

Pitfalls of Managing Malignant Pain

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Conflict of Interest Declaration: Nothing to Disclose

- Presenter: Kathy Simpson
- Presentation: Pitfalls of Managing Malignant Pain
- I have no financial or personal relationship related to this presentation to disclose

#10. Feeling Discouraged



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Cancer Care Ontario Symptom Management

- 23 Items
 - Constipation
 - Fever
 - Fatigue
 - Sleep Disturbance,
 - Etc, etc

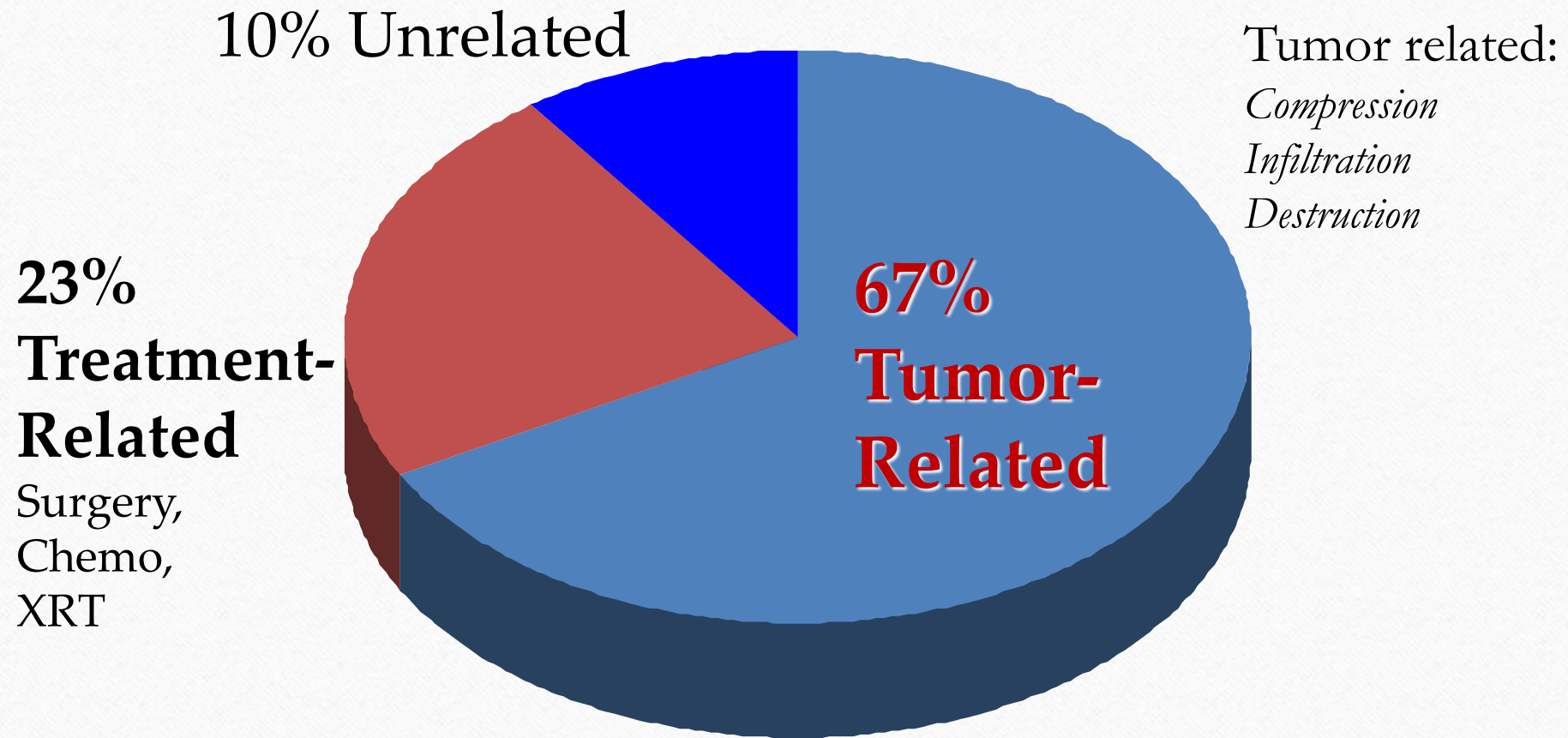
Prevalence Of Pain With Stages of Cancer and It's Treatment

<i>Stage of Disease</i>	<i>Prevalence of Pain</i>
Active anti-cancer treatment	24% to 73%
Advanced Cancer	58% to 86%
Cured of Cancer (in remission)	21% to 46%

* Pooled prevalence of pain was > 50% in all cancer types with the highest prevalence in Head/neck cancer patients (70%; 95% CI 51-88%)

* Of the patients with pain, >1/3rd graded their pain as moderate or severe.

