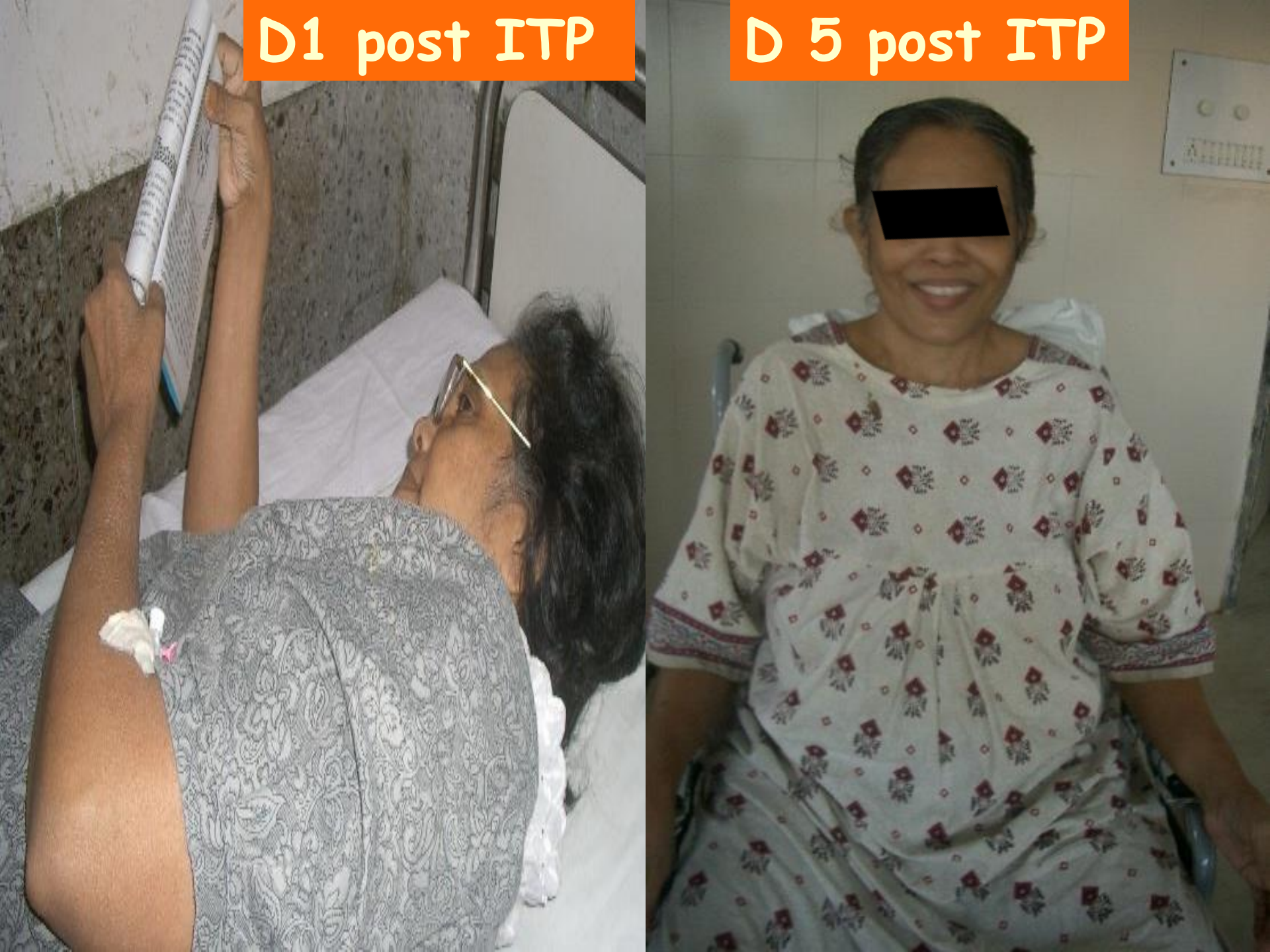
Intrathecal pump implantation for continuous micromg dosing ((0.4mg-4mg/d)of morphine to the spinal cord. Pump requires filling through the skin once in 2-3 m.





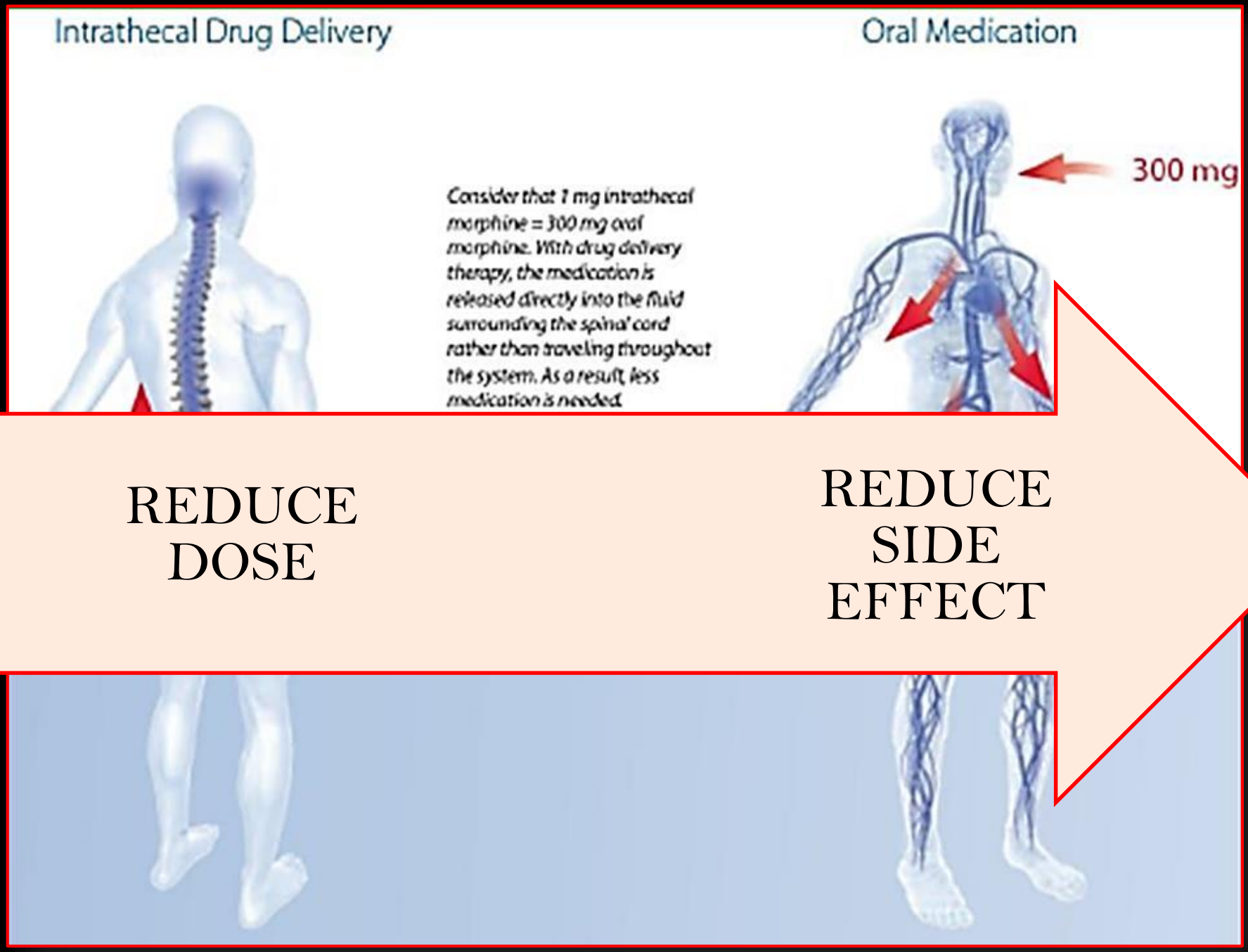


Woman severely demoralized losing weight, exhausted.

