Palliative Care 2021
General Practitioner Webinar Series

Opioids and Cancer Pain Management

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- Launceston School of Medicine, UTAS

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Learning Objectives

- Understand pain within a biopsychosocial model
- Know the commonly used potent opioids
- Know the relative conversion ratio of different opioids
- Know what prn 'rescue' dose to prescribe
- Know the 'ABC' of prescribing opioids
- Understand the role of adjuvant drugs
- Understand the changing risk/benefit ratio of various agents in early and advanced disease

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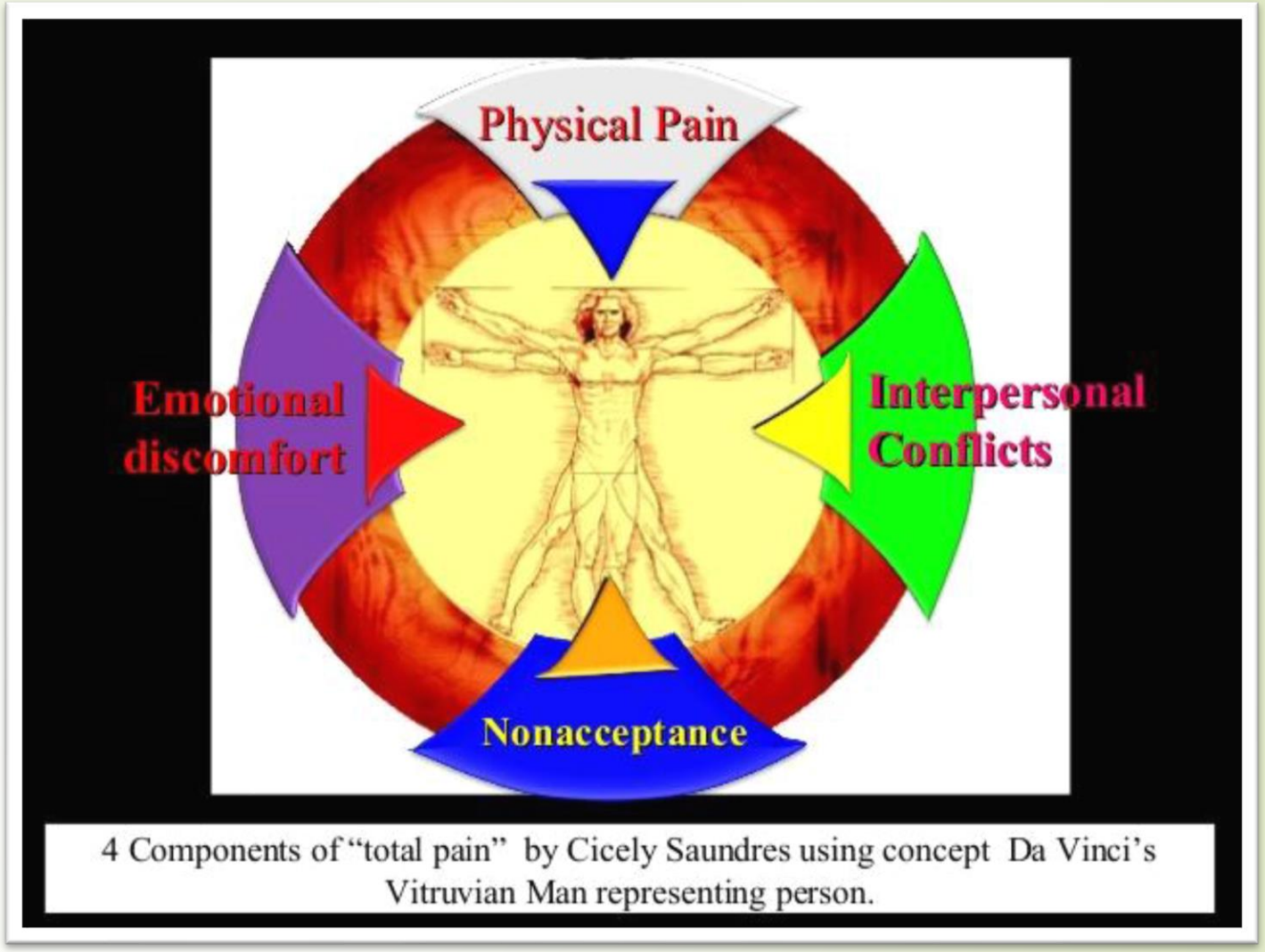
Total Pain The Vitruvian Man



4 Components of "total pain" by Cicely Saundres using concept Da Vinci's Vitruvian Man representing person.

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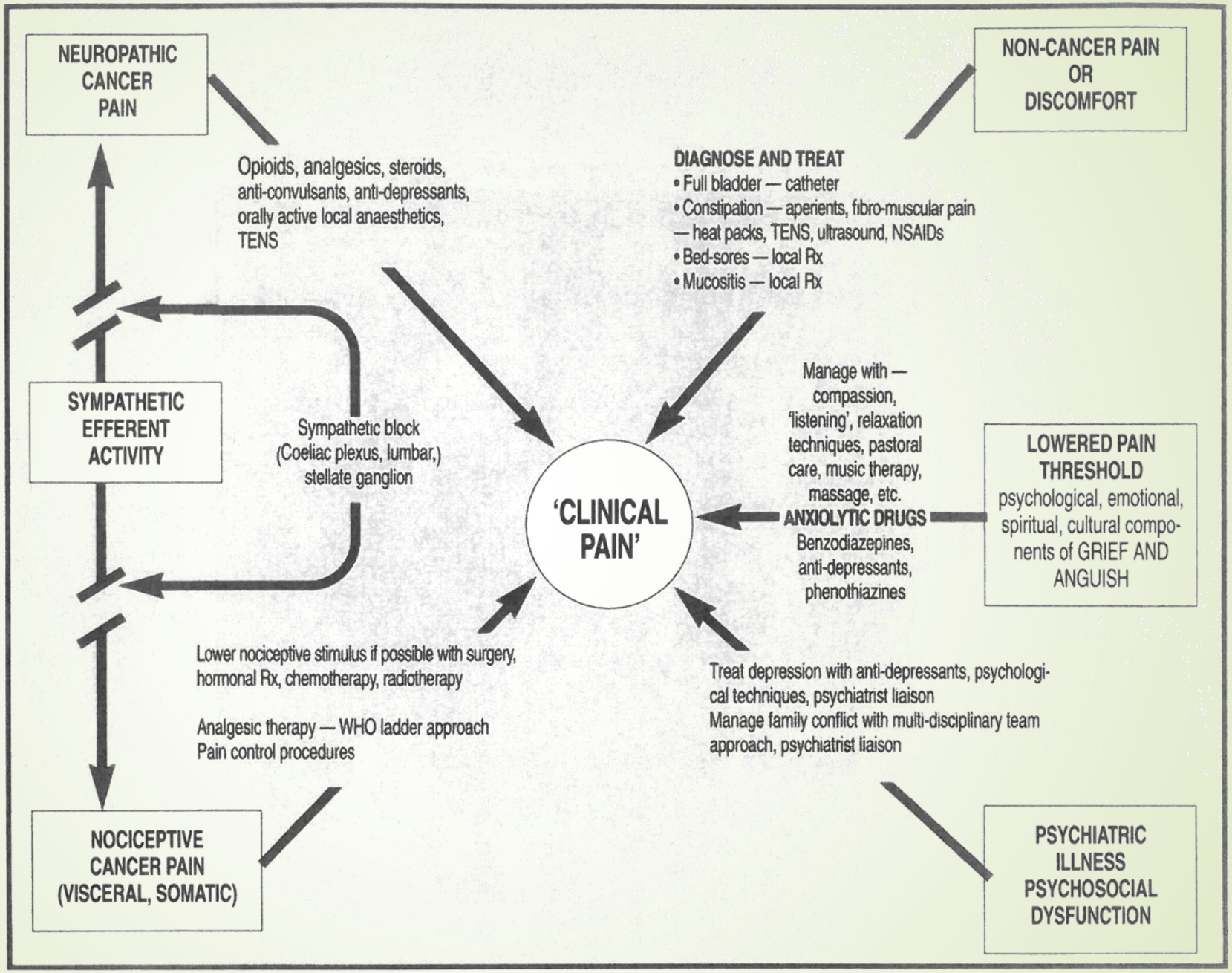

