Opioids, Adjuvant Analgesics and Pain Procedures

Dr Lindy Turner

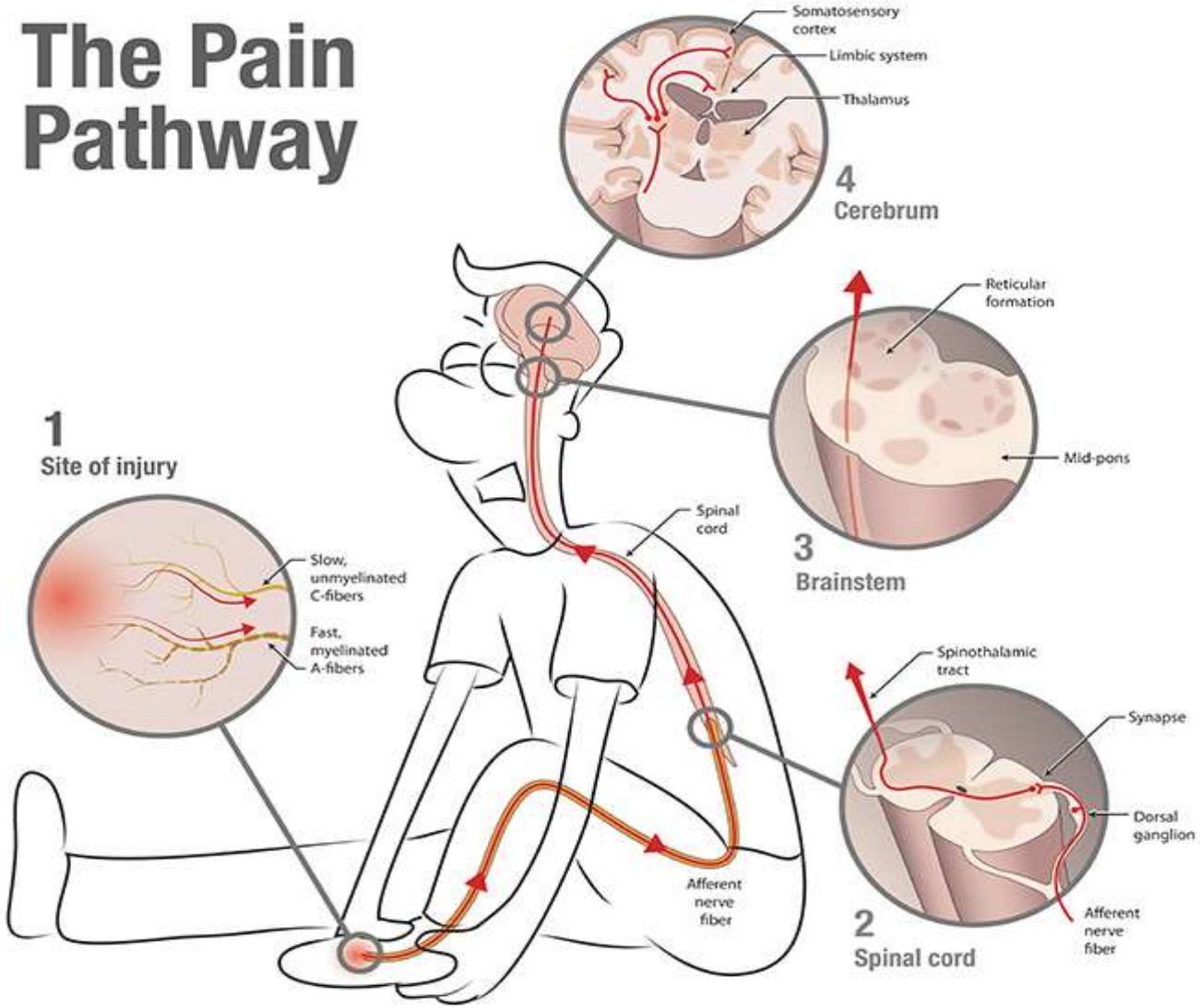
Dept of Palliative Care

Calvary Mater Newcastle

Outline

- Challenging case
- Nociceptive versus neuropathic pain
- General aspects of opioids, specific opioids
- Adjuvant analgesics
- Pain procedures

The Pain Pathway



Nociceptive vs Neuropathic Pain

- Nociceptive Pain
  - More common
  - Experienced when injury or any localised inflammatory process occurs in the tissues
  - Fast pain fibres (A delta) – relay sharp, stinging pain sensation to dorsal horn of spinal cord (not intensity)
  - Slower C fibres relay aching, type pain sensations, more responsible for relaying intensity of pain
  - Treatment involves resolution of condition activating nociceptive fibres
    - E.g. radiotherapy to a painful bone metastasis, suppression of inflammation
- Neuropathic Pain
  - Caused by damage to or pathological changes in peripheral or central nervous system e.g. central neuronal sensitisation, damage to nervous system inhibitory functions, abnormal interactions between peripheral and central NS
  - Hallmarks are allodynia and hyperalgaesia

Neuropathic Pain: Peripheral Mechanisms

- Injury to peripheral nerve → sensitisation
  - spontaneous activity by the neurone
  - lowered threshold for activation
  - increased response to a given stimulus

- Sodium channels in damaged nerves differ pharmacologically and have different depolarization characteristic

- Neurogenic inflammation – inflammatory peptides and cytokines (subst P and prostaglandins) → spreading activation of surrounding neurones

Neuropathic Pain: Central Mechanisms

- Sensitisation of neurones in dorsal horn
- Peripheral nerve injury leads to altered gene expression in nerves of dorsal horn, e.g:
  - increased production of neurotransmitters (e.g. substance P)
  - reduced opioid binding sites
- “wind up” phenomenon
  - repetitive noxious stimulation of unmyelinated C-fibers → prolonged discharge of dorsal horn cells
  - progressive increase in number of action potentials per stimulus in dorsal horn neurons
  - repetitive episodes of "wind-up" can lead to long-term potentiation (LTP), → long lasting increase in the efficacy of synaptic transmission
- Reduction in inhibitory neurones → spinal hyperexcitability

Case: RS

- 62 yo man
- Married (Thai, limited English, visually impaired)
- 2 teenage sons and a 8yo son
- Diagnosed with rectal carcinoma 2004 – radical surgery at diagnosis and no adjuvant treatment
- Small bowel tumour resected at the time – carcinoid
- 2006
  - Anastomotic recurrence
  - Pre-operative chemo-radiation followed by abdomino-peroneal resection
- son born in 2008

Case: RS

- 2012
  - Left testicular granulosa cell tumour resected
  - No adjuvant treatment
- Late 2014
  - Developed pre-sacral recurrence
  - Underwent pelvic exentration surgery at RPA in February 2015
    - Removal of bladder, lower third ureters, prostate, sacral bone from S3 to S5 and coccyx
    - Urostomy created
    - Needing tissue flap from thighs due to large excision area
    - Pathology revealed narrow surgical margins
  - Stormy post-operative course requiring multiple re-admissions

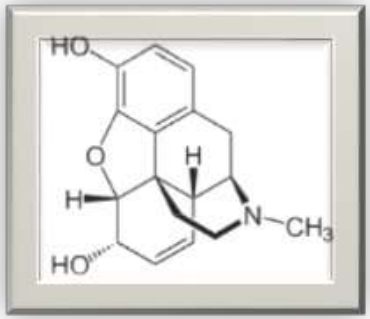
Case: RS

- Complications of surgery
  - Bilateral foot drop – required splints to walk
  - Neuropathic pain both feet
  - Pre-sacral abscess (chronic) and recurrent sepsis – requiring multiple drainages and antibiotics over many months
- May 2015
  - Required admission due to re-accumulation of abscess and sepsis
  - Referred to Palliative Care Service – no evidence of active malignancy at that stage
  - Pain reasonably well controlled on PRN endone (2-3 doses per day)

"Opioids" – originally the term was used to describe drugs derived from opium.

