A PRIMER ON PAIN MANAGEMENT FOR THE PALLIATIVE PATIENT

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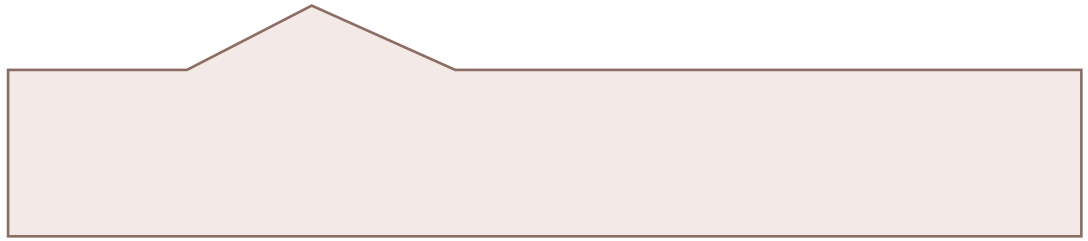
FACULTY/PRESENTER DISCLOSURE

- Faculty: Dr Ohunene Audu

- Relationships with financial sponsors: None



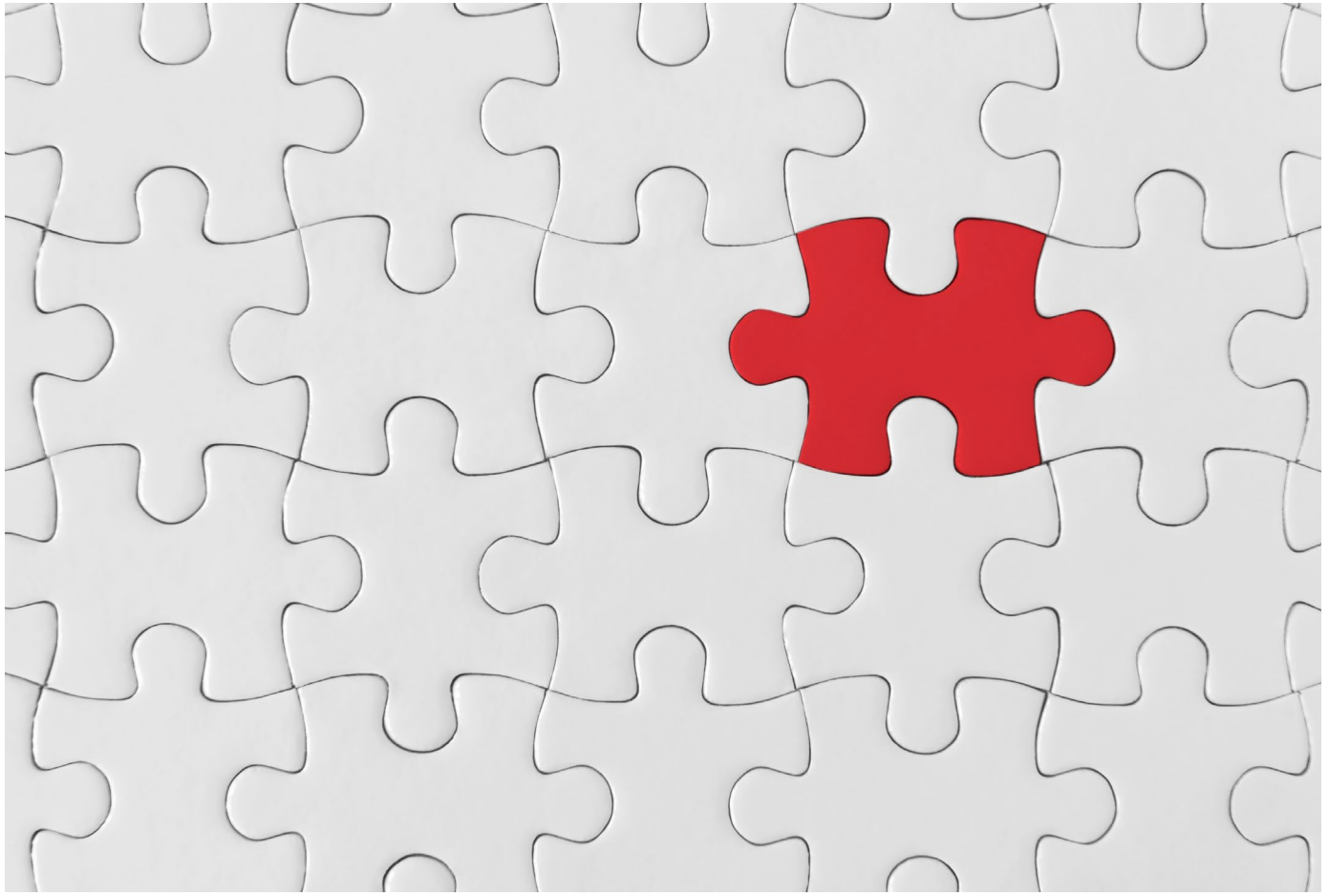
LEARNING OBJECTIVES

1. Refresh basics around opioids in general and specifically in Palliative pain management

2. Manage different types of pain in the palliative patient by selecting appropriate treatment modalities


DISCLAIMER

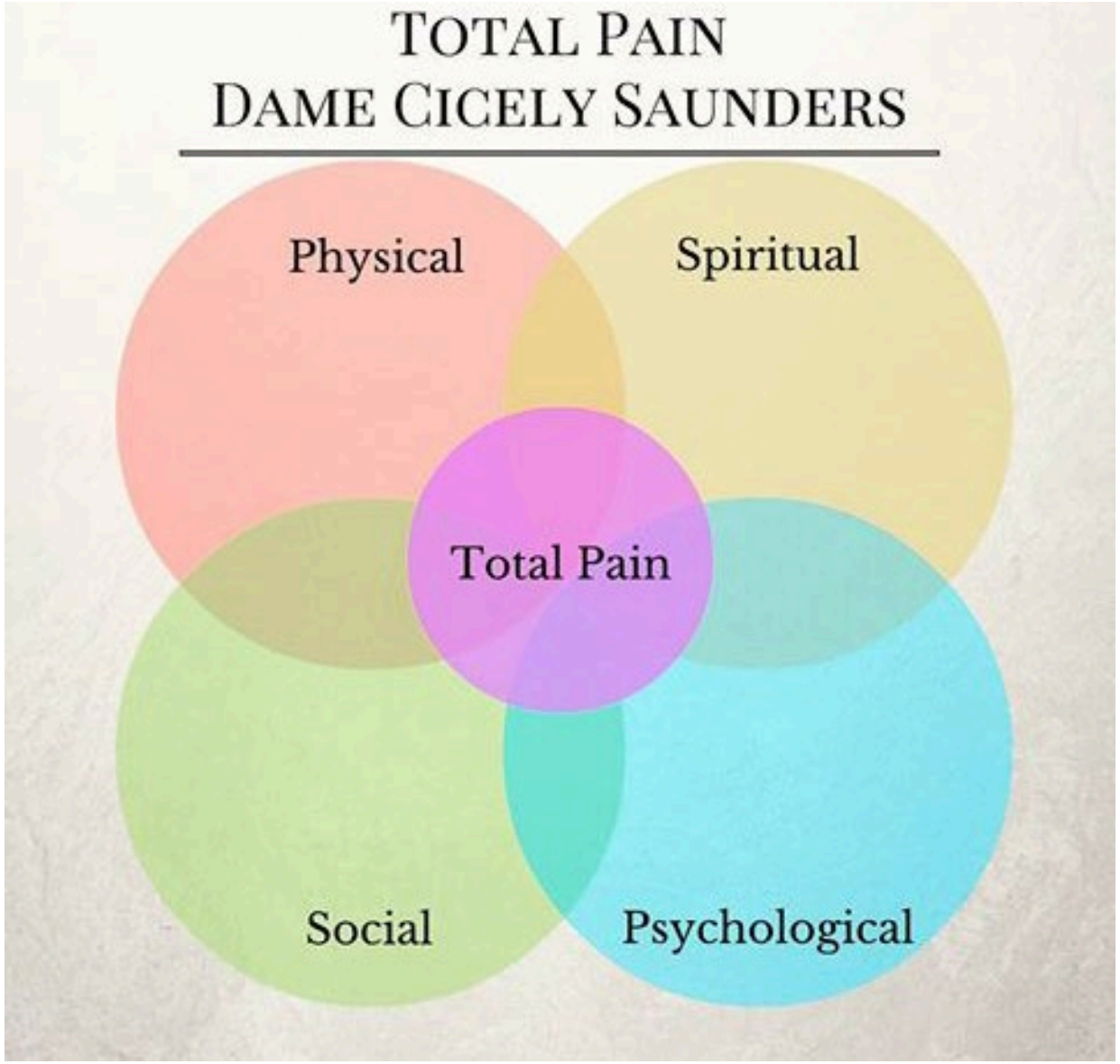
PATIENT X



DEFINITION OF PAIN

- An unpleasant sensory and emotional experience associated with actual or potential tissue damage or described in terms of such damage

CONCEPT OF TOTAL PAIN



APPROACH TO PAIN MANAGEMENT

- History and physical
- Explore with patient and family- expectations, wishes, goals
- Investigations – only if will affect management and is in line with goals
- Ongoing reassessment

ESSENTIALS OF OPIOID THERAPY

OPIOIDS 101 (A REFRESHER)

- All opioids are renally excreted except methadone which is excreted fecally
- All opioids produce both active and inactive metabolites except fentanyl and methadone; both produce only inactive metabolites
- IV and subcut doses are half of the oral dose
- Use short acting (immediate release) opioids for titration in poorly controlled pain
- In renal failure preferred options: Methadone and fentanyl, can consider Hydromorphone and oxycodone but avoid morphine and codeine

OPIOIDS 101- BREAK THOROUGH PAIN

- Three types of BT pain:
    - End of dose failure
    - Incident pain
    - Spontaneous

