Long Term Use of Opioids in Cancer Pain – Implications & Complications

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Overview

- Opioid Induced Hyperalgesia
- Long-term effects of opioids
- Tramadol and Tapentadol
- Buprenorphine – key points
- Management of patients with pain or in EOLC on OAT

Opioids

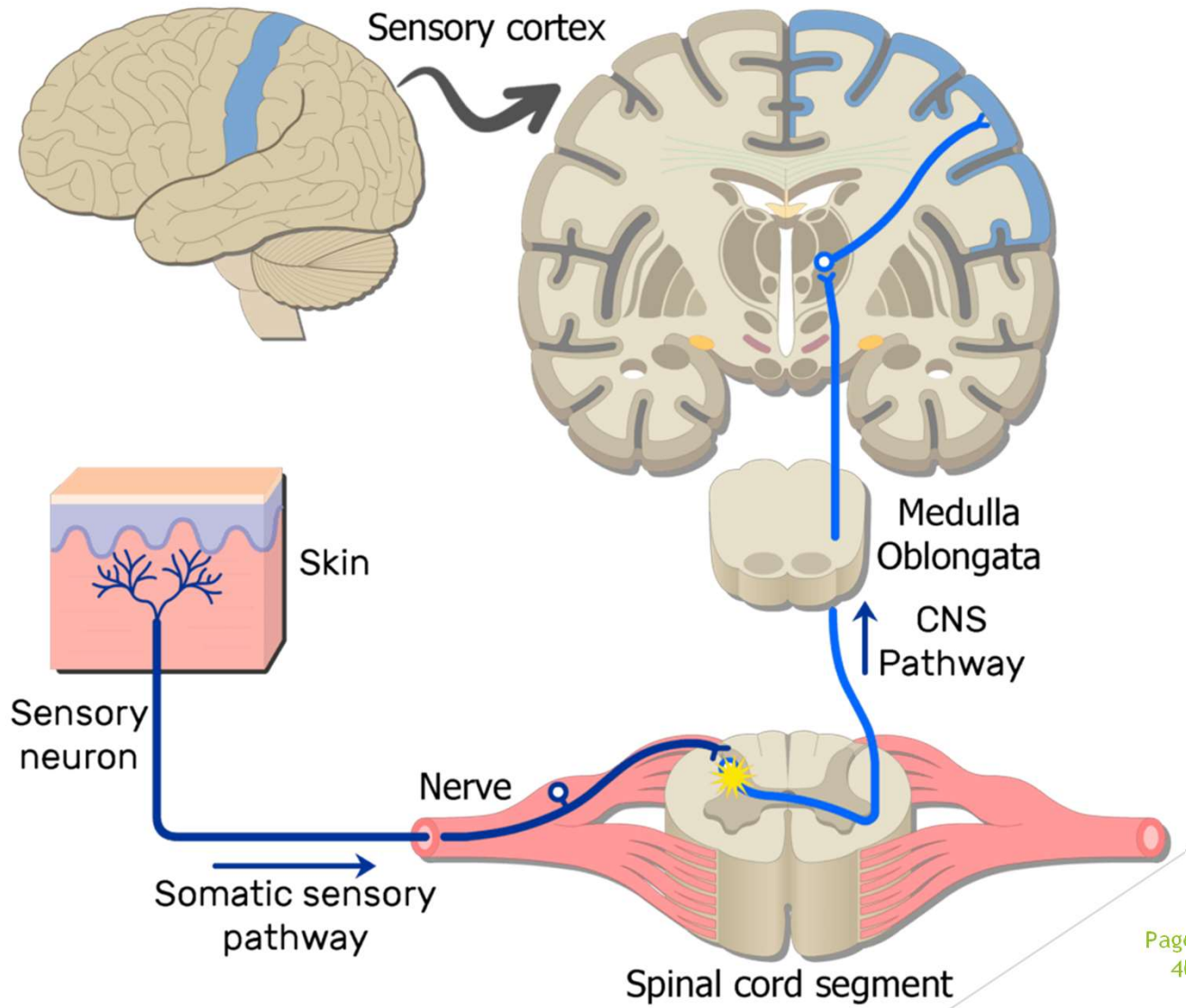
- Family of substances originally derived from the opium poppy
- First seen as long ago as 5700BC
- Used by most civilisations since. Most commonly used as an analgesic and sedative
- Greeks used it for its soporific properties and for pain (Morpheus origin)
- The Latin phrase “Sedare dolorem opus divinum est” is used to describe its benefits (alleviating pain is the work of the divine)
- Paracelsus in the early 1500s reintroduced it as Laudanum
- Thomas Sydenham used a tincture of opium and alcohol that he called Laudanum.
- 1874 – diamorphine (heroin) synthesised
- 1959 – Fentanyl developed