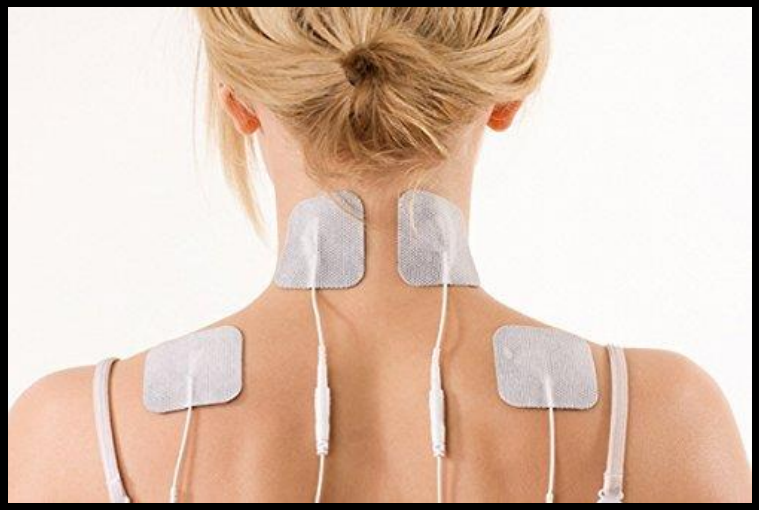

D1 post ITP
D 5 post ITP

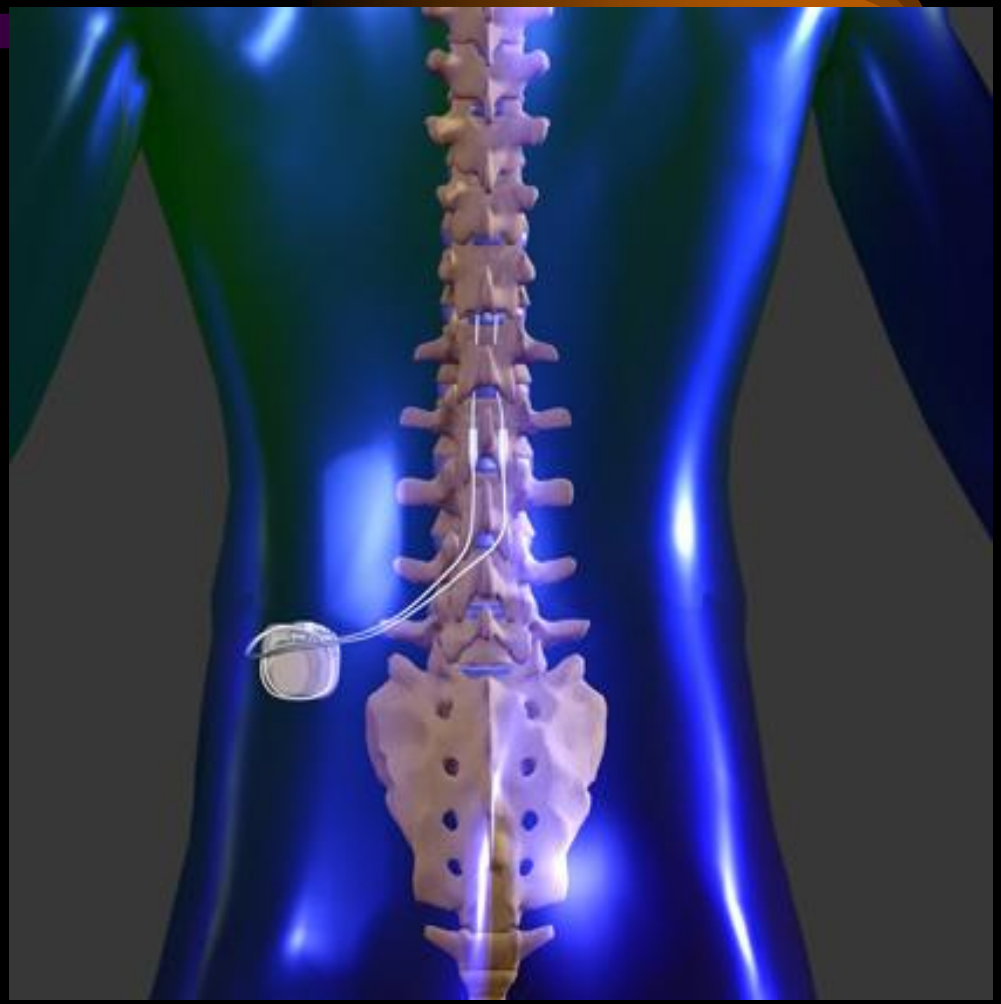
Conversion

ROUTE	DOSE (MG)
ORAL	300
INTRAVENOUS	100
EPIDURAL	20
INTRATHECAL	1

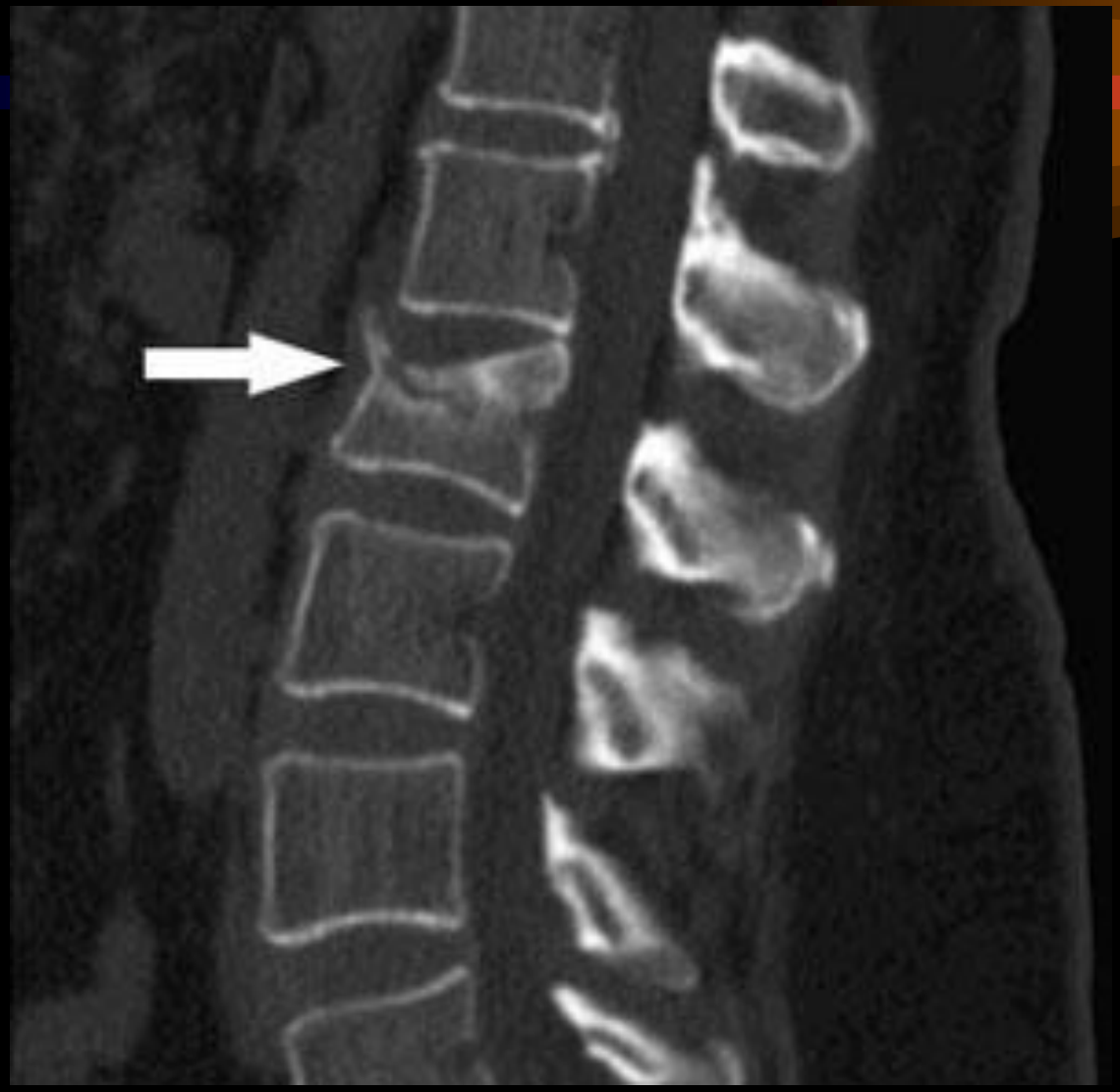

Intrathecal Drug Delivery
Oral Medication
300 mg
Consider that 1 mg intrathecal morphine = 300 mg oral morphine. With drug delivery therapy, the medication is released directly into the fluid surrounding the spinal cord rather than traveling throughout the system. As a result, less medication is needed.
REDUCE DOSE
REDUCE SIDE EFFECT

