Chronic cancer related pain management

Yoko Tarumi

Symptom Control and Palliative Care, Cross Cancer Institute

Clinical Professor, Palliative Care Medicine, Oncology, UofA

April 23, 2022 FP -CCA strengthening linkages workshop

- No conflict of interest to declare
- Off label drug use

Objectives

01

Identify the key terminologies and risk factors associated with chronic cancer related pain management

02

Recognize the impact of opioid therapy in chronic cancer related pain

03

Discuss approaches to mitigate risks related opioid use in cancer care

Terminologies

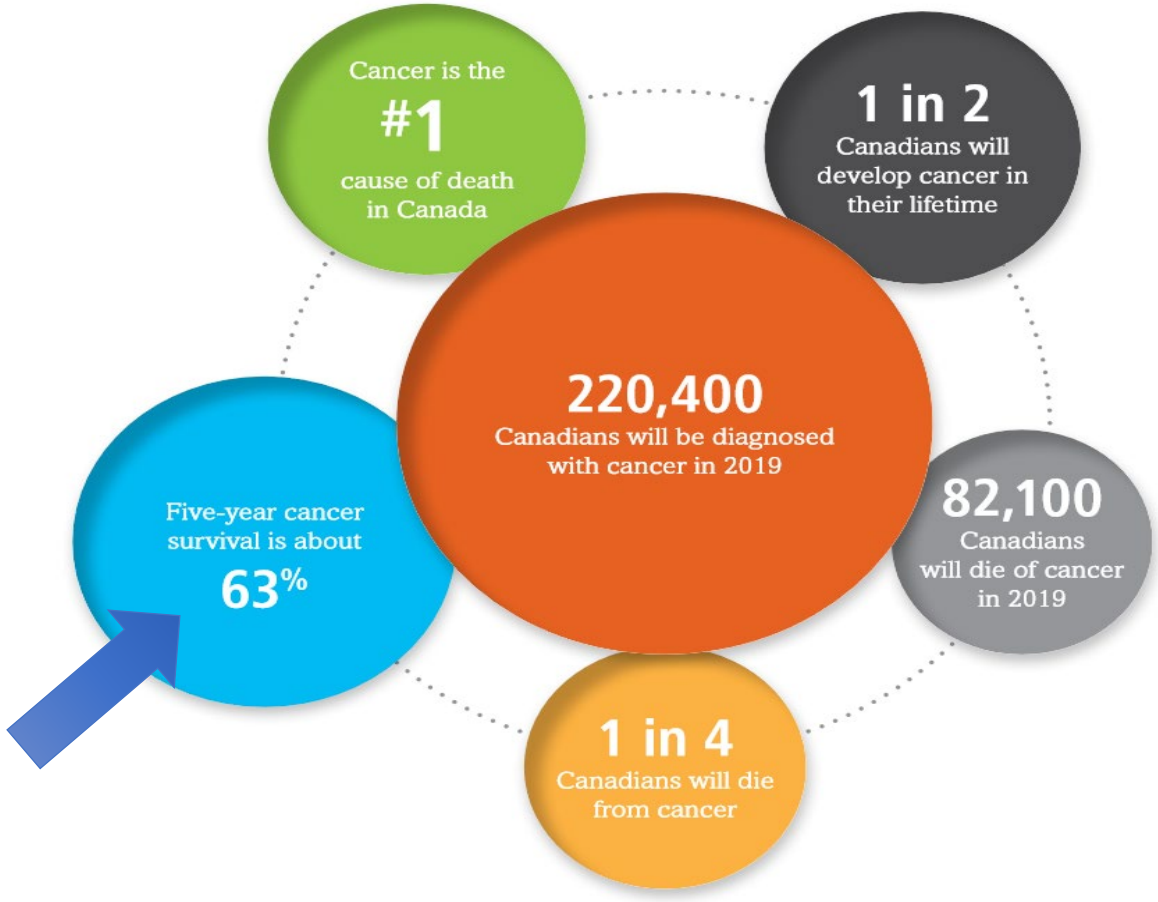
- ✓Cancer survivors
- Chronic cancer related pain
- LTOT: long term opioid therapy
- Opioid related harms (risks)
- SUD/OUD: substance or opioid use disorder

Cancer survivors

Those living beyond three months since the diagnosis and active cancer treatment, maintenance or prophylactic treatment, such as hormone therapy

J.A. Paice, R. Portenoy, C. Lacchetti, *et al.* Management of chronic pain in survivors of adult cancers: American Society of Clinical Oncology clinical practice guideline J Clin Oncol, 34 (2016), pp. 3325-3345
American Cancer Society Survivorship Compendium https://www.asco.org/news-initiatives/current-initiatives/prevention-survivorship/survivorship-compendium
P.A. Glare, P.S. Davies, E. Finlay, *et al.* Pain in cancer survivors. J Clin Oncol, 32 (2014), pp. 1739-1747.
Office of Cancer Survivorship, National Cancer Institute. Washington, DC: Office of Cancer Survivorship, National Cancer Institute; 2012. About Cancer Survivorship Research: Survivorship Definitions, Cancer Survivorship Research. http://cancercontrol.cancer.gov/ocs/researcher_factsheet.pdf.

