Analgesia

Pain = unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage

Treat cause and relieve pain symptomatically.

**WHO ladder, 1996 (ish!)**

**Mild pain**  
Non-opioid analgesics (paracetamol, NSAIDs)

**Moderate pain**  
Add weak opioid

**Severe pain**  
Add strong opioid

**Overwhelming pain**  
Add strong opioid plus anxiolytic (e.g. diazepam) or major tranquilliser (e.g. chlorpromazine)

**Adjuvants**

- Secondary analgesics
  - Antidepressants: esp. TCAs
  - Antiepileptics: carbamazepine, phenytoin, valproate, gabapentin, pregabalin
  - Muscle relaxants
  - Steroids
- Control of adverse effects
- Also consider non-pharmacological measures

**Note**

- Keep it simple
- Become familiar with a couple of agents from each class
- Avoid fixed combination analgesics
  - E.g. co-proxamol/distalgesic no better than paracetamol and dextropropoxyphene alone  
  tend to forget what is actually in it!  
  this particular combination lost its licence in 2007 due to excessive involvement in drug-related suicide
- Specific types of pain
  - Bone secondaries: NSAIDs
  - Neuropathic pain: low-dose antidepressants/antiepileptics
  - Severe back pain (e.g. disc prolapse) with muscle spasm: low-dose BZs as muscle relaxant

**Paracetamol (acetaminophen)**

**Mechanism**

- Analgesic: efficacy equivalent to aspirin
- Antipyretic: lowers set-point in hypothalamus
- Not anti-inflammatory or anti-platelet

Used for mild to moderate pain, but NSAIDs are preferred if due to inflammatory process

**Target unknown**

- Does it act by inhibiting the newly identified COX-3 (see below)? Probably not – paracetamol has less activity against COX-3 than most NSAIDs.

IV formulation now available (Perfalgan®)
**Metabolism**
- Hepatic conjugation to inactive glucuronide and sulphate
  - Pathway saturated in overdose
- Minor P<sub>450</sub> oxidation products incl. N-acetyl p-benzoquinone imine (NABQI) are also formed (4%)
  - Non-saturating pathway
  - NABQI is highly chemically reactive and is usually inactivated by conjugation with SH (thiol) groups of glutathione
  - Supply of glutathione is limited and exhausted in overdose
  - NABQI then reacts with cellular macromolecules and causes cell death
- NAC = glutathione donor (glutathione itself cannot permeate cell membranes)

**Adverse effects**
Therapeutic usage: side-effects rare (skin rash, allergy)
Overdose: can result in fulminant hepatic necrosis and liver failure

**Paracetamol overdose**
Ingestion of >7.5g of paracetamol may be fatal
Ingestion of >5g may be fatal if hepatic enzyme induction has occurred due to chronic alcohol abuse or drug therapy e.g. carbamazepine, phenytoin, rifampicin (more rapid synthesis of NABQI)

**Clinical features**
In severe poisoning
- <24h: none or N&V
- >24h: N&V, RUQ pain, jaundice, encephalopathy

**Management (NPIS guidelines)**
- **Staggered**
  - Plasma levels meaningless
  - Strongly consider NAC
  - Medically fit for discharge after NAC treatment completed, or if not given 24h after last paracetamol dose, provided that criteria below met
- <8h
  - 50g activated charcoal PO if
    - Suspected dose >150mg/kg
    - Able to give charcoal within 1h of overdose
  - Paracetamol/salicylate level, INR, creatinine and ALT at 4h after overdose, or ASAP after 4h
  - Start NAC if
    - Either plasma level above relevant line on nomogram
    - Or plasma level not available within 8h, and >150mg/kg or >12g ingested (whichever is smaller)
      - Stop if plasma level result subsequently indicates that not required
  - On completion of treatment, medically fit for discharge if criteria below met
- 8-15h
  - If >150mg/kg or >12g ingested (whichever is smaller), start NAC immediately without awaiting levels
  - Paracetamol/salicylate level, INR, creatinine and ALT
  - If already receiving NAC, stop only if paracetamol level, INR, creatinine and ALT normal, and patient asymptomatic
  - If not already receiving NAC, start NAC if
    - Either paracetamol level above relevant line on nomogram
    - Or INR, creatinine or ALT abnormal
  - On completion of treatment, medically fit for discharge if criteria below met
- 15h-24h
  - If >150mg/kg or >12g ingested (whichever is smaller), start NAC immediately without awaiting levels
  - Paracetamol/salicylate level, INR, creatinine and ALT
  - Prognostic accuracy of treatment lines beyond 15h is uncertain – seek advice
On completion of treatment, medically fit for discharge if criteria below met

