PAIN MEDICINE

Outline the basic concepts of multimodal analgesia and pre-emptive analgesia

Multimodal analgesia = concurrent use of different classes of analgesics → improves effectiveness of acte pain management

Main targets of modulating pain transmission
- peripheral receptors: LA, NSAIDs
- ascending pathways: opiates, NSAIDs, NMDA receptor angagonists, gabapentinoids
- descending pathways: tramadol, clonidine, 5HT antagonists
- central perception: opioids, paracetamol

Pre-emtpive analgesia
- transmission of pain signals evoked by tissue damage → sensitisation of complex peripheral + central pain pathways
- pre-emptive analgesia aims to ↓sensitisation
- administration of analgesic prior to acute nociceptive stimulus more effective than same analgesic given after pain state established
- theory: preventing cascade of sensitisation will limit subsequent doses of analgesia

Preventive analgesia
- persistence of analgesic treatment efficacy beyond its expected duration
- analgesia that persists >5.5 1.2 lives of a medicine – to ensure complete washout of any direct pharmacological effect
- effect of the intervention is suggicient to modify sensitisation + longer term outcomes

Outline the basic pharmacology and clinical use of available analgesic agents

See below

NEUROBIOLOGY

Describe the anatomy of the sensory pathways with particular reference to pain sensation

Pain = unpleasant sensory + emotional experience associated with actual or potential tissue damage

Ascending tracts
- 2 main ascending pathways = spinothalamic tract + spinoreticular tract
- Spinothalamic tract
  - 1st order neuron (C or Adelta fibre) → relays AP from nociceptor to substantia gelatinosa or nucleus proprius in dorsal horn of SC
  - 2nd order interneuron decussates in anterior commissure → ascends SC in spinothalamic tract
  - 3rd order neuron in thalamus relays nociceptive APs to somatosensory cortex
- Spinoreticular tract
  - emotional responses to pain
  - Decussate + ascending CL spinal cord → reticular formation of BS → project to thalamus + hypothalamus → cortex

Nociceptive transmission
- Dull pain: slow, unmyelinated C fibres → synapse at laminae I and II of dorsal horn (substantia gelatinosa)
- Sharp pain: myelinated Adelta fibres → synapse at liminae I and V of dorsal horn
- 2nd order neurons project to BS and thalamus via spinothalamic and Spinoreticular tracts

Modulation/ descending influences
- Transmission of nociceptive info is modulated at several levels → ↑ or ↓ pain
- Occurs:
  - 1. Peripherally
    - Local inhibitory interneurons
  - 2. Supraspinal structures
    - Descending pathways from the brain
    - hypothalamus, PAG, locus coeruleus, nucleus raphe magnus, nucleus paragigantocellularis lateralis
  - 3. Spinal cord:
    - Substances released from descending fibres in dorsal horn
    - serotonin, substance P, cholecystokinin, GABA, somatostatin, encephalin, norAdr

Describe the anatomy of the autonomic nervous system

- regulates visceral functions + involuntary control → haemodynamics (CO, SVR), respiration, GI, urination + defecation, thermoregulation, sexual function
- Subdivided into central ANS + peripheral ANS

Central ANS
- Located in: hypothalamus, brainstem, spinal cord
- Neural + endocrine mechanisms
- Subdivided into 4 regions:
  - 1. Anterior hypothalamus:
    - supraoptic + paraventricular nuclei → hypothalamo-hypophysial tract to posterior pituitary
    - Controls PSY, release of ADH + oxytocin
  - 2. Medial hypothalamus:
    - Ventromedial + dorsomedial nuclei
    - Controls energy balance + sexual behaviour
  - 3. Lateral hypothalamus:
    - Tuberal nuclei + medial forebrain bundle (carries efferent pathways from hypothalamus to BS)
    - Controls: emotions + thirst centre + drive to seek food
  - 4. Posterior hypothalamus:
    - Principal site of SY outflow
    - Controls vasomotor centres of brain, +ve and –ve inotropy and chronotropy
- tonic output to: smooth muscle, heart, exocrine organs, endocrine organs, GIT, GU

	SY	PSY
Location of preganglionic neuron cell bodies	Lateral horn of spinal segments T1-L3	Brainstem, lateral grey areas of spinal segments S2-4
Length of preganglionic neuron	Short	Long
Location of postganglionic cell bodies	SY chain + prevertebral ganglion	Ganglia close to target organ
Preganglionic NT and post-ganglionic receptor	ACh Nicotinic receptor	ACh Nicotinic receptor
Length of post-ganglionic neuron	Long	Short
Post-ganglionic NT	**Norad**	**ACh**
Target organ receptor	**Adrenergic receptor**	**Muscurinic receptor**

3. Enteric plexus

- autonomic nerves in GIT free of CNS control
- sensory + integrative neurons + excitatory + inhibitory motor neurons
- excitatory interneurons + motor neurons release ACh as NT
- other interneurons release serotonin, vasoactive intestinal peptide, NO

Effector Organ	Parasympathetic Innervation	Response
CNS	CN III via the Edinger-Westphal nucleus, CN VII	Pupillary constriction (CN III), lacrimation (CN VII)
Lungs	CN X	Bronchoconstriction, increased mucous production
Heart	CN X	↓ HR, ↓ inotropy, ↓ conduction velocity
GIT	CN VII (submaxillary and mandibular salivary glands), CNIX (parotid gland), CNX (stomach to proximal two-thirds of the transverse colon), hypogastric plexus (distal one-third of the transverse colon to rectum)	Salivation, decreased sphincter tone, increased motility
GU	Hypogastric plexus	Detrusor contraction, erection

Effector Organ	Sympathetic Innervation	Response
Eye	Cervical	Pupillary dilatation
Lungs	Thoracic	Bronchodilation
Heart	Thoracic	↑ HR, ↑ inotropy, ↑ conduction velocity
Vasculature	Sacral	Constriction
MSK	Sacral	Sweating, contraction, lipolysis
Endocrine	Lower thoracic	Adrenaline and noradrenaline release
GIT	Thoracic, lumbar	Decreased salivation and GIT motility, increased sphincter tone, gluconeogenesis
GU	Pelvic	Detrusor relaxation, sphincter contraction, ↑ uterine tone

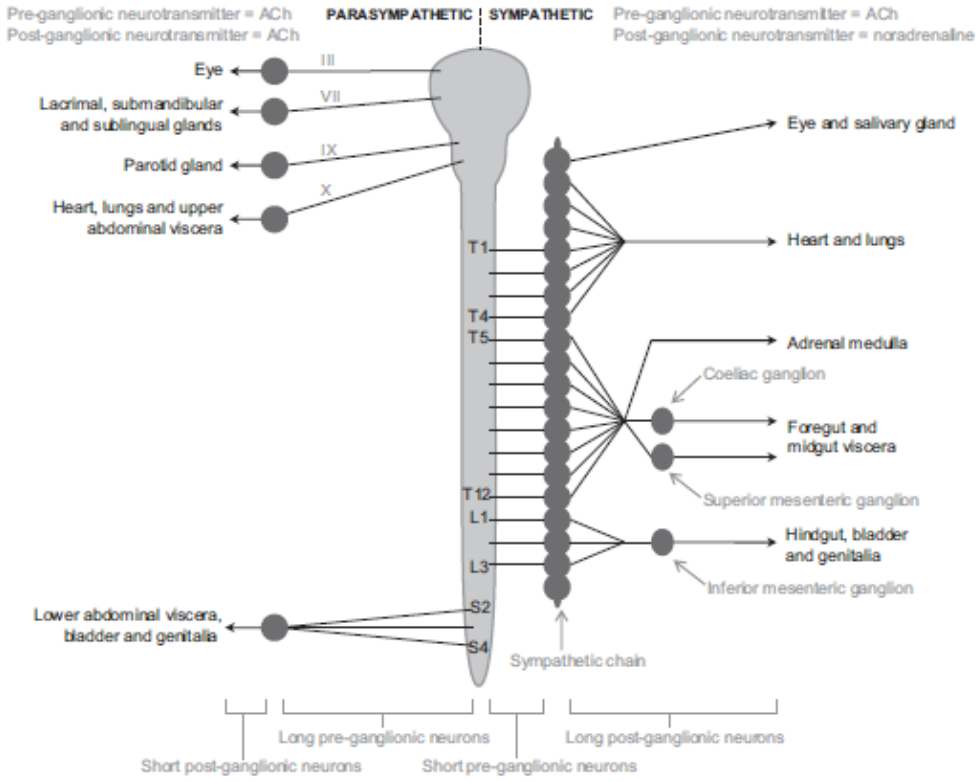


Figure 56.1 Layout of the ANS.

Describe the basic physiological mechanisms of pain including:

Peripheral nociception

- Pain = vital function of nervous system in providing body with warning of potential or actual injury
- Sensory + emotional experience

Nociceptors

- specialised sensory Rs responsible for detection of noxious stimuli → transforming stimuli into electrical signals → conducted to CNS
- free nerve endings of primary afferent Adelta and C fibres
- distributed throughout the body
- Stimulated by: mechanical, thermal, chemical stimuli
- Mediators:
  - Stimulating mediators: H, K, ACh, histamine, 5-HT, bradykinin
  - Sensitising mediators: prostaglandins, leukotrienes, substance P, neurokinin A, calcitonin GRP

Primary afferent fibres

- Pain impulses conducted by 2 types of primary afferent fibres:
- Aβ fibres:
  - highly myelinated; large diameter; rapid signal conduction
  - low activation threshold
  - respond to light touch + transmit non-noxious stimuli
- Adelta fibres
  - Lightly myelinated; smaller diameter; conduct more slowly
  - Respond to: mechanical + thermal stimuli
  - Carry rapid, sharp pain; responsible for initial reflex response
- C fibres
  - Unmyelinated; smallest type of primary afferent fibre
  - Slowest conduction
  - Respond to chemical, mechanical, thermal stimuli
  - Slow, burning pain

	Aβ fibres	Aδ fibres	C fibres
Diameter	Large	Small 2-5μm	Smallest <2μm
Myelination	Highly	Thinly	Unmyelinated
Conduction velocity	> 40 ms-1	5-15ms-1	< 2ms-1
Receptor activation thresholds	Low	High and low	High
Sensation on stimulation	Light touch, non-noxious	Rapid, sharp, localised pain	Slow, diffuse, dull pain

Nociception

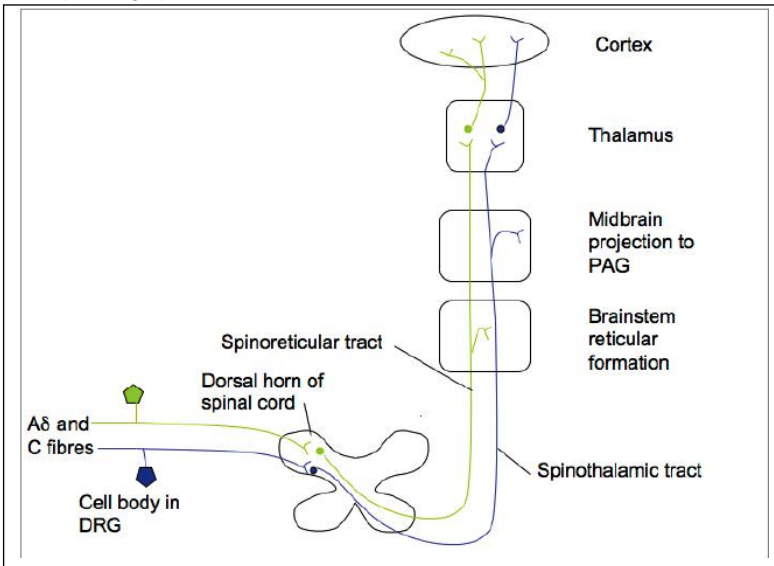
- Process by which noxious signals are encoded as APs and transmitted from peripheries to CNS
- Activation of nociceptors → Na+ channels open → membrane depolarisation
- Voltage dependent Ca2+ channels (VDCC) open → ↑intracellular Ca2+ → substance P, CGRP, neurokinin A released →
  - Inflammation: macrophages, neutrophils, mast cells
  - ↑excitability sensory + SY fibres
  - Vasodilation, extravasation of plasma proteins
  - Inflammatory cells release: histamine, bradykinin, serotonin, NO
  - Voltage gated K+ channels stabilise membrane potential