Cancer survivors are increasing



https://www.cancer.ca/~/media/cancer.ca/CW/cancer%20information/cancer%20101/Canadian%20cancer%20statistics/Canadian-Cancer-Statistics-2019-EN.pdf?la=en

Terminologies

- ✓Cancer survivors
- ✓Chronic cancer related pain
- LTOT: long term opioid therapy
- Opioid related harms (risks)
- SUD/OUD: substance or opioid use disorder

Classification of **chronic** cancer-related pain-ICD 11

Level 1	Level 2	Level 3	Level 4
Chronic cancer related pain	Cancer pain	Visceral cancer pain	
		Bone cancer pain	
		Neuropathic cancer pain	
	Post-cancer treatment pain	**Post cancer medicine pain**	**Painful chemotherapy-induced polyneuropathy (CIPN)**
		Post radiotherapy pain	**Painful radiation-induced neuropathy**
		Post cancer surgery pain	

Bennett, Michael I.[a]; Kaasa, Stein[b,c,d]; Barke, Antonia[e]; Korwisi, Beatrice[e]; Rief, Winfried[e]; Treede, Rolf-Detlef[f,*]; The IASP Taskforce for the Classification of Chronic Pain The IASP classification of chronic pain for ICD-11: chronic cancer-related pain, PAIN: January 2019 - Volume 160 - Issue 1 - p 38-44 doi: 10.1097/j.pain.0000000000001363
Nicholas M, Vlaeyen JWS, Rief W, et al. The IASP classification of chronic pain for ICD-11: chronic primary pain. *Pain*. 2019;160(1):28-37. doi:10.1097/j.pain.0000000000001390

Prevalence of chronic cancer related pain

- Up to 40% of cancer survivors experience and often related to the cancer and its treatment
- More likely to receive opioids**, long-term opioid therapy > 3 mo** (**LTOT**), and high-dose than people without cancer, particularly in the early years after their diagnosis

- van den Beuken-van Everdingen MH, Hochstenbach LM, Joosten EA, et al. Update on prevalence of pain in patients with cancer: systematic review and meta-analysis. J Pain Symptom Manage. 2016;51:1070- 1090.e9
- Salz T, Lavery JA, Lipitz-Snyderman AN, et al. Trends in opioid use among older survivors of colorectal, lung, and breast cancers. J Clin Oncol. 2019;37:1001-1011.
- Sutradhar R, Lokku A, Barbera L. Cancer survivorship and opioid prescribing rates: a population-based matched cohort study among individuals with and without a history of cancer. Cancer. 2017;123:4286-4293.
- Lee JS, Hu HM, Edelman AL, et al. New persistent opioid use among patients with cancer after curative-intent surgery. J Clin Oncol. 2017;35:4042-4049.
- Kriplani A, Lavery JA, Mishra A, et al. Trends in chronic opioid therapy among survivors of head and neck cancer. Head Neck. 2021;43:223-228.
- Jones KF, Fu MR, Merlin JS, et al. Exploring factors associated with long-term opioid therapy in cancer survivors: an integrative review. J Pain Symptom Manage. 2021;61:395-415.

Editorial

Approaches to Opioid Prescribing in Cancer Survivors: Lessons Learned From the General Literature

Katie Fitzgerald Jones, MSN, APN [1,2]; and Jessica S. Merlin, MD, PhD, MBA [3]

LAY SUMMARY:

- Guidance on how to approach opioid decisions for people beyond active cancer treatment is lacking.
- This editorial discusses strategies from the general literature that can be thoughtfully tailored to cancer survivors to provide patient-centered pain and opioid care.

Jones KF, Merlin JS. Approaches to opioid prescribing in cancer survivors: Lessons learned from the general literature. **Cancer. 2021 Oct 11**. doi: 10.1002/cncr.33961. Epub ahead of print. PMID: 34633657.

Mr. Jackson

- 47 yo, diagnosis of recurrent laryngeal cancer is discharged home after hospitalization for progressive dysphagia with PEG and nutrition management.
- Prior to admission, he was on Morphine ER/LA 60 mg q12h, Morphine IR 15 mg po q4h prn using 3-4/day past 3 months.
- ESASr Pain 3/10 (average, best 1, worst 6)
- PMx: HTN, EtOH use disorder, laryngeal cancer
- During hospitalization, morphine was given IV/subcut around the clock
- O/E: Normal vital signs, no distress, skin changes post RT, PEG in place, CV/Pulm normal.
- Test: Creat Normal, LFT normal, QTc interval 530 msec

What is the correct discharge RX for Mr. Jackson?