- BT can be taken as often as every hour and is usually scheduled as such
- BT analgesia are 50-100% of scheduled short acting opioid
- BT analgesia are 10% of scheduled long-acting opioids and are always short acting

BT FOR FENTANYL PATCH

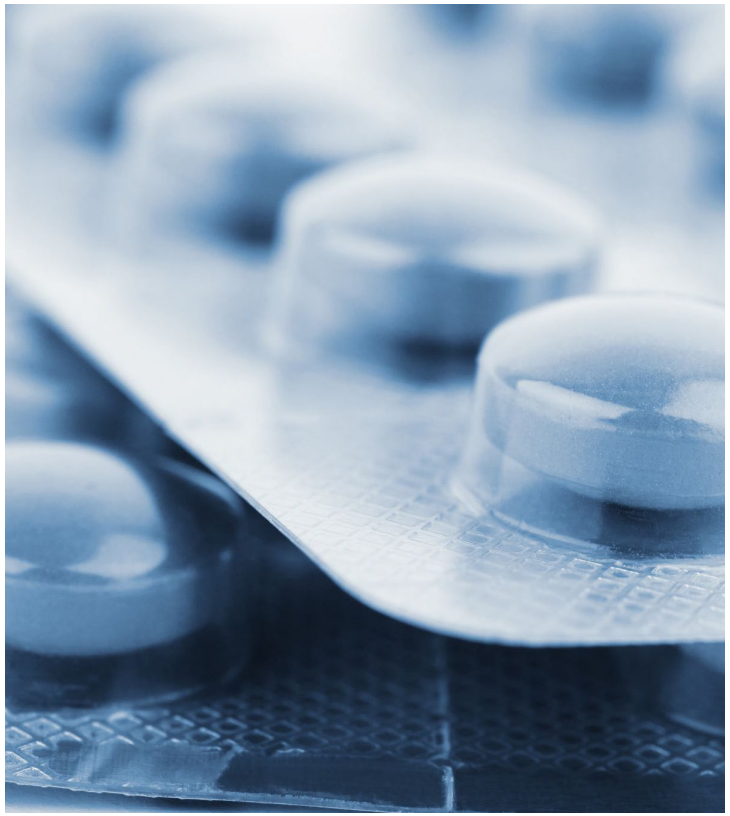
Morphine	10mg	20mg	30mg	40mg	80mg
Fentanyl	25mcg	50mcg	75mcg	100mcg	200mcg
HM	2mg	4mg	6mg	8mg	16mg

OPIOID DOSE CONVERSION RATIOS

Opioid	**Ratio** (Morp: New opioid)
Morphine	
Hydromorphone	5:1
Oxycodone	2:1
Methadone	Variable
Fentanyl	100:1
Codeine	1:10
Tramadol	1:10

GUIDELINES FOR OPIOID ROTATION

1. Calculate 24-hour dose of current opioid
2. Select new opioid you intend to switch to
3. Calculate the equianalgesic dose of new opioid using table
4. Carry out a 25 to 50% dose reduction of the above to account for incomplete cross tolerance
5. Divide the 24-hour dose by 6 to give you Q4h dose



OPIOID INDUCED NEUROTOXICITY (OIN)

- Opioid induced neurotoxicity is neuroexcitation resulting from accumulation of specific opioid metabolites

PRESENTATION

Hyperalgesia
Allodynia
Delirium
Hallucinations
Sedation
Myoclonus/ Seizures

CAUSES OF OIN

- Renal impairment
- Dehydration
- Rapid escalation of opioid dose over short period of time
- Improper use of BT doses

OIN TREATMENT

Hydration

Rotate to another opioid

- Note when rotating from one opioid to another in OIN use a 50% reduction to account for incomplete cross tolerance

OPIOID INDUCED HYPERALGESIA

Paradoxically increase in pain with increase in opioid doses

Pain now described as being generalized

Presence of allodynia

STRATEGIES TO ADDRESS OIH

- Opioid dose reduction
- Opioid rotation
- Addition of NMDA Receptor Antagonists like Ketamine, methadone

WHAT TO DO IN POOR OPIOID RESPONSE

	Options
Identify a more effective opioid	Opioid rotation
Open the therapeutic window	Increase aggressiveness of side-effect management
Add a systemic or spinal co-analgesic to reduce the opioid requirement	Coadministered NSAID or non-traditional analgesic, or a trial of neuraxial analgesia
Add a non-pharmacological approach to reduce the opioid requirement	Neural blockade, a neurostimulatory approach, or a psychological or rehabilitative treatment

NSAID=non-steroidal anti-inflammatory drug.