Pain Physiology - updated

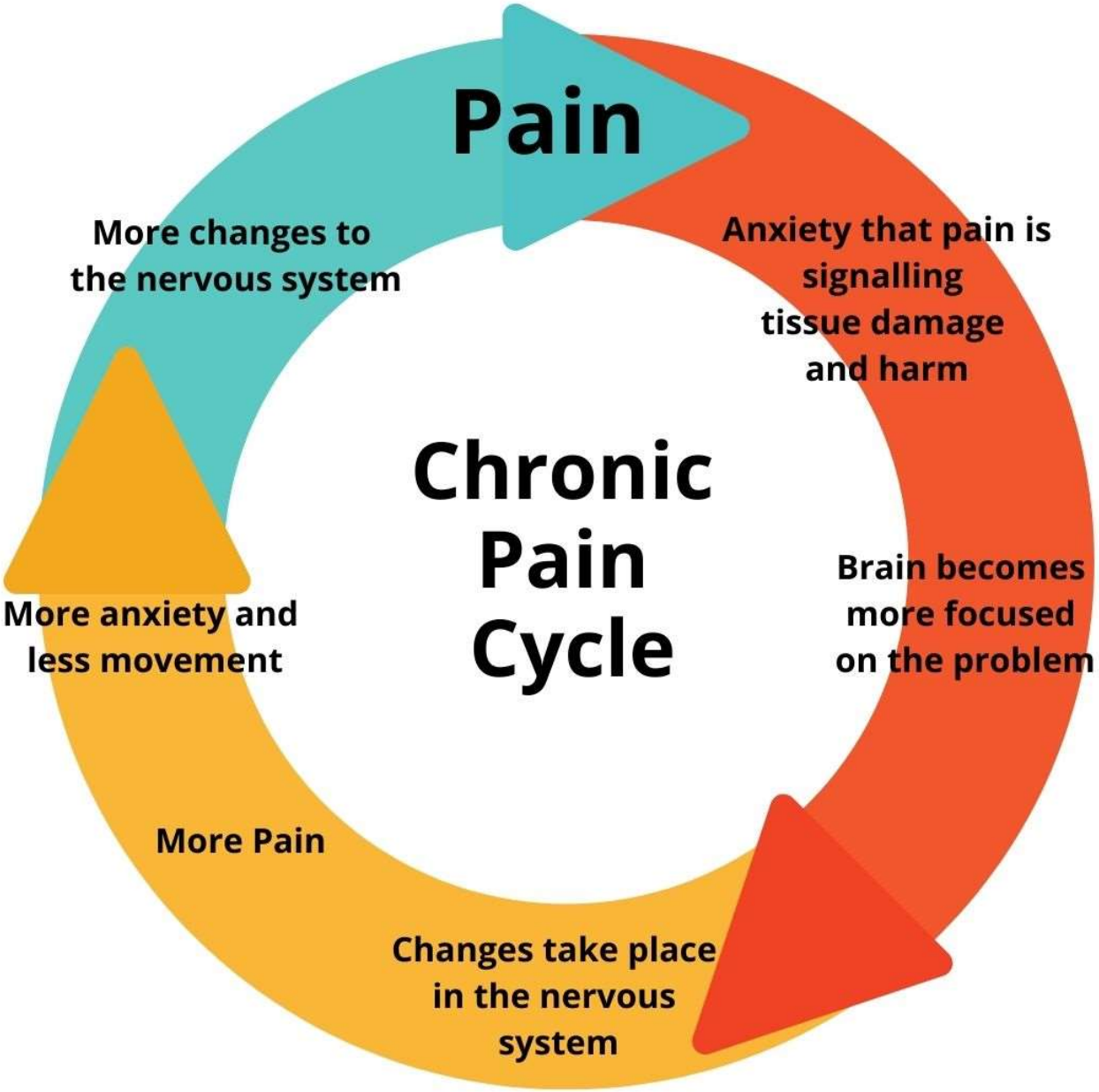
- Neuropathic – pain arising from disease or injury to the somatosensory system – clarified definition in 2010
- Nociceptive – pain arising from the activation of C fibres and A-Δ small fibres.
- C – polymodal activation, but pain specific output
- A-Δ - threshold dependent signalling
- Nociplastic – pain arising due to altered functioning of peripheral and central pathways other than those exclusively defined as neuropathic pain
- Opioids – anti-nociceptive agents – good in acute nociceptive pain – variable effectiveness in other types of pain