Figure 1. The components of cancer pain

Cancer Pain Management

- Pain is one of the most common symptoms in patients with advanced cancer, & often the most feared
- Unfortunately, cancer-related pain is frequently inadequately treated, causing considerable suffering
- Satisfactory pain control is possible in around 90-95% of patients with advanced cancer by pharmacological means

Rome RB et al. The Role of Palliative Care at the End of Life; Ochsner Journal 2011 11(4):348-52 *(Oschner Clinic Foundation)*

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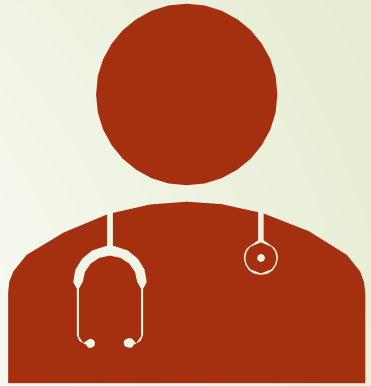
The first step:
Be able to describe your patient, identify the stage of disease, G.O.C., etc



- Diagnosis and Stage of disease
- Pattern of metastases – boney or visceral
- Which area/site is causing the pain
- Overall patient performance status
- Mechanism of the pain(s) – is it malignant pain?
- Imaging correlation if available

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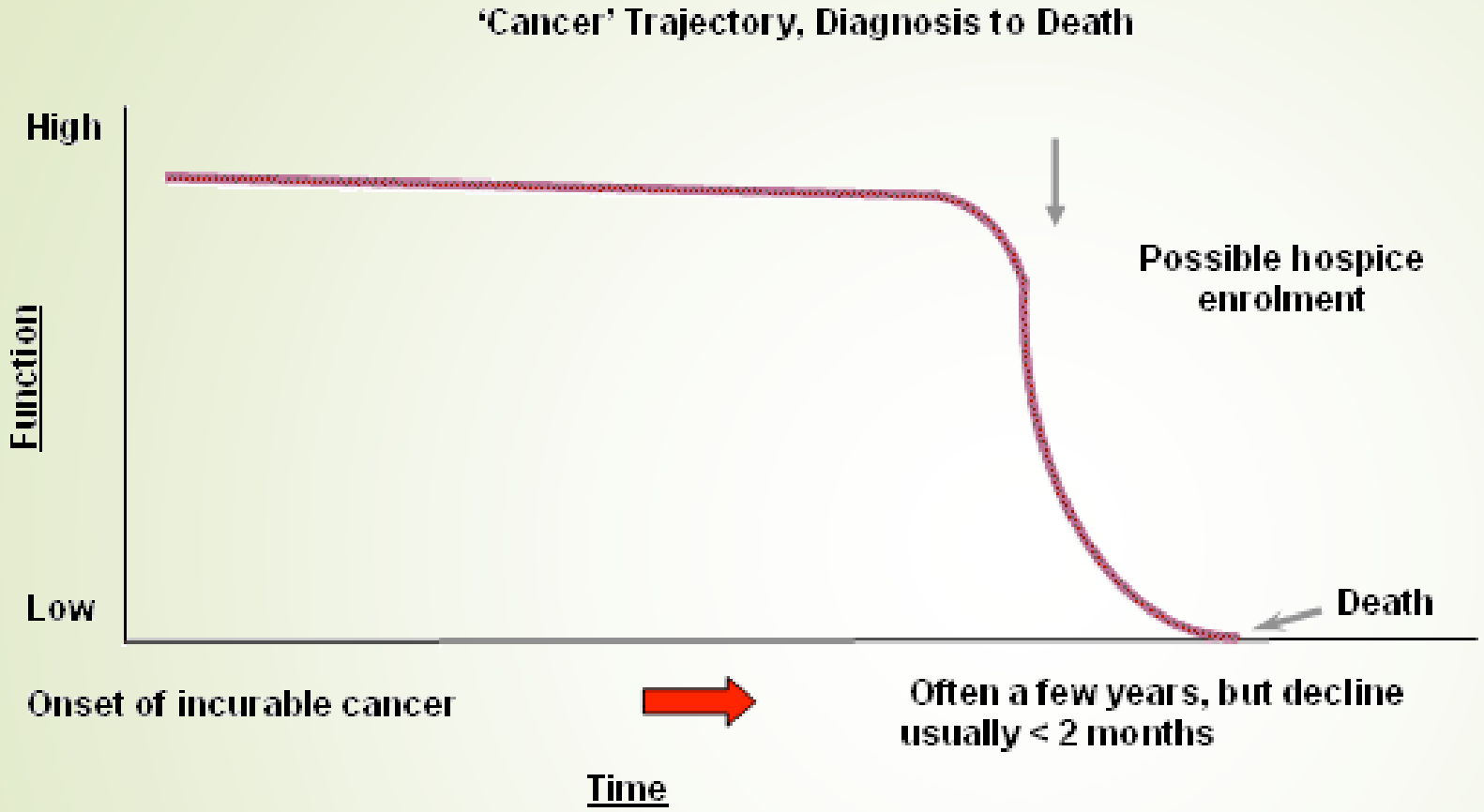

Lunney JR, Lynn J, Foley DJ, Lipson S, Guralnik JM. Patterns of functional decline at the end of life. JAMA 2003

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Performance Status in Cancer How is it measured: Karnofsky Index

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS RATING (%) CRITERIA

Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disable; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

Karnofsky DA, Abelmann WH, Craver LF, Burchenal JH. The Use of the Nitrogen Mustards in the Palliative Treatment of Carcinoma – with Particular Reference to Bronchogenic Carcinoma. Cancer. 1948;1(4):634-56.

