

PAIN

- (a) *To define pain.*
- (b) *To describe pain pathways and mediators involved in nociception. To describe peripheral and central sensitisation, gate-control therapy, preemptive and preventive analgesia.*
- (c) *To describe the pharmacology as pertaining to pain management of:*
 - *Opioids*
 - *Tramadol*
 - *Local anaesthetic agents*
 - *NSAIDs*
 - *Paracetamol*
 - *NMDA antagonists*
 - *Anticonvulsants*
 - *Antidepressants*
 - *Corticosteroids*
 - *Inhalational analgesics – nitrous oxide, methoxyflurane*
- (d) *To describe the different modes of administration of analgesic agents and evaluate their clinical applications.*

(I) Definitions of Pain:

“Pain” – An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage

Note – Pain can be classified according to duration:

- (i) *Acute pain* (< 3 months)
 - o Pain is of recent onset and probable limited duration
 - o It is a symptom of a current pathological process
- (ii) *Subacute pain* (3-6 months)
- (iii) *Chronic pain* (> 6 months)
 - o Pain persists after inciting pathological process has resolved
 - o There may be no clearly identifiable cause → could be due to psychological factors, continuation of pathology, spinal cord “wind-up”, development of “chronic regional pain syndrome”, neural injury, MSk deconditioning, Etc.

Note – Pain can also be classified according to its aetiology:

- (i) *Neuropathic pain* → pain of neural origin caused by a lesion or dysfunction in the somatosensory nervous system
- (ii) *Nociceptive pain* → pain due to activation of a nociceptor by a noxious stimulus

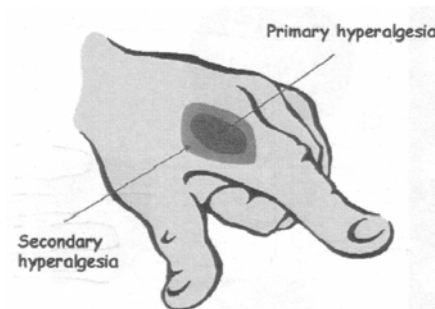
“Pain threshold” – Lowest amount of pain experience that a subject can recognise

“Nociception” – Neural process underlying the encoding and processing of noxious stimuli

“Hyperalgesia” – ↑ response to a stimulus that is normally painful (Ie. pin prick)

Note – Hyperalgesia can be either:

- (i) *Primary* – Local reductions in peripheral nociceptor threshold at site of injury (usually due to mediators of inflammation), lead to ↑ nociceptor firing
- (ii) *Secondary* – Hyperalgesia spreads away from site of injury due to convergence of 1° nociceptive neurons from adjacent dermatomal areas and reduced thresholds of 2° nociceptive neurons in the spinal cord



“Allodynia” – Pain in response to a stimulus that does not normally provoke pain (Ie. clothing)

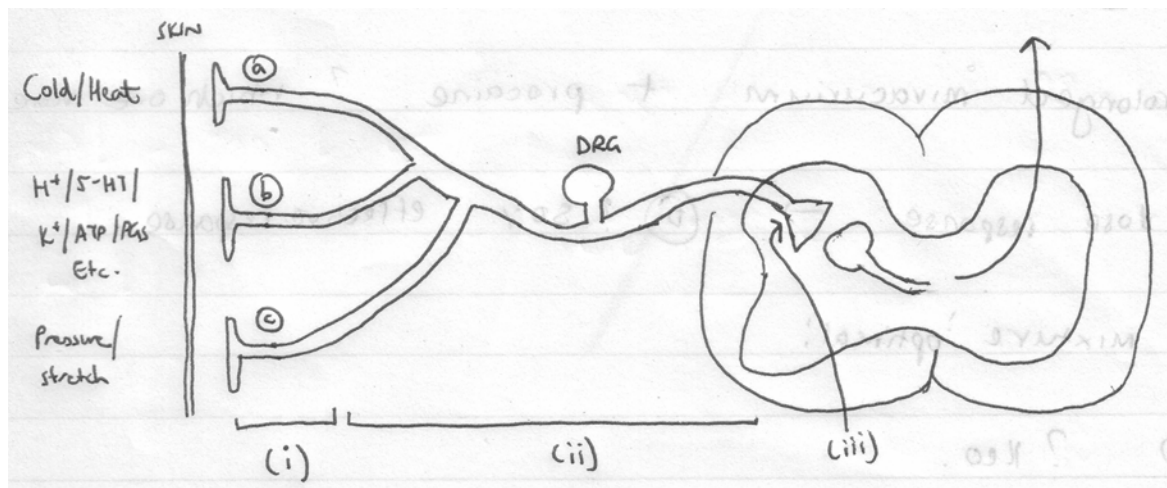
Note – Allodynia occurs when peripheral 1° non-pain afferent fibres forms a pathological synapse in the dorsal horn of spinal cord with a 2° nociceptive fibre