A. Morphine IR (crash or liquid) 20 mg per PEG q4h ATC and 15 mg per PEG q4 h prn
B. Switch to hydromorphone IR (crash or liquid) 4 mg per PEG q4h ATC and 3 mg q4h prn
C. Switch to fentanyl transdermal system at 37 mcg/hr q72 hr
D. Switch to methadone using 8:1 (using Parsons et al. Cancer 2010:116;520-8.) titrate to 6 mg every 8 hours ATC over 3 days

Opioid equianalgesic table

	PO mg	PO:SC	SC mg
Morphine	10	2:1	5
Codeine	100	2:1	50
Oxycodone	6	2:1	3
Hydromorphone	2	2:1	1
Methadone	1 (variable)	-	-
Fentanyl sc	-	-	0.05
Fentanyl TD	Use manufacturer's chart (morphine 90 mg po/d = FTD 25 mcg/hr)		

https://recalls-rappels.canada.ca/en/alert-recall/fentanyl-transdermal-systems-new-changes-dose-conversion-guidelines-health-care

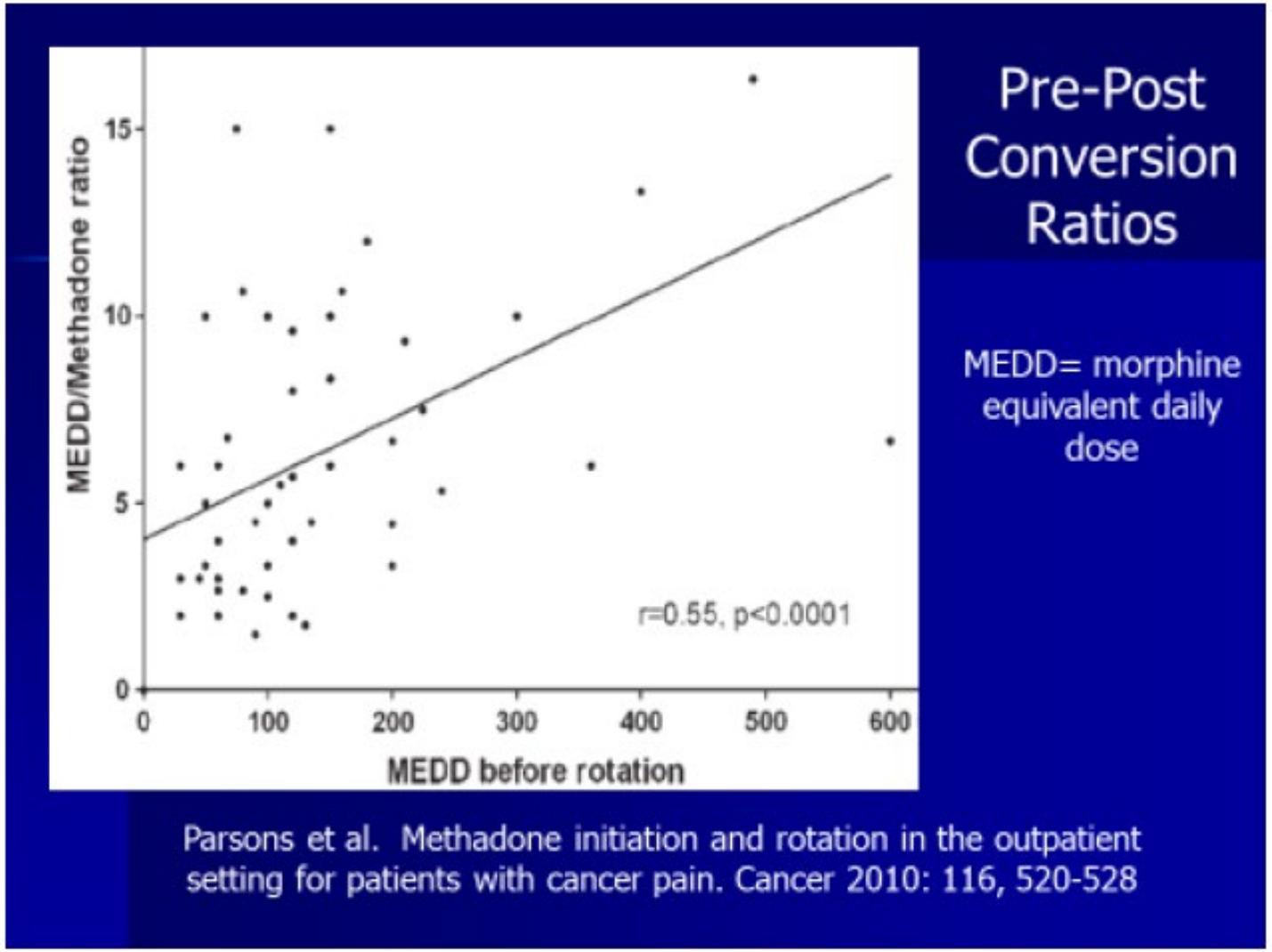
Current Analgesic	**Daily Dosage (mg/d)**						
Oral morphine	60-134	135-179	180-224	225-269	270-314	315-359	360-404
IM/IV morphine (based on a 1:3 IM/IV:PO ratio)	**20-44**	**45-60**	**61-75**	**76-90**	**NA[2]**	**NA[2]**	**NA[2]**
Oral oxycodone	30-66	67-90	91-112	113-134	135-157	158-179	180-202
Oral codeine	150-447	448-597	598-747	748-897	898-1047	1048-1197	1198-1347
Oral hydromorphone	8-16	17-22	23-28	29-33	34-39	40-45	46-51
IV hydromorphone[3]	4.0-8.4	8.5-11.4	11.5-14.4	14.5-16.5	16.6- 19.5	19.6-22.5	22.6-25.5
	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓	↓↓
Recommended Fentanyl Transdermal System (FTS) Dose	**25 mcg/h**	**37 mcg/h**	**50 mcg/h**	**62 mcg/h**	**75 mcg/h**	**87 mcg/h**	**100 mcg/h**