Spinal cord stimulation

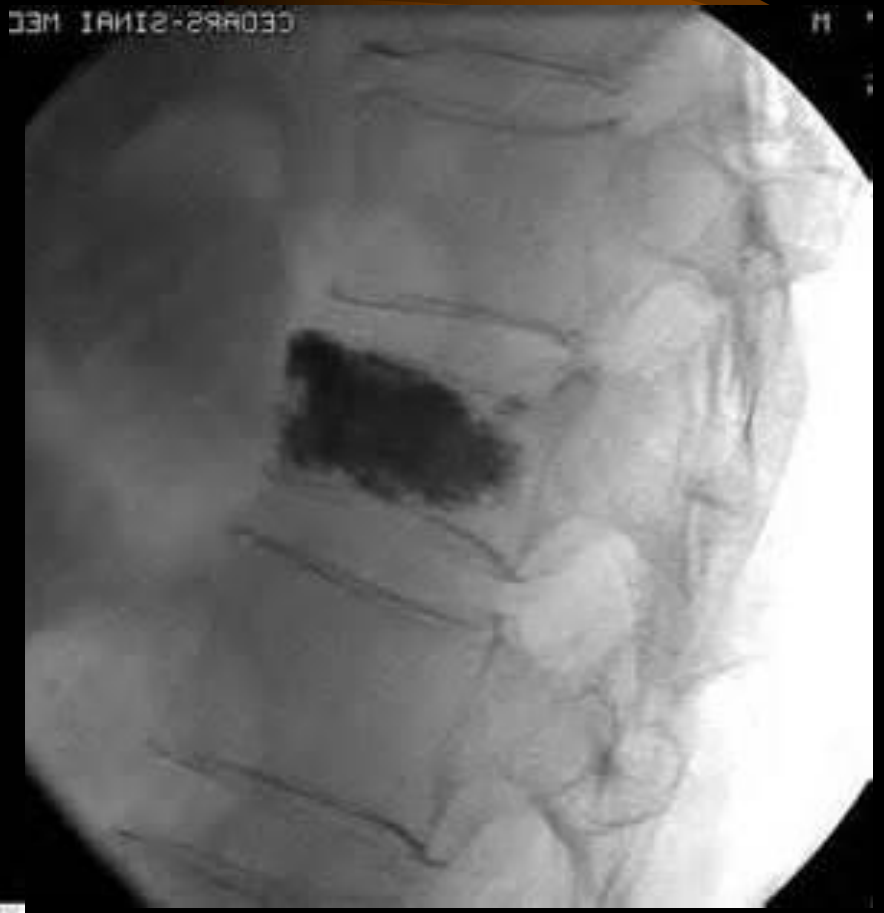




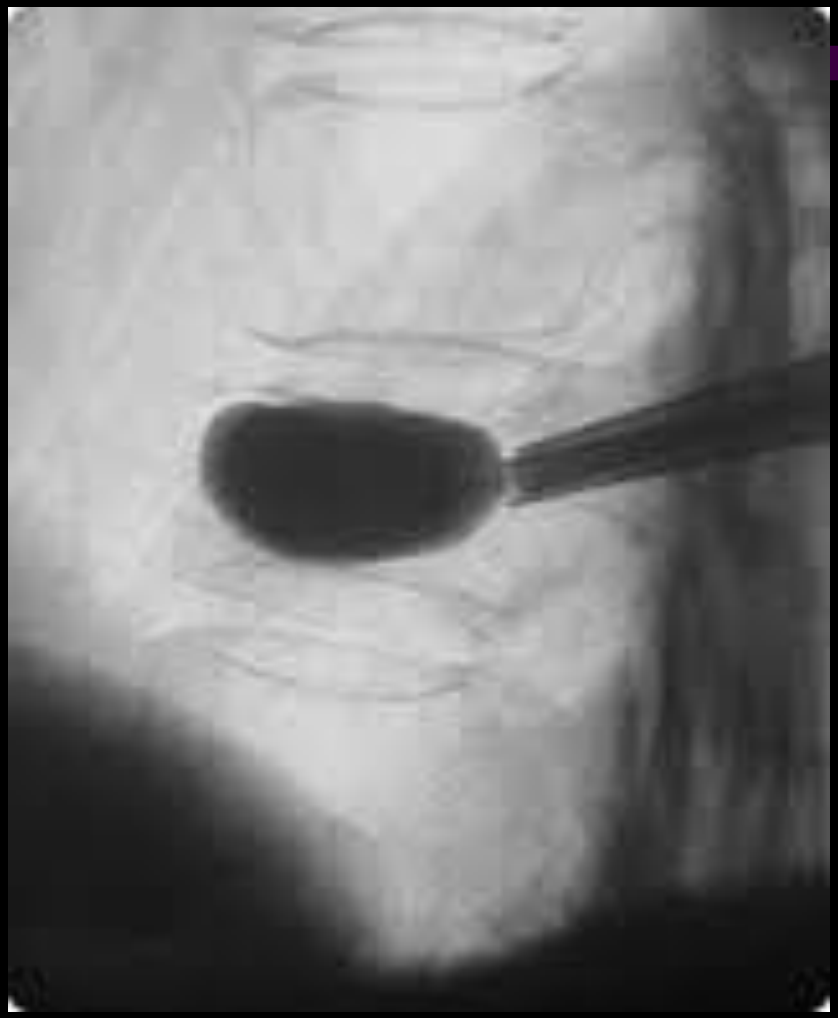
Vertebral fracture

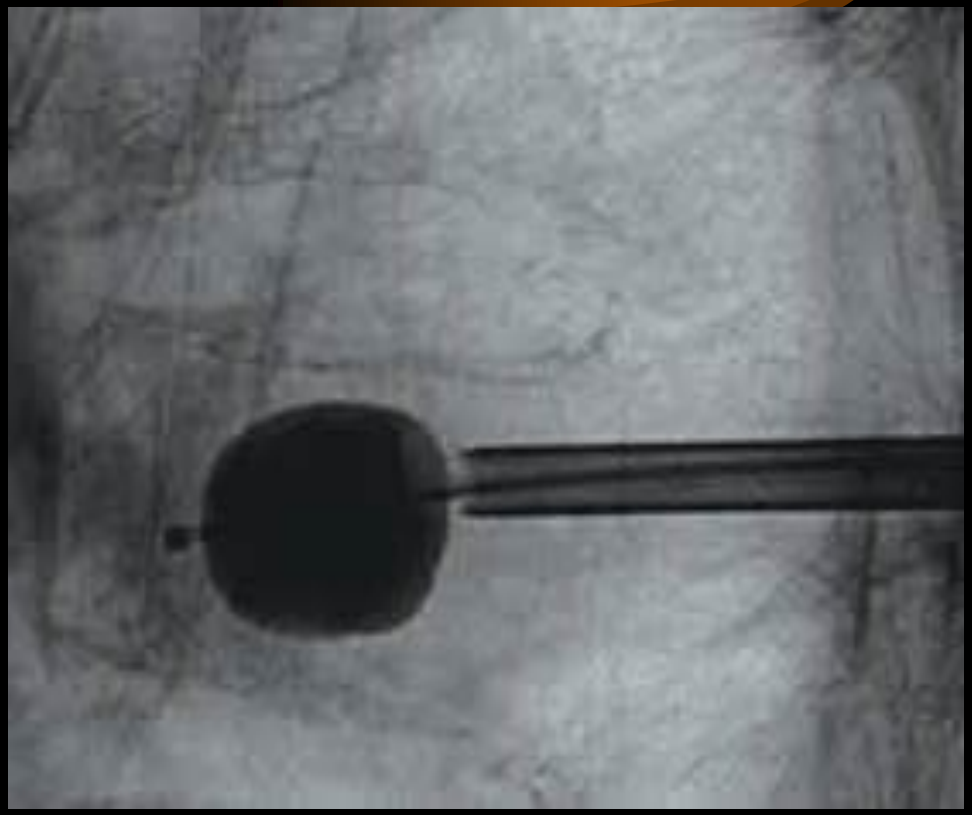


Vertebroplasty

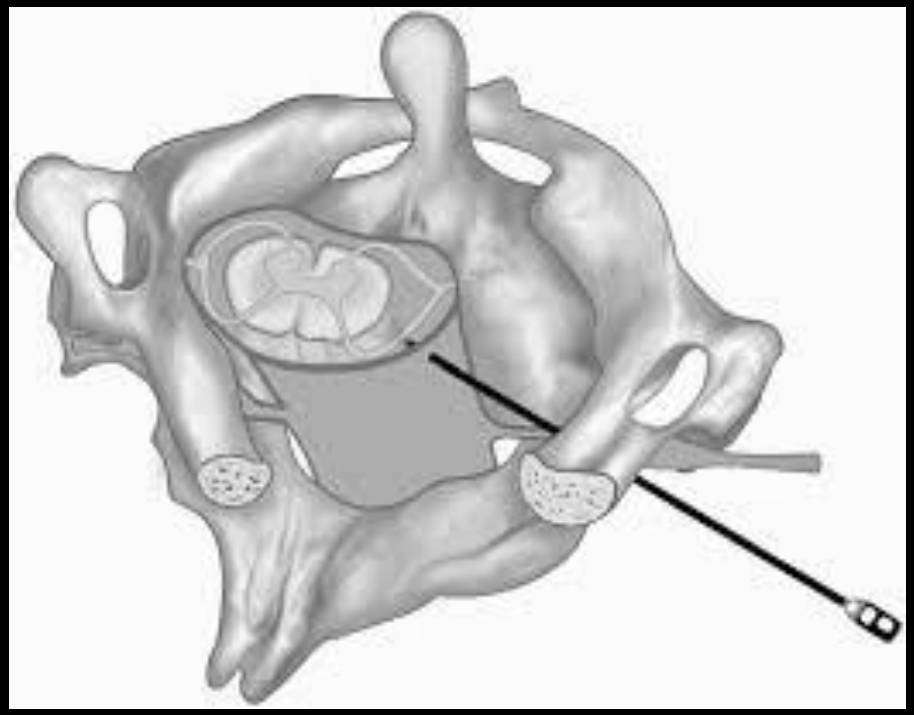


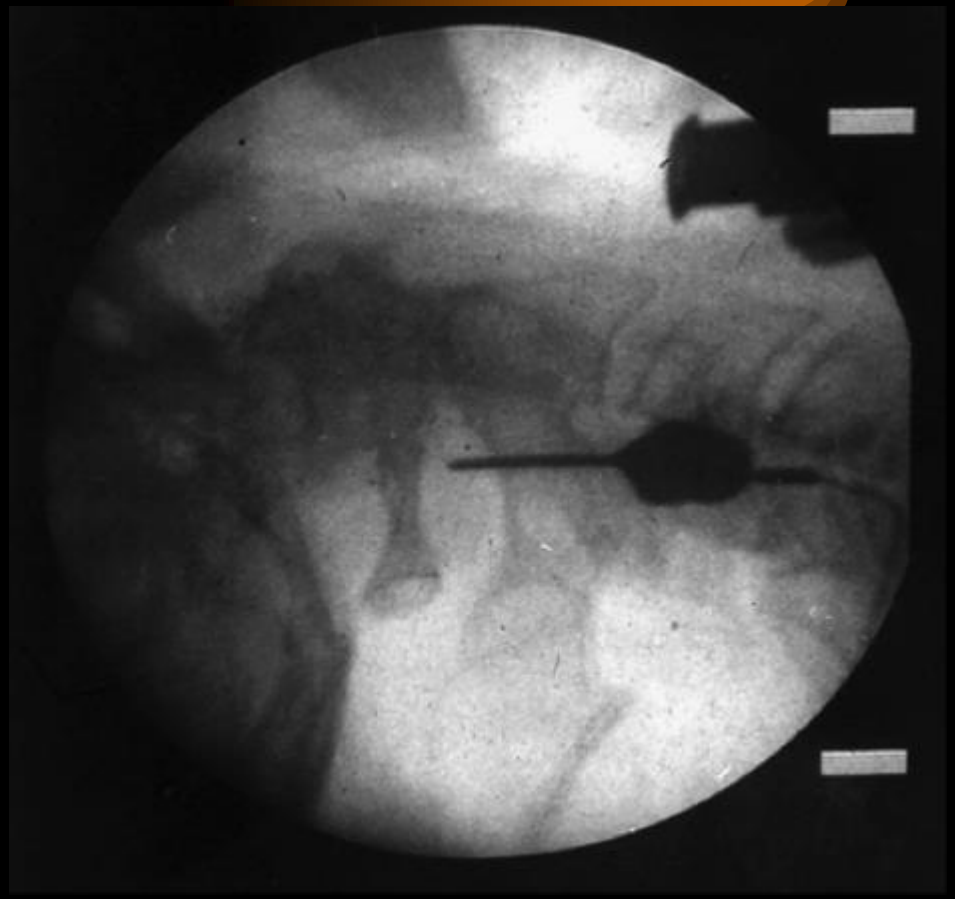
Kyphoplasty





Cordotomy





