Managing cancer pain in primary care

Dr Mark Howard

20th January 2024

Beacon Hospital

THIS IS MODERN MEDICINE

Mr Smith - 68 Years Old

Newly diagnosed metastatic pancreatic cancer on imaging – awaiting histology results and referral to oncology

Complaining of abdominal pain radiating through to his back

Already taking max dose co-codamol 30/500mg

Not sleeping due to the pain

Where do you go next?

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Learning Outcomes

- Define the types of pain and how they are assessed
- Review safe prescribing of opioids, analgesic ladder, opioid titration, recognition of side effects, opioid rotation
- Summarise the use of adjuvant agents in cancer pain management

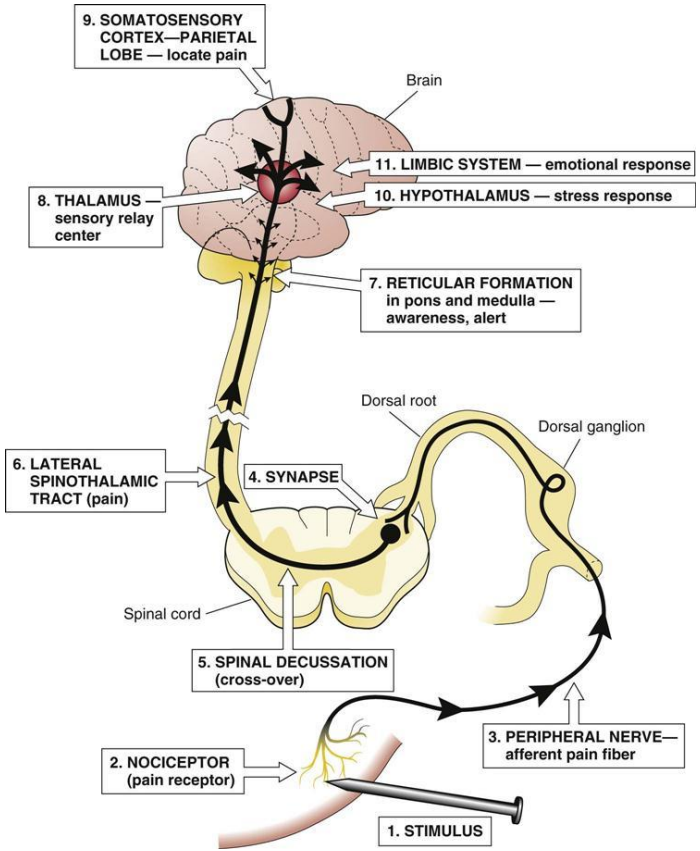
Scope of Talk

- Cancer pain in primary care
    - Cancer with curative or palliative intent
    - Commonly prescribed drugs

- Not being covered today
    - Non-cancer pain
    - Chronic pain
    - Pain in the cancer survivor

Types of Pain

- Nociceptive pain
  - Tissue damage/injury
    - Visceral
    - Somatic
- Neuropathic pain
  - Nerve compression/injury
- Mixed pain
- "Total" pain



https://basicmedicalkey.com/pain-4/

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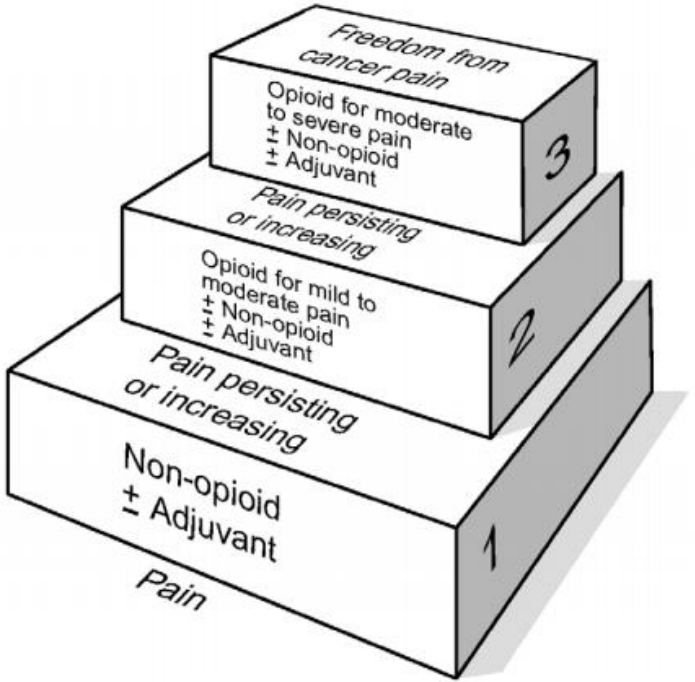
WHO Analgesic Ladder

- 75% of patients will have their pain adequately managed with the WHO pain ladder