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Performance Status in Cancer
How is it measured: ECOG status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g. light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.

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TASMANIAN HEALTH SERVICE | Tasmanian Government

MEDICAL GOALS OF CARE (GOC) PLAN

PT ID

Surname: <<Patient Demographics:Surname>>
D.O.B. <<Patient Demographics:DOB>>

Other Names: <<Patient Demographics:First Name>> <<Patient Demographics:Middle Name>>

Address:

<<Patient Demographics:Full Address Preferred>>

FACILITY: _____

❑Southern Region ❑Northern Region ❑North West Region

FT176800

This form is to communicate the medical decision for appropriate treatment goals of care for this patient. Chose A, B, C or D. If changes are made, this form must be crossed through, marked void and a new form completed.

DIAGNOSIS:

NO LIMITATION OF TREATMENT:	**Hospital**	**Community**
A.The goal of care is CURATIVE or RESTORATIVE. **Treatment aim is PROLONGING LIFE** ❑ **For CPR and all appropriate life-sustaining treatments** ------>	CODE BLUE	For full resuscitation

LIMITATION OF MEDICAL TREATMENT:

❑ Patient has an advanced care directive
and / or has requested the following treatment limitations:

Please specify:

B. The goal of care is CURATIVE or RESTORATIVE with limitations: ❑ **NOT FOR CPR** but is for all respiratory support measures --------> ❑ **NOT FOR CPR or INTUBATION** but is for other active management ----------> *Specific notes:*	For CODE BLUE and MET calls For MET calls Not for CODE BLUE	For treatment and transfer to hospital
C. The goal of care is PALLIATIVE. **Treatment aim is quality of life** ❑ **NOT FOR CPR OR INTUBATION** ---------->*Specific notes:*	MET call ❑ YES MET call ❑ NO	Contact GP for planning
D. The goal of care is COMFORT DURING THE DYING PROCESS ❑ **NOT FOR CPR or INTUBATION** ---------->	For terminal care NOT for CODE BLUE NOT for MET	

Reason for limitation of medical treatment:	❑ medical grounds	❑ patient wishes
Discussed with:	❑ patient	❑ person responsible
DOCTOR'S NAME: <<Doctor:Name>>	**DESIGNATION**:	Family GP
SIGNATURE:	**DATE:**	<<Miscellaneous:Date (short)>>
GP/Consultant responsible:	GP/Consultant informed	❑ YES ❑ NO

This form is endorsed for ambulance transfer, and for the home or care facility

Abbreviation key:	CPR = cardio-pulmonary resuscitation	GP = General Practitioner	MET = medical emergency team

GOALS OF CARE PLAN

THS-TAS-S 97748 7/15 F&P 42202 JULY 15 M10 Template updated by Primary Health Tasmania Oct 2016

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Pain Types

- Somatic- aching, sharp, throbbing, or pressure-like
- Visceral - less well localised, felt over larger areas
- Neuropathic- peripheral or CNS injury
- Referred pain - deep aching or throbbing pain
- Incident pain - pain on movement, common with bone metastases
- Psychogenic - no physical basis, may be opioid insensitive, anxiety is common here

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WHO Analgesic Ladder – circa 1986

- **MILD**: 'SIMPLE' analgesics
  - paracetamol/aspirin/NSAID's/ Coxibs
- **MODERATE**: 'WEAK' opioids
  - codeine/tramadol
- **SEVERE**: 'STRONG' opioids
  - **morphine/oxycodone/hydromorphone**
  - **fentanyl**/methadone/tapentadol
  - buprenorphine

- ***Adjuvant analgesics:***
  - Corticosteroids/psycho-tropics/muscle relaxants
  - pentinoids/ketamine/local anaesthetics/antibiotics
  - ??medical marijuana

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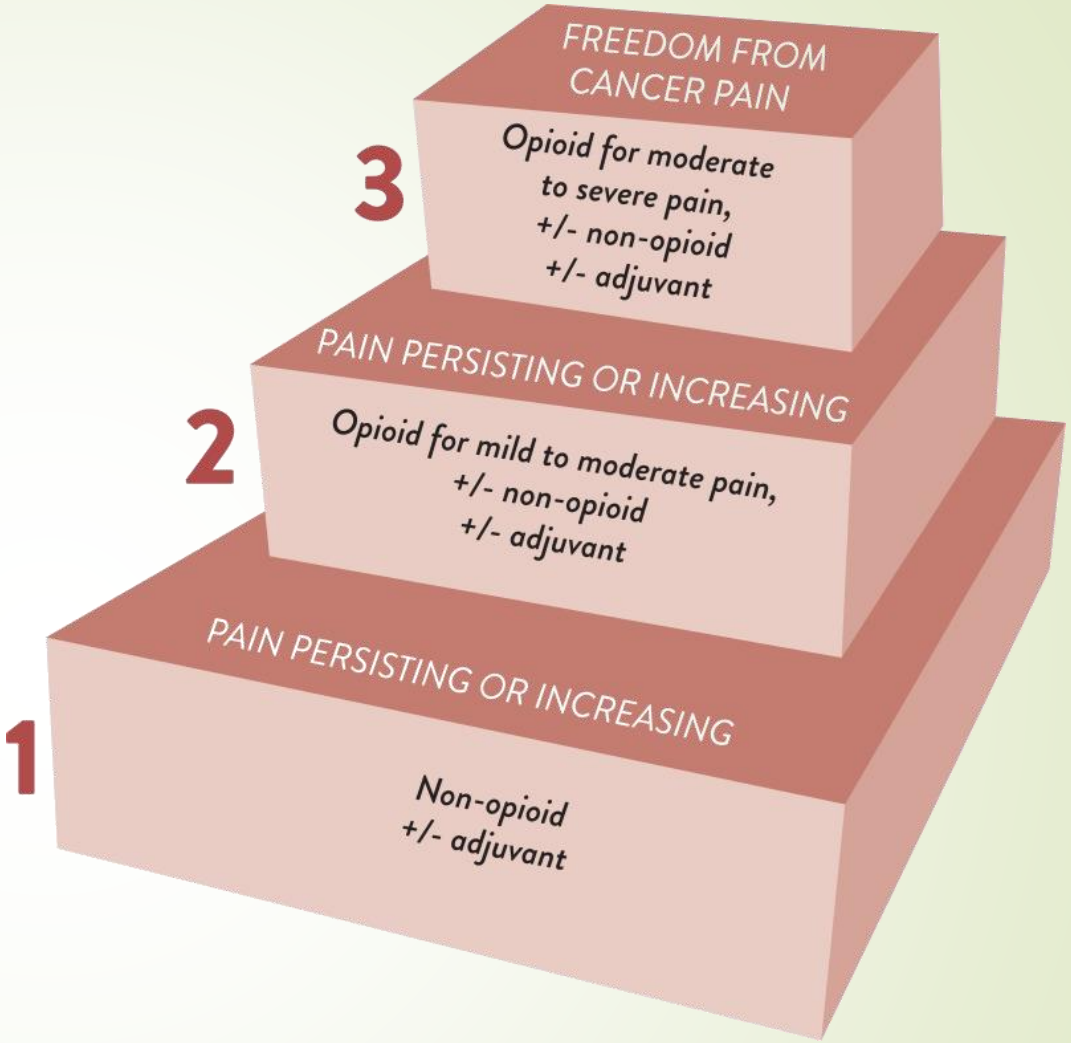
Cancer Pain WHO 3-step Analgesic Ladder – circa 1986