Changing trend

- Rising call for early implementation
- Suggest WHO ladder to be turned upside down

Requirements for success

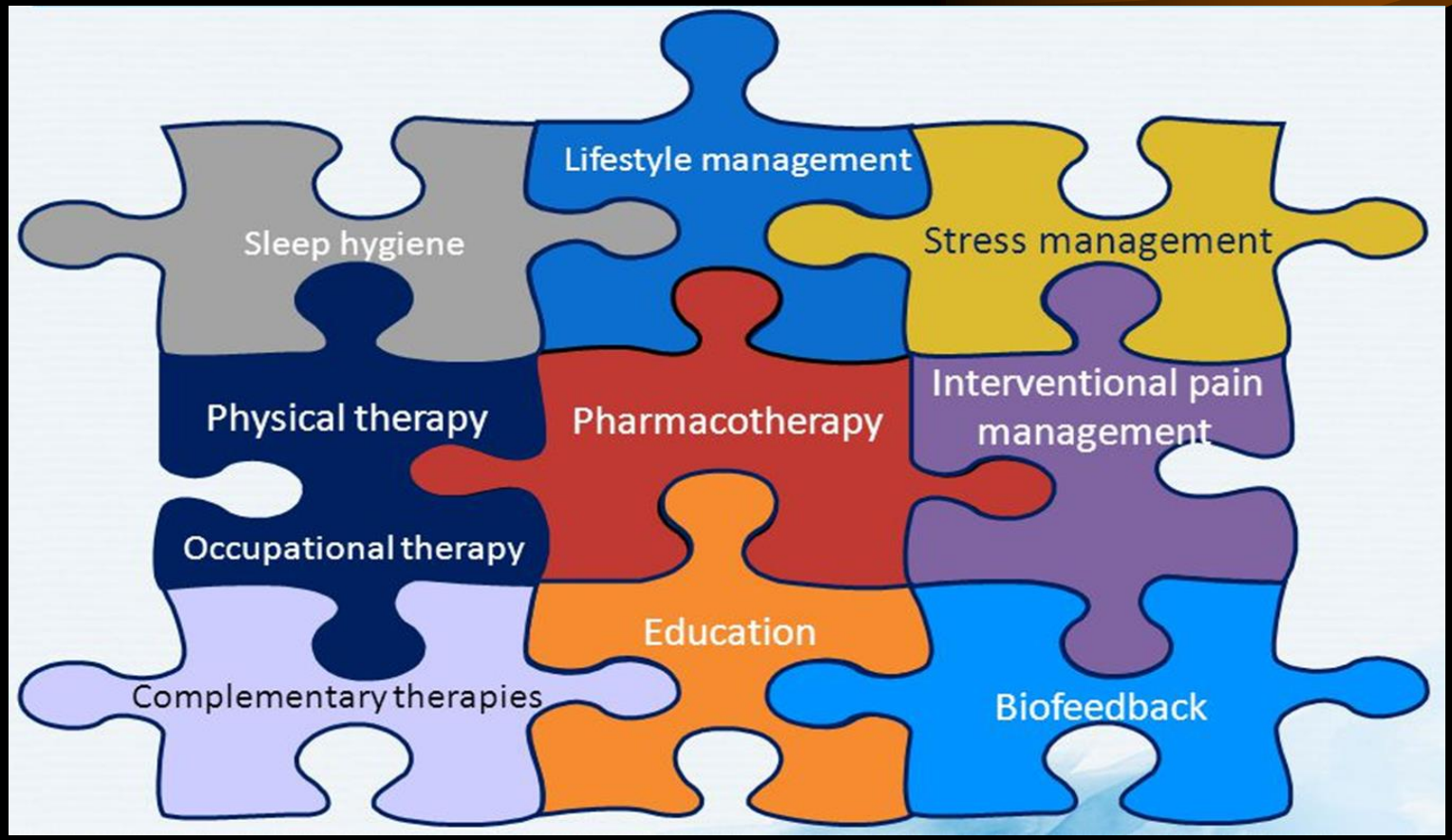
- Accurate diagnosis
- Well defined localized pain
- Trained interventionist
- Patients are not guinea pigs.
- Goal is to reduce the suffering