- Now the term includes synthetic drugs as well.
- Defining factor is their action on opioid receptors.
- Morphine, Hydromorphone, Oxycodone, Fentanyl, Codeine and Endorphins

Morpheus and Iris
Guerin Pierre Narcisse
1811

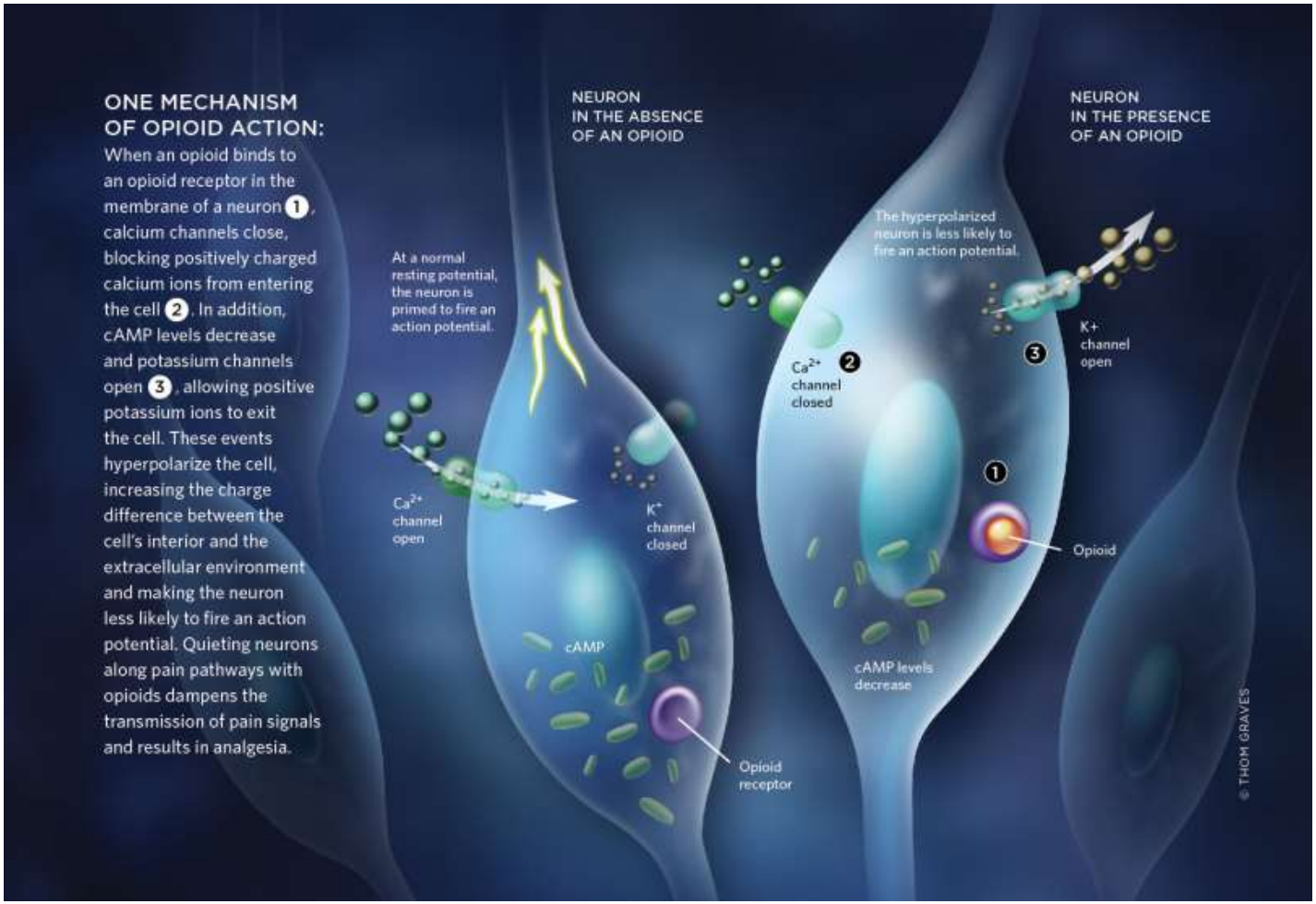


•Morphine is the prototype narcotic and the one against which all others are tested.

•Morphine is a potent agonist of the mu-opioid receptor.

•Central mu-receptors are found in the brain, the spinal cord and spinal ganglia but there are others in peripheral tissue.

•Activation of the mu receptor leads to analgesia, sedation and physical dependence.


ONE MECHANISM OF OPIOID ACTION:
When an opioid binds to an opioid receptor in the membrane of a neuron 1, calcium channels close, blocking positively charged calcium ions from entering the cell 2. In addition, cAMP levels decrease and potassium channels open 3, allowing positive potassium ions to exit the cell. These events hyperpolarize the cell, increasing the charge difference between the cell's interior and the extracellular environment and making the neuron less likely to fire an action potential. Quieting neurons along pain pathways with opioids dampens the transmission of pain signals and results in analgesia.
NEURON IN THE ABSENCE OF AN OPIOID
NEURON IN THE PRESENCE OF AN OPIOID
At a normal resting potential, the neuron is primed to fire an action potential.
Ca2+ channel open
K+ channel closed
cAMP
Opioid receptor
The hyperpolarized neuron is less likely to fire an action potential.
Ca2+ channel closed
K+ channel open
Opioid
cAMP levels decrease
© THOM GRAVES

Morphine

- Predominant liver metabolism
- Metabolites:
    - morphine-6-glucuronide (M6G)
        - most potent
        - analgesic activity through direct interaction with opioid receptors
        - accumulate in renal failure → neurotoxicity
    - morphine-3-glucuronide (M3G)
        - complex pharmacologic activities including partial antagonism of morphine-induced analgesia

- Even in cases of high burden of disease in liver
    – morphine toxicity not a big clinical problem

High Tolerance Develops	Moderate Tolerance	Minimal or No Tolerance
Analgesia	Bradycardia	Miosis
Euphoria, dysphoria		Constipation
Mental clouding		Convulsions
Sedation		
Respiratory depression		
Antidiuresis		
Nausea and vomiting		
Cough suppression		

Opioids are not equipotent.

- Oxycodone is approximately 1.5 x stronger than morphine
- Hydromorphone is approximately 5 x stronger than morphine
- Fentanyl is approximately 100 x stronger than morphine

Which opioid??

- Degree of pain
- Allergy
- Previous opioid use
- Currently opioid naïve?
- Renal impairment?
- Liver impairment?

OXYCODONE and MORPHINE

- 2 different drugs and not equipotent
- Oxycodone is 1.5 (at least) times stronger.
- There is a parenteral form of oxycodone – but not widely used in Australia.
- Morphine is cheap, available and well-tolerated.
- The availability of Targin has led to an increasing reliance on oxycodone in primary care.
- Oxycodone is metabolised in the liver (19% excreted unchanged in urine).
- Use with caution in renal failure - CNS toxicity and sedation
- Fentanyl and hydromorphone generally better in renal failure
- In advanced liver disease oxycodone's maximum concentration can increase by up to 40% and it's half life increases significantly

Targin

- Combination of Oxycodone & Naloxone (2:1).
- Oxycodone = full opioid receptor agonist
- Naloxone = competitive opioid receptor antagonist
- Developed to reduce opioid induced constipation in chronic pain.

Targin

Oxycodone

- Up to 87% oral bioavailability
- CYP3A4 and CYP2D6 mediated hepatic metabolism.
- Renal excretion of metabolites.

Naloxone

- Less than 3% oral bioavailability.
- Extensive first-pass metabolism.
- Renal excretion of metabolites

Targin

"Caution must be exercised in administering Targin to patients with mild hepatic impairment. Targin tablets are contraindicated in patients with moderate to severe hepatic impairment"

- Liver impairment reduces the first-pass metabolism of Naloxone leading to increased bioavailability.

- **Increased systemic antagonism of opioid receptors.**

- Study OXN1006: Naloxone plasma concentrations affected to greater extent than oxycodone. Clinical relevance is not yet known.

Targin in Palliative Care

- Case reports of opioid toxicity occurring during opioid rotation and liver impairment are increasing.