Credit for update to A/Prof Michael Vagg - Geelong

Processing pain



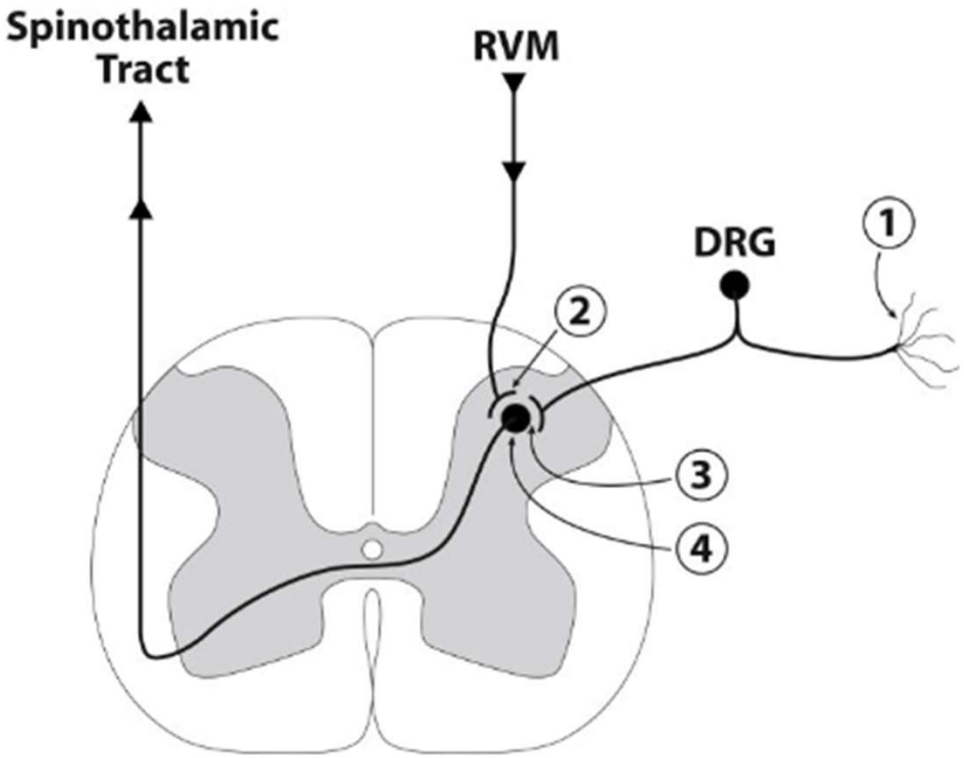
Becoming chronic

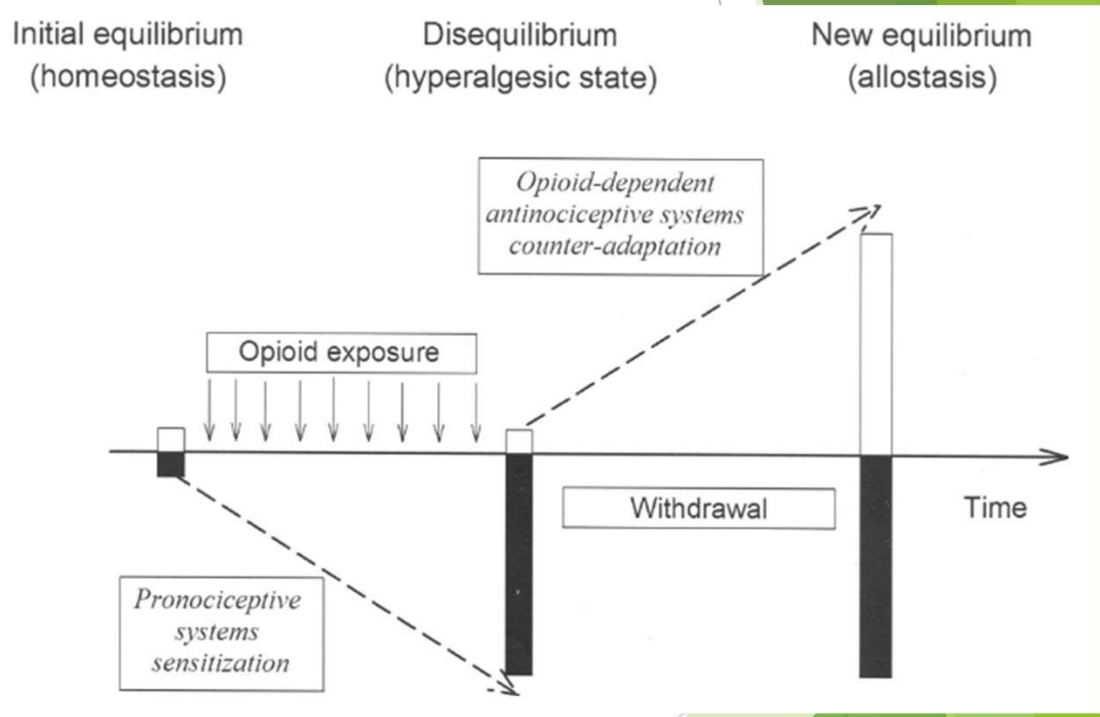


Opioid Induced Hyperalgesia

- Anti-nociception usually regulated by endogenous endorphins
- Sensitisation of nociceptors due to exposure to opioids
- More sensitive to painful stimuli
  - Same or different to original pain cause
- Upregulation of nociceptive neurons due to alterations in response from the brain in the repeated presence of exogenous opioids
- Worsened in the setting of withdrawal, increased opioid agent
- NMDA receptor activity increases – increases opioid tolerance and OIH.