Take home message

- Cancer pain is dynamic
- Resistant pain – a challenge.
- Interventions help to overcome.
- As part of multimodal approach.
- Need for an expert interventionist.
- Simple techniques to be considered
- Evidence based

Combination therapy and multimodal approach

IDEAL



‘We must all die. But that I can save him from days of torture That I feel is my great and ever new privilege ‘

Albert Schweizer

Nobel laureate


I CANNOT PREDICT THE FUTURE
I CANNOT CHANGE THE PAST
I HAVE JUST THE PRESENT MOMENT
I MUST TREAT IT AS MY LAST
Thank you

PHARMACOLOGY OF PAIN MANAGEMENT – NEONATES, INFANTS, CHILDREN, ADULT, GERIATRICS, DISABLED, AND PREGNANCY

PHARMACOLOGY OF PAIN MANAGEMENT IN PEDIATRIC POPULATON:

PEDIATRIC POPULATION AND PAIN

The field of pediatric pain management continues to evolve, with ongoing changes in our appreciation of the impact of pain on pediatric population, a better understanding of how to assess pain and refinements in medication and methods of providing analgesia.There is a pressing need for further research and clinical development in the management of pain in children.

Misconceptions hold that neonates, infants and children do not feel pain, experience, or react to pain like adults, given the immaturity of their peripheral and central nervous system (CNS).Investigations have demonstrated that this immaturity of the CNS preferentially involves the inhibitory pathways that process nociceptive input. So, newborns have an exaggerated response to painful stimuli.

Studies have shown that infants and children experience a similar severity of postoperative pain as adults.This lead to the realization that changes were needed in the approach and management of acute pain in children.

Inadequate treatment of pain during infancy may have long-lasting consequences, including the development of chronic pain syndromes or a heightened sensitivity to subsequent painful stimuli. Inadequate analgesia will result in decreased tissue oxygenation due to vasoconstriction which in turn will result in increased incidence of wound infections.

MEASUREMENT OF ACUTE PAIN IN CHILDREN

Pain scales can be of two types:

A) Self report scales

1.Visual analog scale

2.Faces scale

3.Beyer and Wells picture scale

B) Observational scales

Changes in the heart rate, blood pressure, facial features, body positioning, presence or absence of crying

The treatment should incorporate a graded approach similar to the treatment of cancer-related pain

PAIN RATING	RECOMMENDATION
MILD	NSAID,Acetaminophen or Salicylate
MODERATE	1. NSAID, Acetaminophen with weak opioid (Oxycodone, Hydrocodone, Codeine, Tramadol) 2. Intravenous opioids - I.V opioid by PCA (Patient controlled analgesia) or NCA (Nurse controlled analgesia) - Continuous infusion of opioid with as needed rescue doses of opioid - Fixed interval dosing of opioid 3. Regional anesthetic techniques
SEVERE	Continue fixed interval dosing of NSAID or Acetaminophen, consider use of adjuvants like 1. Intravenous opioid by PCA or NCA 2. Regional anaesthesia techniques

STEPS INVOLVED:

1. Primary assessment of the severity of pain
2. Initiation of therapy
3. Hospitalization if effective control of pain cannot be achieved as an outpatient.

PHARMACOTHERAPY IN CHILDREN:

Acetaminophen and Ibuprofen are the most commonly prescribed NSAIDs.

Available in several preparations, including

1. chewable tablets
2. elixirs

3. infant drops
4. Rectal suppositories
5. sustained-release tablets.

Dose: Acetaminophen (15 mg/kg) or ibuprofen elixir (10 mg/kg).

With rectal administration, a larger dose of acetaminophen (40 mg/kg) is required to achieve analgesic plasma concentrations of 10 to 20 μg/mL.

Recent additions: Intravenous preparations of acetaminophen and ibuprofen.

PHARMACOKINETIC DIFFERENCES BETWEEN PEDIATRIC POPULATION AND ADULTS:

The statement that children are not small adults is valid particularly in pediatric clinical pharmacology.The application of pharmacokinetic and pharmacodynamic knowledge to the pediatric field implies the understanding of the maturing process in a continuing changeable organism at every age, from preterm to neonates to adolescence.

PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetics studies the passage of the drugs through the organism. It is given by LADME :

- L- Liberation
- A- Absorption
- D- Distribution
- M- Metabolism
- E- Excretion

Pharmacodynamics refers to the relationship between drug dosage and effect in a certain organ or system.

PHARMACOKINETIC PARAMETERS

The concentration of a drug attained after a single dose depends on its volume of distribution, which in turn depends on the volume of plasma and tissue and on the fractions of unbound drug in plasma and tissue.After multiple dosing, mean steady state concentrations reflect the dose and dosage interval, clearance, and bioavailability.Pharmacokinetic parameters such as clearance, volume of distribution and bioavailability are age-related.This affects the dose and dosage interval needed to maintain therapeutic concentrations.

ABSORPTION:

Developmental changes in absorptive surfaces, especially the gastrointestinal tract, can influence the rate and extent of the bioavailability of a drug.Physio-pathological factors such as shock cause hypoxia and hypoperfusion and therefore reduce the absorption of drugs.

FACTORS AFFECTING ORAL ABSORPTION:

1. GASTRIC PH:

At birth, pH is practically neutral (6-8), then falls to approximately 1-3 within the first 24 hours following birth, and later on gradually returns to neutrality by day 10.By the age of three years, the amount of gastric acid excreted per kilogram of body weight is similar to that excreted in adults, thus reaching the same pH values (2-3).These initial changes do not occur in premature infants, who seem to have little or no free acid during the first 14 days of life

Gastric pH and Absorption:

Acid labile drugs such as ampicillin, erythromycin or amoxycillin are more efficiently absorbed when orally administered in the neonate and infant than in the adult .Weak organic acids such as phenytoin and phenobarbital have a decreased absorption. Thus, bioavailability of the enteral formulation of phenytoin is 75% in neonates and infants up to four months compared with nearly complete absorption in adults.Basic drugs are absorbed more rapidly than in adults

2. GASTRIC EMPTYING

In normal adults, gastric emptying is biphasic, a rapid (10-20 min) first phase is followed by an exponentially slower phase.In the preterm infant, gastric emptying is slow and linear. It approaches adult values within the first 6-8 months of life.Drugs might have an improved absorption rate in young infants, owing to prolonged contact with the gastrointestinal mucosa secondary to slow gastric emptying.

3. INTESTINAL TRANSIT

Intestinal transit time is prolonged in neonates because of reduced motility and peristalsis.The transit time appears to be reduced in older infants as a result of increased intestinal motility.This seems to be responsible, together with other factors, for the incomplete absorption of some sustained release formulations.

4. OTHER FACTORS AFFECTING ABSORPTION

Immaturity of secretion and activity of bile and pancreatic fluid leads to impaired fat digestion in neonates and infants in the first few months.The absorption of fat-soluble vitamins (vitamin D and E) is reduced in neonates, because of the inadequate bile salt pool in the Ileum. Immaturity of the intestinal mucosa is characterized by lower intestinal motility and proteolytic enzymatic activity, reduced IgA secretion, diminished number of linfocites B and higher intestinal permeability.

The potential consequences of these characteristics are

1. an abnormal bacterial colonization of the superior gastrointestinal tract
2. an insufficient protein digestion
3. lower defensive capacity
4. higher absorption of proteins, immunoglobulins, carbohydrates, bacteria, virus, and toxins.
5. High levels of intestinal beta-glucuronidase activity.
6. Immaturity of transport systems: Gabapentin is absorbed through a L-amino acid transporter in the gastrointestinal mucosa and is excreted by the kidney as

unchanged drug. Its absorption process is saturable, therefore its bioavailability is dose dependent.

