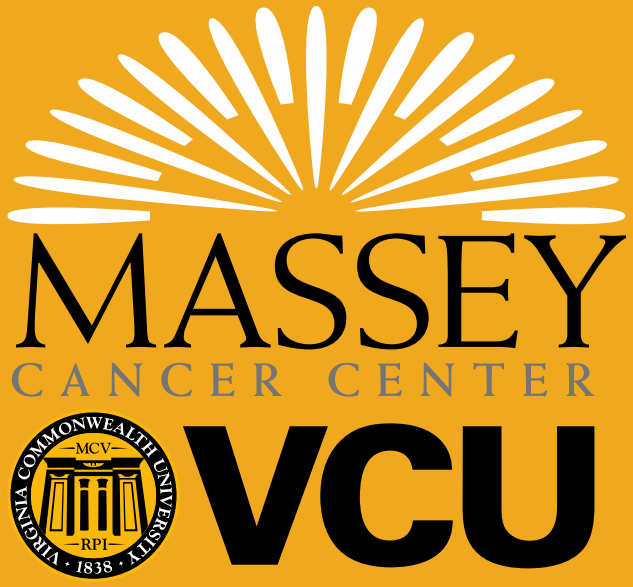

Primum non nocere: First Do No Harm
Opioid Use Among Cancer Survivors

Susan Hong, MD MPH FACP
Director of Cancer Survivorship
VCU Massey Comprehensive Cancer Center

NCI Comprehensive Cancer Center

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Objectives

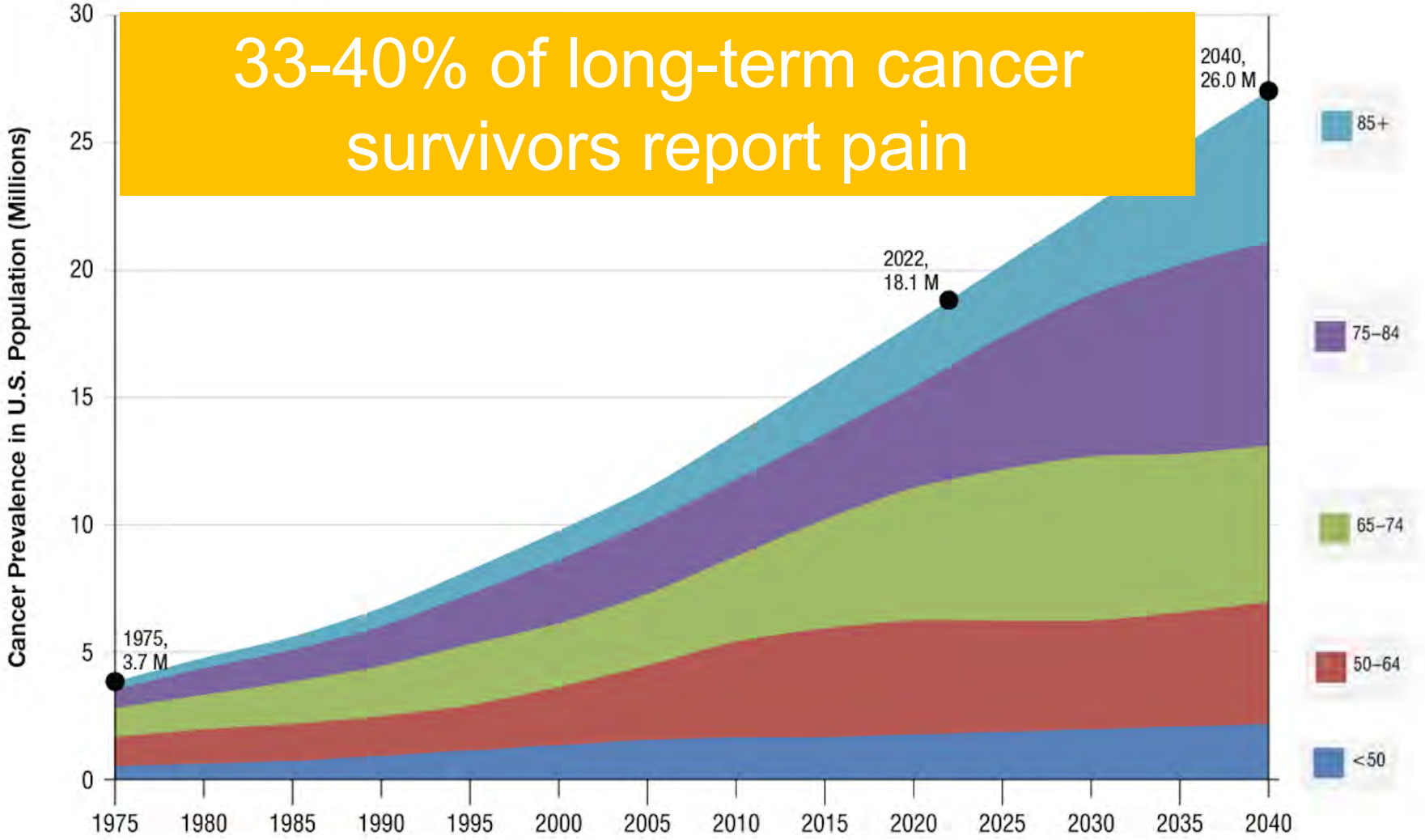
- Describe the burden of pain in CS
- Discuss the rates of the opioid use in CS
- Discuss the potential harms of chronic opioid use

Case

- DS is 59 yo NHW male diagnosed with BRAF+IV melanoma of R UE.
- Dx in 2009 for which he had WLE, AND,and received temozolimide and RT.
- Given advanced stage at diagnosis he was on maintenance immunotherapy with ipilumumab 3/2013.
- He presented to CS 10/22 on the following medications:
  - Oxycodone 30 mg po Q4
  - Neurontin 600 mg po QHS
  - Morphine 90 TID
  - **Total 540 MME**