Cancer Pain: Multiple Causes



#9. Not Considering Pain Type

- Assessment of the pain descriptors improves the choice of therapy. Pain can be:
- Nociceptive: caused by ongoing tissue damage, either somatic (such as bone pain) or visceral (such as gut or hepatic pain)
- Neuropathic: caused by damage or dysfunction in the nervous system, such as in brachial plexopathy or in spinal cord compression by tumour
- Most cancer patients have mixed

Complexity of Cancer Pain Syndromes

- **Frequent co-existence of multiple pain etiologies in an individual patient.**

Neuropathic pain - 10%

Somatic pain - 41%

“Mixed” pain - 49%

● *Cherney et al 1989*

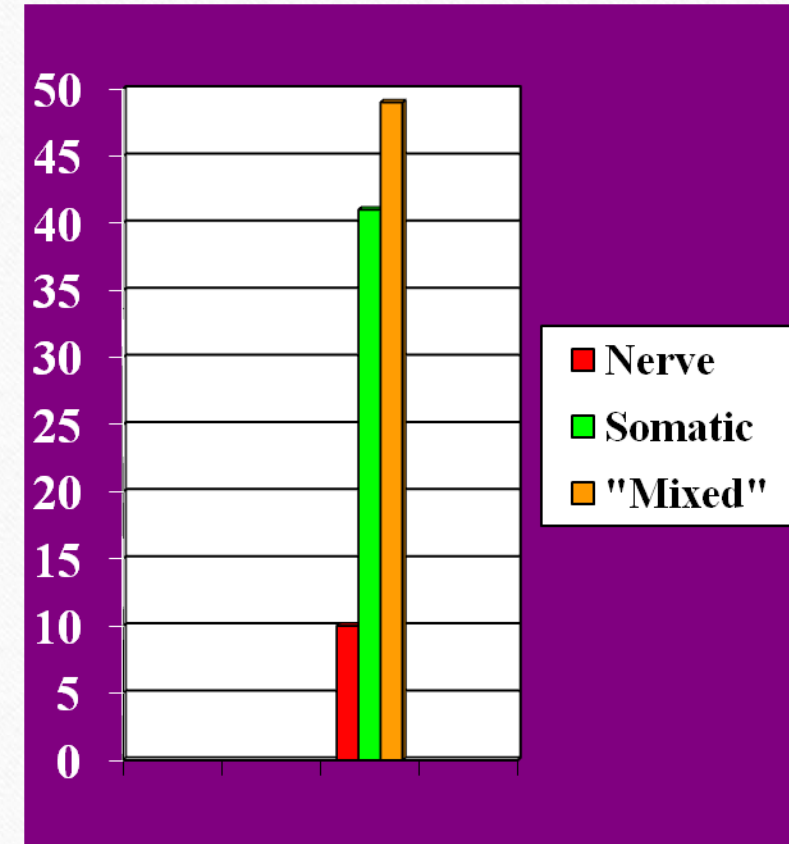
- **Multiple sites involved:**

1 site - 30%

2 sites - 39%

3+ sites - 31%

- Frequent Sites: Lower back 36%, Abdomen 27%, Thorax 23%
Lower limbs 21%, Head 17%, pelvis 15%.





BRIEF PAIN INVENTORY SELF REPORT

The purpose of the questionnaire is to tell us about the severity of your pain and how the pain affects your day to day activities

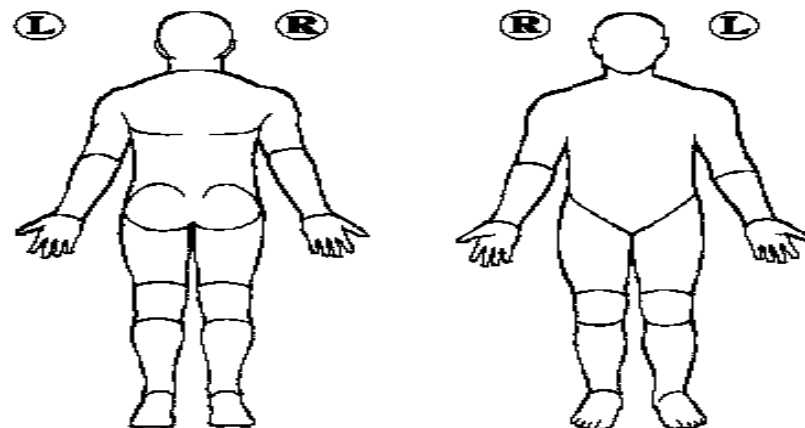
Completed by: ☐ patient ☐ family/care giver
DATE

1 Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these everyday kinds of pain today?

