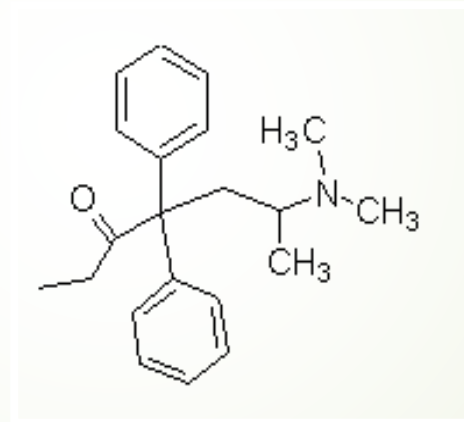
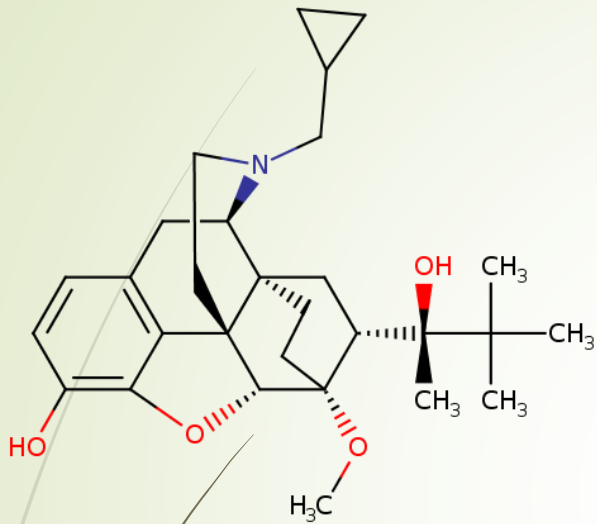


Complex Medication Management

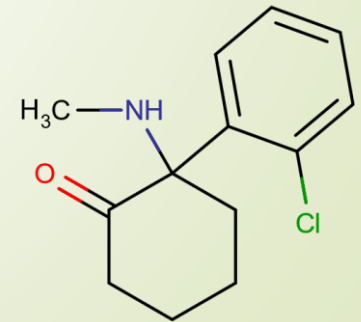


Analgesics

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Why these?

- Pharmacologically complex medications
 - Complex medication regimes
 - Complex regulations with use
 - Psychosocial complexity in prescribing
-
- Pain remains a significant problem
 - Safe use of opioids is NB
 - Responsible prescribing is important

Tasmanian Health Pathways

[Home](#) / [Medical](#) / [Palliative Care](#) / Pain Medications in Palliative Care

Pain Medications in Palliative Care


See also: [Opioid Conversion Guidelines](#)

Management

Practice point

Request [palliative care advice](#) if:

- uncertain about medication use or the use of multiple agents, or
- no improvement in 24 to 28 hours.