Conduction

- Adelta and C fibres synapse with secondary afferent neurons in the dorsal horn of the SC
- Adelta + C fibres transmit info to nociceptive specific neurones in Rexed lamina I and II
- Interactions occur in dorsal horn between: afferent neurones, interneurons, descending modulatory pathways → determine activity of secondary afferent neurons
- Neurotransmitters involved:
  - Excitatory: glutamate; substance P
  - Inhibitory: glycine; GABA

Ascending tracts in the spinal cord

- 2 main pathways that carry nociceptive signals to higher centres in brain
- **Spinothalamic tract**
  - 1st order neuron (C or Adelta fibre) → relays AP from nociceptor to substantia gelatinosa or nucleus proprius in dorsal horn of SC
  - 2nd order interneuron decussates in anterior commissure → ascends SC in spinothalamic tract
  - 3rd order neuron in thalamus relays nociceptive APs to somatosensory cortex
- **Spinoreticular tract**
  - emotional responses to pain
  - Decussate + ascend CL spinal cord → reticular formation of BS → project to thalamus + hypothalamus → cortex



NB Face via trigeminal pathway

- 1st order neuron → trigeminal nerve (some from VII, IX, X) → trigeminal n. → synapse on 2nd order neurons (substance P = NT)
- Trigem n. extends from medulla to midbrain
  - Spinal trigeminal n: receives pain + temp
  - Main trigeminal n: touch + proprioception from face and mouth
  - Mesencephalic: proprioception from jaw
- 2nd order neurons decussate + ascend through BS to thalamus → synapse with 3rd order neurons → relay to somatosensory cortex

Modulation of pain

Inhibition of pain transmission

Gate control theory

- proposed by Melzack and Wall in 1965 to describe a process of inhibitory pain modulation at the spinal cord level
- helps to explain why rubbing an injury can help relieve pain → activating Aβ fibres with tactile, non-noxious stimuli → inhibitory interneurons in dorsal horn are activated → inhibition of pain signals transmitted via C fibres

Descending inhibition

- Transmission of nociceptive info is modulated at several levels → ↑ or ↓ pain
- Peripherally
  - Local inhibitory interneurons
- Supraspinal structures
  - Descending pathways from the brain
  - PAG in midbrain + rostral ventromedial medulla are 2 important areas involved in descending inhibitory modulation → both contain ↑[opioid Rs] + endogenous opioid
  - Other: hypothalamus, PAG, locus coeruleus, nucleus raphe magnus, nucleus paragigantocellularis lateralis
- Spinal cord:
  - Substances released from descending fibres in dorsal horn
  - NAd, serotonin, substance P, cholecystokinin, GABA, somatostatin, encephalin,

Modulation by drugs

- Transduction
  - **NSAIDS**: inhibit COX1 + COX2 → ↓prostaglandins → ↓sensitisation of nociceptors
- Transmission
  - **LAs**: inhibit fast Na+ channels → block Adelta and C fibres
  - **Paracetamol**: inhibit central COX3 + act on serotonin + cannabinoid pathways → ↓CNS transmission of pain
  - **Opioids**: activate mu Rs → GiGPCR → hyperpolarise membrane → ↓transmission of pain signals in SC + ↑descending pain pathways
  - **Ketamine**: NMDA antagonist + weak mu opioid agonism → ↓central sensitisation
  - **N2O**: NMDA antagonist
  - **Mg2+**: NMDA antagonist
  - **Tricyclic** antidepressants (e.g. amitriptyline): ↑NA + 5HT in SC + BS → inhibit pain signal transmission
  - **Gabapentinoid** (e.g. gabapentin, pregabalin): CCB → stabilise membrane
  - **a2 adrenergic agonists** (e.g. clonidine, dexmed) → pre + postsynaptic inhibitory effects at dorsal horn + BS → inhibit pain transmission
  - **tramadol** → (s)-tramadol = SSRI + mu agonist; (R)-tramadol is SNRI
  - **cannabinoids** → CB1 receptor agonist → modulate central patin pathways

Central processing of pain

Pain processing in the brain

- experience of pain affected by: cognition e.g. distraction or catastrophising; mood, beliefs; genetics
- Areas activated during acute pain experience = pain matrix. Includes
  - 1o and 2o somatosensory cortex
  - insular
  - anterior cingulate cortex
  - prefontal cortex
  - thalamus

Mediators, pathways, reflexes

See above

Peripheral + central sensitisation

Peripheral sensitisation

- Mediators released in response to tissue damage → ↓threshold for nociceptor activation
- Mechanism
  - Tissue injury → release of inflammatory mediators (histamine, bradykinin, leukotrienes, PLA2) + degranulation of mast cells → induction of enzymes e.g. COX-2 → ↑arachidonic acid → synthesis of PGs → direct ↓activation threshold for A-delta + c fibres nociceptors → ↑basal (unstimulated) rate of discharge + supranormal ↑discharge strength in response to any stimulus (i.e. hyperalgesia extending beyond boundary of surgical incision)
  - Other factors ↑ pain transmission: substance P, CGRP
- Result: ↑sensitivity to noxious + non-noxious pain

Central sensitisation

- "secondary hyperalgesia"
- changes occur within SC + brain that ↑nociceptive transmission + perception
- innocuous stimuli felt as painful e.g. allodynia = central sensitisation
- implicated in development of chronic pain states
- mechanism
  - glutamate binds to **NMDA R** → influx of Ca2+ + K → depolarisation + ↑sensitivity to NTs
  - Alteration in 2nd order neurons: phorphorylation of NMDA + AMPA Rs

Preemptive + preventative analgesia

Pre-emptive analgesia

- preop treatment is ↑effective than the identical treatment administered after incision or during surgery
- key clarification point is the timing of administration pre insult
- treatment given pre-emptively can also be preventive if satisfies the below definition

Preventative analgesia

- the persistence of analgesic treatment efficacy beyond its expected duration
- Defined as analgesia that persists for >5.5 half lives of a medicine to ensure complete washout of any direct pharmacological effect
- Postop pain and/or analgesic consumption is ↓relative to another treatment, a placebo treatment or no treatment with the effect obsevsed at a point in time beyond the expected duration of action fo the intervention. The intervention may or may not be initiated before surgery
- I.e. the effect of the intervention is sufficient to modify sensitisation and hence longer term outcomes

Describe the physiological mechanism of progression from acute to chronic pain

- central + peripheral sensitisation = most likely underlying factors
- individual "primed" (e.g. pre-existing pain) or susceptible → intense surgical stimulus induces central + peripheral changes
- maintenance of intense nociceptive inputs by poorly controlled post op pain, peripheral nerve damage, and complications → chronic pain state
- leads to neuroplastic processes → peripheral + central sensitisation
  - include inflammation + ectopic discharges after nerve injury → afferent input that produces changes in peripheral nerves, spinal cord, higher central pain pathays, somatosensory cortex + SYNS
- NB: psychological factors are important in development of CPSP

Describe the injury response to acute pain

Pain transmission / response to painful stimulus

Involves:

1. **Transduction**
   - Noxious stimuli sensed by nociceptors (chemical/ mechanical/ thermal stimuli) → transduction of stimuli to neural impulse
2. **Transmission**
   - Dull pain: slow, unmyelinated C fibres → synapse at laminae I and II of dorsal horn (substantia gelatinosa)
   - Sharp pain: myelinated Adelta fibres → synapse at liminae I and V of dorsal horn
   - 2nd order neurons project to BS and thalamus via spinothalamic and Spinoreticular tracts
3. **Perception**
   - 3rd order neurons from thalamus project to higher centres e.g. somatosensory cortex + limbic system → sensory + emotional perception of pain
4. **Modulation**
   - Modulation = inhibit or sensitise
   - Descending pathway modulation e.g. gate control theory of pain
   - Ascending pathway modulation e.g. central sensitisation

The injury response – APMSE

Triggers + predisposing factors	Mediators	Injury response
Surgical trauma or injury Preoperative pain Psychological factors Social + environmental factors Genetic factors Anaesthesia/ analgesia/ other medications	Neural Immune factors Proteins + other molecules - growth factors - eicosanoids - nitric oxide - others Endocrine metabolic	Pain experience, primary + secondary hyperalgesia (peripheral + central sensitisation) Inflammation Haemodynamic Catabolism Physical deconditioning Psychological effects

Clinically significant injury reposnses that are associated with nociceptirv stimuli trigger diffuse physiological responses such as stress + inflammation → hyperalgesia, hyperglycaemia, protein catabolism, ↑FFA (lipolysis), and changes in water + electrolytes

Metabolic, immunological, and endocrine responses to injury

- endocrine:
  - ↑catabolic hormones: ↑ACTH, cortisol, ADH, GHm catecholamines, ATII, aldosterone, glucagons
  - ↓anabolic hormones: ↓insulin, testosterone
- Immune
  - Mitochondrial initiation
  - Proinflammatory followed by compensatory response: ILs, chemokines
- metabolic
  - carbohydrate: hyperglycaemia, glucose intolerance, insulin resistance → ↑glycogenolysis, gluconeogenesis (cortisol, glucagon, GHm adrenaline, FFAs)
  - protein: muscle protein catabolism, ↑synthesis acute phase proteins → ↑cortisol, adrenaline, glucacons, IL, TNF
  - lipid: ↑lipolysis + oxidation → ↑catecholamines, aldosterone, ADH, cortisol, ATII, PGs,

Describe the applied physiology and psychology of neuropathic pain

Neuropathic pain

- Pain arising as a direct consequence of a lesion or disease affecting the somatosensory system, rather than a stimulus itself
- Divided into:
  - central neuropathic pain:
    - CNS injury e.g. spinal cord injury or MS
  - Peripheral neuropathic pain
    - Diabetes: ischaemia of schwann cells → demyelination → exposed axon generates APs inappropriately
    - Trauma: transected axons regrow with endings that spontaneously fire or that have altered threshold potentials
- Mechanisms
  - Neuroma
  - Wind up
  - Phantom limb pain
- Features
  - Injury or disease that causes nerve injury
  - Burning or electrical quality
  - ↓or absent sensation
  - poor response to typical analgesia

Main drugs used to treat neuropathic pain

- Simple analgesi (multimodal approach)
- anticonvulsants: gabapentoids (gabapentin, pregabalin), carbamazepine
- antidepressants: amitriptyline, duloxetine, venlafaxine

Class	MoA	Adverse effects
Simple analgesia (multimodal approach): **paracetamol**	- inhibits synthesis of PG in CNS + blocks pain impulse generation peripherally	hepatotoxic, renal toxicity
Simple analgesia (multimodal approach): **NSAIDs**	- selective/ non-selective COX blockade → ↓PG synthesis → ↓pain pathway activation	GI ulceration (COX1) Renal impairment (COX1/2) Analgesic nephropathy Bronchoconstriction in asthmatics ↑risk AMI
Anticonvulsants: carbamazepine, Na valproate Gabapentin, pregabalin	- stabilises inactivated Na channels in CNS → ↓APs - blocks voltage gated Ca2+ channels in CSN → ↓central sensitisation	Sedation N+V Ataxia
Antidepressants: TCA SSRI	- activates descending noradrenergic + serotenergic pathways in spinal cord → blocking pain signals	Dry mouth Sedation Cardiotoxic in OD
Membrane stabilisers: LAs	- frequency dependent blockade Na+ channels → ↓propagation AP 1st order neuron (↓glutamate release) / 2nd order neuron (↓ transmission AP up spinal afferent)	Motor blockade; cardiotoxicity/ neurotoxicity
$GABA_BR$ agonist: baclofen	- activate GABABR (metabotropic R) → ↑K conductiance → call nyperpolarisation → ↓presynaptic release glutamate	Sedation, N+V, ↓MAP
NMDA R antagonist: ketamine	- block NMDA R → ↓activation → prevent Ca2+ influx → stop protein kinase cascade activation	Dysphoria, ↑secretions, addiction
Alpha2R agonist: clonidine	- ↓cAMP → ↓Ca2+ available for activation of protein kinase cascades / ↓glutamate release presynaptic terminal	↓MAP, sedation, weakness