- "By the mouth"
- "By the clock"
- "By the ladder"
- "Individual dose titration"
- "Use adjuvant drugs"
- "Attention to detail"

(WHO Cancer Pain Relief 1986/1996)



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NSAIDs

- Valuable drugs for cancer pain if they can be safely used
- Increased risk of upper GI and CVS complications
- From RA/OA taking NSAID ± gastroprotection for >2 months
    - the risk of a bleeding ulcer or perforation is about 1 in 500 patients
    - risk of dying from gastroduodenal complications is about 1 in 1,200

Tramer M et al. (2000) Quantitative estimation of rare adverse events which follow a biological progression: a new model applied to chronic NSAID use. Pain. 85: 169–182.

Choice of NSAID

Usually low dose celecoxib (100mg BD) or ibuprofen (400mg TDS)

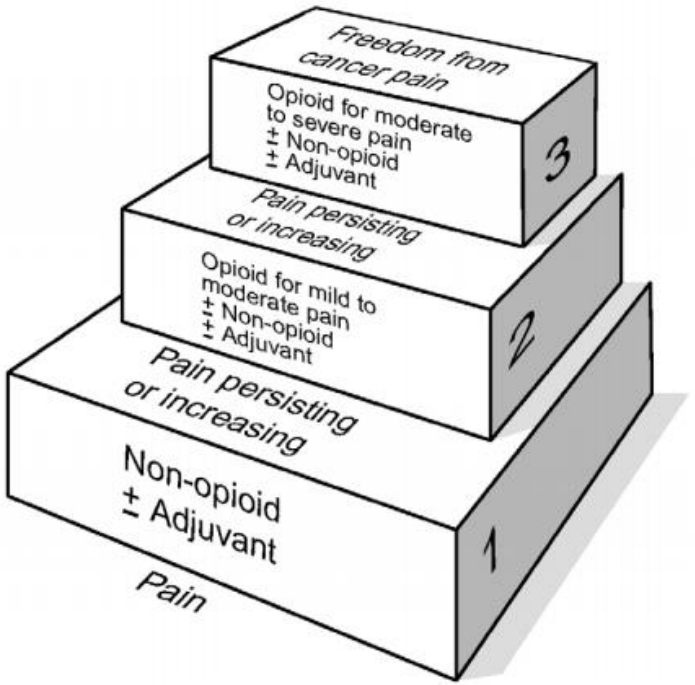
- Low risk of GI toxicity; prob low risk of major cardiovascular event

Patients with high risk of cardiovascular event:

- Naproxen / Celecoxib / Diclofenac / ibuprofen have equal risk

Weak Opioids

- Codeine phosphate (ineffective in 5-10% Caucasian population)
- Tramadol ("sits on the fence" between weak and strong opioid)
- Combination products



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Weak Opioids Equivalent Strength

Weak opioid	Morphine dose
Codeine phosphate 30mg	3mg
Tramadol 50mg	5mg

- Beacon oncology service (IPU and day-ward)
    - 13,703 opioids administered in 2023
    - Weak opioids only accounted for 10%

Strong Opioids - Morphine Sulfate

- is the strong opioid for moderate to severe cancer pain
- It acts on the mu and kappa opioid receptors

Metabolised to

- morphine-3-glucuronide (M3G)-accumulation may cause clinical excitation or agitation

- **morphine-6-glucuronide** (M6G)-the useful analgesic metabolite. Accumulation may account for symptoms of drowsiness, nausea and vomiting, respiratory depression and even coma.

- Shows efficacy with neuropathic pain but evidence quality weak

Morphine metabolites accumulate in renal failure (as do oxycodone and many others)

Morphine-Side-Effects

CNS:

- drowsiness, cognitive impairment, hallucinations, vivid dreams, peripheral shadowing of vision, delirium, agitation, euphoria, myoclonus, hyperalgesia, seizure disorder and respiratory depression

Gastrointestinal

- Constipation, nausea and vomiting (less commonly)

Autonomic

- Dry mouth, urinary retention and postural hypotension

Cutaneous

- Itching (pruritus) and sweating

Starting Doses for Oral Morphine

Adult, not pain controlled on regular weak opioids	5- 10 mg 4- hourly morphine
Elderly and not taking regular weak opioids	2.5 - 5 mg 4-hourly morphine
Very elderly and frail not taking regular weak opioids	1.25- 2.5 mg 4-hourly morphine

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Once the pain is controlled

Calculate the 24-hour dose of four hourly oral morphine needed and split in to two equal doses of 12 hourly morphine.

e.g. Patient took 40mg of oramorph (20mls) in a 24 hr period

⇒ MST 20mg BD

PRN breakthrough dose? **1/6 of the total 24-hour dose**

⇒ Oramorph 5-7.5mg 2-4 hrly PRN

The first dose of the modified-release preparation is given with, or within four hours of, the last dose of the immediate-release preparation (BNF)

Opioids - don't forget!