- 24h+
- INR, creatinine, ALT, venous gas – discuss any abnormalities

**NAC/Parvolex infusion regime**

- 150mg/kg in 200ml 5% dextrose over 15min
- 50mg/kg in 500ml 5% dextrose over 4h
- 100mg/kg in 1000ml 5% dextrose over 16h

**Anaphylactoid reaction to NAC**

- Usually within 30min of starting NAC
- Stop NAC, give IV antihistamine
- Once adverse effects have settled, can usually resume infusion at 50mg/kg over 4h

**Criteria for discharge**

- Asymptomatic
- Paracetamol level below treatment line, or NAC course completed
- INR, creatinine and ALT normal
- Advise patient to return if vomiting or abdominal pain develop or recur

**Possible indications for referral to liver unit**

- Rapid development of Grade 2 encephalopathy
- pH<7.3 more than 24h after ingestion
- PTT >45s at 48h or >50s at 72h
- Rising plasma creatinine

**In such patients prior to transfer**

- Monitor conscious level 8 hourly
- Start 5% dextrose infusion 1litre/12h, and monitor blood glucose 4°
- Monitor CVP and UO, correct hypovolaemia with colloid
- Check PTT 12° and creatinine daily
• Start prophylaxis against stress ulceration with sucralfate 1g 6° PO or by NG tube

**NSAIDs**

**Mechanism**
Structurally heterogeneous group of drugs that act by inhibiting cyclo-oxygenase (prostaglandin G/H synthase) that is responsible for conversion of arachidonic acid to cyclic endoperoxides.

<table>
<thead>
<tr>
<th>Isoforms:</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>• COX-1 constitutive</td>
<td>present in platelets, endothelium, stomach and kidney</td>
</tr>
<tr>
<td>• COX-2 induced by inflammation</td>
<td></td>
</tr>
<tr>
<td>(COX-3)</td>
<td></td>
</tr>
<tr>
<td>(pCOX-1a)</td>
<td></td>
</tr>
<tr>
<td>(pCOX-1b)</td>
<td></td>
</tr>
<tr>
<td>All are generated from one gene by RNA splicing, and possess varying pro- and anti-inflammatory effects</td>
<td></td>
</tr>
<tr>
<td>Future questions</td>
<td></td>
</tr>
<tr>
<td>o Is there a ‘COX continuum’ where differential activation of different isoforms causes a predominantly pro- or anti-inflammatory action?</td>
<td></td>
</tr>
<tr>
<td>o What is the pathophysiological role of the hitherto unknown isoforms? How are they affected by the known NSAIDs/paracetamol, and is there any point in developing specific inhibitors?</td>
<td></td>
</tr>
</tbody>
</table>

Such agents are thus
- Analgesic
  - Effective against pain of mild to moderate intensity
  - Do not cause dependence
- Anti-pyretic
- Anti-inflammatory
- Anti-platelet
  - Prevent production of thromboxanes, which cause platelet aggregation

In addition they are
- Useful in treatment of dysmenorrhoea (esp. mefanamic acid)
  - Associated with increased prostaglandin synthesis and increased uterine contractility
  - Could be used to prevent labour but is contraindicated because of effect on ductus arteriosus
- Used to close PDAs (esp. indomethacin)

**Adverse effects**
- Bronchoconstriction in asthmatics\(^1\) (pseudoallergic reaction)
  - Asthmatic patients sensitive to aspirin usually cross-react to other NSAIDs, but seldom (2%) react to paracetamol.