7. Renal clearance reaches adult levels at 1-2 years of age.

8. Variable microbial colonization:

During fetal life, the gastrointestinal tract is sterile. From birth, microbial colonization occurs and bacteria are detected within 4-8 hours. The digestive tract colonization influences the bile salts metabolism and gastrointestinal motility. The types of bacteria that colonize the digestive tract of the full-term neonates are different depending on whether the neonate receives maternal or artificial milk. The bioavailability of some drugs is influenced by the metabolism (hydrolysis and reductions) by the intestinal microflora, which is different in infants, children and adults.

ROUTES OF ADMINISTRATION:

INTRAMUSCULAR ADMINISTRATION:

The bioavailability of drugs after intramuscular injection depends on the perfusion in the area of the injection, the rate of drug penetration through the capillary endothelium, and the apparent volume into which the drug has been distributed.A decrease of the blood flow to muscle, which varies quite considerably over the first 2-3 weeks of life, less muscular mass and a higher proportion of water.Intramuscular administration of drugs is unreliable in neonates and the pharmacokinetics are unpredictable.For Aminoglycosides and ampicillin, the time needed to achieve peak concentration is comparable for infants, children and adults when administered by intramuscular route.

RECTAL ADMINISTRATION:

The rectal area is small but well vascularized, and the absorption occurs through superior, medial and inferior hemorrhoidal veins.The local pH of the rectum is close to neutral in adults, but alkaline in most children.Drugs administered low in the rectum are delivered systemically before passing through the liver.Drugs administered high in the rectum are usually carried directly to the liver and therefore are subject to metabolism and the enterohepatic

circulation.Depending on the absorption site of the rectum, bioavailability is expected to vary between neonates, infants, children and adults.

Ketoprofen has a similar absorption in children and adults after rectal administration.A prolonged absorption time of paracetamol was shown in preterm neonates in comparison with term neonates, possibly due to differences in rectal temperature. The bioavailability of paracetamol seems to decrease with age, likely because of an increase in the first-pass effect of the liver by maturation of liver enzymes. Apparently there are differences in the degree of absorption after rectal administration of tramadol between children and adults, probably due to the pH difference.

PERCUTANEOUS ADMINISTRATION:

The thickness of the epidermal stratum corneum is inversely related to absorption, whereas the state of skin hydration directly influences absorption.A greater body surface area related to weight, may cause excessive absorption of an agent applied to the skin in the neonate and small infants.Examples include Transdermal patches of Fentanyl and Buprenorphine.Systemic toxicity can be seen with the percutaneous administration of drugs, such as lidocaine and corticosteroids during the first 8-12 months.

INTRAPULMONARY ADMINISTRATION:

Intrapulmonary administration of drugs (inhalation) is increasingly being used in infants and children.Developmental changes in the architecture of the lung and its ventilatory capacity alter the absorption after the intrapulmonary administration of a drug.

INTRANASAL ADMINISTRATION:

Intranasal administration of drugs including ease of administration, speed of action, good tolerance and not having hepatic first-pass effect.Examples: Midazolam, fentanyl, butorphanol, ketamine, sufentanil, corticosteroids, antihistamines, sumatriptan and desmopressin

DISTRIBUTION:

After absorption, a drug is distributed to various body compartments according to its physiochemical properties, such as molecular size, ionization constant, and relative aqueous and

lipid solubility.Factors including plasma protein binding and water partitioning are continuously fluctuating throughout the first years of life, thus affecting the distribution of drugs.

MEMBRANE PERMEABILITY:

At birth, the blood-brain barrier (BBB) is still not fully mature and drugs may gain access to the central nervous system with resultant toxicity.This neonatal greater permeability in turn allows some drugs with low penetration capacity to achieve higher concentrations in brain than those reached in children or adults, as it has been described with Amphotericin B.

PLASMA PROTEIN BINDING:

Plasma protein binding of compounds is dependent on the amount of available binding proteins, the number of available binding sites, the affinity constant of the drug for the protein(s), and the presence of pathophysiological conditions or endogenous compounds that may alter the drug-protein binding interaction.In general, acidic drugs mainly bind to albumin, whereas basic drugs bind to globulins, α1-acid glycoprotein (AAG) and lipoproteins.The unbound fraction is higher in neonates and infants for several reasons.

Physiological and pathological increases in bilirubin and free fatty acid plasma concentrations are often present in the neonatal period.Increased concentrations of non-esterified fatty acids reduce drug binding, as also occurs by the increased levels of bilirubin and other endogenous substances competitively binding to albumin.The lower concentration of AAG in newborns and infants probably accounts for the decrease in protein binding of sufentanyl in these age groups compared with that in older children or adults (the free fraction of sufentanyl is 20% in newborns compared with 12% in infants and 8% in children and adults).

BODY WATER:

In very young infants, the total body water is high (80-90% of the body weight (BW)) while fat content is low (10-15% BW). The amount of total body water decreases to 55-60% by adulthood.The extracellular water content is about 45% in neonates, and especially large in neonates with low birth weights, compared with 20% in adulthood.This will result in a relatively higher volume of distribution of water-soluble drugs in pediatric population than in adulthood.

Examples:

Gentamicin (0.5-1.2 l/kg in neonates and infants and 0.2-0.3 l/kg in adults)

Linezolid

Phenobarbital

Propofol

The volume of distribution will be similar or lower for fat-soluble drugs such as diazepam.

METABOLISM:

The liver is quantitatively by far the most important organ for drug metabolism. It constitutes 5% of the BW at birth but only 2% in adults.The hepatic clearance depends on several factors, including blood flow, hepatic enzyme activities (intrinsic metabolism), transport systems and plasma protein binding.The primary objective of drug metabolism is to transform drugs into more water soluble substances to facilitate their excretion.

Drug metabolisms can be

1. phase I, involving structural alteration of the drug molecule, and
2. phase II reactions, consisting of conjugation with another often more water-soluble moiety.

At birth, both phase I and II metabolic enzymes may be immature. The different capacity to metabolize drugs in children may result in higher or lower drug plasma levels than those reached in adults.

PHASE I REACTIONS:

CYP SYSTEM:

The CYP isoenzyme superfamily comprises over 50 proteins located in the lipophilic membranes of the smooth endoplasmic reticulum of the liver and other tissues in vesicles called microsomes. Total cytochrome P450 content in the fetal liver is between 30 and 60% of adult values and approaches adult values by 10 years of age.

CYP3A: Is the most abundant cytochrome in the human liver and the intestinal tract, which accounts for approximately 30-40% of total hepatic cytochrome.It is probably essential for the metabolism of steroid hormones of maternal, placental or fetal adrenal origin. It is essential for metabolizing more than 50% of the drugs, including ciclosporin, tacrolimus, cisapride,

midazolam, fentanyl, lidocaine, nifedipine, indinavir, verapamil.The clearance of intravenous midazolam, a CYP3A4 substrate, is markedly lower in neonates than that in infants aged >3 months.

Different half-lives (hours) between neonates, infants, children and adults:

Isoenzyme	Drug	Neonate	Infant	Children	Adult
CYP1A2	Caffeine	95	7	3	4
	Theophylline	24-36			3-9
CYP 2C9	Phenytoin	30-60	2-7	2-20	20-30
CYP2C19	Phenobarbital	70-500	20-70	20-80	60-160
	Diazepam	22-46	10-12	15-21	24-48
CYP3A	Carbamazepine	8-28	—	14-19	16-36
	Lidocaine	2,9-3,3	—	1-5	1-2,2

PHASE II REACTIONS:

1. Methylation
2. Acetylation
3. Glucuronidation - In the fetal liver, activities toward bilirubin, androsterone, testosterone and morphine were at values of <14% of those of adults.

Morphine is extensively metabolized by glucuroconjugation with formation of both 3- and 6-glucuronides (M3G and M6G). M6G has been shown to be a potent analgesic.The metabolism of morphine was studied in children and premature neonates, finding detectable concentrations of M3G and M6G.The M3G/morphine and M6G/morphine ratios were significantly higher in children than in neonates, suggesting that morphine glucuronidation capacity is enhanced after the neonatal period.Therefore, weight-corrected doses (mg/Kg) of drugs predominantly metabolized by glucuronidation must be decreased in neonates.