Outline the effects of pain and analgesia on injury-induced organ dysfunction

Pain from injury actiates range of adverse physiological effects:

- ↑SY activity:
  - CVS: ↑HR, ↑contractility, ↑BP; ↑myocardial O2demand, ↓myocardial O2 supply →risk of cardiac ischaemia
  - ↓GI motility → ileus
- Upper abdo/ thoracic pain
  - Inability to cough + ↓FRC → atelectasis, V/Q abnormalities, ↑pulmonary complications
- Suppression of cellular + humoral immune function
- Hypercoagulable state
- Alterations to glucose metabolism + accelerated protein breakdown

Describe the alterations to physiology and perception of pain in the older patient

Nervous system changes

- PNS nervous system
  - nerve deterioration
  - ↓myelination
  - ↓conduction velocity
  - ↓range + speed of ANS responses
  - ↑resting SY tone
- CNS
  - ↓pain perception
  - ↑sensitivity to anaesthetic + analgesics: reach ceiling effects more rapidly
  - degeneration of myelin: subsequent cognitive dysfunction due to neuronal circuit dysfunction
  - generalised atropy
  - ↓NT production

PHARMACOLOGY

Describe the pharmacology of the following agents applicable to pain management, including:

Opioids / tramadol
See Pharmacology of specific agents: opioids

Local anaesthetics
See below

NSAIDs
See Pharmacology of specific agents : NSAIDs

Paracetamol
See Pharmacology of specific agents : NSAIDs

NMDA antagonists
See Pharmacology of specific agents: NMDA R antagonists

Anticonvulsants
See Neurological pharmacology

Antidepressants
Divided into 4 groups:

- TCA
  - E.g.: amitriptyline, nortiptyline, dothiepine
  - MoA: inhibit reuptake of monoamines → ↑concentration of NA + 5HT at Rs
  - SE: antimuscarinic (dry mouth, urinary retention, constipation); antihistaminergic (sedation), blocks alph-1 adrenergic (postural hypotension); prolongs QTc
- SSRI
  - Fluoxetine, paroxetine, sertraline
  - MoA: selectrively inhibit neuronal reuptake of 5HT → ↑synaptic centration of 5HT
  - SE: serotonin syndrome: triad of behaviour, motor, autonomic instability
- MAOI
  - Tranylcypromine, phenelzine, moclobemide
  - Older drugs: non-selectively inibit MAO
  - Newer drugs: reversibly + selectively inhibit MAO-A (MAO-A metabolises monoamines NA, 5HT, DA → therefore MAO-A inhibition → ↑synaptic concentration of monoamine)
  - SE: non selective: unable to metbaolise tyrmaine → hypertensive crisis; serotonin syndrome
- Atypicals
  - Venlafaxine: low dose SSRI
  - Mirtazapine: alpha2 adrenergic antagonist → potentiates NA + 5HT neurotransmission
-

	Tricyclics – amitriptyline	SSRI – paroxetine	SNRI – venlafaxine	MAOI – phenylzine
Chem	Dibenzocycloheptadiene derivative			
Uses	Depression Nocturnal enuresis Adjunct in rx chronic pain syndromes			
Pres	Tablet: 10/25/50mg Clear, colourless solution for injection: 20mg/ml amitriptyline hydrochloride Syrup: 2mg/ml			
Action	Antidepressant, sedative, analgesic Potentiate action of biogenic amines within CNS by inhibiting pre-synaptic reuptake of norad + serotonin Antagonize muscarinic cholinergic, alpha-1 adrenergic, and H1, H2 histaminergic receptors			
CNS	antidepressant; sedation, weakness			
CVS	postural hypotension, tachycardia, dysrhythmias, ↑conduction time through AV node			
Resp	resp depression at high doses			
AS				
Other				
Toxicity/ SE	Anticholinergic effects: blurred vision, dry mouth, constipation, urinary retention			
Reversal				
Route/ dose	PO: initially 75-150mg/day → 50-100mg/day for maintenance IV: 10-20mg 6hrly			
Onset	Takes from 3-30days to become fully effective			
Duration				
pKa				
A	bioavailability 50%; peak serum time 4hr			
D	95% protein bound VD ~20L/kg			
M	N-methylation + hydroxylation → subsequent conjugation to glucuronide + sulfate hepatic CYP2C19, CYP3A4; metabolites = nortriptyline			
E	urine (20%); small amounts in faeces Clearance 10-15ml/min/kg Elimination ½ life 13-36hours			
Special points				

Inhalational analgesics – nitrous oxide

See below

Inhalational analgesics - methoxyflurane

Describe the effect of physiological change and pathological disturbance on the pharmacology of the agents listed ABOVE, with special reference to the elderly

- Changes may ↓ the dose (maintenance +/- bolus) of drug required for adequate analgesia and may lead to accumulation of active metabolites
- Linear ↓ in functional capacity of major systems from age 45
- Alterations are predominantly a consequence of polypharmacy and drug interactions

Pharmacokinetics

- Changes 2o to changes in body composition + function of drug eliminating organs
- **Absorption**
  - Absorption unchanged with age
  - Comorbidities/ drug interactions: e.g. laxatives + prokinetics
- **Distribution**
  - Altered Vd
    - ↑fat 10-50% then ↓s → accumulation of lipid soluble drugs
    - ↓lean body mass (muscle mass)
    - ↓total body water 10% → ΔVD for water soluble drugs
    - plasma vol: little change
  - protein binding
    - ↓albumin → ↑free fraction of PB drugs; ↑hepatic clearance of drugs with ↑extraction ratio; ↑cerebral uptake of drug
    - ↑AAG: ↑30-50%; ↓free fraction of PB drugs
  - CO↓ 0-20%: ↓central compartment vol + ↑peak concentration following bolus
  - ↓CBF + cerebral metabolism → ↓distribution to CNS
  - disease states: may ↓circulating proteins + can lead to ↑free drug + potency
- **Metabolism**
  - ↓hepatic size + blood flow 25-40% → ↓hepatic clearance of drugs with high extraction ratio
  - ↓enzymatic activity:
    - phase I metabolism ↓25% → ↓drug metabolism via hepatic clearance
    - phase II metabolism: little change
  - ↓muscle mass: remifentanil is significantly metabolised by muscle esterases
  - hepatic disease: cirrhosis, hepatitis, disease → impairment of drug metabolising enzymes
  - ↓CO → ↓blood flow to liver → modifying clearance of flow depdnent drugs
- **Excretion**
  - ↓renal function
    - Loss of nephron mass 30% → ↓renal clearance
    - ↓RBF + ↓RPF + ↓GFR → ↓renal clearance of hydrophilic drugs + clearance of active/ toxic metabolites

Pharmacodynamic

- ↑sensitivity to sedatives, opioids, hypnotics
- ↓sensitivity to B-agonists and antagonists, ↓MAC
- polypharmacy ↑potential for drug interactions
- more likely to have co-existing disease: effect of disease process + drug interactions

Describe the different modes of administration of analgesic agents and evaluate their clinical application

Route	Features

PO	- Absorption through GUT mucosa either: transport mechanisms; unionised
	  ○ Drug factors: MW, conc gradient, lipid solubility (pH and pKa), pharmaceutical preparation
	  ○ Pt factors: blood flow, pH, motility, enzymes, bacteria, disease
	  ○ Drugs must be lipid soluble enough to cross CM and water soluble enough to cross interstitium
	- Lowest bioavailability due to:1st pass metabolism; gut metabolism of drugs; bacterial metabolism of drugs

Sublingual	- Rapid onset → bypass portal circulation (drains into SVC)
Inhalational	- Systemic absorption dependent on particle size → large particles reach bronchioles; <1micron may reach alveolus - Rapid diffusion to circulation due to high surface area
IV	- Rapid onset; 100% bioavailability - Direct + ↑reliable - Some drugs still undergo metabolism in the pulmonary circulation e.g. fentanyl, lignocaine, Propofol, catecholamines
Epidural	- Bolus/ infusion - Onset determined by proportion of unionised drug available
Subarachnoid/ intrathecal	- Very small dosing; minimal systemic spread - Extent of subarachnoid spread is dependent on vol and type of solution - Appropriate positioning of patient with higher specific gravity solution is required to avoid superior spread of the block

Transdermal	- Systemic absorption depends on:
	  ○ Dose requirement: large dose requirements cannot be effectively given transdermally
	  ○ Fick principle: conc, regional blood flow, surface area, skin thickness, lipid solubility (pH, pKa), MW
	- Advantages: convenient, painless, no 1st pass metabolism, steady plasma concentration once established
	- Disadvantages: slow onset, variable plasma concentration initiall

IM	- Bioavailability close to 1; absorption dependent on regional blood flow - Potential local complications: abscess, haematoma
Subcut	- Dependent on regional blood flow

Rectal	- Variable absorption
	  ○ Distal rectal absorption bypasses portal circulation
	  ○ Proximal rectal absorption does not and may result in hepatic 1st pass metabolism

PHARMACOLOGY OF SPECIFIC AGENTS: OPIOID AGONISTS AND ANTAGONISTS

Opioid receptors

- opiates = naturally occurring substances with morphine-like properties
- opioids = substances with an affinity for opioid receptors
- opium = mixture of alkaloids from poppy plant

Classification of opioids according to structure

- Naturally occurring:
  - Endogenous opioids: endorphins, encephalins, dynorphins
  - Opium derivatives
  - Phenanthrenes: morphine, codeine
- Semisynthetic
  - Buprenorphine
  - Oxycodone
- Synthetic
  - Phenylpiperidines: fent, alfent, remifent, pethidine
  - Diphenylpropylamines: methadone

Classification of opioids according to activity

- Full agonist: morphine
- Partial agonist: buprenorphine
- Agonist-antagonist: pentazocine
- Antagonist: naloxone

Classification of opioid receptors

- All opioid receptors are Gi receptors
- Activation → ↑adenylyl cyclase, ↓cAMP →
  - Presynaptically: inhibits voltage-gated Ca2+ channels → ↓ca2+ influx + ↓NT release
  - Postynaptically: stimulates K channels → K efflux → membrane hyperpolarisation

Receptor	Actions	Notable properties
MOP (mu)	Mu1: analgesia: spinal/ supraspinal, euphoria, miosis, urinary retention Mu2: analgesia: spinal, resp depression, bradycardia, N+V, Constipation, Physical dependence	Only opioid R to cause N+V
KOP (kappa)	Analgesia (mainly spinal) Sedation, dysphoria Miosis	Minimal resp depression
DOP (delta)	Analgesia: spinal/ supraspinal Urinary retention Physical dependence	Minimal constipation
NOP (nociception)	Anxiety Analgesia: low doses → hyperalgesia; high doses → analgesia Depression Change in appetite	Hyperalgesia at low doses Analgesic at high doses