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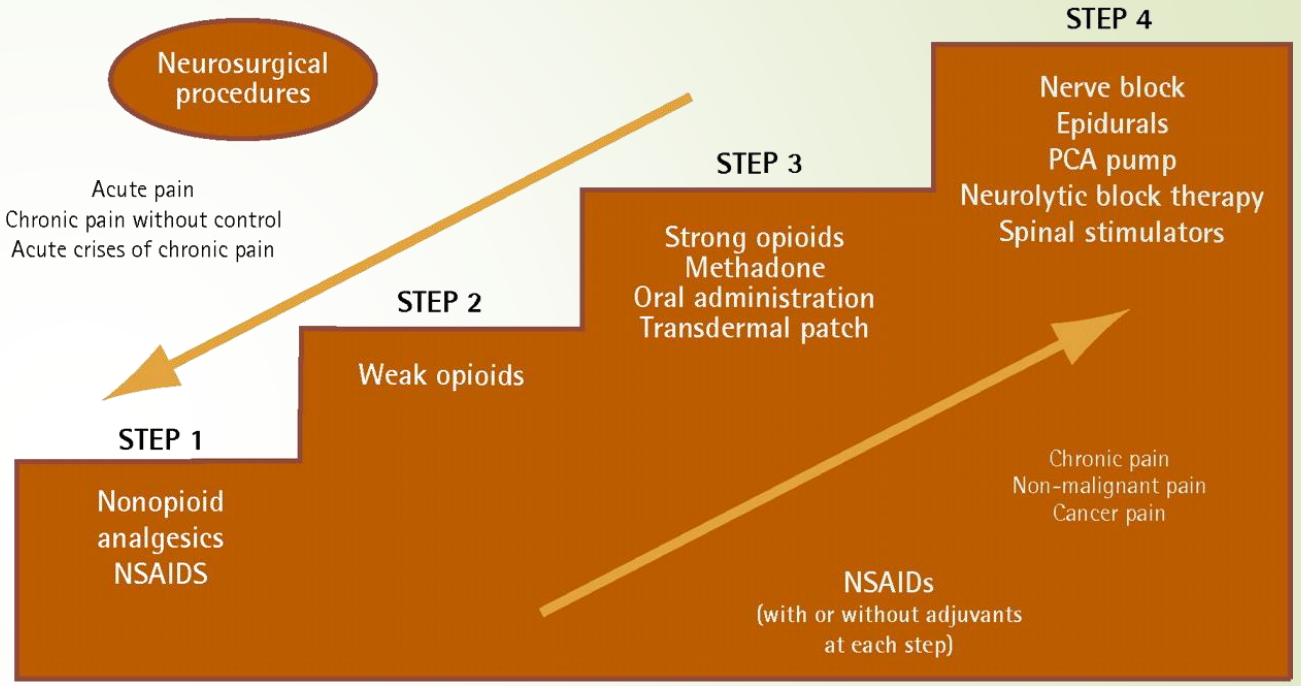
Modified WHO Analgesic Ladder The 21st Century Vargas-Schaffer G. Can Fam Physician 2010 Jun; 56(6): 514-17

Figure 2. New adaptation of the analgesic ladder



NSAID—nonsteroidal anti-inflammatory drug, PCA—patient-controlled analgesia.

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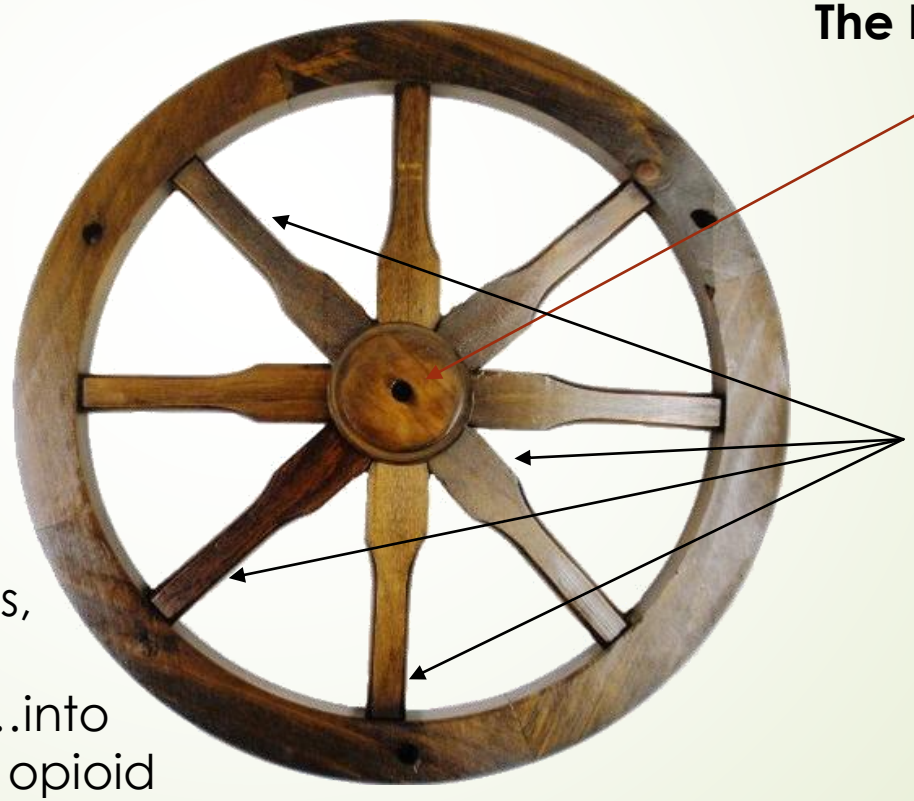
Effective Analgesia for Cancer Pain
The therapeutic 'Wagon Wheel' model
'Hub & Spoke'….a Multimodal Approach