- Laxatives e.g. senna and docusate/lactulose
- Anti emetics PRN for the first couple of days
- Warn patients about the possibility of initial drowsiness
    - This usually settles down after 24-48hrs
- Advise a patient that they should not drive for a few days – and not if they feel impaired in any way

Strong Opioids - Oxycodone

- Similar properties to morphine
- Shows efficacy with neuropathic pain but evidence quality weak
- Metabolised to noroxycodone and oxymorphone
- Better bioavailability than morphine, hence 2:1 morphine:oxycodone ratio
    - **Oxycodone PO 5mg = Morphine PO 10mg**
- Renally excreted
- Combination products (Targin) – Oxycodone/naloxone
    - 5 fold increase in prescribing 2011-2019 in Ireland

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Strong Opioids - Fentanyl (transdermal)

- Is less likely to cause toxicity in renal failure than morphine (because no known active metabolites)
- Thought to cause less constipation than other opioids (less required to achieve same amount of analgesia)
- 6 to 12 hours to take effect
- 36 to 48 hours to reach stable plasma levels
- If pain uncontrolled can be titrated up in increments after 48 -72 hours

- Fentanyl 12mcg transdermal patch = **40-60mg PO morphine / 24hrs**
- **Fentanyl 25mcg patch = 80-120mg PO morphine /24 hrs**
- Ideally patient should be on PRN opioid first for a few days before starting a patch

Strong Opioids - Buprenorphine (transdermal)

- Classed as a partial opioid agonist (mu opioid receptor)
- Comes in a variety of preparations-sublingual tablet, injection, transdermal patch (Butrans & Transtec)
- BuTrans patch (the **seven** days)- 5,10 & 20 mcg/hr strengths
- Transtec patch (the **four** days)- 35,52.5 & 70 mcg/hr strengths
- Useful in renal failure (no centrally active metabolites)
- Buprenorphine TD 5mcg patch = **12mg PO morphine / 24 hrs**

Transdermal opioid preparations

- Generally not suitable for unstable pain
- Useful for patients with head and neck cancers, oesophageal Ca, gastric outlet obstruction or bowel obstruction
- Be mindful of sources of increased body heat – causes ↑ absorption
    - Sunbathing
    - External heat source (sauna, hot tub, electric blanket, hot water bottle)
    - Avoid hot bath (swimming/shower ok)

Tapentadol (Palexia)

- Should be considered a strong opioid
- μ-opioid agonist and inhibitor of norepinephrine
- Tapentadol 50mg = 10mg oral oxycodone = **20mg oral morphine**
- Maximum dose usually 600mg / 24hrs
- Dramatic increases in prescribing in Ireland 2012-2019[1]

1. Norris, B.A., Smith, A., Doran, S. and Barry, M., 2021. Trends in strong opioid prescribing in Ireland: a repeated cross-sectional analysis of a national pharmacy claims database between 2010 and 2019. Pharmacoepidemiology and Drug Safety, 30(8), pp.1003-1011.

Mr Smith - 68 years old

- Metastatic pancreatic cancer confirmed – awaiting appointment to start chemotherapy
- Commenced on Oxycontin and Oxynorm. Dose gradually increased over a week to Oxycontin 20mg BD and oxynorm 5mg PRN – taking 2-3 doses of PRN per 24 hrs for over a week
- Experiencing nightmares
- Wife reports he is having conversations to himself or to people that are not in the room
- Very drowsy, sleeping a lot more
- Pain still a problem

Strategies for managing adverse effects

- Opioid toxicity
  - **If pain controlled – <u>reduce dose of existing opioid</u>**
  - **If pain not controlled – <u>switch/rotate opioid</u>**
- Patients starting on either morphine or oxycodone[1]
  - One third require a rotation to the alternate
  - 95% patients will find an effective and tolerable dose
  - 5% will require a further opioid rotation to another strong opioid

1. Riley J et al. (2015) Morphine or oxycodone for cancer-related pain? A randomized, open-label, controlled trial. Journal of Pain and Symptom Management. 49: 161–172.