Describe the mechanisms of action of opioids, including tramadol

- cellular level: activate opioid receptors
- opioid R: CNS; high conc in NTS, PAG, cerebral cortex, thalamus, substantia gelatinosa of SC + peripheral afferent nerve terminals
- all opioid Rs are GPCRs:
  - opioid agonist + receptor → ↓neuronal cell excitability → ↓transmission of nociceptive impulses
  - Achieved by:
    - closing of voltage gated Ca2+ channels → ↓Ca2+ influx into presynaptic terminal → ↓NT release
    - opening K channels on post-synaptic membrane → ↑K efflux → hyperpolarisation 2nd order neurons → ↓neuronal excitability
    - ↓cAMP production
  - Pure opioid agonists (morphine, pethidine, fent): bind to opioid Rs avidly + demonstrate high intrinsic activity at cellular level
  - Partial opioid agonists (cup) bind to opioid Rs → produce submaximal effect

	Morphine	Fentanyl	Alfentanil	Remifentanil
Chem	phananthrene derivative	phenylpiperidine derivative	phenylpiperidine derivative	phenylpiperidine derivative of fentanyl
Type	Natural opioid	Synthetic opioid	synthetic opioid	Synthetic opioid
Uses	Analgesic	analgesia: GA, PCA, palliative care	analgesia, sedation, intubation	Ultra short acting analgesia, sedation, intubation
Pres	Tablets: 5/10/30/60/100/200mg Syrup; suppositories CCS morphine sulfate 10/15/30mg/ml	CCS fentanyl citrate Transdermal patch	CCS for injection containing 0.5/5mg/ml of alfenanyl hydrochloride	white powder in glycine buffer in 1/2/5mg vials for dilution prior to infusion
Action	Full agonist at mu receptor	highly selective mu agonist 100x more potent than morphine	highly selective mu agonist	Pure mu agonist
CNS	Analgesia; drowsiness; anxiolytic; miosis	Little hypnotic/ sedative activity ↑ICP 2o ↑cerebral vasodilation	10-20x more potent than morph; as per fent	Minimal hypnotic/ sedative; analgesia
CVS	↓SVR	More CVS stable cf morph ↓HR 2o VA No effect on CO, MAP, PVR, SVR	As for fent	VA activity → ↓HR + ↓MAP may ↓myocardial contractility + CO
Resp	Resp depression; ↓response to hypoxia + hypercapnia; antitussive	potent resp depressant: ↓RR ↓vent response to hypoxia + hypercapnia; antitssive	As for fent	As for fent No histamine release
AS	↓GI motility; ↑CBD pressure; spasm sphincter of oddi, N+V	↓GI motility, ↑CBD pressure		↓GI motility low incidence N+V
Other	Urinary retention Pruritis			
Toxicity/ SE	↓HR; bronchoconstriction; resp depression Seizure + rigidity; N+V; hallucinations; dependence	N+V; resp depression	As for fent	Wooden chest / truncal rigidity Post infusion hyperalgesia
Reversal	Naxlone fully reverses			
Route/ dose	PO: 5-10mg q4hr IV: 0.05-0.1mg/kg q3hr	IV/ IM/ SC/ transdermal Epidural: 50-100microg Intrathecal: 5-25microg	IV: boluses of 5-50migro/kg IVI: 0.5-1microg/kg/min	IV only Bolus 1microg/kg over 30sec TCI (0.05- 1microg/kg/min)
Onset	IV <1min; PO 30mins	<30sec (peak 3-5min)	<30sec (peak 1-2min)	<60s
Duration	3-4hrs		5-10mins	Rapid offset 2° rapid metabolism
pKa	7.9	8.4	6.5	weak base; pKa 7.3
%UI	25%	<10%	90%	60%
A	PO bioav: 20-30% extensive 1st pass metabolism	PO bioav 30% Transdermal absorption 98% at 72hrs		
D	Vd 4L/kg Relatively lipid insoluble → slower OOA	Vd 4L/kg Sig 1st pass pulmonary endothelium uptake	Vd 0.5-1L/kg	Low lipid solubility → Vd 0.1 - 0.4L/kg
PB	30%	80%	90%	70%
Relative lipid sol	1	600 → rapid onset + cross BBB rapidly	90	20
M	**liver** **glucuronidation** to: M3G 85% M6G 10% (active; 13x ↑potent than morph) **Demethylation** to: normorphine	**Liver** **N-dealkylation** to **norfent** (inactive) → hydroxylation to hydroxypropionyl derivatives **hydroxylation** + **amide hydrolysis**	**Liver** **N-dealkylation** to noralfentanil Aromatic hydroxylation, demethylation, amide hydrolysis → acetylation Major phase II: conjugation to glucuronide CYP450 3A3 and 3	Organ independent metabolism → **ester hydrolysis** carboxylic acid derivative (clinically inactive) CSHT: 3-5 mins (fixed)
E	**90% urine**; 10% faeces clearance 15ml/kg/min	10% urine clearance 13ml/kg/min	90% urine (1% unchanged) Clearance 6ml/kg/min	40ml/kg/min organ independent 95% urine as remifentanil acid
t½β	160min	190min (↑than morph 2o ↑lipid solubility + ↑Vd)	100min	10min
Special points	↑M6G renal failure → ↓dose Not effective for neuropathic	intrathecal doesn't cause delayed resp depres	↓lipid solubility – but, faster OOA than fentanyl due to its ↓pKa → ↑unionized drug Brief DoA cf fentanyl 2° ↓Vd + shorter t1/2β	Crosses placenta DoA dependent on metab (not distribution - cf alfent / fent) due to small Vd + rapid effect site equilibration kinetics

	Oxycodone	Codeine	Tramadol	Hydromorphone
Chem	opium alkaloid derivative	phenanthrene alkaloid - methylated morphine derivative	Aminocyclohexanol group Raceimix mix of 2 enantiomers (R) and (S) tramadol	
Type	Semi synthetic	natural opioid; prodrug	**Chemically not an opioid**	Semi synthetic opioid
Uses	Analgesia	Analgesia/ antitussive/ anti-diarrhoea	Mod- severe pain; neuropathic pain; anti-shivering	
Pres	IV 10mg/ml and 50mgml PO: 5/10/2-mg; liquid 1mg/ml Immediate + CR preparations	15/30/60mg tablet; syrup 5mg/ml CCS for IV 60mg/ml codeine phosphate	CCS for IV/IM 50mg/ml tablets 50/100/150/200/300/400mg tramadol hydrochloride	
Action	Analgesia + anxiolytic + antitussive + sedative Opioid agonist: mu, kappa, delta MoA as per fent	Low affinity for opioid Rs; 10% metabolized to morphine Antitussive: specific high-affinity codeine receptors	**Weak opioid R agonist:** non-selective mu, kappa, delta **Non-opioid action:** blocks reuptake of NAd + 5HT; stimulates presynaptic 5HT release; NMDA R antagonist (R)-tramadol = SNRI (S)-tramadol = SSRI + partial mu	5x ↑potent than morph when PO 8x ↑potent morph when IV
CNS	analgesia, drowsiness, anxiolysis, euphoria, miosis	10x ↓potent than morphine; few central effects associated with opioids	10x ↓potent than morph ↓sedation, ↓dependency Ceiling effect (↑dose yields no ↑in efficacy)	↑lipid sol than morph → ↑penetration BBB + ↑OOA
CVS	↓SVR (histamine)		Nil clinically sig CVS effects ↑MAP, SYS; no histamine release	
Resp	As for fent	antitussive; resp depression with ↓vent response to hypoxia + hypercapnia	RR, MV, PaCO2 unchanged	
AS	↓GI motility, N+V, constipation; urinary retention	↓GI motility; constipation	no effect on bile duct sphincter activity; ↓constipation	
Other				
Toxicity/ SE	N+V, hallucinations, dependence; pruritis		**Interacts with TCA, SSRI, 5-HT3 antagonists**	
Reversal			**Naloxone reverses 30% of analgesic effect**	
Route/ dose	PO: 5mg q4hr IV: 1-10mg over 1-2min titrated	PO 30-60mg 4-6hr Not for IV due to ↓BP ?2` histamine release	PO, IM, slow IVI, infusion 50-100mg 4-6hourly	
Onset	10-15min	15-30min		
Duration				
A	PO bioavailability 70%	PO 60-70%; little 1st pass metabolism	bioavailability 80%	Extensive 1st pass
D	Vd 2L/kg; pKa 8.5 (<10% UI)	VD 5.4L/kg	Vd 4L/kg	
PB	40%	7%	20%	
M	**liver**; - CYP450 3A to noroxycodone (↓potent) - CYP450 2D6 to oxymorphone (14x ↑potent) + conjugated glucuronides	**liver** by 3 methods: - 20% glucuronidation to codeine-6-glucuronide - 20% N-demethylation to norcodeine - 10% O-demethylation to **morphine** - minor metabolites: normorphine + norcodeine-6-glucuronide	**Liver** 85% by CYP2D6: demethylation; O-desmethyltramadol (**active)**	Liver to hydromorphone 3-glucuronide (**inactive**)
metab	**Active**	**Active**	**Active**	**Inactive**
E	**urine** (20% free drug, 50% conj oxycodone, 14% conj oxymorphone) Clearance 13ml/kg/min	**urine**: free + conjugated codeine, norcodeine, morphine; 17% unchanged Clearance 98L/hr PO	90% urine; 10% faeces Clearance 8ml/kg/min	Renal
t½β	3hr (immediate); 4.5hr (CR)	3hr	300-450min	120-180
Special points	Crosses placenta	Genetic variability with CYP450 enzyme CYP2D6 causes conversion to morphine; fast metabolisers ↓dose in renal failure	80% crosses placenta elimination ½ life doubled in renal / hepatic dysfunction CI in ESRF Precipitates when mixed with diaz/ midaz Slowly removed by dialysis Precipitates serotonin syndrome	

	Methadone	**Buprenorphine**	**Pethidine**
Chemical	Racemic mix of 2 enantiomers: - L-methadone: opioid agonist - D-methadone: NMDA antagonist	Derivative of alkaloid thebaine	phenyl piperdine derivative
Type	Synthetic	Semi-synthetic	Synthetic
Uses	Severe pain Detoxification	Detoxification Severe pain	Analgesia during labour, delivery, surgery Post op shivering
Pres		CCS 300microg/ml of buprenorphine hydrochloride 200/400microg tabs/ transdermal patch	Tablets 50mg CCS for IV/IM injection containing 10/50mg/ml
Action	Full agonist at MOP, KOP, DOP receptors NMDA R angatonist Inhibits reuptake of serotonin + NAd Analgesia, respiratory depression, sedation	**partial agonist- antagonist at mu receptors** Agonist at mu: ↑affinity, dissociates slowly → prolonged analgesia Antagonist at kappa: antianalgesic effect (predominates with ↑dose)	-
CNS	↓sedative than morph	25x ↑potent than morphine 50x affinity for mu-R than morphine ↓CMRO2, sedating	Analgesia + sedation; 10x less potent than morphine Mydriasis (atropine/ anticholinergic effect) LA activity; antishivering
CVS	May cause QT prolongation	minimal; may ↓ SBP	Orthostatic hypotension 2° to α-blockade + histamine release ↑HR large dose: ↓contractility (myocardial depressant)
Resp		↓risk resp depression 2o ceiling effect ↓MV ↓Cough histamine + tryptase release from lung parenchymal mast cells	potent resp depression ↓response to ↑PaCO2 + ↓PaO2 ↑chest wall rigidity + ↓compliance + FRC not effective antitussive
AS			↓N+V cf morph, constipation, spasm of CBD than morphine
Other			↓ureteric tone; may ↑amplitude of contractions in pregnancy ↑ADH and ↓adrenal steroid secretion
Tox/ SE	Agitation, angina, anticholinergic effects, ↓HR ↑interindividual variability in response	N+V (can be severe + prolonged)	interact with MAOI → serotonin syndrome (hypertensive crisis)
Route/ dose	Tablet: 5/10mg/ Dispersible tablet: 40mg IV: 10mg/ml	IM and IV: 300-600microg q6-8hr SL 200-400microg q6-8hr Epidural: 300microg Transdermal: evaluate after 24-72hrs and adjust	
Onset	PO 0.5-1hr; parenteral 10-20min;		<1min
Duration	4-8hr single; 24-48hr repeated		
Reversal		**Not completely reversed by naloxone**	
pKa			8.7 (5% unionized)
A	bioavailability 75%; low 1st pass metabolism	sig 1st pass metabolism → SL preferred bioavailability 40-90% IM; 45-95% SL	Bioavailability 50% due to 1st pass metabolism Not given SC due to excessive histamine release
D	Vd 1-8L/kg	only unchanged bup reaches CNS VD 3 L/kg	Vd 4L/kg 30x more lipid soluble than morphine → fast onset of action
PB	90%	95%	60% (α-1 acid glycoprotein)
M	liver via N-demethylation to **inactive** metabolites	**Liver** Norbuprenorphine (**active**) dealkylation → conjugation to glucuronide (**inactive** metabolites) polar conjugates excreted in bile + hydrolysed by bacteria in GIT	Liver N-demethylation to norpethidine → 50% potency; marked convulsant hydrolysis to pethidinic acid → inactive
Metab	Inactive	**Active + inactive**	Active
E	urine (40% unchanged)	Bile (faeces) as unchanged bup urine as conjugated bup + dealkylated derivatives clearance: 930ml/min	Renal (10% unchanged) Clearance 15ml/kg/min
t½β	15-60hr **(longest of all)**	40hr	3-5hr