The Hub – Strong Opioid



The Spokes

- Steroids
- NSAID's/Cox_2 Inhibitors
- Antidepressants
- Benzodiazepines
- Baclofen
- Pentins – pregab, gab
- Anticonvulsants
- Ketamine
- Methadone
- Local anaesthetics
- Clonidine
- Nifedipine
- ??Medical Marijuana

If there are no spokes,
there is no wheel
It may just fall apart…into
uncontrolled pain or opioid
toxicity

Avoid continuing opioid dose escalation despite a less than adequate response… and subsequent severe side effects or even narcosis

A case of ‘putting all your eggs in the one basket’

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Cancer Pain Management Some less common non-opioid agents used in hospital

- Ketamine infusion – IVI or CSCI
- Ketorolac tromethamine (Toradol) – potent NSAID
- Parecoxib sodium (Dynastat) – potent Cox_2 inhibitor
- Lignocaine infusion (Xylocaine) – CSCI
- Sodium Valproate (Epilim) – IV infusion
- Methylphenidate (can also be used in community)

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Starting Opioid Drugs – the opioid naiive

- **As with all opioids, 'start low and go slow' and remember the ABC:**
  - **A** = Anti-emetic sometimes for the first week
  - **B** = Breakthrough medication provision
  - **C** = Constipation – always prescribe laxatives
- **Ongoing opioid dose escalation**
  - Dose increases should usually be no more than 30-50% of previous daily dose
  - The higher the daily dose, the less the % increase
  - Methadone always requires involvement of palliative care physician

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Classification of Potent Opioid Drugs
Structural

- **Phenanthrenes**
  - Morphine
  - Hydromorphone
  - Oxycodone
  - Buprenorphine
- **Phenylpiperidines**
  - Fentanyl
  - Sufentanil, alfentanil, remifentanil
- **Diphenyl-heptylamines**
  - Methadone

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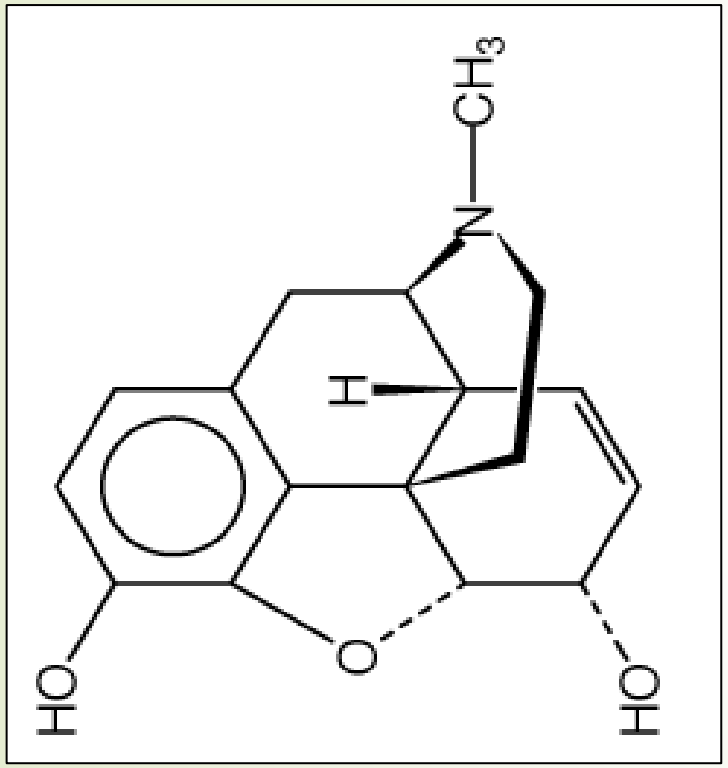
Morphine
5 Ring Structure of all Phenanthrenes



3 position

6 position

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Morphine

- Morphine is now less often prescribed c.f. oxycodone for cancer pain
- In most situations it is still the easiest opioid to use
- Morphine may not be suitable in moderate to severe renal failure due to accumulation of conjugated metabolites, M-3-G and M-6-G
- M-3-G – morphine-3-glucuronide – accumulates in
- RF and may cause seizures and delerium

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Morphine and routes of administration

- Use ratio of between 2-3:1 converting from oral to subcutaneous morphine
- Other opioid doses can be expressed as oral equivalent daily dose (OEDD) or SC equivalent daily dose
- There is little or no need to give morphine by the intravenous route in palliative patients, although this is used more commonly in the USA

Hanks et al. Morphine and alternative opioids in cancer pain. the EAPC recommendations. British Journal of Cancer (2001) 84(5), 587–593. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2363790/pdf/84-6691680a.pdf

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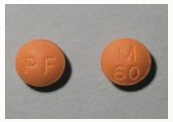
Morphine
Oral preparations

- **Immediate Release**
  - Morphine mixture – Ordine – commonest preparation
  - Sevredol tab 10 mg 20 mg 
- **Slow Release**
  - MS Contin 15 mg  30 mg  60 mg 
  - Kapanol 10 mg 