Opioid Induced Hyperalgesia





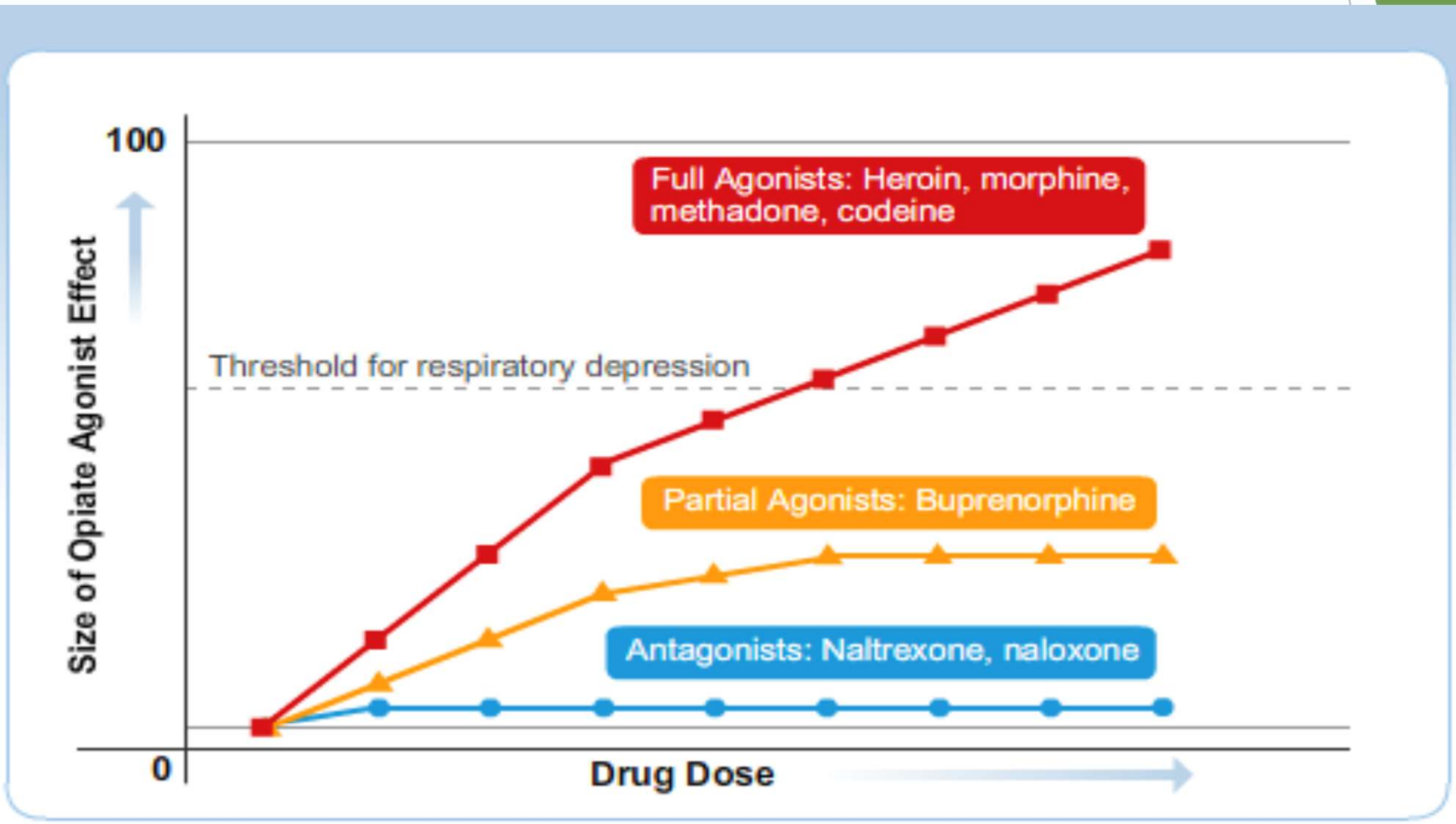
OIH Management

- Opioid cessation/weaning/rotation
- Non-opioid analgesia, antidepressants, anticonvulsants
- Behavioural management
- Unique opioids – methadone, buprenorphine
  - Methadone = NMDA antagonist
  - Buprenorphine = κ antagonist (needed for spinal dynorphin increase)
- ?Ketamine
  - NMDA antagonist, analgesic agent
- Clonidine
  - α-2 agonist, reduces OIH symptoms

Opioids

- Method of action via endogenous opioid receptors (μ, κ, δ)
- Most opioids act as full agonists at all opioid receptors