Pharmacokinetic properties of some opioids

Opioid	*Protein binding (%)*	*$t_{1/2}\beta$ (min)*	*V_d (l/kg)*	*Clearance (ml/kg/min)*	*pK_a*	*Relative lipid solubility*	*% unionised at pH 7.4*
Morphine	35	160	3.5	15	8	1	23
Pethidine	70	210	4	12	8.5	30	< 10
Fentanyl	85	190	4	13	8.4	600	< 10
Alfentanil	90	100	0.6	6	6.5	90	90
Sufentanil	90	160	1.7	13	8	1700	23
Remifentanil	70	10	0.4	40	7.3	20	58
Methadone	90	15-60 (h)	6	= 0.5	8.6	115	< 10
Oxycodone	45	200	2.5	13	8.5	1	< 10

Discuss the pharmacokinetic and clinical implications of different routes of administration for commonly used opioids, including the oral, transdermal, subcutaneous, intramuscular and intravenous routes

Clinical implications

- Which opioid to use depends on:
  - Drug factors: availability + cost; available formulations
  - Surgical factors
  - Patient factors: dependence, age, renal/ hepatic disease, GI

Pharmacokinetics (general)

Route	Features
PO	- Absorption through GUT mucosa either: transport mechanisms; unionised - Lowest bioavailability due to ○ 1st pass metabolism ○ gut metabolism of drugs ▪ Drug factors: MW, conc gradient, lipid solubility (pH and pKa), pharmaceutical preparation ▪ Pt factors: blood flow, pH, motility, enzymes, bacteria, disease ○ bacterial metabolism of drugs - Drugs must be lipid soluble enough to cross CM and water soluble enough to cross interstitium
Sublingual	- Rapid onset - Bypass portal circulation (drains into SVC)
Inhalational	- Systemic absorption dependent on particle size → large particles reach bronchioles; <1micron may reach alveolus - Rapid diffusion to circulation due to high surface area
IV	- Rapid onset; 100% bioavailability - Direct + ↑reliable - Some drugs still undergo metabolism in the pulmonary circulation e.g. fentanyl, lignocaine, Propofol, catecholamines
Epidural	- Bolus/ infusion - Onset determined by proportion of unionised drug available
Subarachnoid/ intrathecal	- Very small dosing; minimal systemic spread - Extent of subarachnoid spread is dependent on vol and type of solution - Appropriate positioning of patient with higher specific gravity solution is required to avoid superior spread of the block
Transdermal	- Systemic absorption depends on: ○ Dose requirement: large dose requirements cannot be effectively given transdermally ○ Fick principle: amount of drug given, amount of drug in skin (regional blood flow), surface area, skin thickness, lipid solubility (pH, pKa), MW - Advantages: convenient, painless, no 1st pass metabolism, steady plasma concentration once established - Disadvantages: slow onset, variable plasma concentration initiall
IM	- Bioavailability close to 1; absorption dependent on regional blood flow - Potential local complications: abscess, haematoma
Subcut	- Dependent on regional blood flow
Rectal	- Variable absorption ○ Distal rectal absorption bypasses portal circulation ○ Proximal rectal absorption does not and may result in hepatic 1st pass metabolism ○ Small SA availabl

Outline the dose conversion between commonly used opioids

Morphine = standard drug against which other opioids are compared

Opioid	*Parenteral*	*Oral*	*Relative potency*
Morphine	10	20-30	1
Pethidine	100	300	0.1
Fentanyl	0.1	N/A	100
Alfentanil	1	N/A	10-20
Sufentanil	0.01	N/A	500-1000
Remifentanil	0.05	N/A	200
Hydromorphone	1.3	4-6	5-8
Codeine	N/A	200	0.1
Oxycodone	5	15-20	1.5-2

Consideration when changing from IV morphine to oral opioid analgesia in post op period

- surgical factors
  - Post op: pain is ↓
  - Fasting status: PO opioid ineffective; delayed gastric emptying, ↑transit time
- patient factors
  - age: ↑age → ↓dose
  - previous opioid use
    - tolerance/ dependent → ↑dose
    - partial agonist use → unpredictable opioid requirements, difficult to titrate
- analgesia factors
  - choice of PO agent: immediate or sustained release
  - equianalgesic dosing
    - based on previous 24hr morphine use
    - PO agents ↓potency compared to IV morphine: 1mg IV morphine = 2mg PO oxygodone
    - Incomplete cross tolerance
  - Dosing: PRN rather than regular; max dose interval
  - Multimodal analgesic approach to ↓opioid use
  - Other medication: may potentiate effects/ ↑risk SE

Pharmacokinetics of intravenous opioids and their clinical applications

Opioid	Morphine	Oxycodone	Fentanyl	Alfentanil	Remifentanil	Pethidine
Chemistry	Phenanthrene	Phenanthrene	Phenylpiperidine	Phenylpiperidine	Phenylpiperidine	Phenylpiperidine
Dose equivalent (i.v.)	10 mg	15 mg	100 microg	1 mg	100 microg	100 mg
Absorption						
Routes	IV/IM/SC IT/ED,PO,PR,TOP	IV PO	IV IT/ED,PO,IN,TOP	IV	IV	IV/IM PO
Bioavailability (oral)	20 ~ 30%	60 ~ 80%	30%	-	-	50%
Distribution						
Vd (steady state)[†]	3.5 L/kg	2.5 L/kg	4 L/kg	0.4 L/kg	0.2 L/kg	4 L/kg
pKa[‡] %unionised (pH=7.4)	8.0 23%	8.5 7%	8.4 10%	6.5 90%	7.1 67%	8.5 5%
Relative lipid sol.[§]	1	~ 1	600	90	20	30
Protein binding[§]	35%	45%	83%	90%	70%	60%
t(iv peak effect)	19 min	5 ~ 10 min (?)	4 min	2 min	1 ~ 2 min	6 min
Metabolism						
Site	hepatic + extra-hepatic (renal)	CYP3A4 (major) CYP2D6 (minor)	CYP 3A4	CYP 3A4	plasma and tissue esterases	hepatic CYP

Opioid	Morphine	Oxycodone	Fentanyl	Alfentanil	Remifentanil	Pethidine
Metabolites	glucuronidation: M3G (70%) - inactive M6G (10%) - active demethylation: nomorphine (5%) codeine	demethylation: noroxycodone (3A4) oxymorphone (2D6)	demethylation: norfentanyl (inactive)	N-dealkylation: noralfentanil (inactive) N-phenyl-propionamide	remifentanil acid (essentially inactive)	demethylation: norpethidine (90%, active) → norpethidinic acid hydrolysis: pethidinic acid
Elimination						
Renal	1 ~ 2% parent	15% parent	minimal	< 0.5% parent[Δ]	–	pH dependent (acidic urine → more parent) 25% parent (@ pH 5)
Clearance	16 mL/kg/min	7 mL/kg/min	13 mL/kg/min	6 mL/kg/min	40 mL/kg/min	12 mL/kg/min
$t_{1/2}\beta$	2 ~ 4 hrs	3 ~ 4 hrs	2 ~ 4 hrs	1.5 hrs	6 min[Δ]	3 ~ 5 hrs
CSHT (4 hr infusion)	–	–	4 hrs	60 min[§]	4 min[Δ]	–
Pharmacodynamics						
Special properties	histamine release sphincter of Oddi spasm w/d start 6~12 hrs w/d duration 7~10 d		muscle rigidity w/d start 2~6 hrs w/d duration 4~5 d	muscle rigidity	muscle rigidity	anticholinergic LA effects addictive +++ norpethidine → induces seizures w/d same as fentanyl

	Morphine	Pethidine	Fentanyl	Alfentanil	Remifentanil
pKa	8.0	8.5	8.4	6.5	7.1
Unionised at pH 7.4 (%)	23	5	9	90	68
Plasma protein bound (%)	30	40	84	90	70
Terminal half life (hrs)	3	4	3.5	1.6	0.06
Clearance (ml/min/kg)	15-30	8-18	0.8-1.0	4-9	30-40
Volume of distribution (L/kg)	3-5	3-5	3-5	0.4-1.0	0.2-0.3
Relative lipid solubility	1	28	580	90	50

Alfentanil vs. fentanyl

	Alfentanyl	Fentany
Effect site equilibrium	- Fast: 1.4min → due to low pKa 6.5; weak base = 90% unionised + crosses BBB more rapidly than fentanyl despite lower solubility - Lower potency → larger dose administered → rapid onset	- slower at 7min despite ↑lipid solubility due to ↑pKa 8.4 → 8% unionised -
Duration of action	- 10mins due to: ○ redistribution ○ fast elimination ½ time (100mins) despite smaller clearance (5ml/kg/min) → due to small Vd (0.5L/kg) as more drug in plasma → metabolised by liver	- 30-60mins due to: ○ redistribution ○ large Vd (4.5L/kg) → slower elimination ½ time (190mins) despite faster clearance (13ml/kg/min) → ↓frequency of intermittent dosing
CSHT 4hr infusion	- 60mins - high due to rapid equilibirium of smaller Vd after infusion has stopped - plateaus at 3hrs – representing complete saturation of peripheral compartments → used as nfusion where prolonged action wanted	- 260mins - when indusion >2hrs → CSHT fent > alfent and continues to ↑ reflecting saturation of inactive tissue dites + returning opioid from peripheral compartments to plasma when infusion stopped - less suitable for prolonged infusion (long CSHT) - single lrge doses (>50microg/kg) last up to 4-6hrs

Morphine vs. fentanyl PCA

- PCA = analgesia method whereby patient controls amount of analgesics received within certain predefined constraints
- Aim: achieve adequate analgesia without causing excessive sedation
- Typical implementation: pt activates computerised pump via remote → drives syringe containing analgesic → preset dose delivered
- Successful implementation requires:
  - Patient understanding + compliance
  - Analgesic agent + appropriate pharmacokinetic/ pharmacodynamics profiles
  - Appropriate equipments: PCA machine, circuit, IV access
- Typical settings
  - Morphine PCA: 0.5-2mg boluses with 5-10min lockout
  - Fent PCA: 10-20microg boluses with 5-10min lockout