Isoenzyme	Pediatric population activity	Drug class	Examples

CYP1A2	↓ until 2 years	Antidepressant Bronchodilator Diuretic	Duloxetine Theophylline Triamterene
CYP2C9	↓ until 1-2 years	Anticoagulant Antidepressant Nonesteroidal antiinflammatory	Warfarin Phenytoin Diclofenac,ibuprofen, naproxen, tolbutamide
CYP2C19	↓ until 10 years	Antidepressant Benzodiazepine Proton pump inhibitor	Citalopram, sertraline Diazepam Lansoprazole, omeprazole, pantoprazole
CYP2D6	↓ until 12 years	Analgesic Antidepressant	Codeine, tramadol amitriptyline, desipramine, doxepin, imipramine, fluoxetine, nortriptyline,

			paroxetine, venlafaxine
		Antihistamine	Diphenhydramine
		Antipsychotic	Risperidone
		ß-Blocker	Labetalol, metoprolol
CYP3A4	↓ until 2 years	Analgesic	Alfentanil, fentanyl
		Antiepileptic	Carbamazepine
		Antifungal	Itraconazole, ketoconazole
		Antihistamine	loratadine
		Antiretroviral	Indinavir, lopinavir ritonavir, saquinavir
		Benzodiazepine	Alprazolam, midazolam
MAO A	↑ until 2 years		
MAO B	≈		
N-Methyltransferases	≈		
		Analgesi	Morphine

		c	
UGTs	↓ until 7-10 years	Antiepileptic Benzodiazepine	Lamotrigine Clonazepam, lorazepam
NAT2	↓ until 1-4 years	Antihypertensive Antiinfectious	Hydralazine Isoniazid

EXCRETION:

Excretion of drugs by the kidneys is dependent on three processes, glomerular filtration (GFR), tubular secretion and reabsorption.At birth, renal blood flow is only 5 to 6% of cardiac output, 15 to 25% by one year of age and reaches adult values after two years of age. During the neonatal period, the elimination of many drugs that are excreted in urine in unchanged form is restricted by the immaturity of glomerular filtration and renal tubular secretion.

A similar or greater rate of elimination from plasma than in adults has been observed in late infancy and/or in childhood for many drugs including as digoxin, phenytoin, carbamazepine, levetiracetam, diazoxide, clindamycin, cimetidine, chlorpheniramine and cetirizine.

Therefore, larger doses of these drugs (mg/kg) are required in children in order to achieve the same plasma concentrations as in adults.Infant urinary pH values are generally lower than adult values. Urinary pH may influence the reabsorption of weak organic acids and bases.

GLOMERULAR FILTRATION:

Inulin or creatinine are often used as a marker of GFR, the former has lower concentration at birth, increases considerably during the first two weeks of life and reach adult levels by six months.For drugs whose renal clearance is governed by GFR, the rapid improvement in efficiency of glomerular filtration leads to rapid enhancement in renal drug clearance and a diminished risk of significant drug accumulation, such as aminoglycosides.

AGE RELATED CREATININE CLEARANCE:

Age	Creatinine clearance (mL/min/m^2)
Preterms	5-10
1-2 weeks preterms	10-12
Neonates	10-15
1-2 weeks of age	20-30
6 months	73
Adults	73

TUBULAR SECRETION:

The renal tubular secretion capacity increases over the first months of life to reach the adult level at approximately seven months. Therefore, active tubular secretion takes somewhat longer to reach adult values than glomerular filtration. The tubular secretion may be greater in children and teens than in adults.

TUBULAR REABSORPTION:

Tubular reabsorption is generally a passive phenomenon especially important with non-metabolized liposoluble drugs.The glomerular permeability and the tubular reabsorption are gradual and continuous processes from birth to adolescence, but the key stage of their maturation may be between one and three years, respectively.

To conclude, pediatric studies entail difficulties and ethical limitations, however, they are necessary to determine the posologic regimen of drugs and estimate their fate once administered. Children cannot be considered as miniature adults and extrapolation from adults' data should not be done, especially in long-term treatments.

PHARMCOLOGICAL CHANGES IN PREGNANCY:

Pregnancy is a complex state where changes in maternal physiology have evolved to favor the development and growth of the placenta and the fetus. These adaptations may affect pre-existing disease or result in pregnancy-specific disorders. Similarly, variations in physiology may alter the pharmacokinetics or pharmacodynamics that determines drug dosing and effect. Understanding both pregnancy physiology and the gestation-specific pharmacology of different agents is necessary to achieve effective treatment and limit maternal and fetal risk.

CARDIOVASCULAR CHANGES DURING PREGNANCY:

Cardiovascular changes during pregnancy include an increase in cardiac output starting in early pregnancy, plateauing by 16 weeks of gestation ~7 L/min and remaining elevated until delivery.An increase is also noted for stroke volume starting at 20 weeks of gestation and a gradual increase occurs with maternal heart rate reaching 90 beats per min at rest in the third trimester.Pregnancy is also marked by ~42% increase in plasma volume, reaching over 3.5 L at 38 weeks of gestation, with parallel increases in total body water and in all body fluid compartments.

Pregnancy-induced physiologic changes during near term:

System (reference)	Parameter	Non-pregnant	Pregnant
Cardiovascular[64,71,72]	Cardiac output [L/min]	4.0	6.0
	Heart rate [beats per min]	70	90
	Stroke volume [mL]	65	85
	Plasma volume [L]	2.6	3.5
Respiratory[73,74]	Total lung capacity [mL]	4225	4080
	Residual volume [mL]	965	770
	Tidal volume [mL]	485	680
Liver[75]	Portal vein blood flow [L/min]	1.25	1.92
	Hepatic artery blood flow [L/min]	0.57	1.06[a]
Renal[76]	Glomerular filtration rate [mL/min]	97	144
	Serum creatinine [mg/dL]	0.7	0.5

[a]Not statistically significant.

DRUG ABSORPTION:

Nausea and vomiting in early pregnancy may decrease the amount of drug available for absorption following oral administration. Therefore, oral medications should be administered when nausea is minimal.

Gastric acid production is also decreased during pregnancy, whereas mucus secretion is increased, leading to an increase in gastric pH. These changes can increase ionization of weak acids (e.g., aspirin) and reduce their absorption, and weak bases (e.g., caffeine) will diffuse more readily since they will be primarily unionized.

The slower intestinal motility and decreased gastric acid secretion in pregnancy could alter drug absorption and oral bioavailability.

DRUG DISTRIBUTION:

The volume of distribution (Vd) is used to indicate how extensively a systemic dose of medication is ultimately dispersed throughout the body. Drugs that predominantly remain within the vascular system will have a Vd estimate close to plasma volume. Drugs that are not bound to any proteins in the body will have a Vd estimate close to total body water. Drugs that are highly bound to tissues, with a small proportion remaining in the intravascular space, will have a very high Vd. Variations in Vd mainly affect the plasma concentration of the drug, which can directly impact a drug's therapeutic and adverse effects.

CHANGES IN DRUG DISTRIBUTION DURING PREGNANCY:

Expanded extracellular volume and total body water will increase volume of distribution for hydrophilic drugs, leading to lower plasma concentrations. Also, maternal body fat expands by approximately 4 kg, increasing the volume of distribution for lipophilic drugs.

Plasma protein binding of drugs decreases during pregnancy due to reduced concentrations of both albumin and alpha 1-acid glycoprotein. Decreased protein binding leads to higher concentrations of free drug (for drugs that have limited clearance) and favors more distribution to tissues. Example: Phenytoin and Tacrolimus

GESTATION-SPECIFIC CHANGES:

Gestation-specific changes also include an increase in uterine perfusion and the addition of the feto-placental compartment. In general, small-molecular-weight and lipophilic drugs readily cross the placenta. The fetus and the amniotic fluid can act as additional compartments, leading to increased drug accumulation which in turn leads to an apparent increase in volume of distribution of certain drugs.

DRUG METABOLISM:

Oxidative phase I reactions are predominantly carried out by the cytochrome P450 (CYP) family of enzymes. The activities of CYP3A4 (50–100%), CYP2A6 (54%), CYP2D6 (50%), and CYP2C9 (20%) are all increased during pregnancy. Changes in CYP3A4 activity lead to increased metabolism of drugs such as glyburide, nifedipine, and indinavir. By contrast, some

CYP isoforms demonstrate decreased activity during pregnancy. CYP1A2 and CYP2C19 appear to undergo a gradual decrease in activity with advancing gestation.