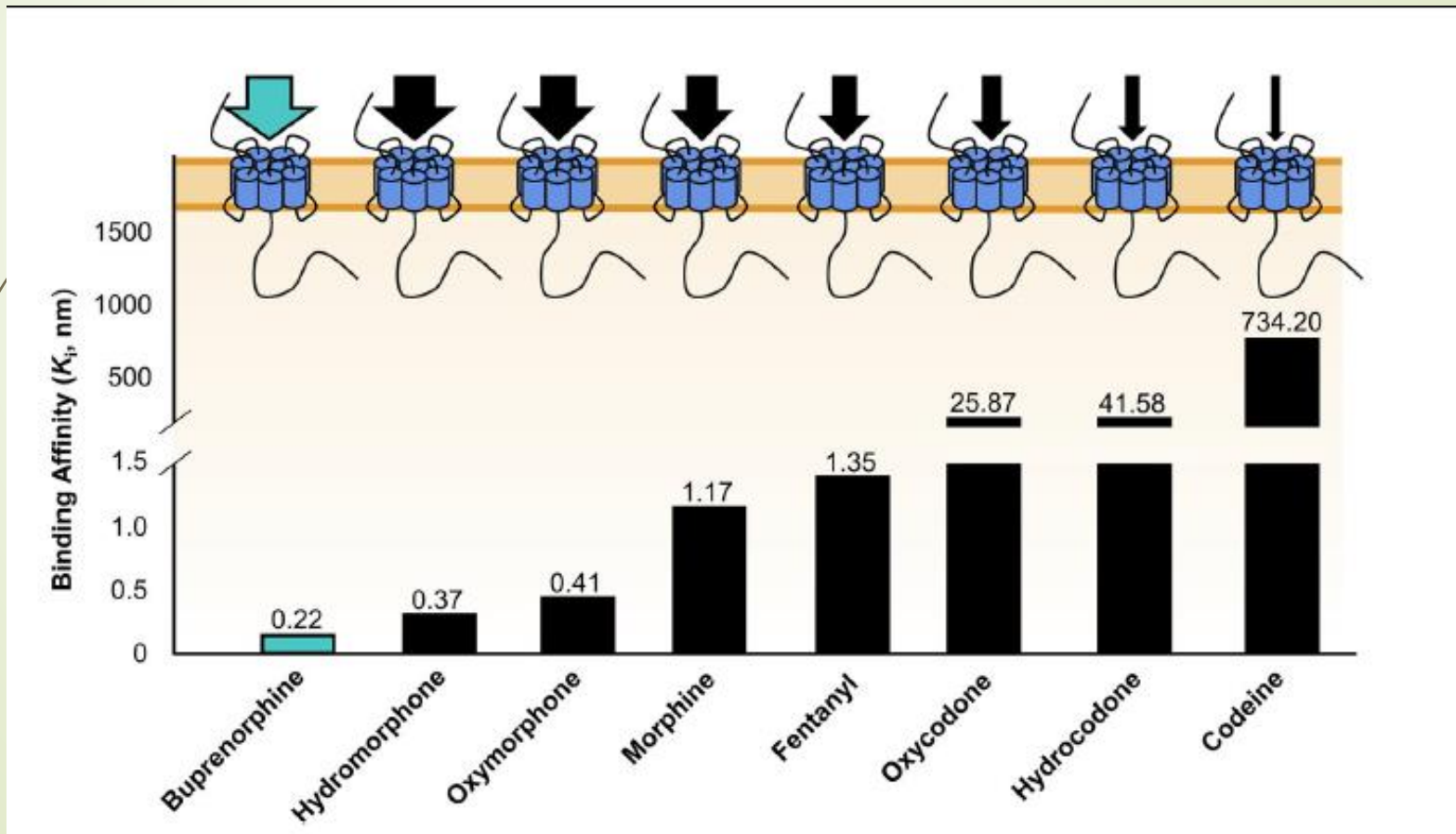
In general, do not use [weak opioids](#)  in palliative care due to low ceiling for toxicity and limited dosing range.

Complex Medications: Opioids₁

- Opioids mimic endogenous 'hormones'
- Their action is via μ , κ , δ receptors and ORL-1 receptor
- Used for:
 - Pain, cough & dyspnoea
 - Slowing of GI
 - Illicit recreation
- Incomplete cross tolerance

Complex Medications: Opioids₂

- Affinity (bonding) for the receptor:



Complex Medications: Opioids₃

- ▶ Potency or magnitude of effect:

Codeine	0.1
Morphine	1 oral = 0.3 SC
Oxycodone	1.5
Hydromorphone	5
Buprenorphine	100
Fentanyl	300