Properties	Morphine	Fentanyl	Comparison
Distribution			
Lipophilicity	Lower	Higher (600x more than morphine)	High lipophilicity → ↑rapid diffusion across BBB
pKa %unionised (pH7.4)	8 23%	8.4 9%	High unionised fraction → more rapid OOA
Equilibration time	5hrs	5min	Fent faster
Protein binding	35%	85%	↑PB → ↓Vd ↑PB = effect more affected by plasma [protein]
Vd	3.5L/kg	4L/kg	Similar
Overall onset	Slow Peak effect in 20mins	Rapid Peak effect <5mins	Overall morphine slower OOA than fent due to less lipophilis → repeated boluses may stack → ↑SE
Overall offset	Slow	Rapid	Morph has slower offset → longer lasting analgesia than fent → ↓fluctuations
Metabolism			
Mode	Hepatic Glucuronidation	Hepatic N-dealkylation + hydroxylation	Plasma and effect site [drug] ↑liver failiure
Metabolites	Active (M6G) + inactive (M3G)	Inactive (norfentanyl)	Morphine has active metabolites → may accumulate in renal failure
Elimination			
Clearance	20ml/kg/hr	13ml/kg/hr	Similar clearance rates
Elimination ½ time	2-4hrs	2-4hrs	Similar terminal elimination ½ time because CL and Vd are similar
Renal elimination	Of active metabolites	Of inactive metbaolites	Renal impairment: M6G will accumulate → morphine PCA inappropriate

Overall

- fentanyl PCA
  - advantages: predictable onset + offset pharmacokinetics
  - disadvantages: rapid offset → short lasting bolus; may need background infusion
- Morphine PCA
  - Advantages: boluses rapid onset; longer lasting; avoids fluctuations in drug leel
  - Disadvantages: prone to oversedation; less tolerant in elderly due to SE

Pharmacology of opioids deposited in the epidural space or cerebrospinal fluid

Opioids injected into spinal intrathecal space

- opioids are injected into the IT space, commonly in conjunction with LA to provide surgical analgesia + anaesthesia
  - preservative free formulations to avoid neurotoxicity
- due to proximity to effect site, doses are significantly ↓ cf IV + epidural routes
- MoA of opioids:
  - Act presynaptically vai GPCR → ↑K+ conductance + ↓Ca2+ release → hyperpolarises cell:
    - ↓release of excitatory NTs (Glu, ACh, substance P) at spinal cord + higher centres
    - may ↓inhibitory NT (glucine, GABA) release in higher centres → CNS excitation
  - Important factors
    - Lipid solubility: affects onset; ↑lipid sol → rapid diffusion across meninges to site of action + faster ↑[plasma]
    - Receptor affinity: ↑affinity → ↑DoA
    - Site of action: opioid Rs in SC; mainly MOP (substantia gelatinosa)
- Main effect of IT opioids = segmental analgesia; little motor or SY effects
  - Extent of distribution determined by lipid solubility of agent
  - Effects via 3 mechanisms:
    1. Local effect at spinal cord level (main effect)
    2. Cephalad spread in CSF → action at supraspinal sites
    3. Systemic spread: through venous plexus

1. Local effects at spinal cord level

- Analgesia
  - Opioid diffuses across meninges (pia mater) → bind to MOP (mu) Rs in substantia gelatinosa of SC → inhibitory
  - Prevents transmission of pain signals along primary afferent neurons Adelta + C fibres
- Hypotension (esp. orthostatic)
  - Blockade of SY chain → vasodilation + venodilation → hypotension
- Urinary retention
  - Block PSY sacral plexus → contracts internal urethral sphincter +relax detrusor mm.
- Priaprism/ anejaculation
  - Blockade of sacral PSY
- ↓temp:
  - inhibition of shivering

2. cephalad spread

- spread of opioid via CSF circulation → action at higher centres
- dose dependent effect
- movement depends on lipid solubility of opioid
- effects
  - sedation: direct action on MOP in reticular formation; indirect effect via precipitating hypercapnia +/- hypoxaemia
  - resp depression:
    - direct opioid depression of brainstem resp centre → ↓RR + ↓chemoreceptor response to ↑PaCO2 → ↓MV
    - early resp depression with lipophilic agents (fent)
    - later resp depression with hydrophilic agents (morphine) → bound less to SC → slowly carried rostrally to brainstem
  - confusion: anticholinergic (pre-synaptic blockade of ACh release)
  - pruritis: interacts with MOP in trigeminal n
  - N+V: stimulate DA Rs at CTZ
  - Paradoxical excitation: at supratherapeutic doses may ↓release of inhibitory NTs (glycine, GABA)
  - Viral reactivation: interaction at trigeminal n.
  - SIADH:
  - Miosis

3. Systemic absorption

- via epidural venous plexus
- rare due to small doses used
- effects
  - ↓gastric emptying/ ↓gut motility → direct effect on smooth muscle
  - ↓MAP: mast cell degranulation → histamine release → vasodilation

commonly used intrathecal opioids are:

- morphine: 200-1000microg
  - lower lipid solubility → slower onset
  - late resp depression >2hrs
- fentanyl 10-25microg
  - high lipid solubility
    - rapid local augmentation of block + short lived effect
    - Diffuses rapidly from CSF into SC + circulation
  - Early resp depression: <2hr of administration

Epidural opioids

- have to penetrate dura and arachnoid to enter the CSF before diffusing into the SC and producing analgesia (bypassed in IT opioids)

- ↑vol → ↑rate of diffusion
- solubility affected by:
  - pKa and pH: determines inuoinised portion available to cross into CSF
  - protein binding: determines free drug able to cross into CSF
  - lipid solubility: determines rate of penetration across arachnoid
    - drugs with low lipid solubility (morphine) cross arachnoid slowly → slower onset of action; cleared slowly → longer duration
- CSF flow: alters concentration gradient between epidural + subarachnoid space

Adverse effects of opioids administered by systemic and neuraxial routes + prevention and management

Adverse effects of opioid receptor agonists

- Adverse effect: any unwanted effects associated with drug administration
- Due to:
  - Acting on opioid receptors: MOP, KOP, DOP
  - Acting on other receptors: e.g. 5HT
- Type + severity of adverse effects governed by:
  - Pharmacokinetic factors
  - Pharmacodynamic factors: type/ dose/ threshold/ tolerance/ pregnancy
  - Pharmacogenetics: enzymes/ metabolism

CNS

- Sedation
  - Directly: opioid R activation → presynaptic neuron hyperpolarisation → ↓release of excitatory NT (ACh, 5HT, glu, DA, NA)
  - Indirectly: ↓resp centres → ↓MV → ↑PaCO2 → sedation
- Confusion: ↓presynaptic release of ACh
- Euphotia: MOP + KOP
- Dysphoria: KOP
- Miosis: Edinger-Westphal n → efferent via occulomotor n.
- N+V: activation of DA + 5HT R at CTZ

CVS

- ↓HR, ↓MAP: inhibit SNS tone
- ↓SVR: histamine release
- ↑QTc: methadone can interfere with voltage gated K channels

Resp

- Effects are dose dependent BUT occur within therapeutic dose range (narrows therapeutic window)
- ↓RR → ↓MV: MOP activation → direct depression of medullary resp centre; ↓RR > TV
- blunt chemoreceptor response to ↑PaCO2: direct depression of medullary resp centre → R shift of PaCO2 response curve → ↑resting PaCO2
- blunt airway reflex/ cough suppression: depresses medullary cough centre
- bronchospasm: histamine release
- ↓ciliary action

GIT

- ↓GI motility: activation of GIT + central MOP + anticholinergic effect
- biliary duct spasm, ↑sphincter tone: MOP

GUT

- urinary retention: detrusor muscle relaxation + ↑urethral sphincter tone
- ureter spasm
- SIADH

MSK

- truncal rigidity: MOP activation → interferes with GABA + DA transmission in brainstem/ basal ganglia (esp. with remifent)

Other

- pruritis: histamine
- adverse effects more likely at extremes of age + with ↑dose

Prevention

- ↓dose/ titrate to effect
- appropriate agent
- multimodal analgesia; education; non-pharmacological mx

management

- naloxone
- change med/ ↓dose

Describe the potential adverse drug interactions between opioids and other agents

- CNS depressants: potentiates effects of opioids → ↑risk resp depression, sedation, coma
- BP lowering meds: opioids may cause hypotension → combination can worsen effects
- Opioids slow GI motility → ↑ or ↓absorption of other drugs being taken
- Some opoids may result in serotonin toxicity if iven with MAOI e.g. fentanyl + MAOI
- Methadone can prolong QT interval → ↑risk of arrhythmia e.g. carbamazepine + methadone

Pharmacology of opioid antagonists – Naloxone

Chemical	N-alkyl derivative of oxymorphine
Uses	reversal of mu-opioid R effects e.g. resp depression, sedation, hypotension, dysphoria, pruritis clonidine overdose
Presentation	clear solution for injection of 200-400microg/ml of naloxone hydrochloride
Action	**competitive mu R antagonist** → small effect at delta + kappa
CNS	Reversal of all mu-opioid R effects in dose dependent manner Rapid onset of withdrawal symptoms in opioid drug addicts Antanalgesic in opioid naïve patients
CVS	
Resp	Reversal of opioid induced ↓RR
AS	N+V
Toxicity/ SE	Ventricular dysrhythmias in pts with irritable myocardium ↑↑doses: ↑SNS activity → ↑HR, ↑MAP, dysrhythmias, APO, drowsiness
Route/ dose	IV: 100-200microg incremental doses titrated to effect IM/ subcut
Onset	<2min
DoA	30mins (infusion may be required)
pKa	8 (25% unionized at pH 7.4)
A	extensive 1st pass metabolism → bioavailability 2%
D	50% protein bound (alpha1-acid glycoprotein) highly lipid soluble → readily crosses BBB Vd 2L/kg

M	**Liver** Conjugation to naloxone-3-glucuronide Small amount of N-dealkylation (<2%)
E	Urine Clearance 25ml/kg/min Plasma ½ life 60-90mins
Special points	Crosses placenta → acute withdrawal in foetus

Describe the pharmacodynamics of individual opioids and evaluate their clinical applications

See above

PHARMACOLOGY OF SPECIFIC AGENTS: NSAIDS

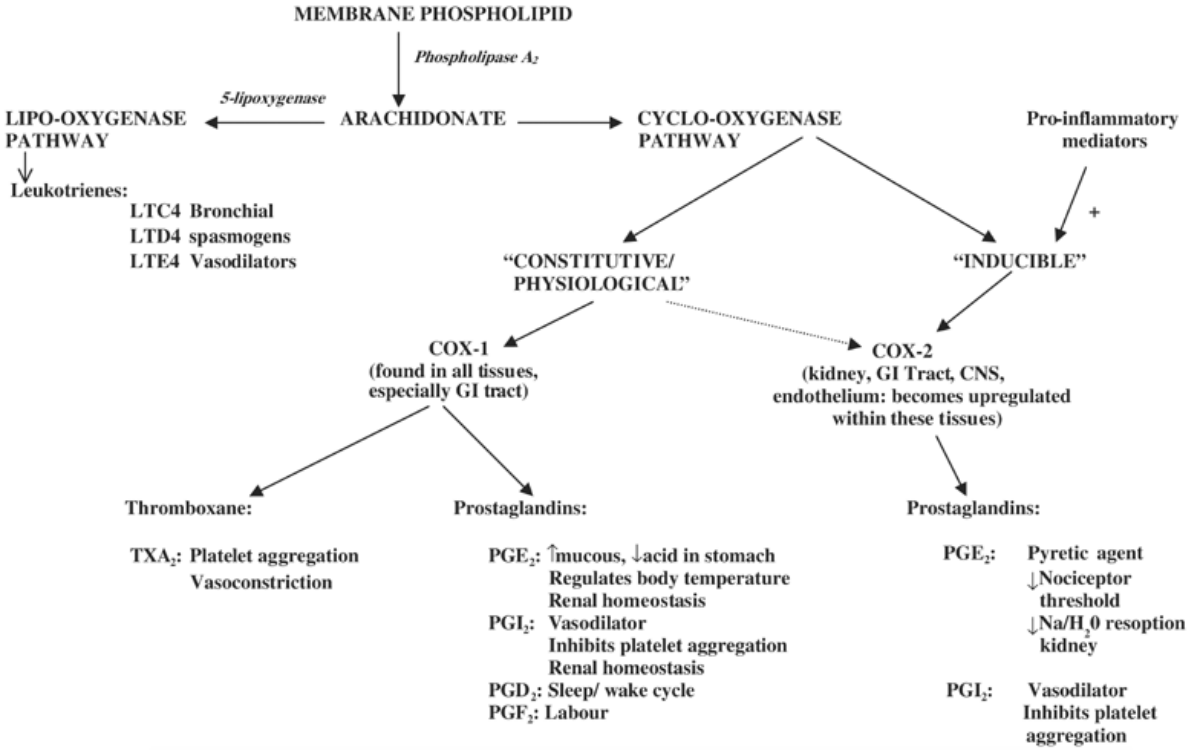
Describe the prostaglandin pathways and their physiological role in the production of pain