☐ yes

☐ no

2 On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



ADDITIONAL TOH ASSESSMENTS

Circle the words that best describe your pain.

tingling	cramping	exhausting
shooting	heavy	continuous
stabbing	aching	nagging
burning	throbbing	excruciating
deep	sharp	unbearable
numb		

3 Please rate your pain by circling the one number that best describes your pain at its **WORST in the past 24 hours.**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

4 Please rate your pain by circling the one number that best describes your pain at its **LEAST in the last 24 hours.**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

5 Please rate your pain by circling the one number that best describes your pain on **AVERAGE.**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

6 Please rate your pain by circling the one number that tells how much pain you have **RIGHT NOW.**

0	1	2	3	4	5	6	7	8	9	10
No pain										Pain as bad as you can imagine

Pain Assessment

- Ask a key screening question, which is not paraphrased and is used consistently. That question should be: 'What has been your worst pain in the last 24 hours on a scale of 0–10?', where 0 is no pain and 10 is the worst imaginable

Pain Assessment and Treatment

1. History of Cancer + History of Pain.
2. Standard assessment tools
3. Document pain syndromes involved.
4. **Is cause known? Need for further investigations?**
5. **Formulate treatment plan - 'realistic goals'.**
6. **Target treatment at pain and cause of pain.**

Cancer Pain

Higher Pain Scores are associated with:

- Presence of Breakthrough Pain
- Neuropathic pain
- Lower Performance status (KPS <70%)
- Younger patient (<60yrs)
- More advanced disease.
- Cognitive impairment

Caraceni. Pain 82 (1999) 263-274

Challenges in Managing Cancer Pain

- Features of both acute and chronic pain syndromes.
- Multiple sites.
- Multiple Pain Pathophysiologies
- Sick population...unstable disease.
- Multiple symptoms.
- Multiple treatments: Polypharmacy
- Multiple doctors!

RESULT = High Probability of Patients with complex Pain Syndromes.

Cancer Pain: 'Hard to treat'

- Opioid responsiveness and optimal pain control is inversely related to the presence of:
- Neuropathic pain.
- Breakthrough pain.
- Previous opioid exposure.
- Cognitive impairment and psychological distress.

Bruera . JPSM. 1989

#8. Not sure where to start

HERMAN®

by Jim Unger



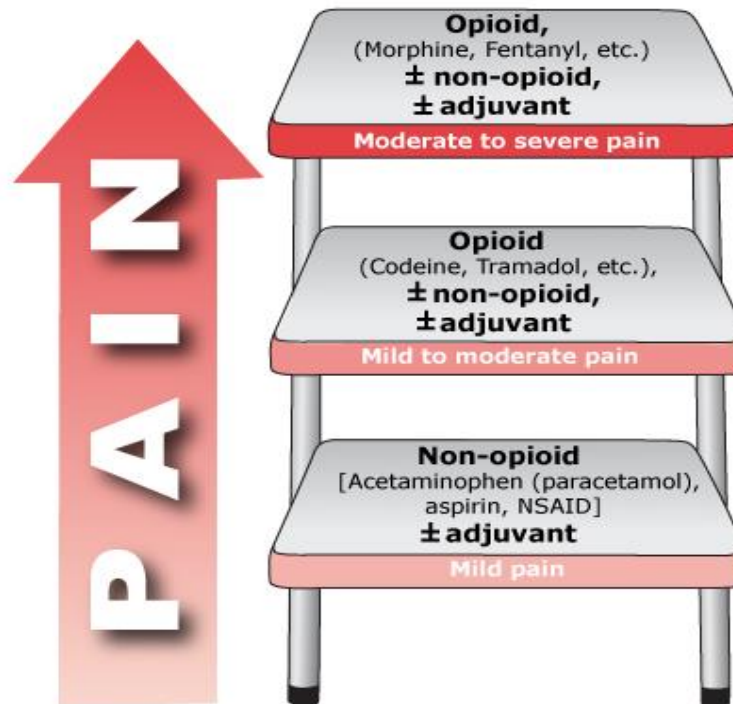
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“Here we go! Step one: Take off your shirt.”

The WHO Analgesic Ladder

World Health Organization (WHO) analgesic ladder



“This three-step approach of administering the right drug in the right dose at the right time is inexpensive and 80-90% effective.”