<table>
<thead>
<tr>
<th>Positively identified with aspirin-induced asthma</th>
<th>Avoid NSAIDs; recommend paracetamol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age&lt;40 or not used NSAIDs recently without incident</td>
<td>If NSAIDs necessary, give first dose under medical supervision. Advise patient that aspirin-induced asthma may develop later in life.</td>
</tr>
<tr>
<td>All other asthmatics</td>
<td>Use NSAIDs if required, advise patient to stop them and seek help in case of any respiratory reaction</td>
</tr>
</tbody>
</table>

- Patients with aspirin-induced asthma (AIA) usually have more severe asthma than those without aspirin sensitivity; they also frequently suffer from nasal polyps and sinusitis
- Gastric or intestinal mucosal damage
  - Mucosal prostaglandins

- Inhibit acid secretion
- Promote mucus secretion
- Prevent back diffusion of acid into the gastric submucosa
  - Inhibition thus results in dose-dependent
    - Erosions
    - Ulceration
    - Bleeding
      - There is no evidence that reducing the dose or using modified release formulations reduces the incidence of gastrointestinal haemorrhage; there is also no ‘mucosal tolerance’ with long-term use²

- Perforation
- Disturbances of fluid and electrolyte balance
  - Inhibition of renal prostaglandin production results in
    - Sodium retention and oedema
    - Possible hyponatraemia
    - Hyperkalaemia
    - Antagonism of anti-hypertensive agents

- Analgesic nephropathy
  - Esp. with renal artery stenosis/concomitant ACE-I use
  - Particularly associated with phenacitin \(\rightarrow\) withdrawn
  - Acute interstitial nephritis
  - Papillary necrosis
  - ARF

**Contraindications**
- NSAID-sensitive asthma
- Bleeding tendency/haemorrhage
  - Global
    - Bleeding disorders
    - Uncontrolled HT
  - Local
    - GI
    - Intracranial
- Hepatic/renal impairment
- Known hypersensitivity

**Interactions**
- ↑levels of methotrexate, lithium
- ↓effect of thiazides, loop diuretics, ACE-Is, β-blockers, oral hypoglycaemics

**Classification**
All agents are analgesic but vary greatly in their anti-inflammatory effects

**Weak**
- Anilines
- paracetamol
  - (phenacitin)

**Mild to moderate**
- Propionic acid derivatives
  - ibuprofen
  - naproksen
- Fenamic acids
  - mefenamic acid

**Marked**
- Salicylic acids
  - aspirin
- Acetic acid derivatives
  - diclofenac
  - indomethacin
- Pyrazolone derivatives
  - azapropazone
  - phenylbutazone
- Oxicam derivatives
  - piroxicam

**Strategies for protecting the GI mucosa**

- Add protective agent
  - Misoprostol given in combination with NSAID
    - Combination agents available (e.g. Arthrotec® = diclofenac + misoprostol)
    - CI in pregnancy (should not be used in women of childbearing age), main SE: diarrhoea
  - PPI
  - H2-blocker
  - Cochrane review of above concludes: “Misoprostol, PPIs, and double dose H2RAs are effective at preventing chronic NSAID related endoscopic gastric and duodenal ulcers. Lower doses of misoprostol are less effective and are still associated with diarrhea. Only Misoprostol 800 μg/day has been directly shown to reduce the risk of ulcer complications such as perforation hemorrhage or obstruction.”

- COX-2 selective agents
  - meloxicam, etodolac

- COX-2 specific agents
  - first generation: celecoxib (CLASS trial)
  - rofecoxib (VIGOR trial, withdrawn)
  - second generation: etoricoxib
  - lumiracoxib (TARGET trial)
  - valdecoxib (withdrawn)
  
  - In theory, avoid harmful effects on gastric mucosa (trial evidence as above) and ?kidney (CI in renal impairment)
  - However, they are associated with an increased risk in vascular events
  - On average, 4x more expensive than ibuprofen
  - Should be used in preference to standard NSAIDs only
    - When specifically indicated (i.e. for patients at high risk of gastroduodenal ulceration/bleeding)
    - After an assessment of cardiovascular risk
    - In patients *not* on aspirin (obviates any benefit, trial evidence as above)
  - Patients with IHD or cerebrovascular disease who are already receiving a COX-2 specific NSAID should be switched to alternative treatment as soon as possible (CSM guidance, 2004)

NB other agents have variable selectivity for COX-1/2

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**Salicylates (aspirin)**

<table>
<thead>
<tr>
<th>NSAID</th>
<th>Ratio COX-2 IC50 / COX-1 IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspirin</td>
<td>3.12</td>
</tr>
<tr>
<td>Naproxen</td>
<td>1.79</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>1.78</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>1.69</td>
</tr>
<tr>
<td>Celecoxib (Celebrex)</td>
<td>0.11</td>
</tr>
<tr>
<td>Etodolac</td>
<td>0.11</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>0.09</td>
</tr>
<tr>
<td>Diclofenac (Voltaren)</td>
<td>0.05</td>
</tr>
<tr>
<td>Rofecoxib (Vioxx)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