Prostaglandins are a series of 20-carbon unsaturated FAs containing cyclopentane ring

- derivatives of arachadonic acid
- not stored; synthesised prior to release
- locally acting autocrine or paracrine messengers

Synthesis

- arachadonic acid formed from tissue by phospholipase A2 → converted to prostaglandin H2 (PGH2) by cyclooxygenase 1 (COX1) and COX2
- PGH2 = precursor for other prostaglandins, prostacyclin, and thromboxane via actions of specific enzymes or via free radical oxidation of arachadonic acid



Prostaglandin receptors

- GPCR named according to class of PG binding to it
- Ligand binding → stimulates 2nd messengers
- Effects of PGs largely on smooth muscle → control [Ca2+] ions

Metabolism

- local destruction + metabolism of circulating prostaglandins via renal, pulmonary, and hepatic circulations

Physiological role

Physiological Roles - ("Multitudinous & varied")

Type	Receptor	Physiological Role
Thromboxane (TXA)	TP	blood clot activation and stabilisation (TXA produced by platelets)
(Prostacyclin) PGI2	IP1, IP2	Vasodilation (important renal vasodilator) inhibition platelet aggregation (most potent) bronchodilatation
PGE2	EP1	bronchoconstriction GI tract smooth muscle contraction
	EP2	bronchodilatation GI tract smooth muscle relaxation vasodilatation → patency of ductus arteriosus
	EP3	↓ gastric acid secretion ↑ gastric mucus secretion uterus contraction (when pregnant) GI tract smooth muscle contraction lipolysis ↑ platelet response to their agonists and ↑ atherothrombosis
	Unspecified	Hyperalgesia pyrogenic Promotes wakefulness
PGF2α	FP	Uterus contraction, bronchoconstriction, pulmonary vasoconstriction, vasoconstriction, GIT muscle constriction
PGD2	DP1, DP2	Promotes sleep, renal vasodilator

PGD2, PGE1, PGE2, PGI2 → oppose vasoconstrcition effects of sympathetic nerves or angiotensin II preserving medullary blood flow in high metabolism low perfusion regions.

Classify non-steroidal anti-inflammatory drugs and outline their pharmacology in relation to enzyme inhibition, mode of administration and adverse effects

NSAIDs = class of drugs that exert effects via COX inhibition

Classification of non-steroidal anti-inflammatory drugs

Non-specific COX inhibitors	Preferential COX-2 inhibitors	Specific COX-2 inhibitors
Salicylates • Aspirin	Oxicams • Meloxicam	Pyrazoles • Parecoxib • Celecoxib • Rofecoxib
Oxicams • Piroxicam		
Acetic acid derivatives • Diclofenac • Indomethacin • Ketorolac		Methyl-sulphones • Etoricoxib
Propionic acids • Ibuprofen • Naproxen		Phenyl-acetic acid derivatives • Lumaricoxib
Para-amino-phenols • Paracetamol		
Anthralinic acids • Mefanamic acid		
Pyrazalones • Phenylbutazone		

Pharmacology in relation to enzyme inhibition

COX

- 3 isoforms of COX: COX-1, COX-2, COX-3
- Convert arachadonic acid to endoperoxidases → prostaglandins + TXA2 + prostacyclin
    - Prostaglandins
        - Prostacyclin: promotes vasodilation + inhibits platelet aggregation
        - Involved in the sensitisation of peripheral pain Rs to noxious stimuli
    - Thromboxane
        - Produced by platelets when activated by exposure to adenosine, collagen, or adrenaline
        - Promotes haemostasis by vasoconstriction + platelet aggregation
- Isoforms:
    - COX-1
        - Constitutive form
        - production of PGs that control RBF + protective gastric mucosal barrier
        - Mediates synthesis of thromboxane
    - COX-2
        - Inducible form
        - 2° tissue damage + facilitates inflammatory response
        - Mediates production of prostacyclin (PGI2) in vascular endothelium
    - COX-3
        - Variant of COX-1; centrally + mediates analgesic and antipyretic effects of paracetamol

MOA of NSAIDs

- COX inhibition → prevents production of prostaglandins (incl prostacyclin) + thromboxanes from membrane phospholipids
- Clinical effects:
    - Analgesia: via ↓PGE2
    - Antipyrexia: via ↓PGE2
    - Anti-inflammatory: via ↓PGE2
    - Antiplatelet (aspirin) via ↓TxA2
    - Ductus arteriosus closure: via ↓PGE2

Selective COX-2 inhibitors

- Advantages: ↓risk PUD; ↓platelet disfunction
- Disadvantages: ↑expensive; can precipitate AKI; ↑risk thrombosis e.g. MI, stroke

Adverse effects

- generally 2° COX-1 inhibition
- **platelet dysfunction**: COX1 inhibition → ↓TxA2 → impaired thrombotic function, vasoconstriction, activation of platelets, ↓stability platelet plug.
- **GIT ulcers**: ↓PGI2 + PGE2 (gastroprotective via stimulation of mucus release)
- **↑bleeding:** impairs platelet aggregation via ↓TXA
- **Renal: ↓RBF + ↓GFR**: renal failure in pts who require PEG2 + PGI2 for renal vasodilation (e.g. diabetics); ↑Na+ retention
- **bronchoconstriction**: in asthma 2° ↓PGE2 + PGI2 (anti-inflam) + ↑leukotrienes (pro-inflam); shunting of PG metabolism → ↑[leukotrienes]
- delays onset of **labour**: ↓PGE2
- premature closure of **ductus arteriosus**: ↓PGE2
- **drug interactions**: ↑PB → displace other drugs → ↑effect
- **allergy**: SJS
- **NB COX-2** inhibitors: prothrombotic 2° ratio of Tx to prostacyclin production → MI + stroke

	Aspirin	Ibuprofen	Ketorolac	Parecoxib	Celecoxib	Paracetamol
Chem	Aromatic ester of acetic acid	Phenylpropanoic acid derivative	Dihydropyrrolizine carboxylic acid derivative Structurally related to indometacin	Prodrug of valdecoxib		acetanilide derivative
Type	Non specific	Non specific	Non specific	Specific COX 2	Specific COX 2	Non specific
Uses	Analgesic/ anti-inflam Antipyretic Prevention post MI/ graft Rx pre-eclampsia DVT prophylaxis in ortho	Analgesic Antipyretic Anti-inflammatory	Analgesia → moderate to severe post-op pain Anti-inflammatory	Analgesia	Analgesia	Analgesic Antipyretic Anti-inflammatory
Pres	75/100/300/600mg tablets	Capsules/ tablets/ suspension/ suppositories/ topical gels	Clear/ pale yellow solution for injection in 30mg/ml	Powder in vial; 40mg; reconstitute in 2mL NS		tablet + suppositories containing 60/125/250/500mg syrup 24/50mg/ml IV: 20mg/ml in 50ml and 100ml vials
Action	Irreversible COX inhibitor Low doses → selective platelet COX inhibitor → ↓TXA2 formation As platelets anucleic → unable to regenerate TXA2	Non-specific COX inhibitor	Non-specific COX inhibitor	Prodrug → converted to valdecoxib by hydrolysis in liver **COX2 inhibitor** → prevent conversion of arachadonic acid to PG	COX-2 inhibitor	Non-specific **COX inhibitor** **5HT1B agonist** → analgesia Blocks peripheral generation of afferent nociceptive impulses within bradykinin-sensitive chemoreceptors
CNS	Antipyretic: inhibition of PG synthesis					Analgesia/ antipyretic/
CVS	↓risk MI/ CVA ↑bleeding			↑risk AMI/ ACS 2o ↓prostacyclin production → shift in prostacyclin:TXA2 ratio		
Resp	↑O2 consumption + CO2 production by uncoupling oxidative phosphorylation	Bronchoconstriction in asthma (20%)	Bronchospasm (20% asthmatics)	Bronchospasm (asthmatics)		
AS	↑gastric acid production	Dyspepsia, N+V, ulceration, perforation, diarrhoea	COX-1 effects: dyspepsia, nausea, bleeding, mucosal ulceration, diarrhoea	Inhibits CYP450 → ↑conc flecainide, metoprolo, imeprazole, pheny, diaz Nil inhibition of PG release: ↓risk GI bleed		
Other	Reye's syndrome: mitochondrial damage, hepatic failure, cerebral oedema, encephalopathy in children <12	↓platelet aggregation	Prolongs bleeding time	Renal arteriolar vasoconstriction		
Toxicity/ SE	OD → uncouples oxidative phosphorylation → resp + metabolic acidosis; pulmonary oedema, resp failure GI upset/ bleed + gastric ulceration Renal papillary necrosis Bronchospasm Aplastic anaemia	Rash Analgesic nephropathy: papillary necrosis + interstitial fibrosis	Due to inhibition of COX1	ARF		GI upset, rash, hypotension on IVI Paracetamol overdose: 2o depletion of glutathione store → accumulation of NAPQI → hepatocyte necrosis
Route/ dose	PO: 100mg daily (300mg loading)	PO: 1200mg daily Paeds: 20mg/kg	IM: 30mg IV: 30mg	IV: 40mg; 20-40mg BD-QID		PO: 500mg to 1g 4-6hr
Onset			IM: 10mins IV: <3mins			<1hr

Duration			6-8hrs			4-6hr
A	Bioavailability 70% Extensive 1st pass metabolism	Bioavailability 80%	Rapid; PO + IM 100%	Nil PO		bioavailability 70-90%
D	Vd 10L/kg PkA3: unionized Limited ability to cross BBB	Vd 0.14L/kg	Vd 0.2L/kg			VD 1L/kg pKa 9.5; weak acid; non-ionised, lipid soluble → penetrates tissues, BBB, placenta
PB	80%	90%	99%	95%	97%	10%
M	**Liver** 50% to salicylurate (saturatable) 20% = to salicylphenolic glucuronide (saturatable)	Liver CYP via oxidation to 2 inactive metabolites	Liver Hydroxylation + conjugation	Valdecoxib → hepatic metabolism CYP2C9 / CYP3A4 and glucuronidation One metabolite antagonises COX2	**CYP2C9 to inactive metabolites**	**liver**: - 90% to **sulphate** + **glucuronide** conjugates - 5%by CYP450 to **NAPQI** → inactivated by conjugation with glutathione
E	**Renal** T1/2β aspirin: 15-20min T1/2β salicylic acid: 2-3hr	Urine ½ life 2hrs	Renal (90%) Faeces (6%) Clearance 20ml/kg/hour ½ life 5hrs	Parecoxib t1/2β 20min Valdecoxib t1/2β 8h		1-5% unchanged in **urine** clearance 5ml/kg/min t1/2β: 2-4hrs
Special points	Use in children is associated with Reyes syndrome (fatty liver, encephalopathy, cerebral oedema) OD: mortality 1-2%	ARF: in pts dependent on PG production for renal perfusion Antagonise antihypertensive effects of ACEI via inhibition of vasodilatory PG synthesis Inhibit activity of diuretics		Not affected by renal failure Caution in hepatic failure Interactions: ACEI (potentiare renal toxicity effects)		