WHO advisory panel 2008

If Rx following the WHO ladder’ patients rated their pain relief :

Good 76%

Satisfactory 12%

Inadequate 12%

WHO Analgesia Ladder: Principles of use

- **By the mouth.** Oral meds whenever possible
- **By the clock.** Continuous pain should be treated with regularly scheduled meds + breakthrough meds as needed.
- **By the ladder.** Choose step appropriate for patient's pain. No ceiling for pure opioids as long as patient gets benefit and can tolerate side effects.
- **For the individual.** The “right dose” is the dose of the right drug that adequately relieves the patients' pain with minimum side effects
- **With attention to detail.** Successful implementation requires meticulous follow up once a new prescription is issued. Ascertain compliance, drug efficacy and side effects.

Cancer pain relief, Geneva, Switzerland, WHO 1996.

WHO Ladder: Step 1: Non-Opioids

- Acetaminophen.
- NSAIDs
- Early use of Adjuvants

Acetaminophen

- N-Acetyl-Para-Amino-Phenol (APAP).
- Potent antipyretic, weak anti-inflammatory
- Mild to Moderate Analgesic actions...HOW?
 - *Probable Central Cox 2 inhibitor*
 - *Serotonergic agent, acts via desc inhibitory pathways**
 - *Blocks metabolism Cannabinoids.*
- Oral bioavailability: 70-100%. t_{max} : 0.5 to 1hr, $t_{1/2}$: 1.5-2hrs
- CYP metabolism : 4% to toxic metabolite NAPQI.
- Caution: drug interactions,(Coumadin, and EtOH.)
- Max daily dose 4gm/day.

NSAIDs

- Cox1 and Cox 2 inhibitors: Anti PGE2.
- Opioid sparing.
- Have both peripheral and central antihyperalgesic effects.
- Poor correlation between anti-nociceptive effect and anti-inflammatory effects and doses.
- Anti-hyperalgesic effect related to ability to cross BBB.
- Ceiling effect+ , must individualize dose.
- **Side effects:** Renal, Cardiovascular, GI, CNS, Hypersensitivity reactions, Platelet dysfunction,
- Recommend: 2 week trial with close monitoring.
- If ineffective the can try other NSAID

NSAIDs: Comparative Doses and Pharmacokinetics

(Lexicomp 2013)

Drug	Maximum Recommended Daily Dose (mg)	Time to peak levels (hr)	Half life (hr)
Diclofenac (ER) (Voltaren)	225	2-3	1-2
Indomethacin (Indocid)	200	1-2	4.5
Ketoralac (Toradol)	I.M/ I.V: 120 P.O: 40	0.5 - 1	2-6
Celcoxib (Celebrex)	400	3	11
Meloxicam (Mobicox)	15	4-5	15-20
Ibuprofen	3200	1-2	1.8-2.5
Naproxen (Naprosyn)	1500	2-4	12-15
Naproxen sodium (Anaprox)	1375	1-2	12-13

WHO Ladder: Step 2

'Weak' Opioids

- Codeine
- Tramadol
- Tapentadol
- Early use of appropriate Adjuvants

Tramadol

- Unique , Atypical opioid. Analgesia=Codeine
- Serotonin and Norepinephrine reuptake inhibitor.
- Oral bioavailability: 68 – 90%* (*rpt dosing)
- Metabolism : Hepatic CYP 2D6.active metabolites (M1)
- Renal excretion.....dose reduce in CKD.
- ?Better tolerated in elderly...? Marketing hype.
- Dosing: 50mg o.d. increase to **maximum** 400mg/d.
- Available as Tramacet , + IR and ER formulations

WHO Ladder: Step 3

‘Stronger’ Opioids

- Mainstay of analgesia therapy in treating moderate to severe pain in cancer patients
 - Morphine
 - Hydromorphone
 - Fentanyl
 - Oxycodone
- Early use of appropriate Adjuvants

Organ System Effects of Morphine and its Surrogates

Central Nervous System	Peripheral
<ul style="list-style-type: none"> ↑ Analgesia ↑ Euphoria* ↑ Sedation ↓ Respiratory rate ↓ Cough reflex ↑ Miosis ↑ Truncal rigidity ** ↑ Nausea and vomiting Behavioural restlessness. <p>*addiction potential ** esp Fentanyl/ Sufentanyl</p>	<p>Gastrointestinal system:</p> <ul style="list-style-type: none"> ↑ Constipation ↓ Gastric motility ↓ Digestion in small intestine ↓ Peristaltic waves in the colon ↑ Constriction of biliary sphincter ↑ Esophageal reflux <p>Other Smooth Muscle:</p> <ul style="list-style-type: none"> ↑ Depression of Renal function ↓ Uterine tone ↑ Urinary retention <p>Skin:</p> <ul style="list-style-type: none"> ↑ Itching and sweating ↑ Flushing of face/neck. <p>Cardiovascular System:</p> <ul style="list-style-type: none"> ↓ Blood Pressure + heart rate <p>Immune System:</p> <ul style="list-style-type: none"> ↓ Lymphocyte function ↓ Cytotoxic activity of natural killer cells