- Buprenorphine primary partial agonist at μ, and antagonist at κ & δ
- Effects:
  - Analgesia
  - Sedation
  - Euphoria
  - Sweating
  - constipation
  - Relaxation, drowsiness
  - Respiratory depression
  - Bradycardia
  - Respiratory arrest
  - Cardiac arrest

Opioids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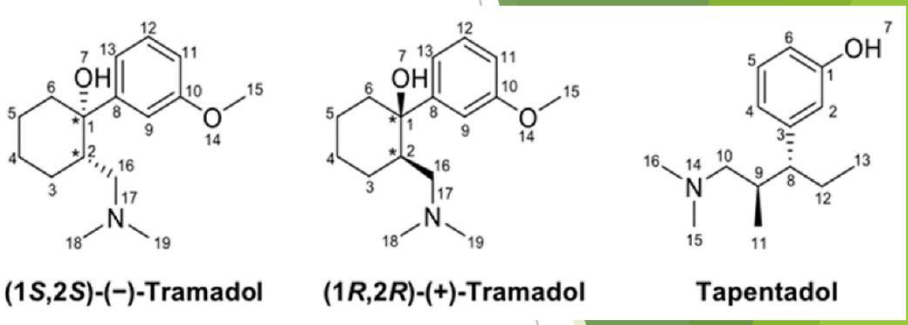
Size of Opiate Agonist Effect
Full Agonists: Heroin, morphine, methadone, codeine
Threshold for respiratory depression
Partial Agonists: Buprenorphine
Antagonists: Naltrexone, naloxone
0
Drug Dose