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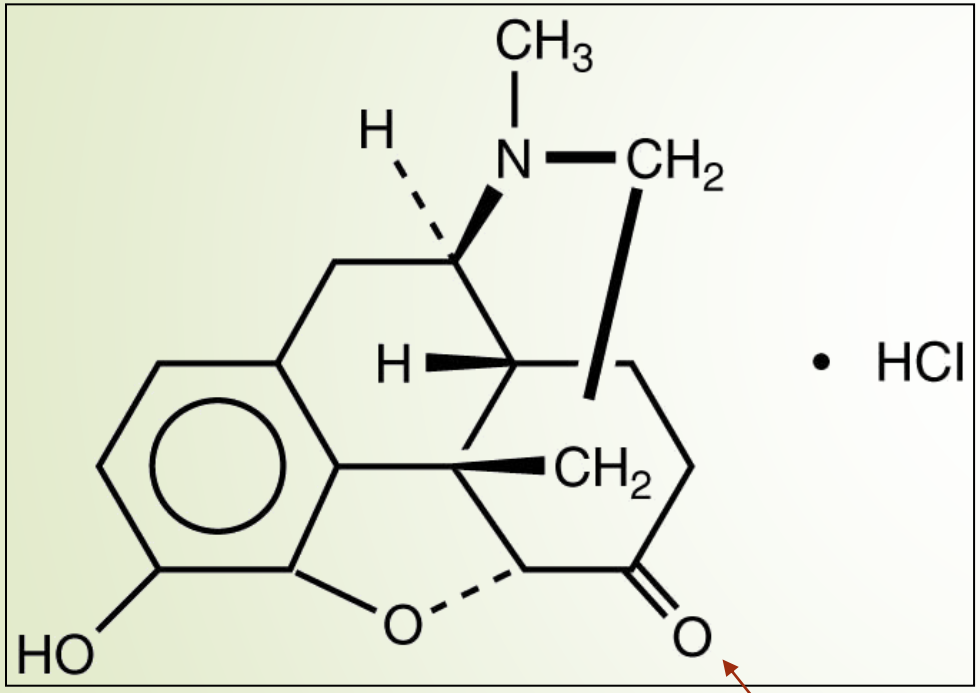
Hydromorphone
Synthesized Germany1924



Double bonded O_2 in 6 position
Increases potency

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Hydromorphone

- Similar profile to morphine, but 6 times as potent by injection, so divide SC morphine dose by 6
- Increased potency is due to the double-bonded oxygen in the C 6-position
- Similar H-3-G and H-6-G metabolites, but accumulation of H-3-G metabolite seems less of a problem c.f. M-3-G
- often less CNS toxicity after a switch from morphine to hydromorphone
- Safer than morphine in renal failure
- Oral bioavailability is similar to morphine but may be lower in some individuals – 25 -30%

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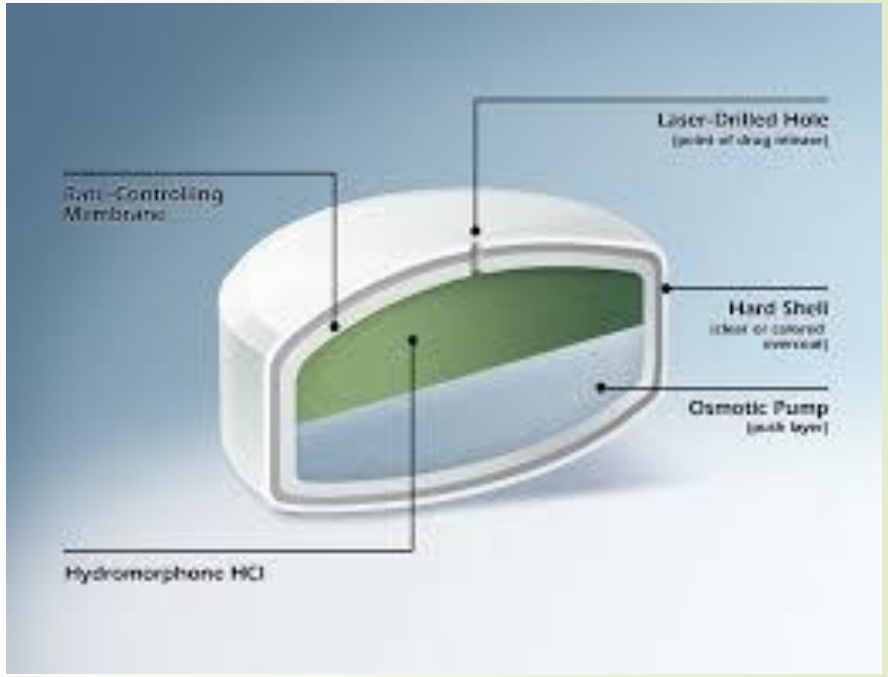
SR (Slow Release) Hydromorphone
Jurnista

Utilises an osmotic pump system for drug delivery



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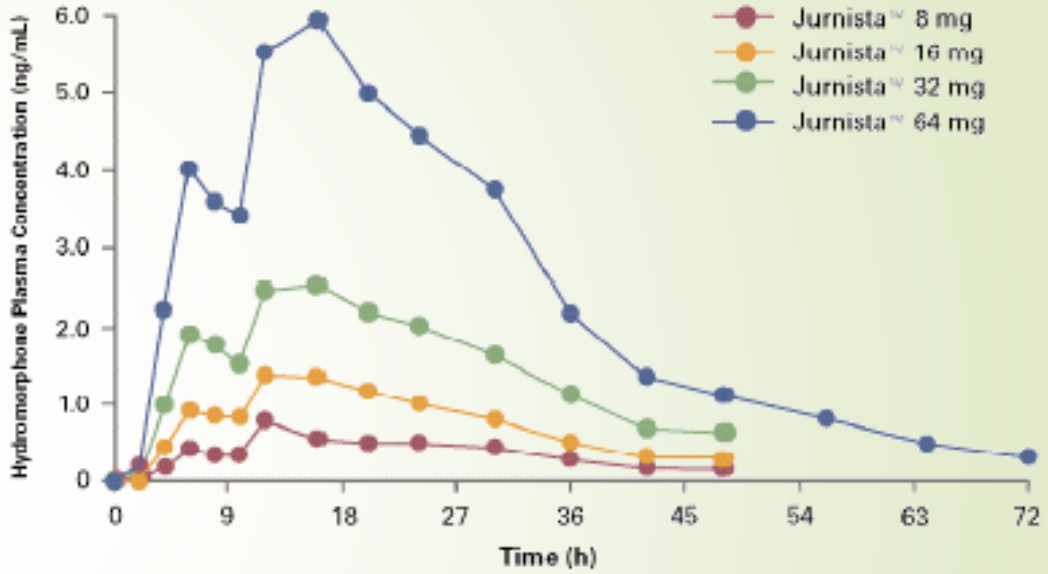
Jurnista - serum levels after single dose

Figure 10. Jurnista™ has a dose-proportional pharmacokinetic profile across all doses[52]



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Jurnista - Learning Point

- Don't prescribe more than once daily
- Don't double the dose with higher dose strengths