- Reports of poor analgesia at higher doses of Targin.(Mercadante S. et al (2010) Support Care Cancer; 19:1471-1472)

- Case reports of opioid-withdrawal syndrome in low doses of Targin (Kang et al (2011) J Pain & Symp Manag; 46(2) e17)

Targin in Palliative Care

- It has limited evidence for use in palliative care patients.
- Do not use if there is evidence of liver impairment.
- Seek advice if switching between opioids.
- Consider the pharmacology of the medication in context of organ failure.

Case: RS

- Aug 2015
  - Saw medical oncologist
  - “adjuvant chemotherapy” not recommended based on:
    - Recurrent sepsis
    - Long time period elapsed since surgery
  - Observation approach
  - Medications at that time:
    - Endone as required (2-3 doses per day)
    - Pregabalin
    - Amitriptyline
    - perindopril, pantoprazole, magnesium, Vitamin D

Adjuvant Analgesics

- Definition:
  - any drug that has a primary indication other than pain, but is analgesic in some painful conditions
- Considerations
  - Overall as a group less reliable analgesics than opioids
  - Higher likelihood of side-effects
  - Slower onset of analgesic effect
  - Significant inter-individual and intra-individual variability
  - Usually reserved for situations when analgesia from opioid inadequate despite dose escalation to limiting side effects
  - Balance between potential for improvement and risks of poypharmacy and adverse effects

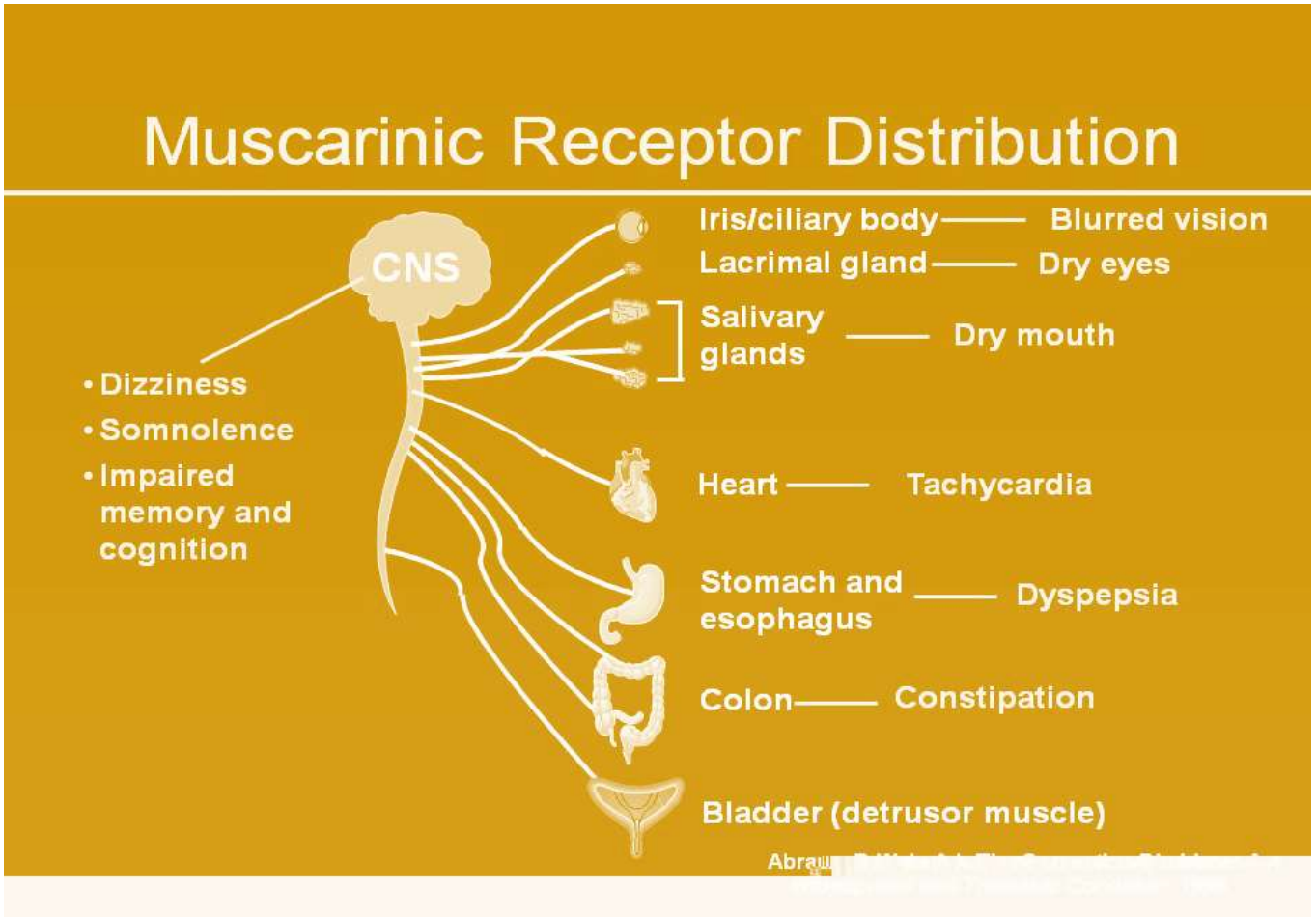
Amitriptyline

- Tricyclic anti-depressant
- Serotonin and noradrenaline (mono-amines) re-uptake inhibitor
- Na channel blockade and NMDA glutamate receptor antagonism may also contribute
- Seems to help 1 in 6 people with a pain reduction of 20-50%
- Time to peak plasma concentration: 4h PO
- Active metabolite nortriptyline 15-39h
- Duration of action: 24 hours

Amitriptyline

- Indications
  - *depression, anxiety and panic disorders, nocturnal enuresis, **neuropathic pain**, urge incontinence, sweating, bladder spasm, drooling, pathological laughing and crying*
- Contra-indications:
  - Concurrent use with MOAIs can lead to hypertensive crisis or serotonin syndrome, CCF, IHD, arrhythmias, mania, severe hepatic impairment
- Cautions
  - Bipolar disorder – can precipitate mania
  - Epilepsy – lowers seizure threshold
  - Hepatic impairment – reduce dose or avoid
  - Cardiac disease – risk of arrhythmia
- Undesirable effects
  - Anti-muscarinic (anticholinergic) effects – “dry as a bone, blind as a bat, red as a beet, hot as a hare, and mad as a hatter”

Amitiptyline



Amitriptyline

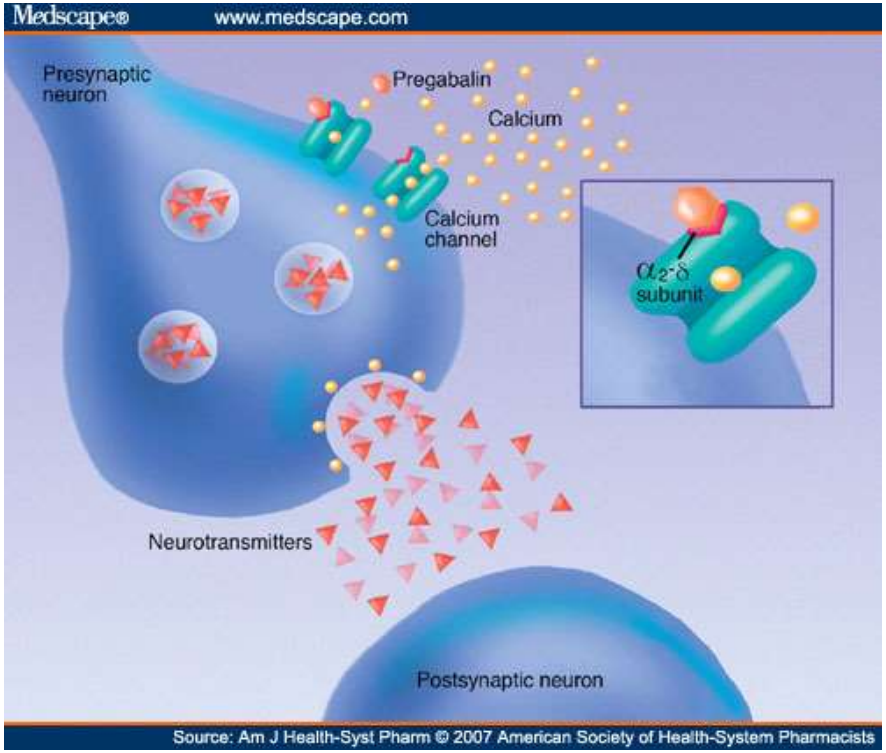
- Metabolised by CYP2D6 → use caution in combination with drugs that are inducers or inhibitors of these enzymes
    - paroxetine, fluoxetine, fluconazole, quinidine (strong CPY2D6 inhibitors) – increase plasma concentrations of TCAs from 20% 10 times
    - Carbamazepine decreases plasma concentrations by up to 60%