Onset + Duration of Opioid Analgesia

Drug	Route	Onset of analgesia (minutes)	Time to Max Analgesia	Duration of action (hours)
Morphine + other short acting opioids	Oral	30 – 40 minutes	1 to 1.5 hours	3 to 5 hours
	SQ	10 -15 minutes	30 to 40 minutes	4 hours
	IV	5 - 8 minutes	10 to 20 minutes	3 to 4 hours
Fentanyl	Buccal	3 to 5	5- 10 min	60 minutes
	SQ	2 to 3	5-10 min	60 mins
	IV	1 to 2	5-8 min	60 mins

Time To Rehabilitate Morphine

“The Gold standard” ESMO 2012

2012:ESMO Clinical Practice Guidelines.

Ripamonti C.I, et al . Management of cancer pain: ESMO clinical practice Guidelines. Annals of Oncology 23 (Suppl):vii139-vii154, 2012.

- “The opioid of first choice for moderate to severe cancer pain is oral morphine.”

There is no evidence ...that other opioids are superior to morphine in terms of efficacy and tolerability.

6% rate of intolerate side effects

2012: Evidence based recommendations from the EAPC.

Caraceni A, et al Lancet Oncol 2012;13:e58-68.

- “The data show no important differences between Morphine, Oxycodone and Hydromorphone.... any of them could be first choice. ”

Hydromorphone vs Morphine

- “In conclusion there is evidence to support the efficacy and tolerability of hydromorphone for moderate to severe cancer pain as an **alternative** to morphine and oxycodone,
- while there is **NO evidence to demonstrate it's superiority or inferiority** in comparison with Morphine as the first choice opioid for the same indication.

Pigni A et al, Palliative Medicine 25(5) 471 -477 (2010)

Quigley C. Cochrane Database Syst Rev 2002 (updated 2009)

Oxycodone

- Morphine like – but not ‘morphine’.
- Twice the potency of morphine (1.5 to 2)
- Combined product – Oxycodone 5 mg + acetaminophen 325 mg.
- Oxycocet, Percocet, Percodan, endone, endocet.
- Limited to 12 pills per day due to acetaminophen (325mg/tab).
- Expected duration of action 4 hours.
- Pure Oxycodone – Peak time to effect 60 minutes
- Partially Active metabolites. Noroxycodone + oxymorphone
- ? Less toxic in renal failure
- Long Acting – OxyNeo 10, 20, 40 & 80mgs.
- Currently NO parenteral formulation in Canada.

Fentanyl

-
- NOT morphine like.
 - Inactive when swallowed.
 - Hepatic metabolism- metabolites are inactive + non-toxic
 - Renal excretion; < 10% of unchanged drug excreted in urine.
 - ? Safer in hepatic + renal failure.
 - Absorbed buccally, sublingually, subcutaneously, intravenously.
 - 75 times more potent than morphine.
 - VERY short acting.
 - SC dose peak time to effect 15-20mins.
 - SC dose duration of action 40-60 mins.

Transdermal Fentanyl

- Fentanyl TD duration of action ~72 hours.
- Slow onset of action when initiated.
- Cachectic patients may require patch changes q48hours.
- Apply above the waist.
- Apply to an area that is well perfused.
- Do not apply over a hairy area.
- Do not shave - but clip if necessary.
- Ensure good adhesion.
- Dose dependent on surface area.
- Rotate patch sites.

Bottom Line.....

- The opioid of first choice for moderate to severe cancer pain is oral morphine [I, A].
- The average relative potency ratio of oral to i.v. morphine is between 1:2 and 1:3 [II, A].
- The average relative potency ratio of oral to s.c. morphine is between 1:2 and 1:3 [IV, C].
- Oxycodone or hydromorphone, in both immediate-release and modified-release formulations for oral administration, and oral methadone are effective alternatives to oral morphine [54].

#7. Failure to titrate long acting opioid and prescribe appropriate breakthrough dose



Titrating opioids

- Titrate to effect
- Short acting (around the clock) starting doses:
 - Morphine 5 mg po q 4 hrs and 5 mg po q 1 hr prn
 - Hydromorphone 1 mg po q 4 hrs and 1 mg po q 1 hr prn
- Change to slow release formulations once pain well controlled
 - Avoid starting with fentanyl patches in opioid naïve patients
- Titration may also be down
 - Ie: after successful radiotherapy