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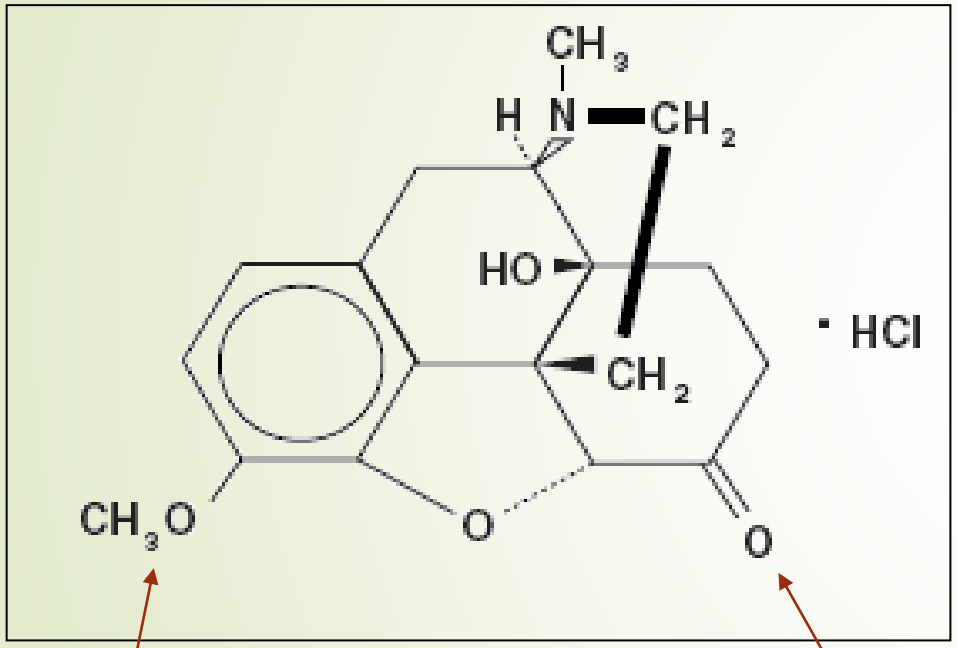
Oxycodone
Synthesised Germany 1916



Methoxy group in 3 position
Inhibits first pass metabolism

Double bonded O_2 in 6 position
Increases potency

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Oxycodone

- Oxycodone has a higher oral bioavailability than morphine – 60 - 85% c.f. 30 - 35%
- The substitution of double bonded oxygen at C 6 position also contributes to higher potency
- It is therefore more potent than morphine by the oral route by a ratio of 1.5:1, or 3:2
- It is, however, less potent than morphine by the injectable route by ratio 2:3
- It comes in both immediate and slow-release tabs

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Oxycodone

- Oxycodone is currently the most commonly used opioid used in cancer care
- Is the most constipating opioid and arguably the most addictive
- Unlike morphine, it is not conjugated to glucuronic acid, but oxidized in the liver to active metabolites (microsomal CYP P450 3A4) - oxymorphone, nor-oxycodone
- Original slow-release formulation is Oxycontin
- Second generation preparation is Targin, (oxycodone/naloxone in 2:1 ratio) which was developed to reduce the constipating effect

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Oxycodone

- SR preparations achieves stable plasma levels within 24 hours
- More constipating than morphine (μ2 opioid receptor activity)
- Slow-release preparation – OxyContin or Targin, may need 8 hourly dosing in younger patients as more rapidly metabolized than morphine
- 8 -10% of all prescriptions for slow release Oxycontin are written with 8 hourly dosing, rather than the usual 12 hourly dosing intervals

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Targin

- Slow release combined oxycodone plus naloxone
- Targin is pharmacokinetically identical to OxyContin in terms of the slow-release oxycodone component
- Naloxone targets the μ2 opioid receptor in the gut and blocks the constipating action of oxycodone
- The oral naloxone results in a reduction in the use of oral aperients by 30-50%, but not usually 100% - some ongoing aperients are usually required

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Targin

Slow release combined oxycodone plus naloxone

- The ceiling dose of Targin is around 80-100 mg daily – higher doses may lead to a central effect of naloxone, potentially interfering with pain control
- With Targin dose requirements higher than 40 mg 12 hourly, it is safest to dose increase with additional OxyContin SR tabs to reduce the likelihood of a central μ1 antagonist effect of naloxone and interference with pain control
- Severe liver dysfunction may result in higher serum levels of naloxone, potentially adversely affecting pain control

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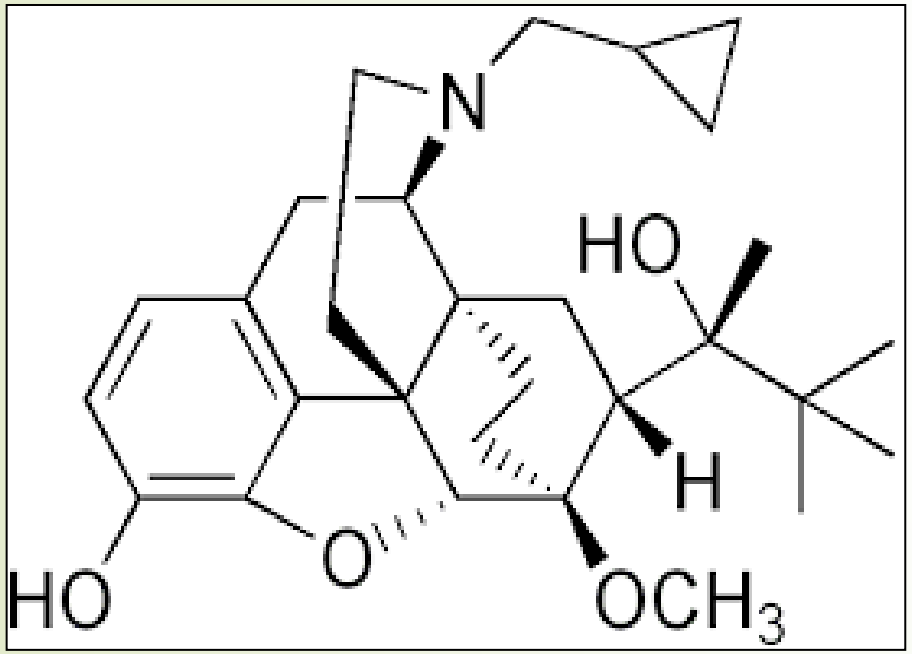
Buprenorphine
Has been labelled an ‘atypical opioid’



Methoxy group in 6 position

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Buprenorphine

Has been labelled an ‘atypical opioid’

- Partial opioid agonist at μ opioid receptors, but high affinity at receptors – i.e. binds more avidly at these receptors than full μ1 agonists
- It is usually well tolerated. A ‘ceiling effect’ to analgesia and may block the action of other opioids concurrently prescribed
- Not active orally. Available as a transdermal patch – Norspan TD – applied weekly, so convenient for patients
- Also available as a sub-lingual tablet (Temgesic) but limited usefulness in cancer pain