PREGNANCY-INDUCED ENZYME-SPECIFIC CHANGES:

Enzyme (references)	Pregnancy-induced change	Potential substrates in obstetrics
CYP3A4[19,20,77,78]	Increased	Glyburide, nifedipine, and indinavir
CYP2D6[77,79]	Increased	Metoprolol, dextromethorphan, paroxetine, duloxetine, fluoxetine, and citalopram
CYP2C9[18,80]	Increased	Glyburide, NSAIDs, phenytoin, and fluoxetine
CYP2C19[18,80]	Decreased	Glyburide, citalopram, diazepam, omeprazole, pantoprazole, and propranolol
CYP1A2[17,23,77,81]	Decreased	Theophylline, clozapine, olanzapine, ondansetron, and cyclobenzaprine
UGT1A4[82–84]	Increased	Lamotrigine
UGT1A1/9[25]	Increased	Acetaminophen
NAT2[17,24,85]	Decreased	Caffeine

DRUG ELIMINATION:

Renal drug excretion depends on GFR, tubular secretion, and reabsorption. GFR is 50% higher by the first trimester and continues to increase until the last week of pregnancy. If a drug is solely excreted by glomerular filtration, its renal clearance is expected to parallel changes in GFR during pregnancy. For example, cefazolin and clindamycin exhibit increased renal elimination during pregnancy. The clearance of lithium is doubled during the third trimester compared to preconception. Digoxin, which is 80% renally-cleared, is merely 20–30% higher during the third trimester compared to postpartum. The clearance of atenolol is only 12% higher across pregnancy.

DRUG TRANSPORT:

Fetal development is dependent upon the transport of nutrients by the placenta toward the fetal side and that of products of fetal metabolism for elimination by the mother. Small, lipid-soluble, ionized, and poorly protein-bound molecules cross the placenta easily. For other substrates, the placenta facilitates maternal to fetal transport through the polarized expression of various transporters.

Table 4. Safety of Over-the-Counter Analgesics and Antipyretics in Pregnancy

Medication	*Drug class*	*Pregnancy risk category**	*Crosses the placenta?*	*Use in pregnancy*
Acetaminophen	Nonnarcotic analgesic/ antipyretic	B	Yes	Drug of choice
Aspirin	Salicylate analgesic/ antipyretic	C in the first and second trimesters, D in the third trimester	Yes	Should be avoided in pregnancy unless needed for specific indications
Naproxen	NSAID analgesic	B in the first and second trimesters, D in the third trimester	Yes	Should be avoided in the third trimester
Ibuprofen	NSAID analgesic	C in the first and second trimesters, D in the third trimester	Yes	Should be avoided in the third trimester

NSAID = nonsteroidal anti-inflammatory drug.

**—Based on pregnancy risk category definitions from the U.S. Food and Drug Administration (Table 2) and other sources.*

Information from references 10 through 16.

PHARMACOLOGY IN GERIATRIC POPULATION:

DRUG METABOLISM AND DISPOSITION IN GERIATRICS:

The elderly (individuals over 65 years of age) constitute more than 13% of the population. It is increasing steadily and is expected to reach 50 million by the year 2020. The most highly drug-treated and accounts for about 25% of prescription drugs dispensed. It is important to keep in mind that chronological aging may not necessarily be an accurate index of biological aging. Age-related alterations in pharmacokinetics (absorption, distribution, metabolism, and excretion) have received considerable attention.

ABSORPTION:

Elderly patients may absorb drugs less completely or more slowly because of decreased splanchnic blood flow or delayed gastric emptying. In addition to this, reduced gastric acidity may decrease the absorption of drugs that require high acidity.

DISTRIBUTION:

Drug distribution in elderly patients may be altered by

- hypoalbuminemia,
- qualitative changes in drug-binding sites,
- reductions in relative muscle mass,
- increases in the proportion of body fat, and
- decreases in total body water. The plasma level of free, active drug is often a direct function of the extent of drug binding to plasma proteins. There is an age-dependent decline (about 20%) in plasma albumin concentration in humans due to a reduced rate of hepatic albumin synthesis.

METABOLISM:

Changes in metabolism occur as a result of reduced hepatic enzyme activity. Metabolism is impaired by a reduction in hepatic mass, volume, and blood flow . Phase I oxidative pathways are decreased with age, while phase II conjugation pathways are unchanged.

Plasma Half-lives of Several

Drugs in Young Adult and

Elderly Patients

	Plasma or serum $t_{1/2}$

Drug	Young (20–30 yr)	Elderly (65–80 yr)
Penicillin G	20.7 min	39.1 min
Dihydrostreptomycin	5.2 hr	8.4 hr
Tetracycline	3.5 hr	4.5 hr
Kanamycin	107.0 min	282.0 min
Digoxin	52.0 hr	73.0 hr
Aminopyrine	3.0 hr	10.0 hr
Phenobarbital	71.0 hr	107.0 hr
Diazepam	20.0 hr	80.0 hr
Lidocaine	80.6 min	139.6 min

EXCRETION:

Renal elimination of foreign compounds changes dramatically with increasing age by factors such as

- reduced renal blood flow,
- reduced glomerular filtration rate,
- reduced tubular secretory activity, and
- a reduction in the number of functional nephrons

Beginning at age 20 years, renal function declines by about 10% for each decade of life. This is important for drugs such as penicillin and digoxin, which are eliminated primarily by the kidney.

ADVERSE DRUG EFFECTS:

The incidence of iatrogenic complications is three to five times greater in the elderly than in the general population. Adverse drug reactions account for 20 to 40% of these complications. Inappropriate drug use has been noted in almost half of hospitalized elderly patients. Poor patient compliance due to cognitive impairment or over dosage are commonly seen in the elderly and disabled patients. Delirium and cognitive impairment are common adverse reactions in

Table 1. Barriers to Geriatric Pain Management	
Patient-Related Factors	Misconceptions: increasing disease, pain as part of aging, non-treatable, medicines should be a last resort
	Fears: addiction, treatment will mask disease progression, being labeled as a weak or bad patient, adverse effects from drugs, loss of independence
	Personality: noncompliance, not wanting to be a complainer, denial, negative attitude towards younger practitioners
	Personal: cultural and religious beliefs, language, monetary status, comfort with health care setting, ambulatory status, social support
	Comorbidities: depression, dementia, altered cognition, etc
	Accessibility: distance, transportation, insurance coverage, economics, social support, etc
Medication/ Intervention-Related Factors	Insurance coverage
	Geographic availability
	Medicine: availability, polypharmacy, complex dosage regimen, adverse effects, generic vs brand name medications, packaging
	Off-label usage of medications or interventions

PAIN IN DISABLED PATIENTS:

Physical disabilities that alter mobility affect a large number of adult population. Some adults with physical impairments who use adaptive mobility might develop chronic pain. Some disabilities result from injury, nervous system changes associated with trauma may produce painful conditions (eg, neuropathic pain with spinal cord injury [SCI], phantom limb pain with acquired limb amputation).

Pain has been frequently documented in persons with acquired amputation. Most people perhaps as many as 85% who undergo limb amputation, experience phantom limb pain. Phantom

pain persists in at least 60% of persons with amputations up to 2 years postsurgery. Persons with acquired amputation also experience residual limb pain (also known as stump pain) and low back pain (LBP).

Among those patients with cerebral palsy, most experienced pain on a daily basis.Studies have shown that severe spasticity may contribute to the pain.For adults with physical disability, functional challenges are associated with specific neuromuscular, musculoskeletal, or systemic impairments.

Pain is a common secondary complication of physical disability. Pain exacerbates limitations in the already disabled population. Only little is known about the nature and scope of pain or how it impacts everyday life of these patients. Also, how people with physical disability communicate their discomfort to family, friends, and health care providers has not been well described.

Understanding pain associated with physical disability can help guide practitioners in their pain assessments, interventions, and related research. When developing interventions, it would be useful to assess the extent to which the different pains are episodic versus persistent; expected versus unexpected; and have physical, emotional, or affective components for the individual. Deliberate probing into a client's pain by clinicians may be necessary because of the tendency by some persons with disability-related pain to hesitate to discuss the phenomenon with others.

Practitioners should make a habit of assessing pain routinely and providing enough time in interactions to discuss pain and pain-related issues. The McGill Pain Questionnaire, short-form McGill Pain Questionnaire, or Neuropathic Pain Scale may be used to assess the multiple qualitative aspects of pain. The Brief Pain Inventory (BPI) includes a pain drawing as well as measures of pain intensity and pain interference.

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