Long-term opioid use

- Tolerance, dependence, withdrawal notwithstanding…
- Hypothalamic-pituitary suppression
  - Loss of libido
  - Sexual dysfunction
  - Infertility
  - Muscle weakness
  - Fluid retention
  - Osteoporosis & fractures
- Sleep apnoea
- OIH
- Dental disease (loss of saliva production)
- Immune suppression & ?contribute to malignancy
- Cognitive slowing
- Constipation
- Depression, anhedonia, fatigue

Tramadol and Tapentadol



- Synthetic opioids
- **Full opioid agonists at all OR**
- Additional properties
  - Tramadol: SSRI/SNRI
  - Tapentadol: SNRI
- Tramadol – variable efficacy – depends on metabolization
- Tapentadol – stable efficacy, better MOR activity
- Neither drug clinically better than other opioids
- BEWARE drug/drug interactions!

Buprenorphine

- Synthetic opioid compound developed in 1969 and available in 1978 for human use
- High binding affinity for the opioid receptors
- **Competitive** partial agonist at μ, and antagonist at κ & δ receptors
- Analgesia via μ-OR
- Has a "ceiling" effect due to partial activation of opioid receptor
- Antagonism of κ & δ receptors reduces respiratory depression, dysphoria and sedation
- No effect on immune system

Binding Affinity

Drug	K_i (nM)	Drug	K_i (nM)	Drug	K_i (nM)
Tramadol	12,486	Hydrocodone	41.58	Butorphanol	0.7622
Codeine	734.2	Oxycodone	25.87	Levorphanol	0.4194
Meperidine	450.1	Diphenoxylate	12.37	Oxymorphone	0.4055
Propoxyphene	120.2	Alfentanil	7.391	Hydromorphone	0.3654
Pentazocine	117.8	Methadone	3.378	Buprenorphine	0.2157
		Nalbuphine	2.118	Sufentanil	0.1380
		Fentanyl	1.346		
		Morphine	1.168		

Volpe, D.A., Tobin, G.A.M., Mellon, R.D., Katki, A.G., Parker, R.J., Colatsky, T., Kropp, T.J., Verbois, S.L., 2011. Uniform assessment and ranking of opioid Mu receptor binding constants for selected opioid drugs. Regulatory Toxicology and Pharmacology 59, 385–390.. https://doi.org/10.1016/j.yrtph.2010.12.007

Buprenorphine & Palliative Care

- Patients regularly on buprenorphine
- Buprenorphine as an analgesic
- Buprenorphine and OAT

Buprenorphine as an Analgesic

- Buprenorphine patches are PBS listed
- Sublingual tablets (200microg) are not PBS listed
- Buprenorphine has fewer side effects than other opioids
  - Mood improved due to κ receptor antagonism
  - Reduced respiratory depression
  - Less sedation
- Pharmacokinetics unchanged in older adults
- No immune suppression – no issue with checkpoint inhibitors for cancer therapy
- Safe in heart failure and long-QT syndrome
- Sublingual absorption/topical

Management of patients with pain or terminal phase on OAT

Opioid Agonist Treatment

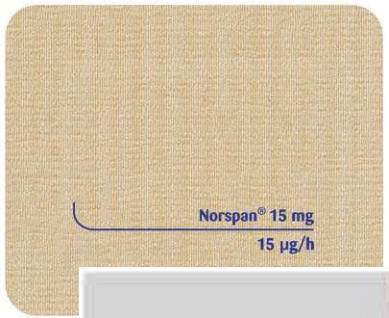
- Management of opioid use disorder with an opioid agonist
- Long history within Australia
- Two agents primarily used in Australia
  - Methadone
  - Buprenorphine

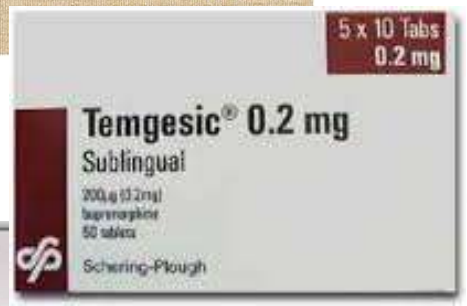
Methadone (OAT)

- Full agonist
- Liquid form, long $t_{1/2}$
- Slow up-titration over weeks
- Daily dosing, usually 40-100mg
- Concerns
  - Prolonged QTc – especially at higher doses (>100mg) RARE
  - Over-sedation + respiratory depression
    - Particularly when used in combination with other sedating medication e.g. benzos, alcohol
- Interactions
  - Methadone metabolised by cytochrome p450 pathways so interacts with inducers and inhibitors of these (e.g. rifampicin)
    - Methadone dosing may need to be adjusted if starting a new medication