Aspirin overdose:

- aspirin
  - acetylsalicylic acid
  - used as: anti-inflammatory, antiplatelet, analgesic
  - typical adult dose: 50-900mg/day
  - overdose >150mg/kg; severe toxicity >300mg/kg
- toxicity
  - salicylate = active metabolite → triphase toxicity
    - 1. Stimulates respiration → resp alkalosis
    - 2. Stimulates renal K and H+ dumping → worsens alkalosis
    - 3. Uncouples electron transport chain → metabolic acidosis
  - symptoms: N+V, confusion, seizures, coma
- Management
  - Supportive: ABC +/- activated charcoal
  - Correct electrolytes
  - NaHCO3 if severe acidosis
  - Dialysis if mod-severe toxicity
  - Psychiatric involvement

Describe in detail pharmacology of paracetamol including mode of action, clinical utility, metabolism and toxicity, advantages and disadvantages of different routes of administration

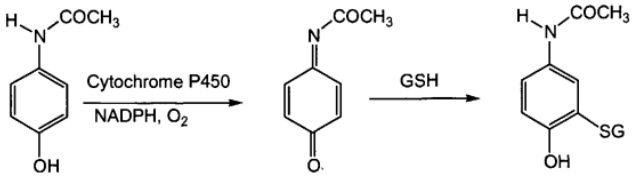
Pharmacology – *See above*

Paracetamol toxicity

- Paracetamol = N-acetyl p-aminophenol
- Used as antipyretic + analgesic; minimal anti-inflammatory properties
- In excess, one of the metabolites of paracetamol: N-acetyl-p-benzoquinonemine (NAPQI) → hepatotoxicity +/- fulminant liver failure

Metabolism:

- 1. Paracetamol → hepatic CYP2E1 oxidation (phase I) → NAPQI
- 2. NAPQI → hepatic flutathione conjugation (phase II) → 3-glutathionyl-NAPQI



Toxicity

- NAPQI = potent oxidant + extremely toxic to liver → causes hepatotoxicity via:
  - ↓liver glutathione stores
  - ↑formation of reactive O2 + N speces
  - oxidative stress on hepatocytes
  - loss of mitochondrial membrane potential → unable to synthesise ATP
  - hepatocyte necrosis
- Normally, NAPQI is made in small quanitities and rapidly eliminationed via phase II metabolism
- Toxicity may result if:
  - Excess paracetamol dose. In healthy patient:
    - >200mg/kg stat
    - >150mg/kg/day over 48hrs
    - >100mg/kg/day over 72hrs
    - >10-15g = lethal
    - Pathway 1 saturated → ↑CYP450 metbaolism → when glutathione <30% NAPQI bonds with hepatocytes causing cell death + centrilobular necrosis
  - ↑risk with:
    - ↑CYP450 activity: chronic EtOH abuse or drug use
    - pre-existing heaptic failure
    - ↓glutathione stores: malnutrition, chronic EtOH abuse

Management

- ABC
- 2. Activated charcoal → 1g/kg up to 50g <1-2hr of ingestion
- N-acetylcystine to ↑glutathione stores
- Methionine (↑glutathione synthesis) can be considered
- Monitor hepatic function
  - Serial LFT: reflects hepatocellular necrosis
  - Serial INR: reflct synthetic function
- Early referral for liver transplantation
  - Consider if high risk criteria:
    - INR>3 at 48hr or >4.5 at any time
    - Oliguria or Cr>200
    - Acidosis with pH<7.3 post resus
    - Ongoing hypotension SBP<80
    - Hypoglycaemia
    - Severe thrombocytopenia
    - Encephalopathy

Notes on NAC

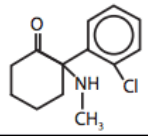
- Treat with NAC if
  - Immediate release
    - <8hrs of ingestion + 4-8hr level above Rumack-Matthew nomogram rx line
    - all pts presenting 8-24hr post ingestion
    - unknown time of ingestion
    - consideration to high risk pts
  - Sustained release
    - Start if >200mg/kg or 10g ingested
- Benefit:
  - Complete protection <8hrs
  - Incomplete protection >8hrs but ↓mortality
- Loading dose: 150mg/kg over 1/24 → then 50mg/kg over 4/24 → then 100g/kg over 16/24
- When to cease:
  - NAC commenced <8hr post ingestion + well after 20hr infusion
  - NAC commenced >8hr post ingection + well + normal transaminases after 20hr
  - If transaminases abnormal: continue infusion at 100mg/kg/16hr until transaminases and INR falling

PHARMACOLOGY OF SPECIFIC AGENTS: NMDA RECEPTOR ANTAGONISTS

Describe the location and role of NMDA receptors

- Ionotropic ligand gated glutamate receptor
- Location: dorsal horn of SC + brain
- Role: central sensitisation; learning + memory; cerebral ischamic damage
- Voltage dependent
  - Channel for Ca2+/Na+(central pore) is "blocked" by Mg2+ ion in resting state (unblocked when partially depolarised)
  - ↑intracellular Ca2+ activates 2nd messengers (e.g. IP3, DAG) → EPSP
  - Secondary events: NO production; activation of 2nd messengers + enzymatic processes
- Agonised by glutamate (Glycine = co-agonist)
- Antagonists
  - Ketamine: binds at site distant to glutamate binding site → conformational change in NMDA R → prevents binding of glutamate
  - N2O, Xe

Describe in detail the pharmacology of ketamine including mode of action, clinical utility, metabolism and toxicity, advantages and disadvantages of different routes of administration

	Ketamine
Chem	phencyclidine derivative alkylated phenol Racemix mix: equal portions 2 enantiomers due to chiral centre of cyclo-hexanone ring ([S-(+)-ketamine] and [R-(-)-ketamine]) 
Uses	Induction, sedation
Pres	clear, colourless solution containing 10/50/100mg/ml of racemic ketamine hydrochloride
Action	Dissociative anaesthesia – profound analgesia + superficial sleep non-competitive antagonist of NMDA-R Ca2+ channel pore + inhibits NMDA receptor activity by interaction with phencyclidine binding site → ↓pre-synaptic release of glutamate + interaction with opioid receptors ?antagonist at monoaminergic, muscarinic, and nicotinic receptors
CNS	Dissociative state 2o separation functionally + electrophysiologically of thalamo-limbic system Eyes open; nystagmus; hypertonus ↑CBF, ↑ICP, ↑IOP, ↑CMR
CVS	↑SNS tone → ↑circulating Ad + NAd → ↑HR, ↑BP, ↑CVP, ↑CO mild direct myocardial depressant
Resp	Bronchodilation ↑pulmonary compliance
AS	↑salivary secretions
Other	
Toxicity/ SE	Emergence delirium, dreams, hallucinations; N+V; rash
Route/ dose	IM: 4-10mg/kg; IV: 0.5-2mg/kg over 60s; IVI for maintenance: 10-50microg/kg/min PO, PR, nasally, intrathecal, extradural
Onset	IV: 30sec IM: 2-8mins;
Duration	IV: 5-10mins IM: 10-20mins
A	PO 20% Nasal 25-50% IM 95%
D	25% protein bound Vd 3L/min pKa 7.5
M	Liver N-demethylation + hydroxylation via CYP450 Norketamine (30% potent) → glucuronide (inactive)
E	Urine Clearance 17ml/kg/min Elimination ½ life 3hrs
Special points	

PHARMACOLOGY OF SPECIFIC AGENTS: ANTICONVULSANTS

Describe the pharmacology of anticonvulsants relevant to pain medicine, including gabapentin and carbamazepine

	Carbamazepine	**Na valproate**	**Pregabalin**	**Gabapentin**
Chem	Iminostilbene derivative – structurally related ot the tricuclic antidepressants	Sodium salt of valproic acid (fatty carboxylic acid)	GABA analogue (S)-3(aminomethyl)-5-methylhexanoic acid	Acetic acid derivative (structural analogue of GABA)
Uses	Anticonvulsant + analgesic Trigeminal neuralgia Bipolar disorder	Primary generalised epilepsy esp. petit mal, myoclonic seizures, tonic-clonic Chronic pain	Anticonvulsant/ analgesic/ anxiolytic Neuropathic pain Partial seizures	Anticonvulsant + analgesic Neuropathic pain Partial seizures
Pres	100/200/400mg tablets 125/500mg suppositories white syrup 20mg/ml carbamazepine	100/200/500mg tablets syrup 40mg/ml ampuoles 400mg lyophilized Na valproate for dilution in 4ml water	25-300mg capsules containing lactose monohydrate	600/800mg tablets + capsules
Action	Unknown ?alterations in adenosine disposition within CNS	GABA-ergic inhibition; ↑brain GABA by inhibition of succinic semialdehyde dehydrogenase in GABA shunt May: - minic action of GABA at post-synaptic Rs - ↓excitatory inhibition	Structurally related to GABA but doesn't interact with GABA Rs Binding site is alpha-2-delta subunit of voltage gated Ca2+ channels	Structurally related to GABA; doesn't interact with GABA Rs Binding site: a-2-delta subunit of voltage gated Ca2+ channels May also: - partially ↓response to glutamate agonist NMDA - ↓release of monoamine NTs - stimulate glutamate decarboxylase - ↑synaptic release of GABA
CNS	↑seizure threshold	Anticonvulsant Minimal sedation Essential tremor	Analgesic Anticonvulsant Anxiolytic	Analgesic Anticonvulsant
CVS	Antiarrhythmic; ↓AV conduction			
Other	Antidiuretic	↑NH4		
Toxicity/ SE	Diplopia, N+V, drowsiness, ataxia Rashes 3% Mild neutropenia Aplastic anaemia	Hepatic dysfunction, acute pancreatitis, GI upset, hair loss, oedema, weight gain Platelet disturbances: ↓aggregation; thrombocytopenia Coagulation disturbances: ↑bleeding time, ↑PT, ↑APTT	Weight gain in DM pts	Dizziness, ataxia, nystagmus, somnolence, tremor, diplopia Leucopenia, weight gain
Route/ dose	100-1600mg daily; divided doses	PO: 600-2500mg daily in 2 divided doses IV: 400-2500mg in divided doses Effective plasma range: 40-100mg/L	PO: 150-600mg/day	PO: initially 300mg TDS up to 1800mg/d
Onset				Peak plasma levels <2-3hrs
Duration				
A	PO: bioavailability 100%	Rapid + PO bioavailability 100%	Rapid; bioavailability >90%	Bioavailability 60%
D	75% protein bound Vd 1L/kg	90% protein bound Vd 0.1-0.4L/kg Brain concentrations 7-30% plasma levels	Not bound to plasma proteins Vd 0.56L/kg	Not bound to plasma proteins Vd 0.85L/kg
M	Liver Oxidation to epoxide (active) Chronic use: induces own metabolism	Liver Oxidation + glucuronidation Some active metabolites	Minimal metabolism 0.9% administered dose excreted as major metabolite N-methylated pregabalin	Not metabolised
E	**Urine** as unconjugated metabolites Clearance 20ml/kg/hr Elimination ½ life 16-36hr	1-3% unahcnaged in **urine** clearance 7-11ml/kg/hour elimination ½ life 8-20hrs	98% unchanged in **urine** elimination ½ life 6hrs clearance directly proportional to creatinine clearance	**Renal**; unchanged Elimination ½ life 5hrs Clearance directly proportional to creatinine clearance
Special points	NaValproate + CCB → ↑[free carbamazepine] ↓efficacy of panc/ vec	CI in acute liver disease Sedative effects additive with other DNS depressants Not removed by dialysis	Removed by dialysis	Should be weaned if discontinuation of therapy regardless of indication ↓in renal impairment