Table 3: Clinical strategies to address poor opioid responsiveness

Portenoy, R (2011) Treatment of cancer pain. The Lancet Vol 377:2236-47

PRACTICAL CONSIDERATIONS

1. Don't forget the concept of total pain, not all pain is purely physical, a multidisciplinary approach may be warranted
2. There is no ceiling limit to pure mu opioid agonists, the only limitation are side effects
3. In opioid naïve, frail geriatric patients **HM 0.25mg po** or **Morphine 2.5mg po** is a good starting dose
4. In opioid naïve, robust younger patient **HM 0.5mg po** or **Morphine 5mg po** is a good starting dose
5. Dose titration/escalation should be 30-100% of fixed scheduled dose
6. Intervals between dose titration should be **2-3 days for oral long-acting formulation** and **3-6 days for patch**
7. For poorly controlled pain stick to short acting opioids as a more rapid dose escalation is needed
8. The need for > 200mg of morphine or equivalent is uncommon and should trigger assessments for OIH, OIN, drug related behaviors, Total pain; and a reassessment of underlying pathology
9. Never start a fentanyl patch in an opioid naïve patient and always consider dose of existing opioid before rotating to a patch- patients on **HM 1.5mg po Q4h or Morphine 7.5mg po Q4h** can tolerate a 12mcg patch
10. Cancer pain in Palliative patients is never eliminated 100%. The goal is to reduce it to such levels that it doesn't impact on quality of life

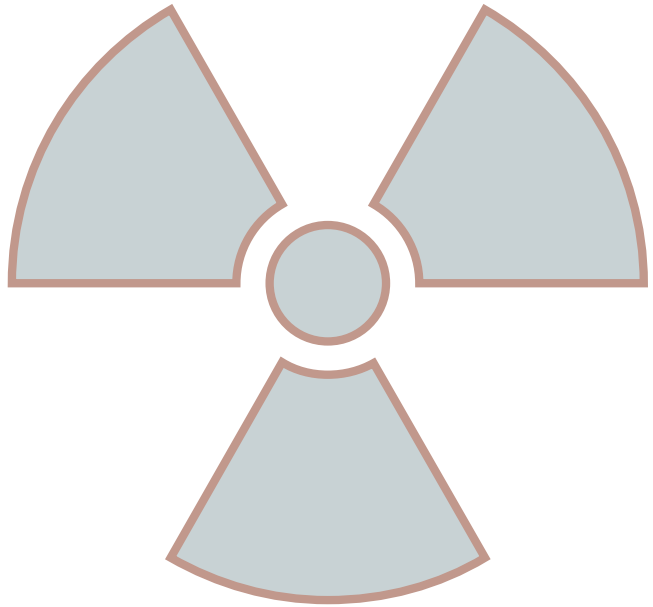
OTHER OPTIONS FOR PAIN MANAGEMENT

CATEGORIES OF TREATMENT FOR PAIN RELATED TO CANCER

Category	Type of Treatment
Pharmacologic	Opioid analgesics
	Nonopioid analgesics
	Nontraditional analgesics (adjuvant analgesics)
Interventional	Injection therapies
	Neural blockade
	Implant therapies
Rehabilitative	Modalities such as heat and cold
	Therapeutic exercise
	Occupational therapy
	Hydrotherapy
	Therapies for specific disorders (eg, lymphedema)
Psychological	Psychoeducational interventions
	Cognitive-behavioral therapy
	Relaxation therapy, guided imagery, other types of stress management
	Other forms of psychotherapy
Neurostimulation	Transcutaneous
	Transcranial
	Percutaneous peripheral nerve and spinal cord/root stimulation
Integrative (complementary or alternative)	Acupuncture
	Massage

PALLIATIVE RADIATION-KEY POINTS

1. Single fraction radiation treatment (SBRT) is as equally effective for pain relief as multi fraction radiation treatment (MBRT)
2. Reirradiation in patients with recurrent pain is possible
3. Pain relief is not noticeable at once but builds up over time with maximum benefit noticed usually around 4-6 weeks post radiation
4. Can provide overall pain relief (complete or partial) in approximately 60% of pts
5. RT can cause temporary pain flare – Dexamethasone a few days before and a few days post
6. Useful in preventing fractures in asymptomatic patients with tumors in weight bearing bones



ADJUVANT ANALGESICS

- A large and diverse group of drugs that were originally developed for primary indications other than pain but have potential for analgesic efficacy in one or more painful conditions