(II) Nociceptive pathways:

(A) Peripheral transmission:

Nociceptive (1° order) neurons consist of:

- (i) Nociceptor:
 - A sensory receptor that is capable of transducing and encoding a noxious stimulus (or a stimulus that would become noxious if it was prolonged)
 - There are three types, each responding to a group of nociceptive triggers:
 - (a) Thermoreceptor → respond to heat/cold
 - Heat > 43 °C and capsaicin → TRPV1
 - Cold < 26 °C and menthol → TRPM8
 - (b) Chemoreceptor → respond to noxious chemical stimuli
 - H^+ → TRPV1
 - 5-HT → 5-HT3R
 - Bradykinin → BK1R/BK2R
 - ATP → P2XR
 - PG's → PGE2R
 - (c) Mechanoreceptor → respond to noxious mechanical stimuli
 - Pressure → TRPA1/ENaC
 - It is covered in “ionotropic receptors” → appropriate noxious stimulus activates nociceptor → causes ion flux that depolarises peripheral termini
- (ii) Axonal projections that extend from nociceptor in tissues (Eg. skin, organs) to cell bodies in the dorsal root ganglia (of spinal cord or trigeminal nuclei)
- (iii) Central termini that form synapses with 2° neurons in dorsal horn of spinal cord → contain NTs (a.a. NTs (glutamate, aspartate) and peptide NTs (CGRP, substance P))



Types of nociceptive neurons:

- (1) Aδ fibres
 - Found in ↑ [] in skin
 - Respond to specific type of mechanical pressure → fast, sharp and localised pain
 - Fibres are medium calibre (2-5 um diameter) and myelinated → conduct AP rapidly (12-30 m/s)
- (2) C fibres (* predominant fibre type *)
 - Found in most tissue types
 - Polymodal → respond to broad range of physical and chemical stimuli → slow, dull and diffuse pain
 - Fibres are small calibre (0.5-1.2 um diameter) and unmyelinated → conduct AP slowly (0.5-2 m/s)

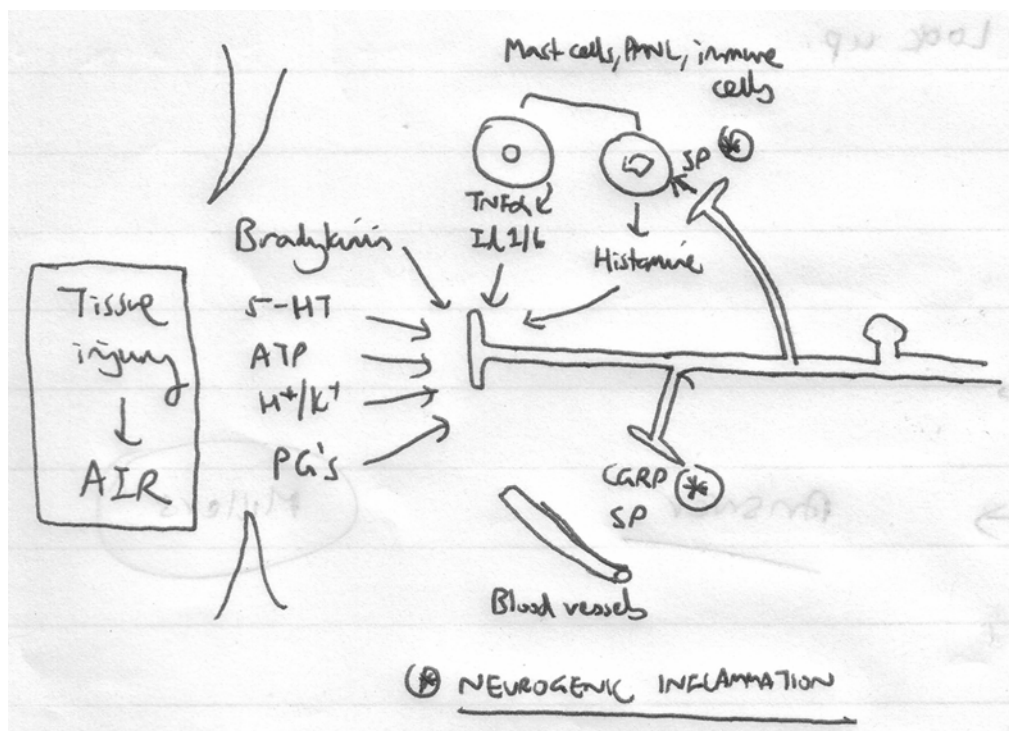
Inflammation as a trigger of peripheral nociceptors:

- Tissue injury (I.e. due to physical injury, infection, ischaemia, burns) produces an acute inflammatory response → involves cellular disruption (releases 5-HT, H^+ , PGs, ATP, bradykinin), mast cell degranulation (releases histamine), inflammatory chemotaxis (Eg. PMNLs), and production of pro-inflammatory substances (Eg. cytokines)
- This involves various pro-nociceptive substances:
 - o (1) “Allogeic substances” (Eg. K^+ , H^+ , 5-HT, ATP)
 - Directly activate ligand-gated ion channels in nociceptor termini → cause influx of ions which depolarises termini → AP initiated and conducted along nociceptive neuron
 - o (2) “Allogetic substances”
 - Inflammatory mediators (Eg. histamine, PGE2, bradykinin, substance P) → sensitise nociceptor termini via metabotropic 2nd messenger systems
 - Cytokines (Eg. TNF- α , IL-1 and -6, Etc.) → sensitise nociceptor termini by altering gene expression of channel receptors

Important to note – “Peripheral sensitisation”:

- ↑ responsiveness of peripheral nociceptors to normal or subthreshold stimulus input → caused by “allogetic substances” in areas of inflammation that sensitise the nociceptor to activation by “allogeic” substances
- Forms basis of “Primary hyperalgesia” (I.e. ↓ pain threshold at site of injury/inflammation)

- In the absence of active inflammation/tissue damage → neuropeptides (substance P and calcitonin gene-regulated peptide (CGRP)) can be released from nociceptors to act as inflammatory chemotactic agents and cause “Neurogenic inflammation”

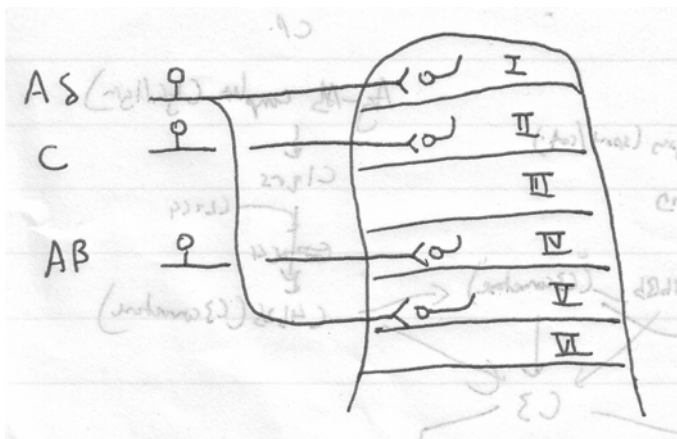


(B) Dorsal horn transmission:

Synaptic connections at the dorsal horn:

- Nociceptive (1^o order) neurons synapse on 2^o order neurons onto specific laminae of dorsal horn of the spinal cord (see picture below)

- These synapses are modulated by various descending pathways that act as either → (i) “Facilitatory pathways” that promote pain transmission, or (ii) “Inhibitory” pathways that inhibit pain transmission (Eg. diffuse noxious inhibitory control (DNIC))