CANADIAN Virtual Hospice

Methadone Conversion Table

Morphine Equivalents and Initial Dose Ratios	
24 hour total dose of oral morphine (or morphine equivalents)	**Conversion ration oral morphine (or morphine equivalents) to oral methadone**
Less than or equal to 30 mg	2:1(2 mg morphine to 1 mg methadone)
31-99 mg	4:1
100-299 mg	8:1
300-499 mg	12:1
500-999 mg	15:1
1000 mg or greater	20:1

Scatter Plot



Terminologies

- ✓Cancer survivors
- ✓Chronic cancer related pain
- ✓LTOT: long term opioid therapy
- Opioid related harms (risks)
- SUD/OUD: substance or opioid use disorder

LTOT (long-term opioid therapy > 3 mo) in cancer survivors

retrospective cohort comparative study designs published 2013-20, N= 976 to 106,732, 21 articles

- Prevalence: 5 to 45 %
- H&N 15-35%, breast, colorectal, lung, cervix: 5-7%
- Factors: opioid use before surgery or radiation tx, medical comorbidities, anxiety disorder, alcohol use disorder
- Pain type: under explored (H&N cancer post tx, painful CIPN,…)
- OME> 90 mg, polypharmacy
- Socioeconomic factors (income, education, employment, disability, tobacco use, etc.)

Jones KF, Fu MR, Merlin JS, Paice JA, Bernacki R, Lee C, Wood LJ. Exploring Factors Associated With Long-Term Opioid Therapy in Cancer Survivors: An Integrative Review. J Pain Symptom Manage. 2021 Feb;61(2):395-415. doi: 10.1016/j.jpainsymman.2020.08.015. Epub 2020 Aug 19. PMID: 32822751.

Opioid related harms (risks) = Biopsychosocial

- Lethal: Fatal opioid over dose
- Physiological: central disordered breathing (esp>OME 100 mg/d), insomnia, gastropathies, endocrinopathies/hypogonadotropic hypogonadism, immune dysfunction, cognitive impairment, osteoporosis
- Pharmacodynamic: tolerance and withdrawal
- Psychosocial behavioural: mood disorder (Hyperkatifeia*), worsened pain (Hyperalgesia), polypharmacy, social consequences, aberrant behaviours, misuse/OUD

*Ballantyne JC, Koob GF. Allostasis theory in opioid tolerance (topical review). Pain 2021 162:2315-2319.
- Carmona-Bayonas A, Jimenez-Fonseca P, Castanon E, et al. Chronic opioid therapy in long-term cancer survivors. Clin Transl Oncol. 2017;19:236-250.
- Kotlinska-Lemieszek A, Klepstad P, Haugen DF. Clinically significant drug-drug interactions involving opioid analgesics used for pain treatment in patients with cancer: a systematic review. Drug Des Devel Ther. 2015;9:5255-5267.
- Prostran M, Vujovic KS, Vuckovic S, et al. Pharmacotherapy of pain in the older population: the place of opioids. Front Aging Neurosci. 2016;8:144.
- Dowell D, Haegerich TM, Chou R. CDC guideline for prescribing opioids for chronic pain—United States, 2016. JAMA. 2016;315:1624-1645.
- Cutrufello NJ, Ianus VD, Rowley JA. Opioids and sleep. Curr Opin Pulm Med. 2020 Nov;26(6):634-641

Mr. Jackson cont'd

- Immunotherapy q3 weekly in stable condition
- 6 months later, his family physician requested advice
- Mr. Jackson calls for requesting early refill multiple times. Is cancer progressing?
- Rx: Morphine liquid 40 mg every 4 hours ATC + 15 mg q1h (unknown times a day)
- ESASr: Pain 9/10; Anxiety 9/10; Depression 8/10; WB 9/10

List differential dx

- Disease progression
- Co-occuring distress
- Organ failure
- Delirium
- Opioid tolerance
- Withdrawal-mediated pain
- Opioid induced hyperalgesia
- Opioid misuse or OUD
- Diversion

What is the right approach?