Titration opioids

- Following selection of a starting opioid dose, adjustment is almost always required
- Titrate with caution in patient with risk factors such as decreased renal/hepatic function, COPD, upper airway compromise, sleep apnea, or poor performance status
- Adjustment may require a dose adjustment of both the regular dose as well as the BTD. As the regular dose increases the BTD must also increase (usually 10-15 % of regular dose)
- Dose adjustments should not be made more frequently for short acting and no more frequently than 3 days in long acting

#6. Using Long Acting Opioids (including Fentanyl Patch) to Treat Uncontrolled Pain

- Long Acting Opioids NEVER first option in acute or uncontrolled pain
- Be aware of the slow rise in serum values.
- Peak time to effect is about 8 hours., however, provides constant opioid release.
- Improved compliance and QoL

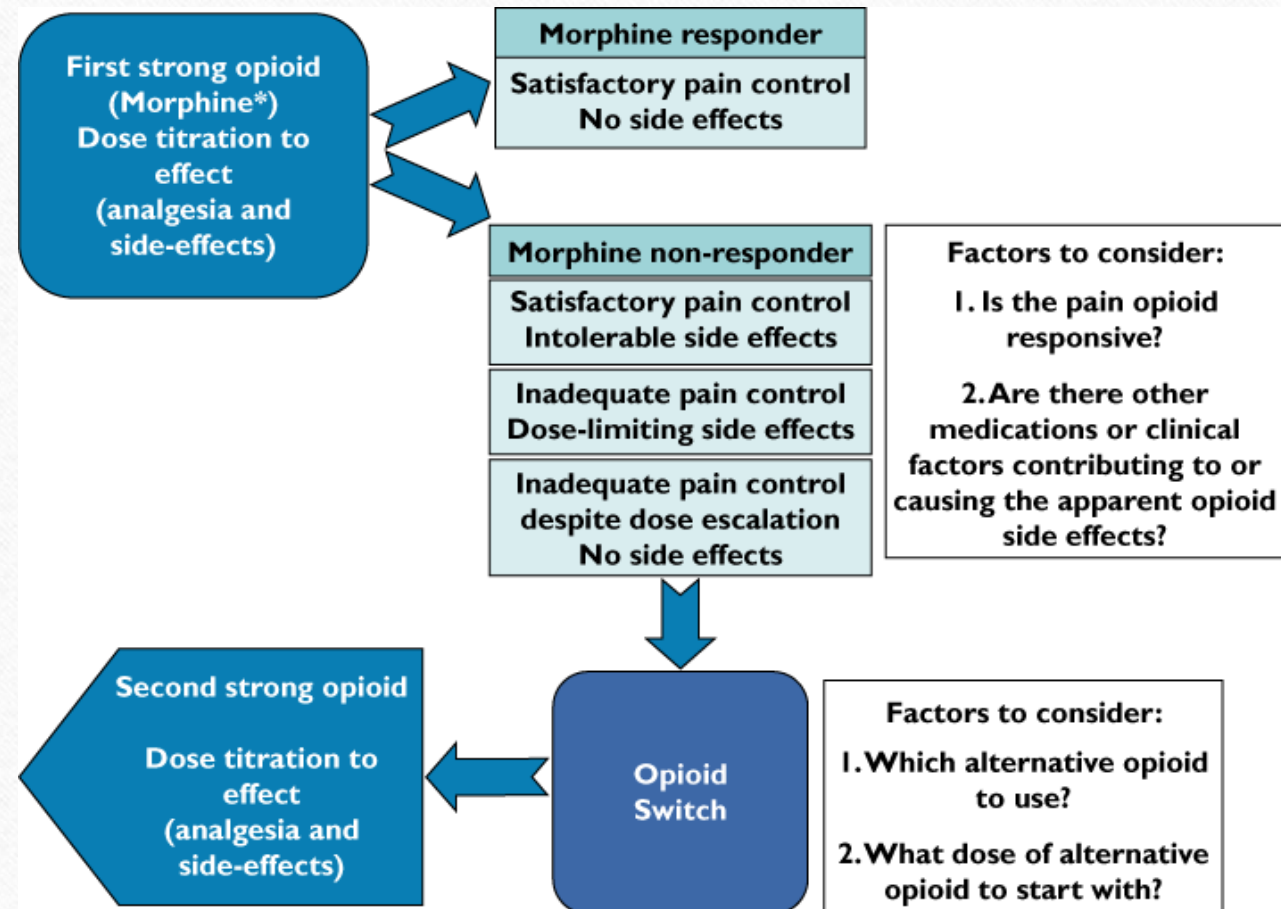
#5. Use of Multiple Opioids

- Use same breakthrough medication as long acting opioid
 - Improved ease and clarity for further dose titrations
- Exceptions include fentanyl patch and methadone