Opioid switching(or rotation)

Useful if:

- Poor response to a particular opioid – side effects
- Intractable constipation (consider change to transdermal fentanyl)
- Intolerable adverse effects (e.g. drowsiness, hallucinations, muddle)
- Poor compliance/adherence (often switched over to transdermal preparation)

- Referral to Specialist palliative care

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Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

SPECIALIST PALLIATIVE CARE REFERRAL FORM

Please forward completed form to your local service provider.
Contact details available at:
http://www.iapc.ie/directory and http://www.icgp.ie/palliative

Patient Details

Name:	**Date of Birth:**	**Gender:** Male Female
Address:	**Phone:**	**Medical Card:** Yes No
	Mobile:	**Health Ins:** Yes No
Current Location:		**Is the Patient Living Alone?** Yes No

Contact Person

Contact Person (Family/Friend):	**Address:**
Relationship:	**Phone:**

Referral For:	**Urgency of Referral:**
Hospice Admission: ☐	(Subject to Triage by Specialist Palliative Care Team)
Community Based Services*: ☐	Two working days* ☐
Hospital OPD: ☐	*Must be accompanied by phone contact from Referrer
Other: ☐	One Week ☐
	Two Weeks ☐
*Subject to availability, services may include OPD, Day Hospital, Community Specialist Palliative Care Team (Home Care Team) or other.	Pending ☐

Diagnosis, treatment to date, further treatment planned (e.g. recent admission(s), radiotherapy, chemotherapy, etc.)
PLEASE ATTACH COPIES OF RECENT CORRESPONDENCE, IMAGING REPORTS AND BLOOD RESULTS

A Late palliative care referral

B Early palliative care referral

Zimmermann, C. and Mathews, J., 2022. Palliative care is the umbrella, not the rain—A metaphor to guide conversations in advanced cancer. *JAMA oncology*, *8*(5), pp.681-682.

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Opioid switching(or rotation)

Recommendation to reduce the calculated equivalent dose of the new opioid by 25-50% (EAPC 2012)

Most common opioid rotations:

- Switching from morphine to oxycodone
- Switching from oxycodone to morphine

Patient taking oxycontin 100mg BD with opioid toxicity and ongoing pain
= oxycontin 200mg in 24 hrs
= morphine 400mg in 24 hrs (2:1 conversion ratio)
Reduce new opioid by 25-50% = morphine 300mg in 24 hrs = MST 150mg BD

Adjuvant drugs - examples of use

Adjuvant drug class	Example of use
Corticosteroid	Pain caused by oedema/inflammation
Antidepressant	Neuropathic pain (or when low mood contributing to pain)
Anticonvulsant	Neuropathic pain
Muscle relaxant	Muscle cramp
Antispasmodic	Bowel colic
Antibiotic	Infection pain (e.g. cellulitis/abscess)
Night sedative	When lack of sleep is decreasing pain threshold
Anxiolytic	When anxiety is contributing to pain

Adjuvant agents – anti-depressants/anti-epileptics

- Question – which of these has the strongest evidence base for the treatment of neuropathic pain?
    - Amitriptyline
    - Pregabalin
    - Gabapentin
    - Duloxetine
- Choice depends on side effect profile

Adjuvant agents – anti-depressants

- Amitriptyline
    - lower doses than for depression eg 10-25 mg at night, titrate up to 75mg
    - Limited by side-effect profile - drowsiness, dry mouth, blurred vision, postural hypotension, urinary retention, constipation, confusion
        - Less useful for frail elderly patients

- Duloxetine
    - SNRI
    - start at 30mg PO once daily and increase to 60mg after 1–2 weeks
    - if necessary, increase to 60mg b.d.

Anti-epileptics

- Pregabalin
    - Lower starting dose 25-50mg BD – max 300mg BD

- Gabapentin
    - Slow titration– 100mg od – tds, increase to 300mg tds after a week, then 600mg tds after another week

    - Fast titration – 300mg od, add 300mg each day until 300m tds then increase by 300mg/day every 3 days as needed (max 1200mg tds)

Toxicity from gabapentinoids often goes under the radar / blamed on opioid

Renal failure – which opioids to use?

National clinical programme cancer pain guideline 2015

- All opioids should be used with caution
- Fentanyl and alfentanil are the safest to use in stage 4 or 5 kidney disease
- Paracetamol for mild to moderate pain
- Reduction in dose and frequency of analgesia

Liver impairment and opioids

Opioids should be used with caution

- Fentanyl – generally safer
- Morphine – use with caution
- Avoid other opioids if possible

Avoid transdermal route

Avoid sustained release (or modified release) preparations

Mr Smith – 68 years old

- Opioid rotated from oxycodone to morphine
- Could there be coeliac plexus involvement?
    - Neuropathic agent e.g. amitriptyline/pregabalin?
- Does he have liver capsule pain?
    - Can he have NSAID/steroids?

Resources for cancer pain

For patients

Irish cancer society - pain

https://www.cancer.ie/cancer-information-and-support/cancer-information/cancer-treatments-and-side-effects/coping-with-side-effects/pain

For clinicians

Pharmacological Management of Cancer pain in adults

HSE National clinical effectiveness committee 2015

Thank you

mark.howard@beaconhospital.ie

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