- Dosage in neuropathic pain
    - Start with 10mg nocte
    - If tolerated increase to 25mg after 3-7 days
    - If necessary increase by 25mg every 1-2 weeks

Gabapentin and Pregabalin

- **Class:** Anti-epileptic (pre-synaptic calcium channel blocker)
- **Indications:** *Adjunctive use in epilepsy,* ***neuropathic pain****, anxiety, intractable itch, hot flushes, sweating, refractory hiccup, restless legs syndrome, refractory cough*
- **Pharmacology**
    - Bind to $\alpha_2\delta$ regulatory subunit of pre-synaptic voltage-gated calcium channels
    - Reduce calcium influx responsible for triggering neurotransmitter release

Gabapentin/Pregabalin



Pregabalin/Gabapentin

- Inflammation and neuropathic pain
  → Calcium channel $\alpha_2\delta$ subunits are upregulated in the spinal dorsal horn
  → Pregabalin and gabapentin counteract this

- Evidence that they cause redistribution of calcium channels away from cell surface rather than blocking them directly

Pregabalin and Gabapentin

- Gabapentin in first-line choice for neuropathic pain because:
    - benefit has been confirmed for a range of causes
    - few drug interactions
    - less expensive than pregabalin
- Efficacy and tolerability of both appear comparable across a range of measures
- Pain relief similar in a head-to-head RCT of 120 patients with cancer-related neuropathic pain
- May be a role in switching from one to the other

Pregabalin and Gabapentin

Drug	Gabapentin	Pregabalin
Time to peak effect	2-3 h	1 h
Plasma half-life	5-7	5-9
Elimination	Renally excreted unchanged	Renally excreted unchanged

Pregabalin and Gabapentin

- Cautions:
  - Absence seizures (may worsen)
  - Psychotic illness (may precipitate or exacerbate psychotic symptoms)
  - Renal impairment (dose adjustment required)
  - Some potential for misuse
- Drug interactions
  - Increased rate of delirium and myoclonus when combined with opioids

Pregabalin and Gabapentin

- Undesirable effects
    - Very common – dizziness, drowsiness, ataxia
    - Common– amnesia, confusion, visual disturbance, dysarthria, tremor, arthralgia, myalgia, peripheral oedema, dry mouth, vomiting, constipation
    - Uncommon– suicidal ideation, impotence, gynaecomastia

- Pregabalin associated with cardiac conduction disturbance, QT prolongation and exacerbating CCF (gabapentin less so)

Gabapentin dose

- Start with 300mg nocte
- If necessary, increase by 300mg/24h every 2-3 days
- In elderly and/or frail patients
    - start 100mg nocte and increase if necessary by 100mg/24h every 2-3 days
- Maximum recommended dose: 1200mg TDS
- Doses should be reduced in renal impairment and dialysis patients

Pregabalin

- In physically robust patients recommended starting dose is 75mg BD
- In reality most palliative care patients fairly frail

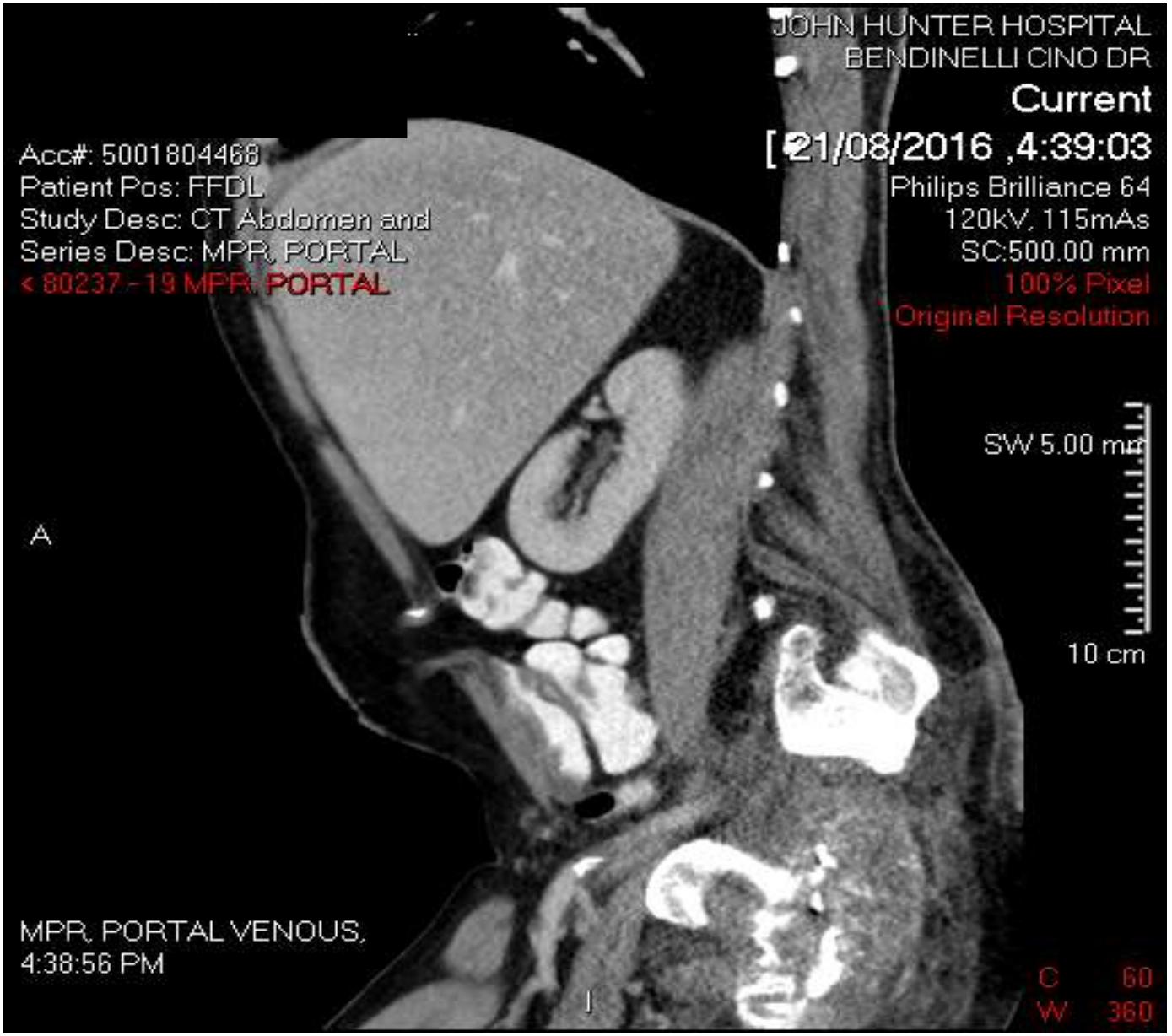
  → therefore better to start at 25mg -50mg BD (or even lower)
- Increase by 25-75mg BD every 3-7 days
- Dose reduction is necessary in renal failure