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Buprenorphine

Has been labelled an ‘atypical opioid’

- Maximum serum levels only attained after 48-72 hours following first application of TD patch, so not as suitable for unstable severe cancer pain
- Has a well accepted role in chronic non-malignant pain and is safe in renal failure
- TD buprenorphine useful as sole opioid in mild to moderate cancer pain in ‘disease stable’ patients – suitable for use in general practice or oncology office-based practice

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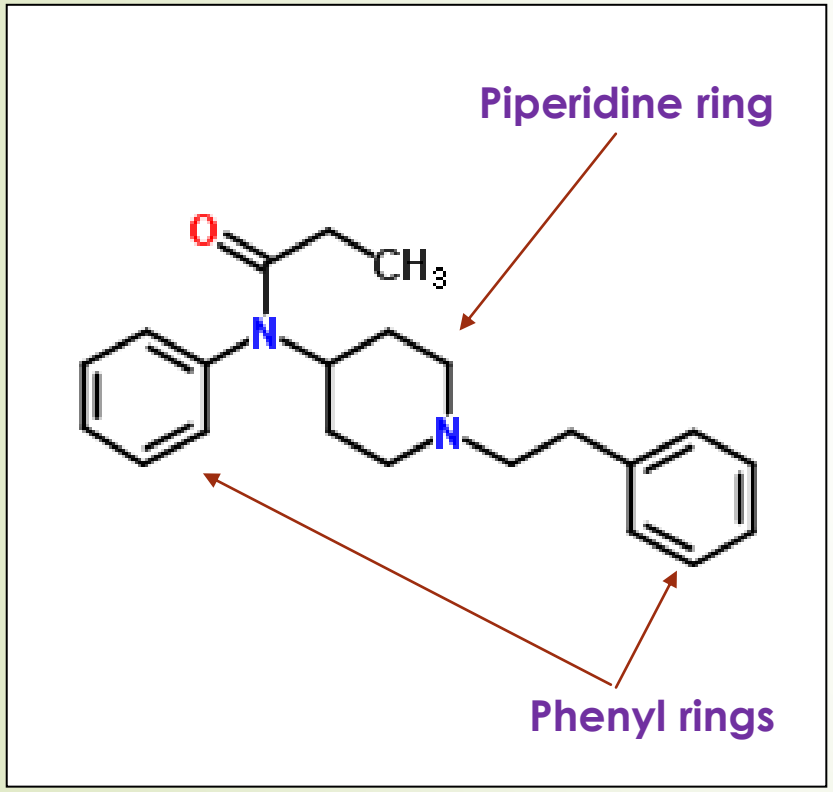
Diphenyl-piperidines
Fentanyl citrate



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Diphenyl-piperidines
Fentanyl citrate

- A very potent opioid (80 -100 × morphine) which has no active analgesic metabolites. Suitable in renal failure
- Pure μ_1 receptor agonist, so less constipating than morphine. It is the least constipating potent opioid
- Available as injection 100 mcg/2 ml ampoule
- Convenient transdermal TD 3rd daily preparation (Durogesic) Patch strengths are 12, 25, 50, 75 and 100 mcg/hr release fentanyl. A 100 mcg/hr strength patch will deliver 2400 mcg fentanyl per 24 hours

Diphenyl-piperidines
Fentanyl citrate

- More fat soluble than morphine so good CNS penetration; can be slightly more variably absorbed into vascular system by SC route, as it is released more slowly from fat stores
- IV analgesic equivalence is usually 100 mcg fentanyl to10 mg IV morphine
- SC analgesic equivalence may be more like 150-200 mcg fentanyl to 10 mg SC morphine, although suggest commence with the usual ratio of 100 mcg fentanyl: 10 mg Morphine

Fentanyl citrate sub-lingual tabs
Abstral

- Rapidly acting tabs suitable for rescue pain
- Indicated for those patients already taking >60 mg/day oral morphine equivalence
- Sublingual absorption and rapid rise in serum levels is not too inferior to IV administration
- Not to be chewed or sucked
- Tablet strength is 100 mcg, 200 mcg, 300 mcg, 400 mcg, 600 mcg, 800 mcg
- Dose must be titrated up, starting with lowest dose -100 mcg strength, irrespective of total opioid dose

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Constipation

The cause of much suffering

Considerations:

- Hydration - assess and address
- Drugs & immobility – deprescribe if possible
- Laxatives
- Any other mechanical causes - ?bowel obstruction

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Constipation
Laxatives

- Docusate/senna (Coloxyl & senna)
- Lactulose
- Macrogol 3350+Electrolytes (Movicol)
- Sodium picosulphate and magnesium citrate (Picolax)
- Suppositories – bisacodyl or glycerin
- Enemas (Microlax, Fleet)
- **μ_2 antagonists**
  - **Injectable – methylnaltrexone (Relistor)**
  - **Oral – pegylated naloxone (Movantik)**

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Constipation - Learning Point

- "The hand that writes (types) the opioid order should also write the aperient order…"
- Aperients should be prescribed on a regular basis, not 'prn'

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Some take home messages..

- Ensure an adequate PRN ‘rescue’ opioid for ‘breakthrough’ pain – should be 1/10 to a maximum of 1/6 total daily dose
- Remember to think of non-cancer causes of pain: urinary retention, constipation
- Always ensure aperients are prescribed and have a low threshold for diagnosing constipation as a cause of abdominal pain
- If the pain stimulus responds to treatment such as palliative radiotherapy, opioid doses may need to be reduced or occasionally even ceased

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Useful websites

- **Tasmanian Palliative Care Formulary**
  http://formulary.health.local/Formulary/SpecialtyFormulary/3

- **Opioid Conversion Ratios**
  http://www.emrpcc.org.au/wp-content/uploads/2016/05/Opioid-Conversions-May-3-2016-final.pdf
  https://www.eviq.org.au/clinical-resources/eviq-calculators/3201-opioid-conversion-calculator
  http://fpm.anzca.edu.au/documents/opioid_calculator_app.pdf

- **Syringe Driver Drug Compatibilities**
  http://www.emrpcc.org.au/wp-content/uploads/2013/08/Syringe-Driver-Drug-Compatibilities-Guide-to-Practice-2013.pdf

- **Cancer Council - Cancer Pain Guidelines**
  https://www.cancer.org.au/news/news-articles/cancer-pain-management-in-adults.html

- **CareSearch – a Palliative Care Website**
  https://www.caresearch.com.au/Caresearch/Default.aspx

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Thank you and questions