Methadone

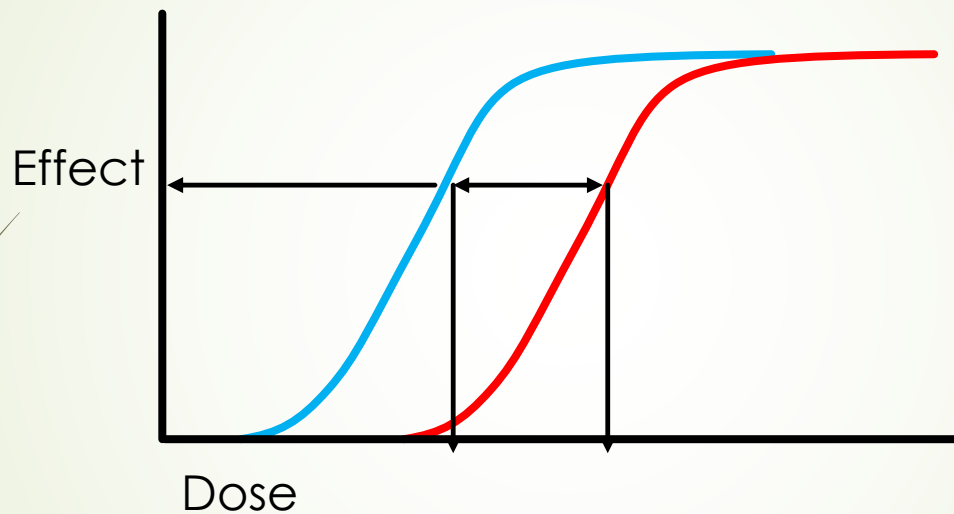
Variable

Complex Medications: Opioids₄

- In 1980's it was thought you just had to use 'enough' opioid.
- Since late 1990's progress in immunology, opioid pharmacology and pain has proposed:
 1. High dose opioids may exacerbate pain.
 2. Opioids influence immune response.
 3. Sensitisation can be due to neuroplasticity and NMDA mediated excitation: **Hyperalgesia**

Opioid tolerance vs pain

- Tolerance results in a right shift



- ? caused by \uparrow nociception.
- ? caused by hyperalgesia.
- ? Caused by non-compliance!!

Hyperalgesia

- Sensitisation is an \uparrow response for the same stimulus.
- Central or peripheral sensitisation is an amplification in nociceptive output.
 - An amplification in processing.
 - Producing \uparrow pain: **Hyperalgesia**
- It is thought caused by:
 - Neuronal maladaptation
 - Activation of Glia via TLR-4
 - Mediated by NMDA receptors

Opioid Induced Hyperalgesia₁

- Opioids may be responsible, **particularly at high doses.**
- Essentially opioids are cytokines (type V)
They are immune modulators.
- They contribute to a dose dependent neuroinflammation which overwhelms analgesia.
- The inflammatory response occurs both centrally and peripherally.

Opioid Induced Hyperalgesia₂

- For this and safety reasons guidelines now suggests maximal doses:

Oral Morphine 90-100mg.day⁻¹

Oral Methadone 40mg .day⁻¹

- Equivalent doses:

Oral Oxycodone 60-80mg.day⁻¹

Oral Hydromorphone 20mg.day⁻¹

Topical Fentanyl 25mcg.Hr⁻¹

Topical Buprenorphine 40mcg.Hr⁻¹

[Oral Tapentadol 250mg.day⁻¹]

Opioid Induced Hyperalgesia₃

- Hyperalgesia is managed using several strategies:
 - **Reducing the opioid dose**
 - **Switching to another opioid**
 - **Using an analgesic adjuvant**

- Management options:
 1. Switch to **Methadone**
 2. Use analgesic adjuvant **Ketamine**

Complex Opioid: Methadone₁

- Wide spectrum analgesic:
 - $\mu > \delta > \kappa$ agonist
 - NMDA antagonist** (weak)
 - SRI** >> **NRI**
 - Lymphocyte Ag 96 binder
 -
- Highly lipid soluble molecule
- Oral bioavailability is 85%
- 96% Protein binding to **α** and **β** globulins.
- Metabolised CYP **2B6** & **2D6**, 3A4 & 2C19

Complex Opioid: Methadone₂

- OK in renal failure
- **Half life varies 8-120hrs.**
- **Intra and inter-individual variability**
- 11.5% opioid related drug deaths

- **No dose equivalence with other opioids**

- **The pre-switch opioid dose correlates with Methadone potency.**

Complex Opioid: Methadone₃

- Rather than using switching strategies

Methadone is commenced by

TITRATION

- Starting dose is usually 2.5mg Nocte and
↑ in 2.5mg increments every few days.
- ↓ the 'pre-switch' opioid is challenging
when doses >100mg OME

Complex Opioid: Methadone₄

- Methadone is a second line agent.
- It is unpredictable and difficult to use.
- Methadone prescribing for addiction is **NOT** the same as prescribing for pain.
- Best left to those familiar with it.

- **Late onset toxicity is NB**

Remember safety is paramount.

Complex Adjuvant: Ketamine₁

- Ketamine is controversial in Palliative paradigm:
 - RCT showed no benefit vs placebo
 - Excluded 2/7 unstable analgesia
- APS Ketamine is beneficial.
- When opioids are escalating, and pain is increasing.
- Used in Continuous SubCutaneous Infusion (CSCI) over 24/24 for 3-5 days.