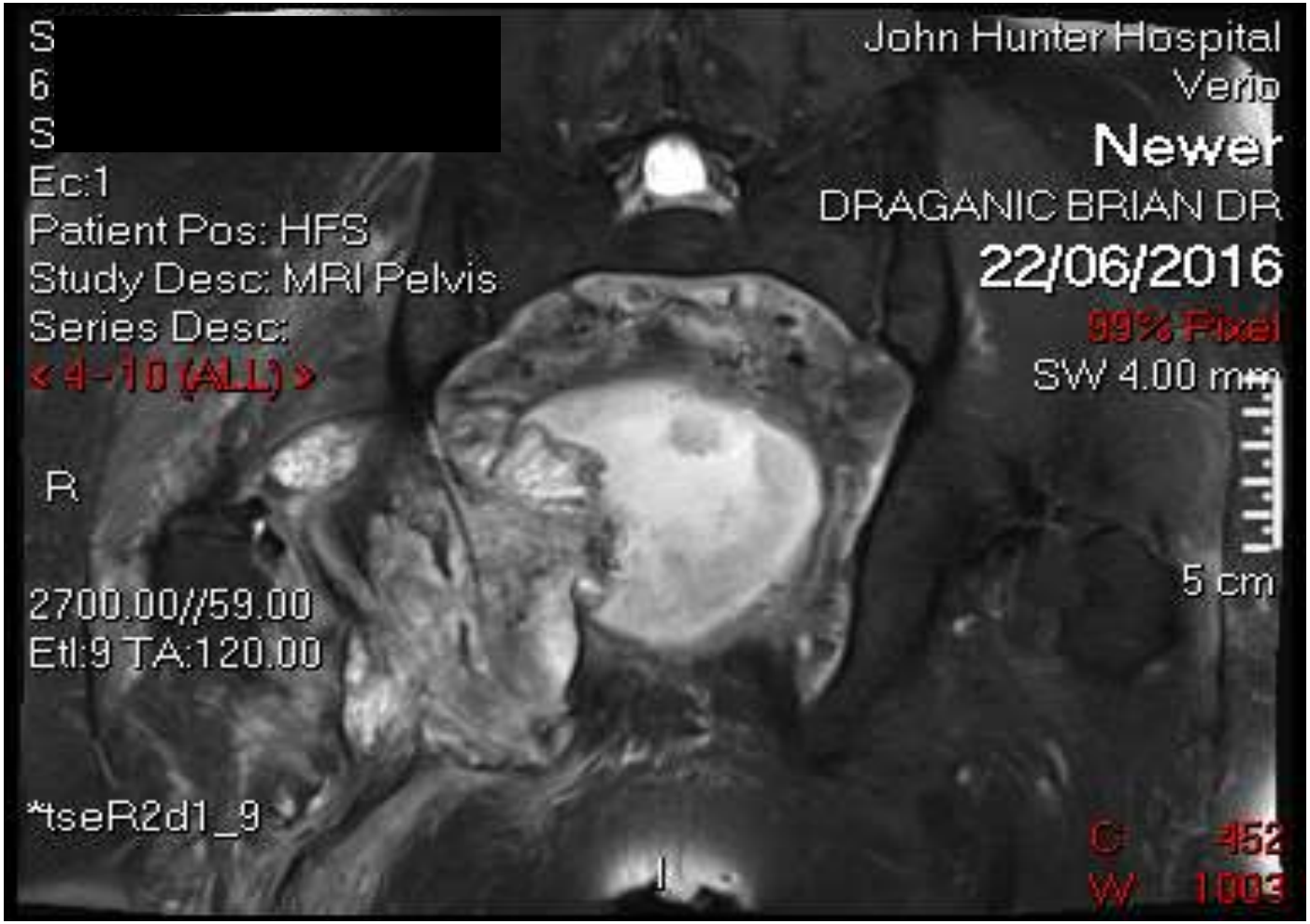
Case: RS

- Aug 2016
  - Re-admitted to JHH
  - Chronic pelvic collection still present, complicated by a severe progressive destructive process in right pelvis eroding through pubic bone, completely infiltrating right gluteal region
  - Felt to be osteomyelitis and/or ? recurrence of cancer
  - Fistula in right gluteal region with bag in-situ collecting
  - Imaging showed increase in size of collection despite antibiotics (fevers ongoing, CRP > 200 persistently) but also ***evidence of recurrence***

Case: RS

- CT and MRI findings
  - Large ill-defined calcified soft-tissue mass gluteal region extending into right inferior pubic ramus and destruction of underlying right ischium
  - Involvement of posterior and inferior aspects of right acetabulum – consistent with progressive destructive malignant process


JOHN HUNTER HOSPITAL
BENDINELLI CINO DR
Current
[21/08/2016 ,4:39:03
Philips Brilliance 64
120kV, 115mAs
SC:500.00 mm
100% Pixel
Original Resolution
Acc#: 5001804468
Patient Pos: FFDL
Study Desc: CT Abdomen and
Series Desc: MPR, PORTAL
< 80237 -19 MPR, PORTAL
SW 5.00 mm
10 cm
A
MPR, PORTAL VENOUS,
4:38:56 PM
I
C 60
W 360


S
6
S
[redacted]
Ec:1
Patient Pos: HFS
Study Desc: MRI Pelvis
Series Desc:
< 4-10 (ALL) >
R
2700.00//59.00
Etl:9 TA:120.00
*tseR2d1_9
I
John Hunter Hospital
Verio
Newer
DRAGANIC BRIAN DR
22/06/2016
99% Pixel
SW 4.00 mm
5 cm
C 452
W 1003

Case: RS

- Mobility significantly impaired
- Pain
    - Gluteal region, radiating to distal leg
    - Described as a constant ache / burning
    - No hyperalgaesia / allodynia
    - Exacerbated by lying on right side, certain movements
    - Reasonably well-managed on current regimen:
        - Oxycontin 40mg BD + PRN oxycodone 10mg
        - Pregabalin 75mg BD
        - Amitriptyline 50mg nocte

Case: RS

- Discussions surrounding cessation of antibiotics and changing focus of care to symptom management alone → eventual decision to cease antibiotics (24 Aug 2016)
- Discharged home on 5 Sept as per RS's wishes and family all very willing to support this wish
- On discharge, medications were:
    - MS Contin 150mg BD
    - PRN oxycodone 25mg
    - Amitriptyline, pregabalin as per previous doses

Case: RS

- Remained at home from 5/9 until 26/9
- Main issue was uncontrolled pain
    - Difficult to describe
    - Felt in right hip and bilateral knees
    - Finds opioids helpful however felt that “nothing takes the suffering away” (MS Contin200mg BD)
- Other symptom issues:
    - Fatigue – no energy, preferring to stay in bed, over past 2-3 days asleep more than awake
    - Existential – loss of hope for a cure and trying to come to terms with this, worried about his youngest son and aware that he hasn’t had conversation to tell him he will die, worried about his wife and wanting to please her and other family members, not afraid of death but fearful of pain and effect on family