CLASSES OF ADJUVANT ANALGESICS

Table 2. Adjuvant Analgesics

	Category			
	Class	Type	Examples	Comment
Multipurpose analgesics	Antidepressants	SNRIs	Duloxetine, milnacipran, venlafaxine, desvenlafaxine	Established analgesics; duloxetine often selected first for chronic pain
		Secondary amine TCAs	Desipramine, nortriptyline	Established analgesics; better tolerated than the tertiary amine TCAs
		Tertiary amine TCAs	Amitriptyline, imipramine	Established analgesics
		SSRIs	Paroxetine, citalopram	Poor evidence of analgesia
	Alpha-2 adrenergic agonists		Tizanidine, clonidine, dexmedetomidine	Tizanidine is oral and better tolerated than clonidine Clonidine used in spinal infusions; dexmedetomidine is used in critical care
	Cannabinoids	Pharmaceutical	Nabiximols, nabilone, dronabinol	Nabiximols not available in the United States; limited evidence for others
		Nonpharmaceutical	Medical cannabis	Available in many states
	Glucocorticoids		Dexamethasone, prednisone	Commonly used in advanced cancer for pain/other symptoms
	NMDA receptor antagonists		Ketamine, memantine, amantadine, dextromethorphan	Evidence mixed but commonly used in palliative care for severe opioid-refractory pain. Efficacy in depression may increase use
	Neuroleptics	First/second generation	Haloperidol, olanzapine	Poor evidence of efficacy
	Topical agents	Local anesthetics	Lidocaine 5% patch or cream, and lower concentration creams, gels, and patches	5% patch used for neuropathic and musculoskeletal pain
		NSAIDs	Diclofenac ketoprofen	Approved for acute musculoskeletal pains
		Capsaicin	.075% patch or cream, 8% patch	.075% used for neuropathic or musculoskeletal pain; 8% patch may relieve PHN for months after short exposure in a monitored setting
		Compounds	Ketamine, amitriptyline, menthol, others	Limited evidence, costly; safety supports trials if available
	Botulinum toxin	Botulinum A, B		Evidence for use in many focal and regional neuropathic and musculoskeletal pain
Drugs used for neuropathic pain	Multipurpose adjuvant analgesics	Antidepressants, α-2 adrenergic agonists, cannabinoids and other systemic drugs, topical drugs, botulinum toxins	See above	Most guidelines emphasize the antidepressants, the gabapentinoids, and the topical drugs for neuropathic pain; glucocorticoids are commonly used for neuropathic pain in advanced cancer
	Gabapentinoids		Pregabalin, gabapentin	Evidence in acute pain and chronic neuropathic pain; used first for neuropathic pain, unless comorbid depression supports antidepressant

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Table 2 (Contd.)

Category				
	Class	Type	Examples	Comment
	Other anticonvulsants		Oxcarbazepine, lacosamide, topiramate	Older drugs may be analgesic, but side effects support use of newer drugs; limited evidence overall
	GABA agonists	$GABA_A$ $GABA_B$	Clonazepam Baclofen	Poor evidence of analgesia
	Sodium channel blockers		IV lidocaine, mexiletine	IV lidocaine used for pain in monitored settings; oral drugs not used for pain due to limited evidence and side effects
Drugs used for musculoskeletal pains	Multipurpose adjuvant analgesics	Antidepressants, alpha-2 adrenergic agonists, cannabinoids, topical drugs, botulinum toxins	See above	
	So-called muscle relaxants		Methocarbamol, carisoprodol, chlorzoxazone, metaxalone, cyclobenzaprine	No evidence in chronic pain; not used for chronic pain due to side-effect liability
Drugs used for cancer-related bone pain	Osteoclast inhibitors	Bisphosphonates RANKL inhibitor Calcitonin	Zoledronate, alendronate, ibandronate, Denosumab	Used to prevent and treat pain and other SREs Poor evidence of efficacy
	Radioisotopes		Samarium-153, strontium-89, phosphorus-32, others	
Drugs used for pain and other symptoms in cancer-related bowel obstruction	Multipurpose adjuvant analgesics	Glucocorticoid	Dexamethasone	Most patients receive a glucocorticoid and an opioid
	Antiemetics	Dopamine antagonist, $5\text{-}HT_3$ antagonist	Metoclopramide, haloperidol, ondansetron, granisetron	
	Antisecretory drugs	PPI, H2 blockers	Omeprazole, ranitidine	
		Anticholinergic drug	Scopolamine, glycopyrrolate	Risk of cognitive side effects probably lessened by using drug with poor BBB penetration (ie, scopolamine, butylbromide, or glycopyrrolate)
		Somatostatin analog	Octreotide, lanreotide	Evidence of efficacy is mixed and may not be a first-line approach for this reason

Abbreviations: 5-HT, 5 hydroxytryptamine or serotonin; BBB, blood-brain barrier; GABA, gamma-aminobutyric acid; NMDA, N-methyl-D-aspartate; NSAIDs, nonsteroidal anti-inflammatory drugs; PHN, post-herpetic neuralgia; PPI, proton pump inhibitor; RANKL, receptor activator of nuclear factor-κB ligand; SNRIs, serotonin norepinephrine reuptake inhibitors; SREs, skeletal-related events; SSRIs, serotonin selective reuptake inhibitors; TCAs, tricyclic antidepressants.