A. Urine drug toxicology
B. Set a personal pain goal
C. Opioid switch to hydromorphone by 50% dose reduction
D. Consult addiction specialist for opioid agonist tx
E. Increase morphine to 60 mg IR every 4 hours based on his using 8-9 PRN
F. Pill count and call pharmacy to confirm that he is taking the correct meds

Terminologies

- ✓Cancer survivors
- ✓Chronic cancer related pain
- ✓LTOT: long term opioid therapy
- ✓Opioid related harms (risks)
- SUD/OUD: substance or opioid use disorder
- ADTB: Aberrant drug taking behaviours such as, taking higher dose, more frequent, running out, multiple prescribers, borrowing, concurrent use, inconsistent, threatening, lost/stolen, selling (diversion)

Diagnose Opioid Use Disorder (OUD)

- "a problematic pattern of opioid use leading to **significant impairment or distress**" over at least 1 year
- 4 **C**'s: **C**ravings, **C**ontrol [loss of], **C**onsequence, and **C**ompulsive use
- "How many times in the past year have you used an illegal drug or a prescription medication for nonmedical reasons?"
- Several studies shown OUD >25 % receiving opioids in chronic pain
- DSM 5 diagnostic criteria classifies mild-moderate-severe

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. American Psychiatric Association; 2013.
*Smith PC, Schmidt SM, Allensworth-Davies D, Saitz R. A single-question screening test for drug use in primary care. Arch Intern Med 2010;170:1155-1160. Just JM, Bingener L, Bleckwenn M, Schnakenberg R, Weckbecker K. Risk of opioid misuse in chronic non-cancer pain in primary care patients: a cross sectional study. BMC Fam Pract 2018;19:92-92.
Vowles KE, McEntee ML, Julnes PS, Frohe T, Ney JP, van der Goes DN. Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis. Pain 2015;156:569-576.
McCaffrey SA, Black RA, Villapiano AJ, Jamison RN, Butler SF. Development of a brief version of the Current Opioid Misuse Measure (COMM): the COMM-9. Pain Med 2019;20:113-118.

Check all that apply	DSM-5 Criteria for Diagnosis of Opioid Use Disorder Criteria from American Psychiatric Association (2013). Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition,. Washington, DC, American Psychiatric Association page 541.
	Opioids are often taken in larger amounts or over a longer period of time than intended.
	There is a persistent desire or unsuccessful efforts to cut down or control opioid use.
	A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects
	Craving, or a strong desire to use opioids.
	Recurrent opioid use resulting in failure to fulfill major role obligations at work, school or home.
	Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids.
	Important social, occupational or recreational activities are given up or reduced because of opioid use.
	Recurrent opioid use in situations in which it is physically hazardous
	Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by opioids.
X	*Tolerance, as defined by either of the following: (a) a need for markedly increased amounts of opioids to achieve intoxication or desired effect (b) markedly diminished effect with continued use of the same amount of an opioid
X	*Withdrawal, as manifested by either of the following: (a) the characteristic opioid withdrawal syndrome (b) the same (or a closely related) substance are taken to relieve or avoid withdrawal symptoms

Total Number Boxes Checked: _____
Severity: Mild: 2-3 symptoms. Moderate: 4-5 symptoms. Severe: 6 or more symptoms

Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis

NNTB: Number of people achieving 50% or greater pain relief compared with placebo
NNTH: Number of people treated to experience harm

Active drug class	Number of comparisons	Participants	Pain relief Active vs. Placebo		NNTB	NNTH	Susceptibility to bias[3]
TCAs	15	948	217/473	85/475	**3.57** (3.0–4.4)	13.4 (9.3-24.4)	1973
SNRIs	10	2541	676/1559	278/982	**6.40** (5.2–8.4)	11.8 (9.5-15.2)	1826
Pregabalin	25	5940	1359/3530	578/2410	**7.71** (6.5–9.4)	13.9 (11.6-17.4)	2534
Gabapentin	14	3503	719/2073	291/1430	**7.16** (5.9–9.1)	25.6 (15.3-78.6)	1879
Tramadol	6	741	176/380	96/361	4.73 (3.6–6.7)	12.6 (8.4-25.3)	982
Strong opioids	7	838	211/426	108/412	4.26 (3.4–5.8)	11.7 (8.4-19.3)	1326
Capsaicin 8%	6	2073	466/1299	212/774	10.64 (7.4–19)	NA	70
BTX-A	4	137	42/70	4/67	1.85 (1.5–2.4)	NA	678

Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpää M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol. 2015 Feb;14(2):162-73. doi: 10.1016/S1474-4422(14)70251-0. Epub 2015 Jan 7. PMID: 25575710; PMCID: PMC4493167.

Meta-analysis in cannabis for cancer related pain

Six RCTs in this systematic review (n=1460 pts) Five studies with low risk of bias for the meta-analysis (1442 pts)

- No difference between cannabinoids and placebo in the change in average Numeric Rating Scale pain scores
- Cannabinoids had a higher risk of adverse events when compared with placebo, especially somnolence (OR 2.69 (1.54 to 4.71), p<0.001) and dizziness (OR 1.58 (0.99 to 2.51), p=0.05)
- No treatment-related deaths
- Dropouts and mortality rates were high

Boland EG, Bennett MI, Allgar V, Boland JW. Cannabinoids for adult cancer-related pain: systematic review and meta-analysis. BMJ Support Palliat Care. 2020 Mar;10(1):14-24. doi: 10.1136/bmjspcare-2019-002032. Epub 2020 Jan 20. PMID: 31959586.