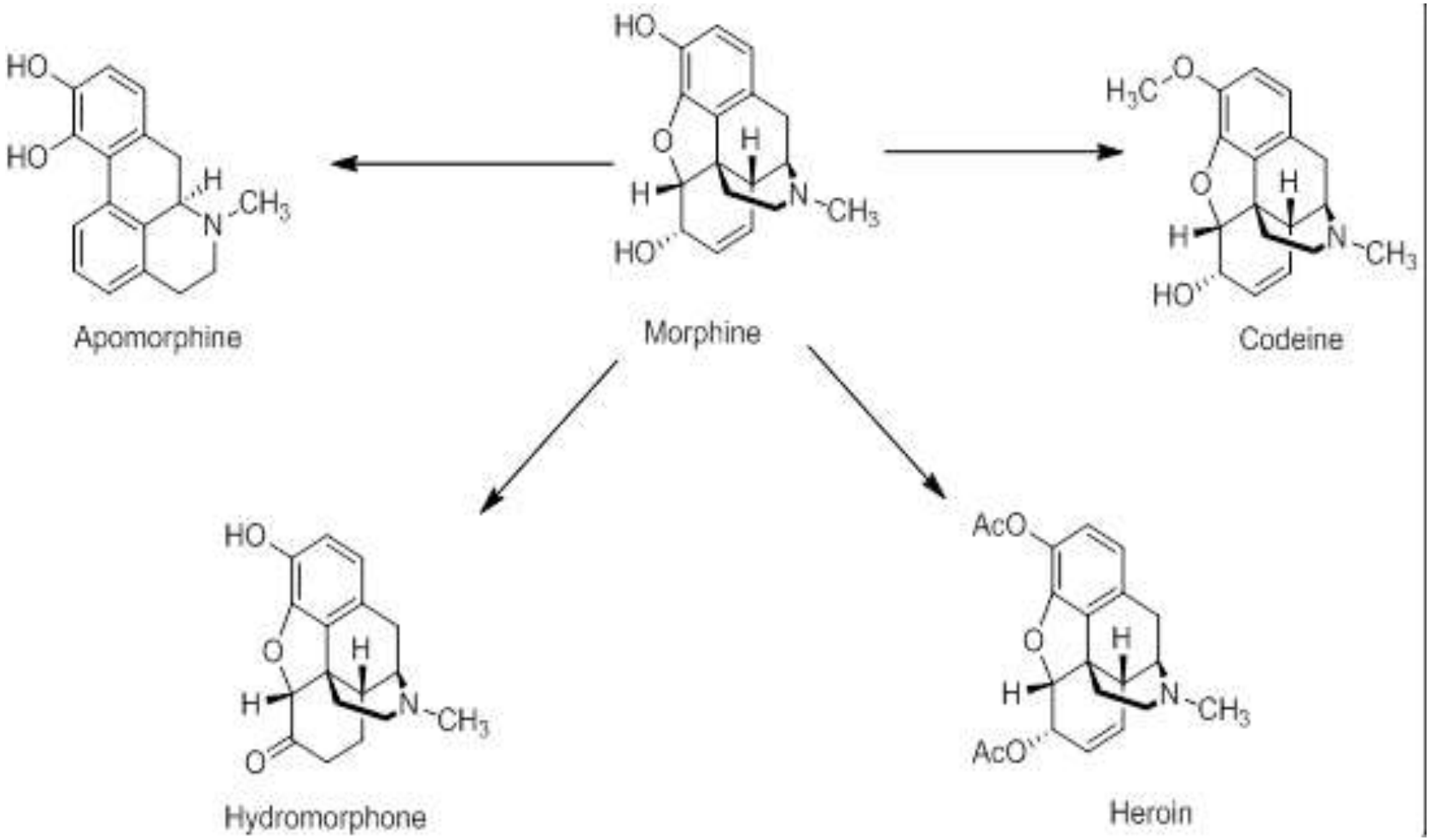
Case: RS

- On examination:
    - Myoclonus, afebrile
    - Dry mouth, no thrush
    - Abdomen – colostomy bag, ileal conduit, bag over chronic discharging fistula right buttock
- Plan on admission:
    - Hydromorphone 20mg, clonazepam 0.5mg SC infusion over 24 hours
    - Hospice admission – Resuscitation Plan completed
    - Wean pregabalin
    - Social work / pastoral care referral
        - Religious issues
        - Support of RS and family members
- Interpreter required for wife

Hydromorphone

- Semi-synthetic opioid agonist,
- Structurally similar to morphine, but addition of 6 keto- group and hydrogenation of double-bond at 7-8 position
- Acts primarily at mu opioid receptors, less so delta (no effect on kappa, sigma or epsilon receptors)
- First synthesised in 1921 in Germany, introduced into clinical practice 1926
- Not commonly used despite supporting evidence until more recently

Structure of opioids



Pharmacokinetics: PO

- PO hydromorphone absorbed mainly in small intestine
- 62% of oral dose eliminated by liver on first pass

- Immediate–release (Dilaudid)
    - onset of action ~30mins
    - duration of action ~4hours

- Modified release (Jurnista)
    - duration of action 24 hours

Pharmacokinetics: Parenteral

- IV, IM, SC
- More fat soluble than morphine therefore onset of action faster
- Can be administered in highly concentrated solutions
- More potent than morphine (5-7 x)
- Therefore able to administer high doses parenterally

- High concentrations can result in painful local reactions

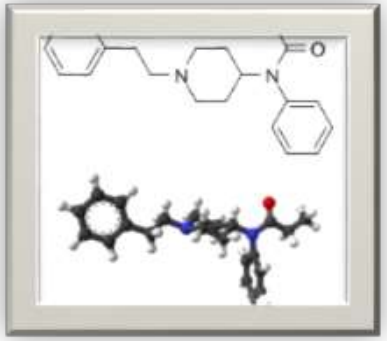
Hydromorphone Metabolites

- Main metabolite is H3G (hydromorphone-3-glucoronide)
    - No analgesic activity but significant neuro-excitatory properties (2.5 > than M3G)
- All metabolites are renally excreted and can accumulate in renal impairment
- Conflicting evidence as to whether it has a more favourable side effect profile compared to morphine
- As with all opioids will depend on individual patient

Hydromorphone:
Take Home Messages

- Hydromorphone is 5-7 times as potent
- Always check dose (convert to morphine)
- Toxic metabolites more potent than those of morphine
- Whilst recommended for use in renal impairment it should still be used with caution
- Site reactions are more common than with morphine

- What other agents could we potentially use at this point??



- **Fentanyl** is a potent synthetic opioid.
- Rapid onset and short duration.
- Onset over 5 minutes (parenteral)
- Hepatic metabolism
- T1/2 is around 20 minutes (parenteral).
- Bioavailability varies significantly based on route of administration-
    - 92% transdermal
    - 89% nasal
    - 50% buccal
    - 33% ingested

Fentanyl

- considered safe in renal failure but minimal pharmacokinetic data around it's use in end-stage renal disease.
- not dialysable because highly protein bound and has a high volume of distribution.
- Oral preparations act rapidly due to high lipid solubility through the buccal mucosa.
- Fentanyl patches are only useful for stable pain and take approximately 4 days to reach steady state.
- Heat – due to fever for example- can cause more rapid absorption and cachexia can reduce effect.
- Seem to have a 'ceiling effect'.

Available Opioid Formulations and Equivalency

eviQ Cancer Treatments Online

ID: 000883 | Approved: 26 Oct 2010 | Last Modified: 13 Oct 2014 | Review Due:01 Jan 2015

The following is a list of the currently available opioid formulations in Australia. Preparations are available as immediate release or as modified released formulations.

Modified-release formulations should never be crushed
large dose being absorbed over a short period.

Please note that all conversions listed are a **guide onl**
patient and previous analgesic requirements.

Conversions from transdermal fentanyl to other opioids are imprecise and poorly studied. The calculator uses conversion figures provided by the manufacturer.

Opioid	Trade name	Release Ra		
Buprenorphine	Norspan®	Slow Release		
Codeine	Codeine	Immediate		
	Codeine/Paracetamol eg.Panadeine Forte®**	Immediate		
	Codeine/Paracetamol eg.Panadeine®**	Immediate		
Fentanyl	Durogesic®	Slow Release	12, 25, 50, 75 and 100 mcg/hr transdermal (TD) patch	Conversions from transdermal fentanyl to other opioids are imprecise and poorly studied. The calculator uses conversion figures provided by the manufacturer.
	Fentanyl Sublimaze	Immediate	50 mcg/ml injection	25 mg PO morphine = 100 mcg fentanyl
Hydromorphone	Dilaudid®	Immediate	2, 4 and 8 mg tablets 1 mg/ml oral liquid 2 mg/ml and 10 mg/ml injection	10 mg PO morphine = 1.67 mg PO Dilaudid 10 mg PO morphine = 1.67 mg PO Dilaudid 20 mg PO morphine = 1 mg IV Dilaudid
	Dilaudid-HP®	Immediate	10 mg/ml injection	20 mg PO morphine= 1 mg IV Dilaudid
	Jurnista® ***	Slow Release	4, 8, 16, 32 and 64 mg tablets	4 mg PO Jurnista = 24 mg PO morphine
	[illegible]®	Immediate	10 and 20 mg tablets	Direct equivalent

Transdermal fentanyl – morphine equivalence

Durogesic **Table 5**

Recommended starting dose of Durogesic based on daily oral morphine dose*

Oral 24 hour morphine (mg/day)	Durogesic dose (microgram/hour)
< 60	12**
60-134	25
135-224	50
225-314	75
315-404	100
405-494	125
495-584	150
585-674	175
675-764	200
765-854	225
855-944	250
945-1034	275
1035-1124	300

* In clinical trials these ranges of daily oral morphine doses were used as a basis for conversion to Durogesic. ** Based on dose proportionality and not clinical trial data on dose conversion.