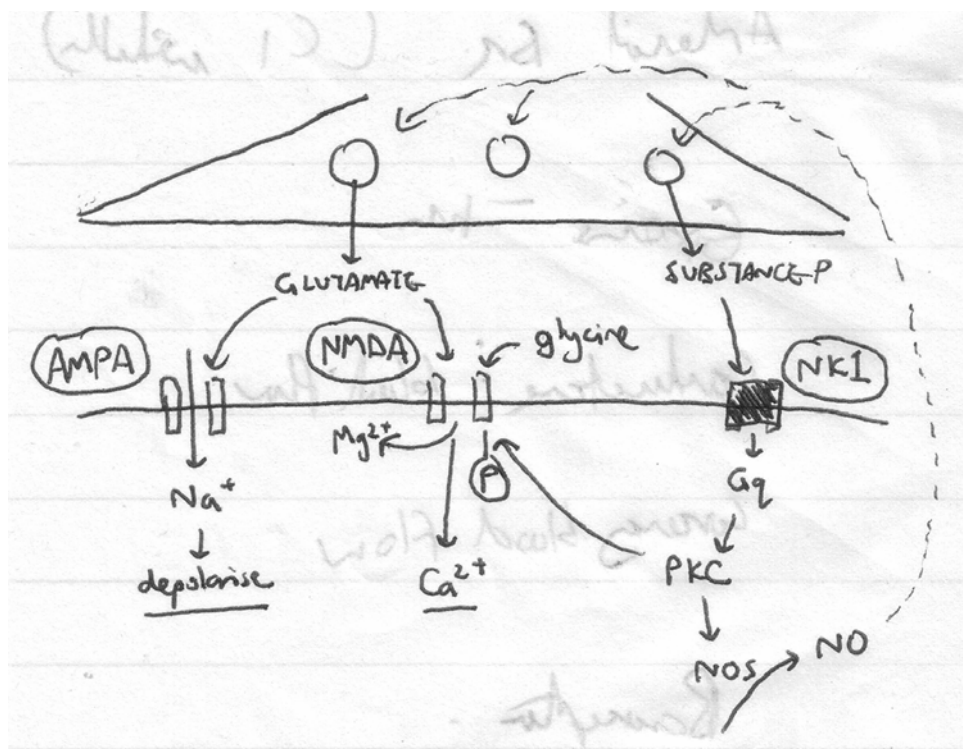


Note:

- $A\delta \rightarrow$ lamina I and V
- C $\rightarrow$ lamina II
- $A\beta \rightarrow$ lamina IV

Pain transmission at dorsal horn:

- Depolarisation of the nerve terminal of the nociceptive (1° order) neuron → causes Ca^{2+} influx → results in exocytosis of NTs – (i) amino acid NTs (glutamate, aspartate) and (ii) peptide NTs (substance P and CGRP) – into the synaptic cleft
- These NTs then act on post-synaptic membrane of 2° order neuron in the spinal cord:
 - Glutamate → activates AMPA and NMDA receptors
 - Substance P → activates NK1 receptors



Normal pain transmission:

- Glutamate activates AMPA receptor (ionotropic mechanism) → causes opening of fast Na^+ channels → results in Na^+ influx and depolarisation of 2° order neuron
- This causes perception of brief localised pain when the signal reaches the brain sensory cortex

“Wind-up” phenomenon:

- Overview – This process ↑ the propensity of 2° order neuron (esp WDR neurons) to reach threshold by augmenting the activation of NMDA receptor → implicated in basis of “allodynia” and “secondary hyperalgesia” (see below)

Aside – NMDA receptor:

- Ligand- and voltage-gated cationic channel
- At “resting state” → channel is closed and held inactive by Mg^{2+} plug
- Activation requires:
 - o (i) Glutamate binding (as endogenous ligand)
 - o (ii) Glycine binding (as co-agonist)
 - o (iii) Release of Mg^{2+} plug
 - o (iv) Membrane depolarisation
- Receptor activation → causes Ca^{2+}/Na^{+} influx and K^{+} efflux across cationic channel → depolarises 2° order neuron

- Process:

- o (1) Repeated stimulation of 2° order neuron by continued release of NTs from 1° order neuron nerve terminal → primes NMDA receptor for activation by removing its Mg^{2+} plug

Substance P stimulates NK1 receptor via “metabotropic” mechanism → activates PKC via Gq mechanism:

- (i) Stimulates NO synthetase → produces NO, which causes ↑ glutamate/substance P release from nerve terminal (+ve feedback)
- (ii) Phosphorylates NMDA receptor → causes release of Mg^{2+} plug

- o (2) Primed NMDA receptor now requires less stimulation to activate the 2° order neuron → activation of NMDA receptor causes prolonged cation flux and 2° neuron depolarisation

NMDA receptor is activated by:

- (i) Glutamate activation of AMPA receptor (via ionotropic mechanism) → opens fast-acting Na^{+} channel to cause Na^{+} influx → depolarises 2° order neuronal membrane
- (ii) Glutamate binding to “primed” NMDA receptor → now lacks Mg^{2+} plug
- (iii) Co-agonist binding by glycine

- o (3) Activation of 2° neuron causes:
 - (i) Transmission of nociception
 - (ii) Altered gene expression (esp cFOS)
 - (iii) ↑ expression of NMDA receptors
 - (iv) Stimulation of WDR neurons → cause “secondary hyperalgesia” (as WDR neurons receive convergent inputs from various nociceptive fibres), and “allodynia” (as WDR neurons sprout onto $A\beta$ fibres)

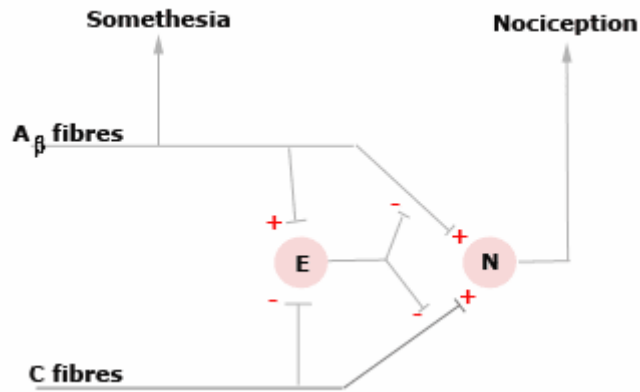
Important to note → these changes are IRREVERSIBLE!

Important to note – “Central sensitisation”:

- ↑ responsiveness of nociceptive neurons in CNS to their normal or subthreshold afferent input → caused by “wind-up phenomenon” that occurs in WDR neurons found in dorsal horn of spinal cord
- Forms basis of “secondary hyperalgesia” and “allodynia”

Wide-dynamic range (WDR) neurons:

- Collection of 2° neurons in dorsal horn of spinal cord that receive synaptic inputs from all peripheral nociceptive fibres (I.e. transmits wide range of nociceptive stimuli ((heat, cold, mechanical, chemical)), but also form synapses with non-nociceptive fibres ($A\beta$)
- They are implicated in:
 - o (1) Gate control theory of pain
 - $\uparrow$ non-nociceptive input (via $A\beta$ fibres) can $\downarrow$ nociceptive transmission by inhibiting ascending pain pathway via an inhibitory interneuron



- o (2) Allodynia
 - Neuroplastic alterations (initiated by “wind-up” phenomenon) cause WDR neurons to sprout and form synapses with non-pain fibres ($A\beta$) in the dorsal horn
 - This causes non-painful stimuli transmitted via $A\beta$ to activate WDR neurons $\rightarrow$ results in non-painful stimulus to be misinterpreted as nociceptive input
- o (3) Secondary hyperalgesia
 - Pathological conditions that induce “wind up” phenomenon enhance the activation of WDR neurons (Nb. WDR neurons are NOT readily stimulated under by “normal” dorsal horn pain transmission)
 - WDR neurons receive convergent input from several peripheral nociceptive fibres $\rightarrow$ causes pain to be perceived in areas away from injury site

(C) Ascending tract transmission:

2° order neurons ascend spinal cord and transmit pain signals via several tracts:

- (1) Spino-thalamic tract (* main *) $\rightarrow$ transmits discriminative sensation
- (2) Dorsal column $\rightarrow$ transmits visceral sensation
- (3) Spinoreticular tract $\rightarrow$ transmits behavioural and emotional reflexes

All 2° order neurons synapse at the thalamus, then proceed via 3° order neurons to various sub-cortical and cortical structures:

- (1) Somatosensory cortex $\rightarrow$ contains sensory homunculus for pain discrimination
 - o (2) Pre-frontal cortex, amygdala and nucleus accumbens $\rightarrow$ emotive/behavioural response to pain
 - o (3) Cingulate gyrus and hippocampus $\rightarrow$ pain memory formation
 - o (4) Nucleus raphe magnus and rostro-ventral medulla $\rightarrow$ descending pathways that modulate pain (I.e. initiation of DNIC)

(III) Neuropathic Pain:

Definition → pain of neural origin caused by a lesion or dysfunction in the somatosensory nervous system

Characteristics:

- (i) History of injury or disease process that could cause nerve injury
- (ii) Brief and spontaneous pain of burning, shooting, stabbing or freezing quality, and associated with dysesthesia (I.e. abnormal sensation)
- (iii) Pain occurs in area of reduced or absent sensation
- (iv) Poorly responsive to conventional analgesics (Eg. NSAIDs, opioids) → generally treated with antidepressants and anticonvulsants

Types:

- (1) Peripheral neuropathic pain → initiated by pathology in PNS (Eg. painful DM neuropathy, post-herpetic neuralgia, severed nerve)

Note – Mechanisms of peripheral neuropathic pain:

- (i) Neuroma formation → occurs at site of nerve injury
 - o Damaged nerve forms a neuroma that has ↓ firing threshold for depolarisation → discharges readily and causes spontaneous pain
 - o Neuroma can sprout into surrounding tissues (Eg. muscle) → movement of tissue discharges neuroma and causes pain
- (ii) Sympathetic efferent “basketting” → occurs at DRG cell bodies
 - o SNS efferents from sympathetic chain grow back along spinal nerve root to DRG and forms a “basket” around it → ↓ firing threshold of A δ and C fibres synapsing in dorsal horn → discharges readily and cause spontaneous pain
- (iii) Spinal cord sprouting → occurs at dorsal horn
 - o Sprouting of A β fibres (non-pain 1° neuron) onto a 2° nociceptive neuron in ascending pain pathways → causes “allodynia”

Aside – There is upregulation of certain ion channels (Eg. NaV1.7, NaV1.8) in nerve tissue that are responsible for ↓ firing threshold and spontaneous depolarisation a/w peripheral neuropathic pain → Nb. these are RESISTANT to blockade by LAs!

- (2) Central neuropathic pain → initiated by pathology in CNS (Eg. post-stroke pain syndrome, spinal cord injury pain)

Note – Mechanism of central neuropathic pain:

- (i) Neuroplastic changes within somatosensory cortex → causes structural changes of normal homunculus
- (ii) Disruption of descending modulation pathways → caused by brain or spinal cord pathology (most commonly CVA of thalamus)

- (3) Mixed peripheral and central neuropathic pain → initiated by pathology in both CNS and PNS (Eg. complex regional pain syndrome, phantom limb pain)

Note – Mechanism of “phantom limb pain”:

- Central basis – Neurons in somatosensory cortex experience deafferentation from amputated area → as a result, they grow and synapse with afferent neurons outside their normal input field
- Peripheral basis – Peripheral nerve injury with spinal cord wind-up

(IV) **Measurement of Pain:**

Objective measurement of pain is DIFFICULT b/c pain is a complex subjective experience → it varies with emotional and psychological state, past experiences, behaviour, Etc.)

Self-reporting of pain using various “pain measurement scales” is the “gold standard” method

Common pain measurement scales include:

- (1) Numerical rating scale (NRS) – Pain is ranked from 0 to 10 (10 as “worst pain possible” and 0 as “no pain”)
- (2) Visual analogue scale (VAS) – Pain is marked along a 10 cm line (with one end as “no pain” and other as “worst pain possible”)
- (3) Faces pain scale (FPS) – Similar to NRS except pain is ranked from a series of faces → useful in children

Limitations of these pain measurement scales:

- (i) One-dimensional assessment → attaches numerical score to pain only; gives no information about its impact to patient (I.e. emotional, behavioural, psychological, Etc.)
- (ii) NRS and FPS provide “ordinal data”, which limits to non-parametric statistical analysis (Nb. Only VAS provides “continuous data” which allows parametric analysis)
- (iii) Condition of pain must be identified (I.e. rest vs movement)
- (iv) Pain value can vary despite same apparent conditions (I.e. resting in bed vs chair)
- (v) Poor inter-individual validity (I.e. cannot compare scores from one person to another)
- (vi) Accurate use depends on appropriate communication/rapport with patient, and intelligence level of patient
- (vii) Stable pain score may offer false security if not related to analgesic delivery (Eg. epidural pain score of 0 can hide an infarcting limb)
- (viii) Scores can be falsified for secondary gain (I.e. to ↑ opioid prescribing)

Multi-dimensional pain measurement scales (Eg. Brief pain index, McGill Pain questionnaire) exist → they are more useful (cf. NRS or VAS) b/c they include pain severity with emotional and functional impact of pain → as a result, they allow for more accurate assessment of benefit of various pain treatment modalities (I.e. pharmaceutical, psychological, physical)

(V) Pharmacotherapy for Pain:

Important definitions:

- “Preemptive analgesia” → Anti-nociceptive intervention commenced before a surgical procedure that proves more effective than the same intervention started afterwards
- “Preventive analgesia” → Analgesic or antihyperalgesic effects of a drug in the post-operative period that exceeds the expected duration of action

Opioids (Eg. morphine, fentanyl, methadone, Etc.)

Mechanism of drug action	Acts on opioid receptor (μ , κ , δ) → GPCR (Gi)
Site of action	- (i) Periaqueductal grey and nucleus raphe magnus → activates descending inhibition pathway - (ii) Dorsal horn of spinal cord → acts pre- and post-synaptically to inhibiting ascending pain pathway
Mechanism of ↓ pain	- (i) Activates Cl ⁻ channels → hyperpolarises nociceptive neurons - (ii) Alters transcription of proteins (I.e. upregulates Cl ⁻ channels) in nociceptive neurons
Side-effects	Sedation, respiratory depression, pruritis, urinary retention, constipation, pupillary miosis, tolerance/dependence/addiction

Tramadol:

Mechanism of drug action	Racemic, with each isomer acting differently but synergistically - (+) inactive but metabolised to M1 → weak μ agonist - (-) has 5-HT reuptake inhibitory activity
Site of action	- (i) Periaqueductal grey and nucleus raphe magnus → activates descending inhibition pathway - (ii) Dorsal horn of spinal cord → acts pre- and post-synaptically to inhibiting ascending pain pathway
Mechanism of ↓ pain	- (i) Activates Cl ⁻ channels → hyperpolarises nociceptive neurons - (ii) Alters transcription of proteins (I.e. upregulates Cl ⁻ channels) in nociceptive neurons - (iii) Stimulates DNIC (I.e. inhibitory descending pathways)
Side-effects	5-HT syndrome if used with SSRI, N/V, sedation

NSAIDs (Eg. celecoxib, diclofenac, indomethacin, Etc.)

Mechanism of drug action	- COX enzyme → 2 isoforms: - COX-1 (“constitutive”) – Widespread (esp GIT, kidney, platelets) → maintain homeostasis (Eg. renal perfusion, gastric mucosal protection, platelet aggregation, Etc.) - COX-2 (“inducible”) – Upregulated in injured tissue → involved in pain, inflammation, pyrexia - NSAIDs inhibit either COX-1/-2 non-selectively, or COX-2 selectively → ↓ metabolism of arachidonic acid into PGs/TXA ₂
Site of action	- COX enzyme is widespread → both centrally and peripherally
Mechanism of ↓ pain	- (i) Peripheral effects (main) → ↓ synthesis of PG at site of tissue damage/inflammation → ↓ peripheral sensitisation of nociceptor (↓ 1° hyperalgesia) - (ii) Central effects → ↓ synthesis of PG in dorsal horn of spinal cord → ↓ central sensitisation (↓ 2° hyperalgesia)
Side-effects	GI toxicity (GI bleeding, PUD, gastritis), bleeding, NSAID-induced asthma, renal dysfunction, hepatic dysfunction

Paracetamol:

Mechanism of drug action	- Mainly a central COX-1 (aka. COX-3) inhibitor - Also has agonists effects on 5-HT ₃ R and Cannabinoid receptor; inhibits nitric oxide
Site of action	1°ly central effects
Mechanism of ↓ pain	- (i) ↓ central sensitisation in spinal cord - (ii) Stimulates DNIC (Ie. inhibitory descending pathways)
Side-effects	Hepatotoxicity with overdose, analgesic-nephropathy

Local anaesthetic agents (Eg. lignocaine, bupivacaine, ropivacaine, Etc.)