Reducing Overdose Risk in Long-Term Opioid Therapy

Risk factors:

- Concurrent use of sedative medications, including benzodiazepines
- Coexisting mental health or substance use disorder
- Higher doses of opioids (especially >100 MMEs daily)
- Prior opioid overdose
- Use of ER/LA opioid formulations
- Older age (>65)
- Sleep-disordered breathing

When high:

- Prescribe naloxone when >50 MMEs esp concurrent BZPs
- Consider buprenorphine vs. taper (rapid 5 to 10% in 2 to 4 wks, slow 2 to 10% in 4 to 8 wks)
- Consider approaches other than benzodiazepines in managing anxiety : Concurrent use of benzodiazepines is seen in 30% of opioid overdoses

Babu KM, Brent J, Juurlink DN. Prevention of Opioid Overdose. N Engl J Med. 2019 Jun 6;380(23):2246-2255. doi: 10.1056/NEJMra1807054. PMID: 31167053..

Opioid taper: lessons learned from general literature

- When risks outweigh benefits, tapering or discontinuing LTOT may be considered
- Clinicians should develop a therapeutic relationship with patients and communicate the tapering rationale, schedule, and symptoms that may be experienced during the tapering process.
- Opioid tapering is an evolving area of research. It should be undertaken with caution in patients at risk for psychological decompensation, but evidence suggests that slow, flexible, and voluntary tapering can improve function, quality of life, mood, and pain management.

- Jones KF, Merlin JS. Approaches to opioid prescribing in cancer survivors: Lessons learned from the general literature. Cancer. 2021 Oct 11. doi: 10.1002/cncr.33961. Epub ahead of print. PMID: 34633657.
- Larochelle M, Lagisetty PA, Bohnert ASB. Opioid tapering practices-time for reconsideration? JAMA. 2021;326:388-389.
- Frank JW, Lovejoy TI, Becker WC, et al. Patient outcomes in dose reduction or discontinuation of long-term opioid therapy: a systematic review. Ann Intern Med. 2017;167:181-191.
- Fishbain DA, Pulikal A. Does opioid tapering in chronic pain patients result in improved pain or same pain vs increased pain at taper completion? A structured evidence-based systematic review. Pain Med. 2018;20:2179-2197.
- Rich R, Chou R, Mariano ER, Dopp AL, Sullenger R, Burstin H; Pain Management Guidelines and Evidence Standards Working Group of the Action Collaborative on Countering the U.S. Opioid Epidemic. Best Practices, Research Gaps, and Future Priorities to Support Tapering Patients on Long-Term Opioid Therapy for Chronic Non-Cancer Pain in Outpatient Settings. National Academy of Medicine; 2020.
- Powell VD, Rosenberg JM, Yaganti A, et al. Evaluation of Buprenorphine Rotation in Patients Receiving Long-term Opioids for Chronic Pain: A Systematic Review. *JAMA Netw Open.* 2021;4(9):e2124152. Manhapra A, Arias AJ, Ballantyne JC. The conundrum of opioid tapering in long-term opioid therapy for chronic pain: a commentary. Subst Abus. 2018;39:152-161.
- Cheng J, Rutherford M, Singh VM. The HHS Pain Management Best Practice Inter-Agency Task Force report calls for patient-centered and individualized care. Pain Med. 2019;21:1-3.

Buprenorphine

- Partial agonist of the MOR: Ceiling effect on respiratory depression < analgesia (unless concurrent BZPs or EtOH)
- Higher affinity to MOR (1.7 times of Hydromorphone)
- Kappa antagonism and Opioid receptor-like 1 (ORL1) agonist: analgesia + blocks analgesic tolerance
- Unlike other opioids, increases MOR expression on membrane surfaces, does not interact with β-arrestin-2 and is uniquely a 6-transmembrane MOR agonist
- Drug clearance dose not affect with age, renal or mild hepatic impairment
- Precipitated withdrawal
- Buprenorphine can facilitate opioid tapers by minimizing hyperalgesia and promoting mood stability attributed to prolonged abstinence syndrome.
- Analgesia: 80 to 100 times of morphine.

Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. J Support Oncol. 2012;10(6):209-219
Grinnell SG, Ansonoff M, Marrone GF, Lu Z, et al. Mediation of buprenorphine analgesia by a combination of traditional and truncated mu opioid receptor splice variants. Synapse. 2016;70(10): 395-407.
Muriel C, Failde I, Mic´o JA, Neira M, S´anchez-Magro I. Effectiveness and tolerability of the buprenorphine transdermal system in patients with moderate to severe chronic pain: a multicenter,open-label, uncontrolled, prospective, observational clinical study. Clin Ther. 2005;27(4):451-462.
Evans HC, Easthope SE. Transdermal buprenorphine. Drugs. 2003;63(19):1999-2010; discussion 2011-2.
Sporer KA. Buprenorphine: a primer for emergency physicians. Ann Emerg Med. 2004;43(5):580-584.
Davis MP. Buprenorphine in cancer pain. Supp Care Cancer. 2005;13(11):878-887.
Davis MP, Pasternak G, Behm B. Treating chronic pain: an overview of clinical studies centered on the buprenorphine option. Drugs. 2018;78(12):1211-1228.