Buprenorphine

- Usually encountered as:
  - Norspan
  - Temgesic
  - Subutex
  - Suboxone
  - Buvidal
  - Sublocade





A note on LAIB

- Approved only for the treatment of opioid dependence
- Long-Acting Injectable Buprenorphine
  - Buvidal
  - Sublocade
- Ultra-long half-lives
  - Buvidal weekly 3-5 days
  - Buvidal monthly 19-25 days
  - Sublocade 43-60 days
- Once they're in, they don't come out
- Reduced pharmacy contact

OAT and Palliative Care

- Consider the situation
- Stigma of “drug seeking”
- Under-reporting of pain due to stigma
- Under treatment due to system related misunderstandings and bias regarding pain and OAT

Myths

- Patients on OAT do not experience pain in the same way as those not on OAT
  - OAT patients (and other opioid dependent patients) experience pain both in the same way and are often more sensitive with lower thresholds for pain
- Opioid dependent patients will receive the same analgesic effect from similar doses of opioids to patients that are not dependent
  - Opioid dependence and tolerance often leads to a lower effect from a similar dosage.
- Palliative care patients on OAT can simply have their OAT doses increased to manage their pain
  - Not always a viable option.
  - May not result in increased analgesia
  - May not be suitable for the situation and symptoms

OAT and acute pain

- Methadone
  - Other full opioid agonists
  - May need larger doses
  - May need more frequent dosing
- Buprenorphine
  - IM/IV injections (300-600microg QID/TDS)
  - Sublingual (200microg 1-2tab QID/TDS)
  - Other full opioid agonists
    - WILL need larger doses and more frequent dosing!
    - Consider high binding affinity agents (e.g. fentanyl, hydromorphone, morphine)
- Don't forget non-opioid analgesia – WHO guidelines, physiotherapy, massage, heat wraps.

Appropriate Management

- Team strategy
- Involve the patient from the word go!
- Flexibility
- Open communication
- Plan for the unexpected

- Breakthrough pain management options
- Methadone liquid to physeptone?
- Buprenorphine OAT – continue or transition?
- EOLC management plan

Caveats

- Not all palliative care patients will be stable with regards to opioid use
- Many patients will have triggers to return to opioid use
- Patients may be on haemodialysis which may interact with some analgesic agents (Methadone and buprenorphine are not affected)
- Palliative care patients are not immune to diversion (individuals as well as family members)
- Palliative care does not always equal end of life care – consider take home naloxone for patients with high opioid requirements

More thoughts

- Consider treating OAT and palliative needs as separate issues
- Involve addiction medicine service for complex patients
- Ensure that palliative medications will not detract from OAT support and efficacy
- If patient is still mobile – consider staged supply of OAT and other opioid analgesia
- Once patient mobility decreases, good communication with local pharmacy and carers is required to ensure medication supply and patient support
- Once a patient is no longer able to take oral medications, adequate opioid agonist will still be required.
- Consider an in-home safe for medication storage to minimize risk of diversion
- Schedule 8 medications may require special treatment after a patient passes away

Typical Agents

- May be appropriate in rare cases
- Closer monitoring
- Patient contracts
- Staged supply
- Opioid rotation
  - Dose reduce 25-50% (OMEDD)
  - Reduced tolerance poorly understood
  - May result in tolerance again and dose escalation
- Regular reviews

Support

- Colleagues
- MATOD education
- Local Pharmacists
- Addiction Medicine Specialist Services
- Local Pharmacotherapy Area Based Network
- PAMS – Pharmacotherapy Advocacy Mediation Support
- SafeScript

Summary

- Palliative care and OAT are complex and need a tailored approach to manage
- The patient should be involved in all steps and discussions
- Patients on OAT are likely to require large doses of opioid analgesia in order to achieve the desired effect
- Consider changing from buprenorphine to methadone as analgesia requirements increase
- A multi-disciplinary approach has the best chance of a dignified outcome
- Take consideration around instability and always remember that diversion is a possibility


any
questions?