Complex Adjuvant: Ketamine₂

- It is also almost 50 years since it was developed
- It is an IV anaesthetic agent with:
 - Potent analgesic properties:**
 - Acute pain**
 - Burns**
 - Neurolept anaesthesia**
 - Antidepressant activity**
- NMDA receptor agonism is associated with:
 - Hyperalgesia**

Complex Adjuvant: Ketamine₃

- It's mechanism of action is:
 - NMDA antagonism
 - κ opioid agonism (NB Naloxone)
 - Nitric oxide synthetase inhibitor
 - ...
- Highly lipid soluble
- 53% bound to plasma proteins.
- **17% bioavailable** (NB cystitis)
- Metabolised by CYP **2B6**
- OK in renal impairment

Complex Adjuvant: Ketamine₄

- ▶ Half life 3-7Hrs
- ▶ Usually used in Palliative Care for patients who have both escalating pain and escalating opioid, especially:
 - Visceral pain
 - Neuropathic pain
 - Hyperalgesia
 - Prolonged opioid exposure
 - Past pain Mx problems

Complex Adjuvant: Ketamine₅

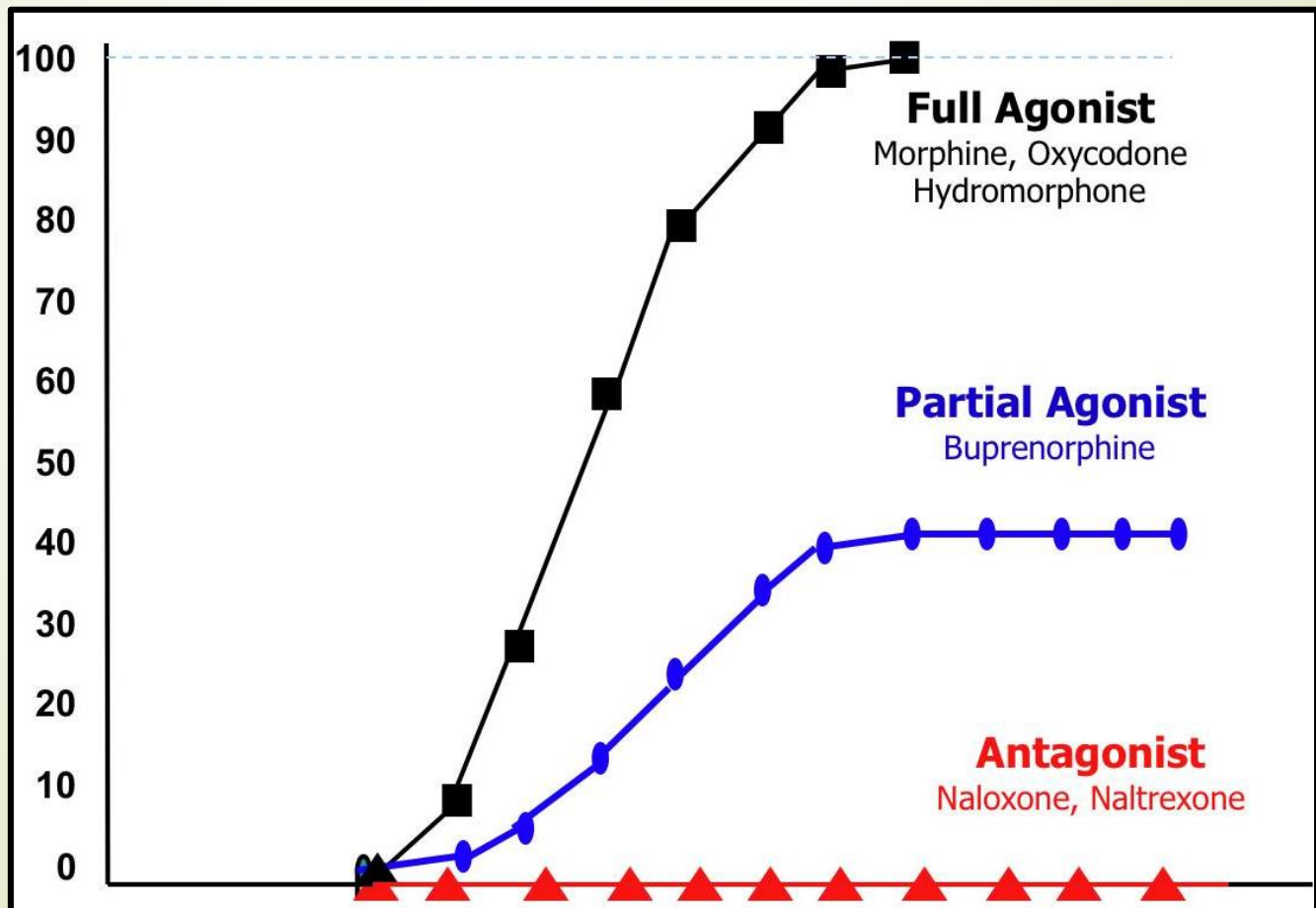
- Major side effect is hallucination, but a dysphoria can also complicate comfort.
- Starting doses vary from 25-150mg.Day⁻¹
- Efficacy may reduce the need for opioid so dose reduction may be prudent. (?Risk respiratory depression)
- Once analgesia established switch to Methadone.