The lower the ratio, the better the COX-2 selectivity. The authors do not appear to draw this conclusion, but given the standing of diclofenac, COX-2 selectivity alone cannot offer a full explanation of protection against GI effects.
Aspirin = acetylsalicylic acid
Rapidly metabolised in plasma to salicylic acid

**Actions**

- Analgesic
  - Central and peripheral action
  - Mild effect and less than codeine
- Antipyretic: lowers set-point in hypothalamus
- Anti-inflammatory
- Anti-platelet

- Metabolic effects
  - Respiratory alkalosis
    - Direct analeptic action on respiratory centre
  - Metabolic acidosis
    - Uncoupled oxidative phosphorylation
    - Direct effect of salicylic acid in blood
    - Compensation for respiratory alkalosis leads to dehydration (↑susceptibility)
  - Hypoprothrombinaemia
    - Occurs with large doses, i.e. >5g/day
  - Hypoglycaemia or even hyperglycaemia can occur
  - Uricosuric effects
    - Reduces renal tubular reabsorption of urate but treatment of gout requires 5-8g/day
    - <2g/day may cause retention of urate.
    - Antagonises the uricosuric action of other drugs

**Adverse effects**

In general those described for NSAIDs but see overdose

Also
- Reye’s syndrome in children (age limit has been raised from 12 to 16)

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**Salicylate overdose**

Ingestion of more than 10g can cause moderate/severe poisoning in an adult

**Clinical features**

‘Salicylism’
- Tremor
- Vasodilatation, sweating
- Deafness, tinnitus
- Hyperventilation
- N&V

**Initial management**

- Activated charcoal effective >1h
- Ix
  - FBC
  - PT may be ↑ due to hypoprothrombinaemia (high-dose salicylate mimics warfarin)
  - UE hyperkalaemia is common
  - Glu hypoglycaemia is common (increased tissue glycolysis)
  - ABG respiratory alkalosis progressing to metabolic acidosis
  - Plasma salicylate (need to repeat)
  - CXR if pulmonary oedema suspected

- Forced diuresis with IV fluids
  - If salicylate level>500mg/l (3.6mM) consider alkalisation
  - If salicylate level>700mg/l (5.1mM)/profoundly acidaemic/pulmonary oedema consider haemodialysis

- Address complications
  - Correct hypokalaemia
  - Correct hypoglycaemia
  - Consider vitamin K 10mg
Opioid analgesics

Opium = mixture of opiates, but predominantly morphine (10%) and codeine
Opiate = derived from opium
Opioid = all substances binding opioid-R

Classification

Low efficacy
- Codeine
- Dihydrocodeine
- Dextropropoxyphene

Medium efficacy
- Buprenorphine
- Meptazinol
- Tramadol

High efficacy
- Morphine
- Diamorphine
- Pethidine
- Oxycodone
- Fentanyl
- Remifentanil

Note
- Codeine
  - Cannot be metabolised to morphine by 8% of the population (P450 polymorphism)
  - Ceiling effect
  - More emetic and more constipating than morphine
- Buprenorphine can be given sublingually and thus often used for surgical pain relief if no access and NBM; can cause confusion/hallucinations in elderly.
- Meptazinol is a useful moderate analgesic in patients in whom morphine is not indicated and who fail to respond to NSAIDs or are unable to take them (e.g. arthritic patients with peptic ulcer disease)
- Morphine available in many preparations
  - Oral (Oramorph) – onset 20min, peak 60min, lasts 4h
  - Oral slow-release (MST) – onset 1-2h, peak 4h, lasts 12h
  - IV/IM/SC – lasts 4h
- Diamorphine (heroin) is
  - Ca. x2 more potent
  - More lipid soluble $\rightarrow$ smaller injectable volume $\rightarrow$ used in emaciated patients and epidurals
  - More venodilating $\rightarrow$ used in pulmonary oedema
- Pethidine is a synthetic analogue
  - Less potent
  - Slower
  - Less smooth muscle spasm $\rightarrow$ used in pancreatitis
  - Repeat doses cause accumulation of norpethidine, a toxic metabolite that can cause seizures
- Oxycodone
  - Ca. 2x more potent (rel morphine)
  - Less SEs
- Fentanyl
  - Poorly titratable
  - No PO form available
  - Marked respiratory depression
  - But
    - Transdermal patches (25-100μg/h) last 72h, avoid 1st pass metabolism and poor compliance habits
    - Transdermal iontophoresis system (Ionsys®) allows PCA without needles
    - Parenteral form lasts ca. 20min, great for short procedures
    - Lozenges/lollipops available
- Remifentanil
A novel, expensive favourite on ITU, given as IV infusion. Has with extremely short half-life, thus can switch on-off/titrate very quickly (akin to e.g. UFH, esmolol); also metabolised by non-specific blood and tissue esterases, thus independent of liver metabolism.