Subcutaneous fentanyl

- Not useful for breakthrough because of lipophilic nature – poor analgesic quality and short duration
- In a CSCI – sometimes used if appropriate
- Often avoided so that regular opioid and breakthrough can be the same drug

Sublingual fentanyl

- Use for breakthrough pain in adult cancer patients already on strong opioids
- Aim to provide rapid onset analgesia

- Successful dose cannot be predicted from baseline analgesia
- Individual titration is required (start with 100mcg dose and monitor)

METHADONE

It is impossible to over-estimate the shame and fear that opioid use engenders for some patients and families. This impact is magnified dramatically for methadone.

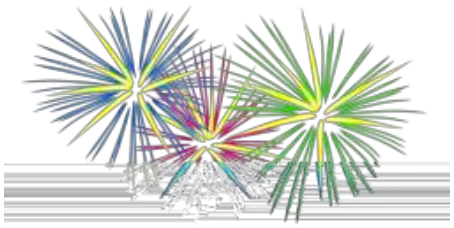
- Potent opioid agonist
- Low-cost, inactive metabolites, several formulations.
- Unlike morphine it is a racemic mix: one stereoisomer acts as an NMDA receptor antagonist and the other is a mu-receptor antagonist.
- Can therefore be useful for neuropathic pain, prevention of opioid tolerance and to potentiate opioid effects.

- Highly lipophilic, rapid GI absorption, rapid onset of action.
- Extended terminal half-life – up to 190 hours. This half-life does not match the duration of analgesia (6-12 hours).
- Long half life leads to increased risk of accumulation – sedation / respiratory depression.
- Half life varies between patients and can vary in the same patient.
- High-dose methadone can cause QT prolongation and Torsades.
- The potency of methadone is patient specific – no easy conversion table.
- Response can vary in the same patient over time.
- A patient's current exposure to other opioids dramatically effects the potency of methadone.

<100mg morphine 24/24 – 3:1
(3mg morphine / 1mg methadone)
800mg morphine 24/24 – 20:1
(20mg morphine / 1mg methadone)

Ketamine

- Main use is as a dissociative anaesthetic.
- Increasing interest in it's role as an analgesic and anti-depressant.
- Acts on the NMDA receptor (n-methyl-D-aspartate/glutamate receptor). This receptor is a calcium channel that is closely involved in the development of central (dorsal horn) sensitisation.
- 'Central sensitisation' is implicated in opioid-resistant pain and opioid-induced hyperalgesia as well as neuropathic pain.
- Ketamine also seems to act on nicotinic, muscarinic and opioid receptors.



- Data for use in pain is poor.
- Side-effects include dysphoria, hallucinations, nightmares, nausea, sedation and tachycardia.
- Concern regarding hepatobiliary, urinary and neuropsychiatric toxicity with long-term exposure.
- Current practice suggests use of burst ketamine in patients with refractory and severe pain not responding to other agents.

Case: RS

- Pain remained difficult to control
- Lignocaine commenced at 500mg/24 hours 4 days after admission
- Pain improved “a bit” the next day → increased to 750mg over 24 hours
- 2 days later – increasing opioid requirement → hydromorphone increased to 28mg over 24h → 35mg
- Referral to HIPS - ? Any local procedures to alleviate pain
- Reviewed by HIPS and offered central neurolytic procedure
  - explained likelihood of significant numbness from waist down, complete paralysis and no bowel/bladder function

Case: RS

- Planned for 2 days time
- Significant deterioration over the next 2 days
    - Fevers, sweats
    - Increasing delirium
    - Pain more manageable (reduced breakthrough requirements)
    - Still excruciating to move but virtually pain-free at rest
    - Increasing drowsiness, interaction with family becoming less and less
- Discussed pros and cons of transporting to JHH for procedure – on balance decision to not go ahead
- Deterioration continued over next few days but symptomatically reasonably stable
- Intensive regular meetings with family and some resolution of conflicts.
- Died 14 October with family surrounding him

Systemic Lignocaine

- Local anaesthetic - mechanism of relief from neuropathic pain not fully understood
- Blockade of sodium channels → stabilises nerve membrane → suppresses injury-induced hyperexcitability in peripheral and central nervous systems
- Animal and human studies demonstrate that injured nerves develop abnormal, spontaneously active sodium channels at sites of nerve injury, along damaged nerves, and at the dorsal root ganglia of damaged nerves.
- Lignocaine can suppress this ectopic, spontaneous firing of aberrant sodium channels at concentrations that do not affect normal nerve or cardiac conduction and thereby modulate neuropathic pain.

Systemic Lignocaine

- Systematic review of 32 RCTs mostly of IV lignocaine and PO mexiletine for neuropathic pain of various causes:
  - Better than placebo
  - Equivalent to gabapentin, carbamazepine, morphine
  - But benefits inconsistent particularly in cancer-related neuropathic pain
- Should be considered only when combination of strong opioid + NSAID + TCA + anti-epileptic is ineffective or poorly tolerated

Systemic Lignocaine

- Narrow therapeutic index
- Important contraindications:
    - Patients at greater risk of cardiac arrhythmia (e.g. cardiac disease, electrolyte abnormalities, on anti-arrhythmic drugs)
- Important cautions:
    - Elderly
    - Cachectic
    - Renal impairment
    - Hepatic impairment
- A normal 12-lead ECG is mandatory
- In reality, at therapeutic levels cardiac arrhythmias are very rare

Systemic Lignocaine

- In cancer-related neuropathic pain one positive RCT
    - Compared to placebo pain relief was faster (40 vs 75mins), of greater magnitude (75 vs 25% reduction) and duration (9 vs 4 days)
- Some case reports in literature
- Various regimens include:
    - CSCI 0.5-1mg/kg/h
- CSCIs have been given for up to 6 months

Pain Procedures

- Anaesthetic, neurolytic and neurosurgical procedures to block or modify sensation of pain as it is transmitted from the source to CNS
- **Options:**
    - Local infiltration of anaesthetic
    - Peripheral nerve blocks
    - Intraspinal nerve blocks
    - Neurosurgical procedures