Buprenorphine available in Alberta (not indicated for cancer pain control)

Buprenorphine transdermal system

- 5 mcg/hr ($75-90 per 4 weeks)
- 20 mcg/hr ($ 250 per 4 weeks)

Buprenorphine-Naloxone sublingual tablet (not buprenorphine only)

- 2-0.5 mg, 4-1 mg, 8-2 mg

Buprenorphine	Oral Morphine Equivalent /24 hours (OME)								
	7	15	30	48	60	80	100	120	300
Transdermal patch	5 mcg/hr		10 mcg/hr	20 mcg/hr					
Sublingual tab						2 mg		4 to 6 mg	

Ms. Marple

- 59 yr, breast cancer on endocrine therapy x 2 years presented to ER with altered mental state
- O/E unresponsive. pinpoint pupils. Resp 7/min: Naloxone was given and improved mental state and respiration.
- Medical Hx: breast cancer, seizure disorder
- Med list:
  - Fentanyl TDS 12 mcg/hr q3d for post mastectomy pain
  - Valproic acid 2000 mg/d recently increased 2 weeks ago from 1500 mg due to several breakthrough seizures
  - Clarithromycin, Amoxicilin and omeprazole started 6 days ago for Helicobactor pylori eradication

Ms. Marple: Which one is the culprit?

A. Valproic acid
B. Clarithromycin
C. Amoxicillin
D. Omeprazole

Drug-drug interactions

Pharmacodynamic

- Concurrent sedative use
- Concurrent SSRIs
- Concurrent agents with prolong QTc interval
- Efflux and influx via transporters

Pharmacokinetic

- Concurrent use of inducers: increase drug clearances
- Inhibitors: increase drug efficacies and side effects
- Autoinduction of cytochrome P-450 enzymes and drug clearance

EtOH affects both phamacodynamic and pharmacokinetics (esp. ER/LA opioids)

Ms Gold

- 59 yr old female with breast cancer and bone metastasis admitted to hospital with decreased renal function after presenting with N+V x 3 days post last chemotherapy with docetaxel given 5 days ago.
- She has been on morphine IR 45 mg q4h ATC with good pain control
- On admission, she was drowsy, S-creat 5 times normal upper limit, S-Ca normal, others all normal
- She is on IV fluids x 3 hrs and mental state improved but pain returns

Ms. Gold: Which is the correct approach?

A. Increase morphine IR to 55 mg q4h ATC orally with BTA
B. Switch to hydromorphone IR 4 mg q4h ATC orally with BTA
C. Switch to fentanyl TDS 75 mcg/hr
D. Start methadone rotation over the next 4 days with planned final dose 10 mg q8h ATC
E. Decrease morphine IR to 35 mg po q4h ATC with BTA

Opioids in renal failure

- Systematic review
  - Poor quality evidence
  - Pharmacological data and clinical experience → fentanyl = methadone > hydromorphone = tramadol > morphine = codeine = oxycodone
- Use all opioids with caution → extend dosing interval, monitor for toxic sx

King S, Forbes K, Hanks GW, Ferro CJ, Chambers EJ. A systematic review of the use of opioid medication for those with moderate to severe cancer pain and renal impairment: a European Palliative Care Research Collaborative opioid guidelines project. *Palliat Med*. 2011;25(5):525-552. doi:10.1177/0269216311406313

Sande TA, Laird BJ, Fallon MT. The use of opioids in cancer patients with renal impairment-a systematic review. *Support Care Cancer*. 2017;25(2):661-675. doi:10.1007/s00520-016-3447-0

Share the understanding of cancer treatment intension/goals: curative, life-prolonging, comfort focused