Key Principles of Opioid Use

- What is the right dose: Look at the effect not at the milligrams.
 - The desired effect is pain relief with tolerable or manageable side effects.
 - Adequate trial by dose titration.
 - Increase the dose up to the appearance of limiting side effects. (Effect OR Toxicity)
 - Genetics of opioid receptors-variants determine analgesic response to a greater degree than differences in opioid metabolism and clearance
- = Individualise treatment plan

Rationalizing Opioid Rotations



Rotating Opioids

Opioids	Analgesic ratio	LoE	GoR	Evaluated studies (N)
Oral morphine to oral oxycodone	1:1.5	II	B	RCTs (4); PCT (2)
Oral oxycodone to oral hydromorphone	1:4	II	B	RCT (1)
Oral morphine to t.d. buprenorphine ^a	75:1	IV	C	PCT (1)
Oral morphine to t.d. fentanyl ^b	100:1	III	B	PCT (4)
Oral morphine to oral methadone	1:5 to 1:12	III	B	PCT (6)
Oral morphine to oral hydromorphone	1:5 to 1:7.5	II	B	RCT (1)

Equianalgesic Table

Drug	S/C (IV)	P.O.
Morphine	10mgs	20mg
Hydromorphone	2mgs	4mg
Oxycodone	N/A	10 to 15mg
Codeine	60mgs	120mg
Fentanyl	100 to 125 mcg sc	
Tramadol	N/A	150mg
Merperidine	75mgs	300mgs
Methadone	N/A	2mgs

#4. Lack of Patient Opioid Education

Discuss the implications of the use of opioids.

- Patients and family members are fearful of impending death, addiction, tolerance, and nothing left for 'later.'
- Discuss the most common side effects.
- Nausea - tolerance.
- Constipation – rarely tolerance.
- Drowsiness especially when initiating therapy or increasing the dose – and tolerance.
 - Drowsiness may be related to pain relief.

Use of Parenteral Opioids

- The s.c. route is simple and effective for the administration of morphine, diamorphine and hydromorphone and it should be the first-choice alternative route for patients unable to receive opioids by oral or t.d. routes [III, B].
- i.v. infusion should be considered when s.c. administration is contraindicated (peripheral oedema, coagulation disorders, poor peripheral circulation and need for high volumes and doses) [III, B].
- i.v. administration is an option for opioid titration when rapid pain control is needed [III, B].

#3. Failure to Consider Liver or Renal Function

- Fentanyl, methadone and oxycodone safest in renal dysfunction
- Morphine and hydromorphone probably safest in liver dysfunction

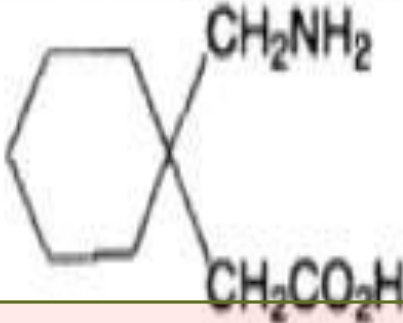
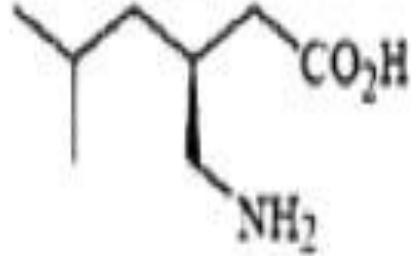
#2. Forgetting about Adjuvants

- Adjuvants for neuropathic pain
 - 1st line: TCA, gabapentin, pregabalin, duloxetine
 - 2nd line: corticosteroids (consider first line in pain crisis)
 - 3rd line: ketamine, lidocaine IV/SC
- Methadone

Tricyclic Antidepressants

- Nortriptylline / Amitriptylline
- Start: 10 mg/day
- Titrate: 3 – 7 days by 10 – 25 mg/day
- Max: usual antidepressant dose
- Limited by side effects
- Alternatives
 - Venlafaxine
 - Duloxetine
 - SSRIs of limited use.

Comparison of Gabapentin and Pregabalin

Structure	Gabapentin	Pregabalin
		
Bioavailability	27%-60%	90%
T _{max} (hrs)	2-3	1
Plasma protein binding	<3%	0
Potency	+	+++++
t _{1/2} (hrs)	5-7	5.5-6.7
Metabolism	None	None
Elimination	Renal (100% unchanged)	Renal (92-99% unchanged)
Dosing Schedule	TID	BID/TID
Controlled Substance	No	Schedule V
Neuropathic pain dose	1800-3600 mg/day	150-600 mg/day
Time to effective dose	9 days ^a	1 day

^a Recommended titration.