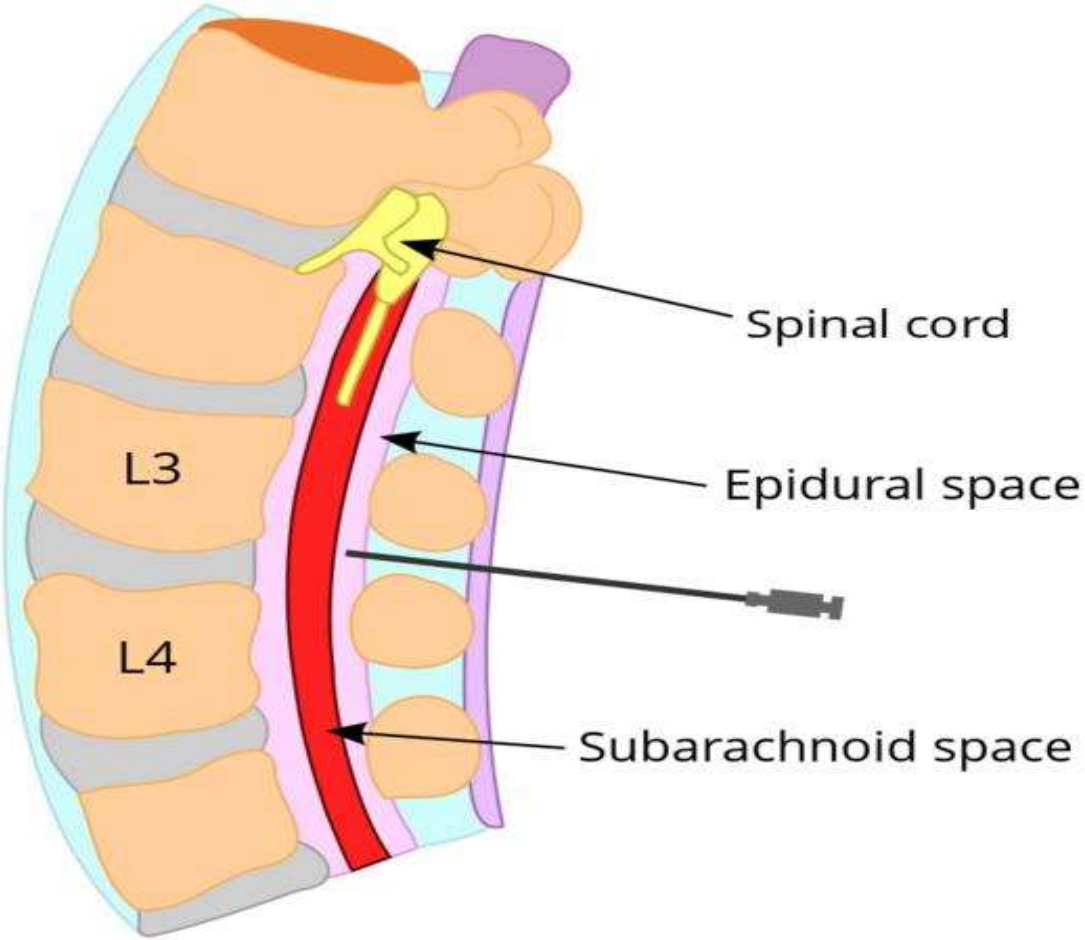
Pain Procedures

- **Local infiltration**
  - Used for discrete painful bone metastases (e.g. ribs) – local anaesthetic and steroid to prolong effect
- **Nerve blocks**
  - **Diagnostic** nerve block to determine which nerve(s) responsible for pain
  - **Prognostic** nerve block to assess adequacy of analgesia and allow patient experience sensory loss/motor and sphincter disturbance
  - **Therapeutic** nerve blocks
    - Temporary (local anaesthetic)
    - Prophylactic – where predictable local progression of cancer likely to produce severe pain, e.g. intercostal nerve block at time of surgery where significant chest wall infiltration
    - Permanent – provide pain relief for weeks to months, only suitable for purely sensory nerves or where loss of motor or other functions deemed an acceptable option

Pain Procedures

- **Spinal nerve blocks**
  - Epidural local anaesthesia – anaesthetic diffuses through epidural space affecting dorsal nerve root (usually minimal motor or autonomic effect)
  - Epidural catheter can be tunnelled SC and connected to a reservoir or continuous infusion pump
    - can provide excellent analgesia over several spinal levels
    - C-T junction → analgesia to both arms
    - Mid T → lower chest and abdomen
    - T-L junction → lower abdomen, upper thighs
    - L-S → both legs
    - Mid-sacral – perineum

Spinal blocks

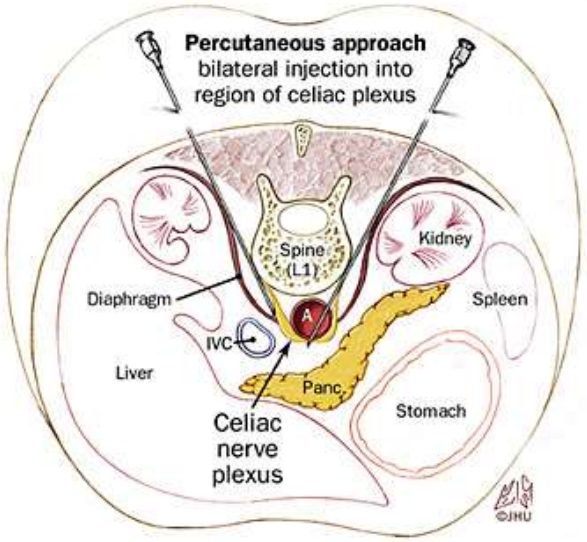


Pain Procedures

- **Neurolytic blocks**
  - Injection of alcohol or phenol into epidural or subarachnoid space
  - Motor and autonomic nerves likely to be damaged causing limb weakness/paralysis and bowel and bladder dysfunction
- **Autonomic nerve blocks**
  - Coeliac plexus block – for severe pain of uppper abdominal viscera e.g. pancreatic cancer → can provide immediate relief of pain for 80% of patients

    - ***Side effects:*** orthostatic hypotension due to splanchnic and lower limb vasodilation (often resolves in a few days), potential for damage to surrounding tissues, vessels and nerves

Coeliac Plexus Block

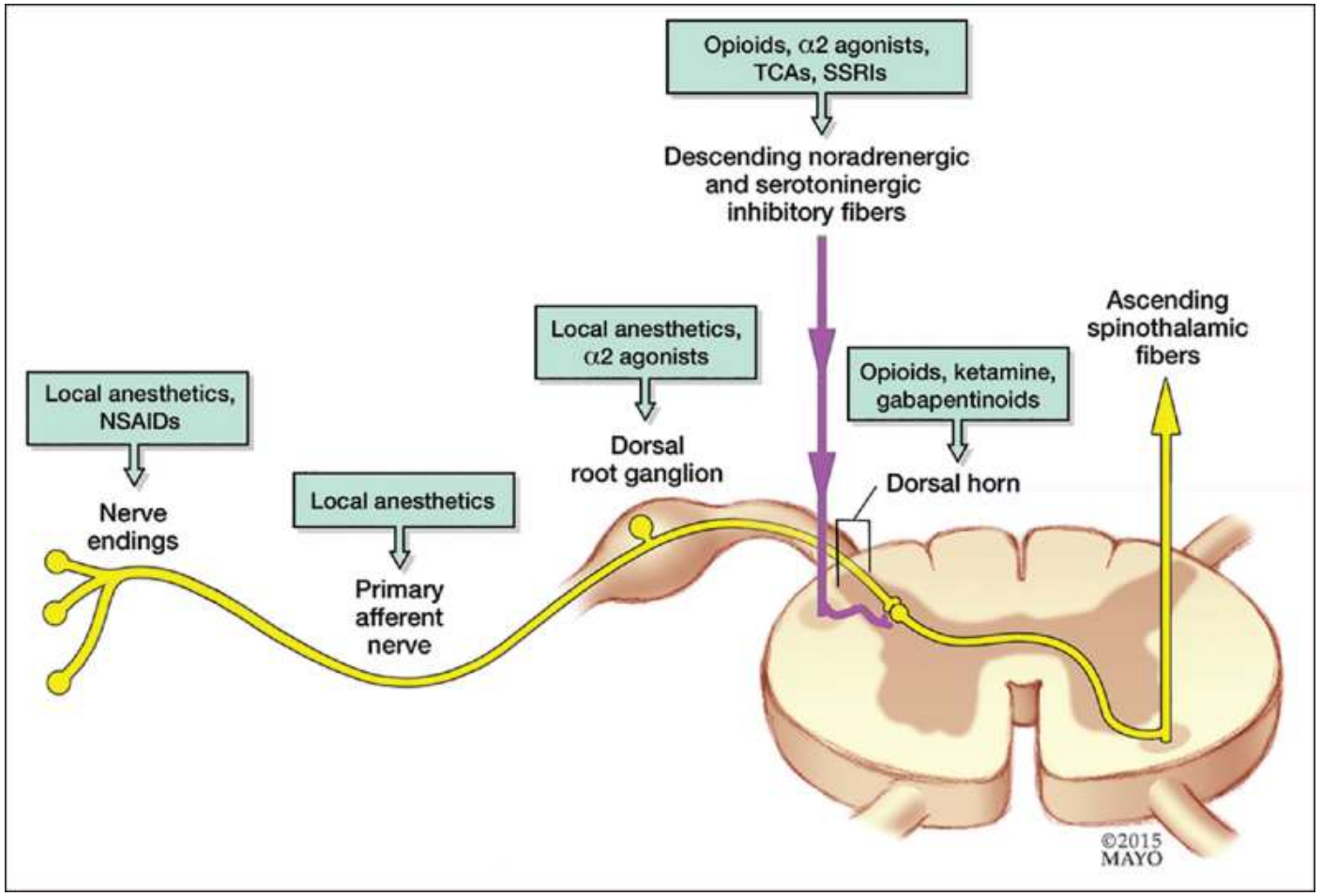


Pain Procedures

- Always worth considering particularly if :
  - opioids and other adjuvants ineffective
  - high doses causing significant toxicity
  - pain is localised to a particular region

- Always a balance between potential side effects and potential for benefit reasonable

Pain Pathways



THANK YOU

ANY QUESTIONS OR COMMENTS?