Complex Opioid: Buprenorphine₁

- Buprenorphine is a semi-synthetic opioid.
- Developed in 1960's used in 1970's.
- Partial μ agonist, κ & δ antagonist.
- Binds to ORL-1 ? Action.
- Mostly used in addiction.
Safest of all Opioids owing to partial agonism
- Reported as having less effect on immune system

Complex Opioid: Buprenorphine₂

- Partial μ agonism causes ceiling effect:



Complex Opioid: Buprenorphine₃

- OK in renal failure
- Rapid onset of action
- Slow offset of action because of affinity and lipid solubility
- Not very effective in neuropathic pain
- ? Reduced risk opioid hyperalgesia.

- Why not in cancer pain?

Complex Adjuvant: Regimes₁

➤ Current paradigm is Multimodal analgesia

➤ Typical oral regime:

Simple analgesic	Paracetamol
Opioid IR & SR	Morphine
Adjuvant	Pregabalin

➤ Opioid is usually background SR dosing
Plus

Breakthrough analgesia 1/24 PRN

Complex Adjuvant: Regimes₂

- When swallowing an issue:
Switch to CSCI & SC breakthrough:
Morphine 5mg CSCI
Plus PRN
Morphine 0.5-1mg 1/24
Haloperidol 0.5mg 4/24
- Remember 15 hrs to steady state!
- Patients & families believe CSCI = death.
- 1-3 breakthroughs a day is normal.

Complex Adjuvant: Regimes₃

- No breakthroughs: ↓ the CSCI Morphine and recalculate breakthrough
- >3-4 breakthroughs ↑ the CSCI morphine and recalculate breakthrough
- Anxiety/ sedation can be managed with Midazolam in CSCI or Clonazepam.

Complex Medications: Regulations

- **PSB:** DORA real time monitoring.
Every patient on opioids
Contact if concerned.
- **PBS:** Recent unwinding of regulations for Palliative Care patients:
Benzodiazepines
Opioids (NB Kapanol for Dyspnoea)
- Ketamine and Midazolam not on the menu yet

Complex Medications: Problems

► Toxicity:

↑ dose

↑ absorption

↓ metabolism

Drug-Drug interaction

Other concurrent medications

► Lack of effect:

↓ dose

↓ absorption

↑ metabolism

Drug at site of action

Drug-Drug interaction

Other concurrent medications

Complex Medications: Tips & tricks

- ▶ **NEVER EVER use codeine for analgesia.**
- ▶ Last drug added may not have caused the side effects that have developed.
 - Pregabalin addition = sedation
 - Check renal function
 - Check opioid requirements
- ▶ **Prolonged pain means:**
 - more distressed patient & family
 - more complicated analgesia
 - complex mechanisms in play

eg opioid nearing ceiling 100mg OME

Complex medications: Tips & tricks

- Drug-drug interactions that involve **enzyme inhibition cause rapid toxicity.**
- Beware of Amitriptyline and opioid in the frail patients. (? Tramadol)
- Keep it simple and keep the doses low, with the ability to increment with B/T



Complex medications: Questions



Questions Please