Mechanism of drug action	Inhibit VG-Na ⁺ channel by maintaining them in a “closed-inactivated state” → prevents depolarisation and AP propagation
Site of action	VG-Na ⁺ channels in central and peripheral nerves
Mechanism of ↓ pain	- (i) Stops neural transmission of pain peripherally or centrally (depending on effect-site []) - (ii) Membrane stabilising effect → inhibit spontaneous discharge of nociceptive neurons implicated in neuropathic pain
Side-effects	CNS toxicity (tinnitus, paraesthesia, convulsions, coma), CVS toxicity (hypotension, arrhythmias, cardiac arrest)

NMDA antagonists (Eg. ketamine):

Mechanism of drug action	Non-competitive antagonist of NMDA receptor (at phencyclidine binding site) → stabilises channel in inactive state
Site of action	- (i) Post-synaptic membrane of 2° neuron of dorsal horn in spinal cord - (ii) Diffusely throughout CNS (esp cortical and associative ctrs)
Mechanism of ↓ pain	Inhibits “wind-up” and “long-term potentiation” → ↓ central sensitisation → ↓ 2° hyperalgesia
Side-effects	Sedation, ↑ secretions, dysphoria/hallucinations, addictive

Anticonvulsants (Eg. valproate, carbamazepine, GABA-pentinoids (gabapentin, pregabalin))

Mechanism of drug action	- Valproate → Na ⁺ channel blockade - Carbamazepine → GABA-ergic effects - GABA-pentinoids → Inhibit N-type Ca ²⁺ channels
Site of action	Central and peripheral
Mechanism of ↓ pain	- (i) Membrane stabilising effects → ↓ spontaneous discharge of nociceptive neurons implicated in neuropathic pain - (ii) Stimulates DNIC (Ie. inhibitory descending pathways) - (iii) ↓ Ca ²⁺ entry into nerve terminal of 1° nociceptive neuron → ↓ release of glutamate/substance P onto 2° nociceptive neuron → inhibits ascending pain transmission
Side-effects	N/V, sedation, dizziness/ataxia, diplopia, rash, liver/renal dysfunction, weight gain, behavioural changes

Antidepressants (Eg. TCA (amitriptyline), SSRI (venlafaxine)):

Mechanism of drug action	Inhibit reuptake of 5-HT and NAd
Site of action	Central
Mechanism of ↓ pain	- (i) Anticholinergic effects (TCAs) → sedation - (ii) Stimulates DNIC (Ie. inhibitory descending pathways)
Side-effects	Sedation, dry mouth, blurred vision, constipation, cardiac arrhythmias, 5-HT syndrome

Corticosteroids:

Mechanism of drug action	↓ expression of phospholipase A ₂ → ↓ conversion of membrane phospholipid into arachidonic acid → ↓ PG, LT and TX
Site of action	Central and peripheral

Mechanism of ↓ pain	- (i) Peripheral effects (main) → ↓ synthesis of PG at site of tissue damage/inflammation → ↓ peripheral sensitisation of nociceptor (↓ 1° hyperalgesia) - (ii) Central effects → ↓ synthesis of PG in dorsal horn of spinal cord → ↓ central sensitisation (↓ 2° hyperalgesia)
Side-effects	↑ BGL, central adiposity, muscle wasting, osteopaenia, fluid retention, euphoria/depression

Inhalational analgesics (Eg. nitrous oxide, methoxyflurane):

Mechanism of drug action	Unknown
Site of action	Central
Mechanism of ↓ pain	Activates neurons in periaqueductal grey matter, which stimulates NAd neurons in locus ceruleus → these neurons descend into dorsal horn of spinal cord and inhibit ascending pain signals
Side-effects	N ₂ O: N/V, vitamin B12 suppression, pulmonary HT, expands air-filled cavities Methoxyflurane: Renal toxicity