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GENERAL PRINCIPLES OF ADJUVANT ANALGESIC USE

- Choose each medication carefully for both intended effect and side effects
- Ensure that patients have realistic expectations
- Begin the use of drugs with known bothersome side effects slowly and increase slowly
-

Farrar J; Portenoy R, 2001

GENERAL PRINCIPLES-2

- Increase the dose of each medication until the desired effect is achieved, side effects are unmanageable or high therapeutic drug levels are obtained before calling the trial a failure

- Different classes of drugs can be used concomitantly

- Be persistent, encouraging and supportive as treatments are implemented

Farrar et al, 2001

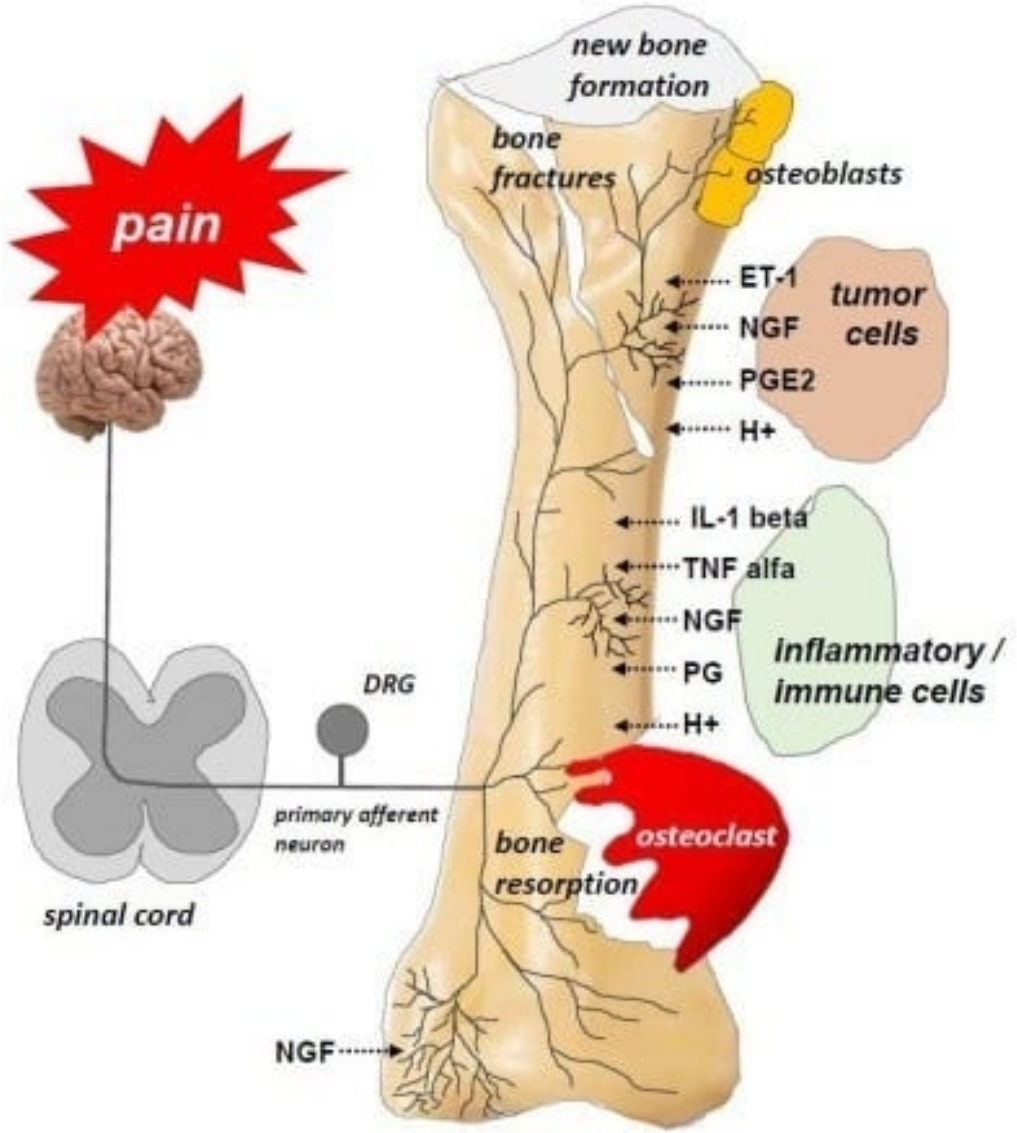
A Comparison of Adjuvant Pain Medications

New evidence states NNT closer to 6- 8

	NNT	Titration	Notes	Side Effects
TCA	2.5-3	2-15 wks	Antidepressant, cheap	Anticholinergic
Duloxetine	4-5	none	Anxiolytic, antidepressant	few
Venlafaxine	4-5	3-5 wks	Antidepressant	few
Gabapentin	3.5-4.5	1.5-6 mo	Min drug interactions	Dizzy/sleepy
Pregabalin	3.5-4.5	1-2 wks	Min drug interactions	Dizzy/sleepy
Methadone	?	variable	Opioid, cheap	Opioid, drug interactions
Ketamine	?	1-4 wks	Opioid sparing	Hallucinations
Tramadol	3.8	4-8 wks	For Diabetes, PHN	Anticholinergic
Carbamezapine	1.7	1-4 wks	For Trigeminal neuralgia	Drug interactions
Lidocaine/Mexilitine	4	none	IV trial then po	Cardiac, neurologic
Capsaicin	?	none/days	Topical	Burning, redness
Cannabinoids	?	none/days	For MS, allodynia	GI, drowsiness
Clonidine	?	none/days	Effective IT, topical	Hypotension