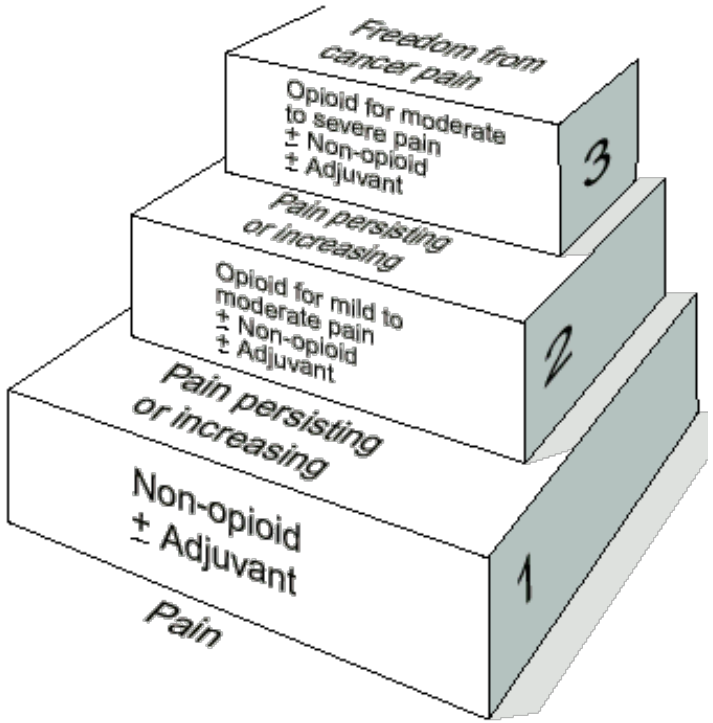
GOALS of care= quality of life

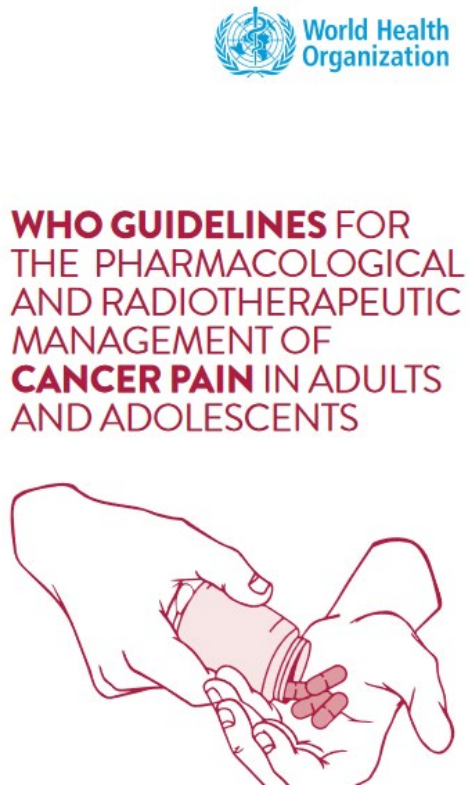
Methadone: Head and Neck cancer during chemo-RT

Design	Measurements	Patients	Rationale for MET	Intervention	Outcome
Open label RCT MET vs FEN Average pain/reduction of 50% , GPE at wk 3	BPI, HADs, AEs , Global perceived effect(GPE), EuroQol 5D at 1, 3, 5 wks	N=26 vs. 26 Dx H+N outpt (NRS≥4 DN4≥4)	Naïve to ATC opioid	1. FEN 12 mcg/hr 2. MET 2.5 mg bid FEN 50 mcg nasal PRN Weekly adjustment	At wk 1 and 3 Statistically significant NRS reduction ARM1
Partial blinded RCT Chemo RT (70Gy+56Gy to nodes + cisplatin)	OME, CTCAE v4 (AE +SAV) OMQW-HN EORTC QLQ-C30/H&N35 at baseline, wk 2, 7, 1, 3, 4-6, 9, 12 mo up to 2 yrs	N=31 vs 29 Dx SCC H+N St II-IV 90% completed	Definitive CRT exd. Chronic pain, recurrent ca, Brain met, Qtc risk	1. FEN TDS + hydrocodone PRN + Gab 2700 mg 2. MET 5 -15mg bid + OXY 5 -10 PRN + Gab 900 mg	ARM2 significantly better QoL (emotional function) and faster to gain baseline global health and less opioid requirement (p=0.11)

- Haumann J, et a;. Methadone is superior to fentanyl in treating neuropathic pain in patients with head-and-neck cancer. Eur J Cancer. 2016 Sep;65:121-9.
- Hermann GM, et al. A single-institution, randomized, pilot study evaluating the efficacy of gabapentin and methadone for patients undergoing chemoradiation for head and neck squamous cell cancer. Cancer. 2020 Apr 1;126(7):1480-1491.

WHO analgesic ladder first published 1986 –Freedom from cancer pain





WHO Guidelines for the Pharmacological and Radiotherapeutic Management of Cancer Pain in Adults and Adolescents. Geneva: World Health Organization2018. Executive Summary.Available from: https://www.ncbi.nlm.nih.gov/books/NBK537479/

“right-to-pain-relief”& “titrate-to-effect” principle

In dying:

- Effective in lowering pain score
- Possible life shortening effects: the double-effect doctrine in dying ?Consent
- Care occurs in the **supervised setting**
- Harm of opioid therapy in end-of-life care are limited by the diminished capacity

In living

- Titrated opioid dosing led to unprecedented dosing level
- Titration tended to select the least suitable candidate/provider for opioids because of the people reporting the highest pain intensity are the most distressed and are most at risk of tx failure and opioid misuse
- When used to “relief” suffering, opioid diminishes the capacity for living =diminishes quality of life and cope with suffering

Sullivan MD, Ballantyne JC. The right to pain relief: its origins in end-of-life care and extension to chronic pain care. Clinical J of pain 2021.DOI:10.1097/AJP.000000000001000

Conclusions

Key message in chronic cancer related pain management

- Differentiate pain mechanism, disease trajectories
- Identify high risk factors in opioid management and approach proactively
- Acknowledge suffering cannot be alleviated by “taking something”
- Goals: quality of life= improve function and more options
- Establish shared goals + empower through education (safe opioid management, adverse effects, multiprofessional teamwork)