40x more potent than morphine

**Mechanism of action**

Bind to CNS opioid receptors (µ, κ) whose natural ligands are endorphins, dynorphins and encephalins (these also bind δ receptors).

**CNS**
- Analgesia
- Sleep
- Miosis (does not tolerate out)
- Delirium
- Mood changes
  - Euphoria
  - Dysphoria
- Dependence
  - Up to 8h Mild psychological withdrawal stress
  - 8-12h Increasing nervousness, restlessness and anxiety
  - 12-24h Yawning, sweating, rhinorrhoea, galactorrhoea
  - 24h Pupils dilate, waves of goose flesh
  - 36h Twitching of muscles
  - Leg and abdominal cramps
  - Vomiting and diarrhoea and anorexia
  - Insomnia
  - Tachypnoea
  - Increased BMR and mild pyrexia
  - 48-72h Peak withdrawal symptoms
  - Up to 10 days Symptoms gradually subside
  - Complete recovery requires 3-6 months

**Note**
- Withdrawal syndrome can be in part alleviated by
  - Long-acting opioids such as methadone
    - Minimal cross tolerance
    - Addictive, hence only given if already opioid dependent
  - Non-opioids such as lofexidine (central α₂-agonist)
    - Reduction of rebound sympathetic activity
    - Less postural hypotension than with clonidine
  - BZs and neuroleptics are less effective

**Respiratory**
- Respiratory depression
- Cough reflex depression (codeine used as antitussive)
- Bronchospasm

**GI**
- Vomiting
  - Use antiemetics, can use haloperidol 1-3mg nocte as well
  - Usually tolerates out within 2 weeks
- GI muscle spasm, causing delayed transit and constipation (codeine used as antidiarrhoeal)
  - Only bothersome side-effect that does not tolerate out at all
  - Use softener and motility agent
  - In palliative care, can use dantron/co-danthramer (has both actions)
  - Less with fentanyl
- Biliary spasm

**Cardiovascular**
- Dilation of resistance vessels (arterioles) and capacitance vessels (veins) → hypotension
**Practical use**

Remember
- Prescribe 4° regular doses and 1° ‘breakthrough’ prn at first, then add up and convert to bd MST with ‘breakthrough’ dose 1/3 of MST dose
- Initial dose
  - Opioid naïve: 2.5-5mg morphine 4°
  - On weak opioid: 10mg morphine 4°
    - 2T co-proxamol 4° = 6mg morphine 4°
- Consider double dose at bedtime to prevent waking
- Converting route bioavailability
  - Oral:SC morphine = 2:1
  - Oral:IV morphine = 3:1
  - Oral morphine:SC diamorphine = 3:1
- Need to review very frequently in first 2-3 days
- Prolonged effect in hepatic and renal impairment (conjugate renally excreted)
- If intolerable side-effects before analgesia achieved: opioid rotation, co-analgesics

**Opioid overdose**

Death usually due to respiratory depression
Cardiovascular function usually well preserved unless severe anoxia

Treatment with naloxone (Narcan), an opioid antagonist
- IV: 0.8-2mg every 2-3min, up to maximum of 10mg
- SC/IM: if no IV access; slower onset of action
- Infusion: 10mg/50ml, rate adjusted to response

$t_{1/2}$ of naloxone is shorter (1h) than most opioids
- In particular methadone (long pharmacokinetic half-life)
- May need long infusion

Buprenorphine binds very tightly – effect reversed incompletely

Naltrexone (Nalorex) acts similarly and is used in detoxified ex-addicts (>7-10d); particularly effective against euphoric action of opioids, hence prevents relapse.

**Nefopam**

Taken PO in mild to moderate pain, 60mg tds
Unknown mechanism of action.