CHRONIC CANCER PAIN SYNDROMES

BONE PAIN


new bone formation
bone fractures
osteoblasts
pain
ET-1
NGF
PGE2
H+
tumor cells
IL-1 beta
TNF alfa
NGF
PG
H+
inflammatory / immune cells
DRG
primary afferent neuron
bone resorption
osteoclast
spinal cord
NGF

TREATMENT OPTIONS

- Opioids +/- NSAIDS
- Dexamethasone
- Palliative Radiation
- Surgery
- Bone modifying agents like bisphosphonates - pamidronate and zoledronic acid

NEUROPATHIC PAIN

TREATMENT OPTIONS

- Methadone
- Adjuvant Analgesics- TCAs, SNRIs, Anticonvulsants
- Topical agents
- ? Ketamine

CHRONIC NON-CANCER PAIN

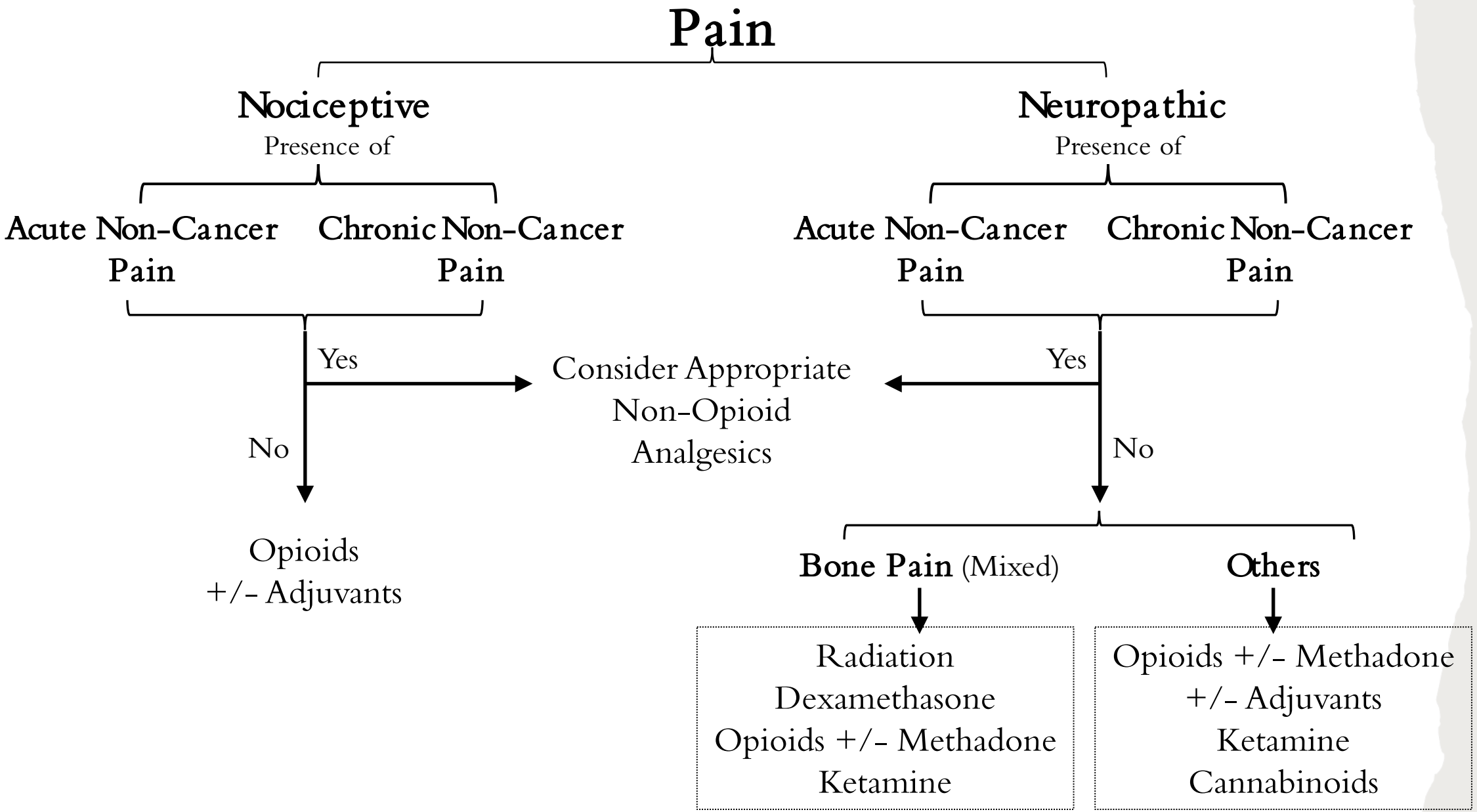
TREATMENT OPTIONS

For Osteoarthritis – NSAIDS, SNRIS, TCAs

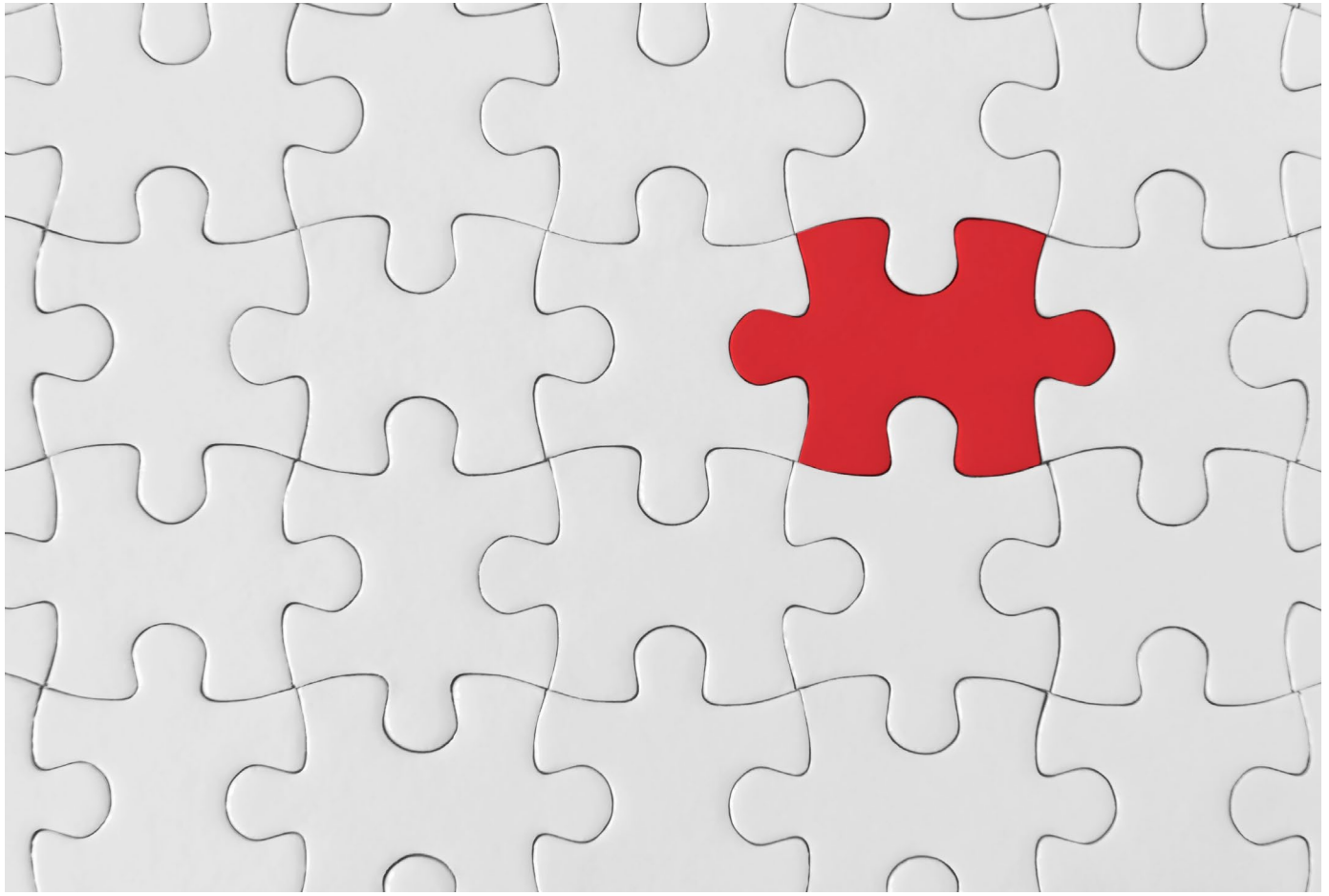
Fibromyalgia- SNRI

Headaches- Acetaminophen

SUMMARY FLOW SHEET



PATIENT X



PHONE CONSULT- APRIL 6TH 2024

Hx of lung cancer with mets to clavicle and ribs

New onset severe back pain – 3 weeks prior to admission

In community was initially on Hydromorph contin 9mg po bid with Hydromorphone 4mg po Q4h prn

As pain got worse, she was started on a Fentanyl 25mcg patch in addition

Admitted to hospital in Brandon on April 4th for further pain management

IN HOSPITAL

Switched from HM Contin to Hydromorphone IR 4mg IV Q4h and Q1h prn

Fentanyl 25mcg patch was continued

For incident pain with movement, Fentanyl 75mcg sublingually added on

Still ++++ pain

MY SUGGESTIONS

1. Get imaging to rule out vertebral bone mets
2. Initial switch to Hydromorphone IR was spot on
3. Treat for possible OIH or OIN by hydrating and rotating off Hydromorphone
4. Add on Ketamine 2.5mg po bid; have Haloperidol as a prn in case of hallucinations
5. Switch Fentanyl from 75mcg to 50mcg sublingual or intranasal
6. Keep fentanyl 25mcg patch with no up titration

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