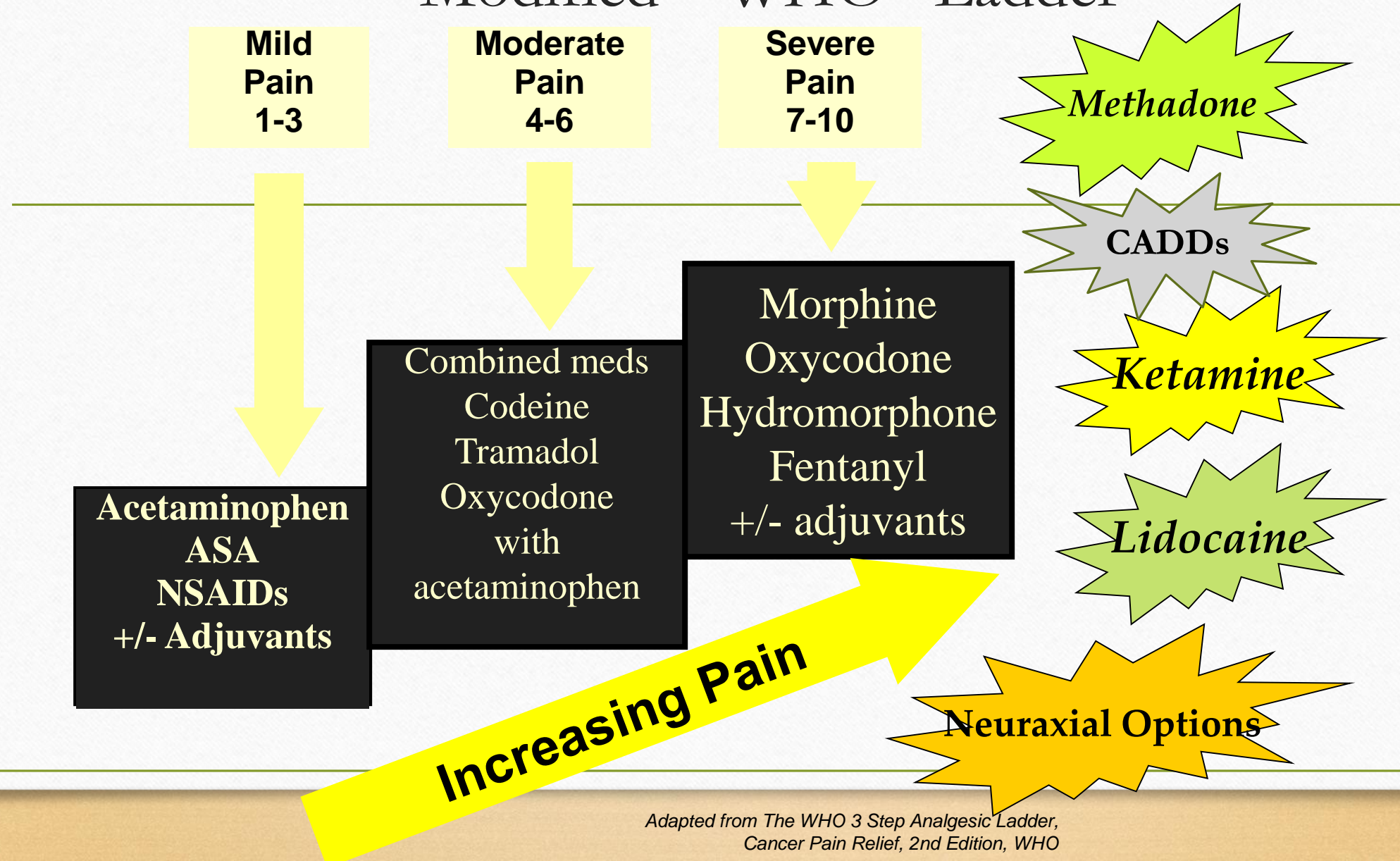
Adjuvants for Bone Pain

- NSAIDS
 - Relatively limited use in severe pain
- Steroids
 - Useful in pain crisis
- Bisphosphonates
 - Reducing skeletal events (path #, need for XRT, hypercalcemia and pain)
 - Requires monthly RX for at least 3-4 months
 - Pamidronate or zoledronic acid

Adjuvants for Visceral Pain

- Liver metastases or malignant bowel obstruction
 - Dexamethasone 2-8 mg po/iv/sc od
- Colic
 - Buscopan sc
 - Octreotide sc
 - dexamethasone

Modified "WHO" Ladder



#1. Failure to consider non-pharmacological RX

- Radiation
 - Very effective, 75-85 % response rate
 - Response within 1-2 wks though may have pain flare
- Palliative surgery
- Celiac Axis Block



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Call a Friend (Nurses Registry)