Cancer Prevalence and Projections in U.S. Population from 1975–2040

33-40% of long-term cancer survivors report pain



Bluthmann SM. et.al. Cancer Epidemiol Biomarkers Prev 2016

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Burden chronic pain in cancer survivors

- Data from National Heath Interview Survey:

  115,901 individuals of which 6.6% had history of cancer
- Median age of entire cohort 48 years
- CS were more than 2 years out from diagnosis

Prevalence CP pain in CS	Prevalence CP w/o hx cancer	AOR [95% CI]
30.8%	15.7%	1.48[1.38-1.59]

Sanford NN. Et.al. Prevalence of chronic pain among cancer survivors in US, 2010-2017. Cancer 2019.

Burden chronic pain in cancer survivors

- CS were > 5 years out from diagnosis

Prevalence CP pain in CS	Prevalence CP w/o hx cancer	AOR [95% CI]
30.5%	15.7%	1.45[1.34-1.56]

Sanford NN. Et.al. Prevalence of chronic pain among cancer survivors in US, 2010-2017. Cancer 2019.

Impact of chronic pain in cancer survivors

	CS with pain %	CS w/o pain %	AOR [95% CI]
Rates of depression	32.8%	11.1%	3.49 [2.95-4.13]
Reported feeling anxious/worried	44.7%	22.8%	2.60 [2.25-3.00]
Inability to work	32.5%	7.7%	4.90 [4.11-5.82]
Assistance w/ ADL	10.6%	2.5%	3.92 [2.93-5.26]
Assistance w/ IADL	19.6%	5.2%	3.86 [3.11-4.79]

Sanford NN. Et.al. Prevalence of chronic pain among cancer survivors in US, 2010-2017. Cancer 2019.

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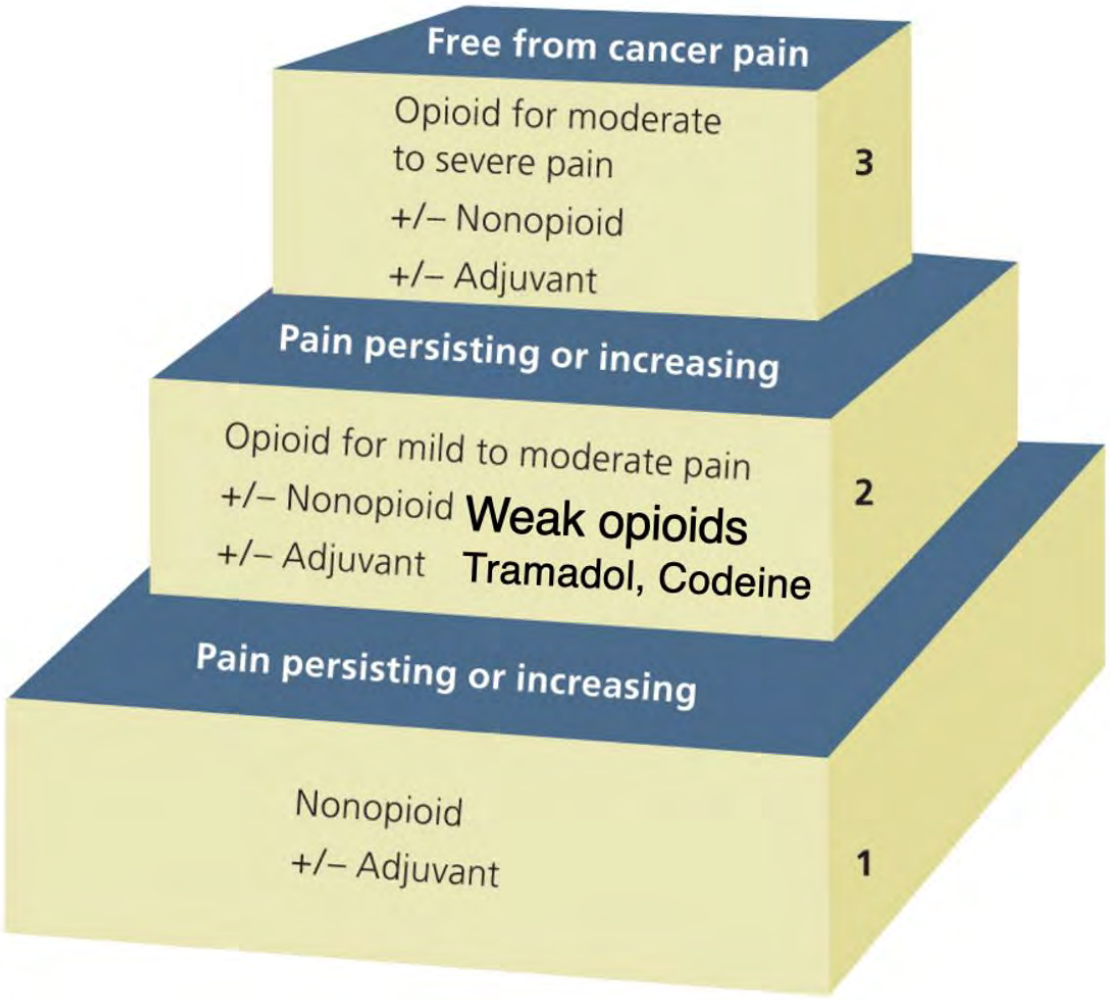
Pain management in cancer patients

World Health Organization's Pain Relief Ladder



More than ½ of cancer patients will be prescribed opioids within first year of diagnosis

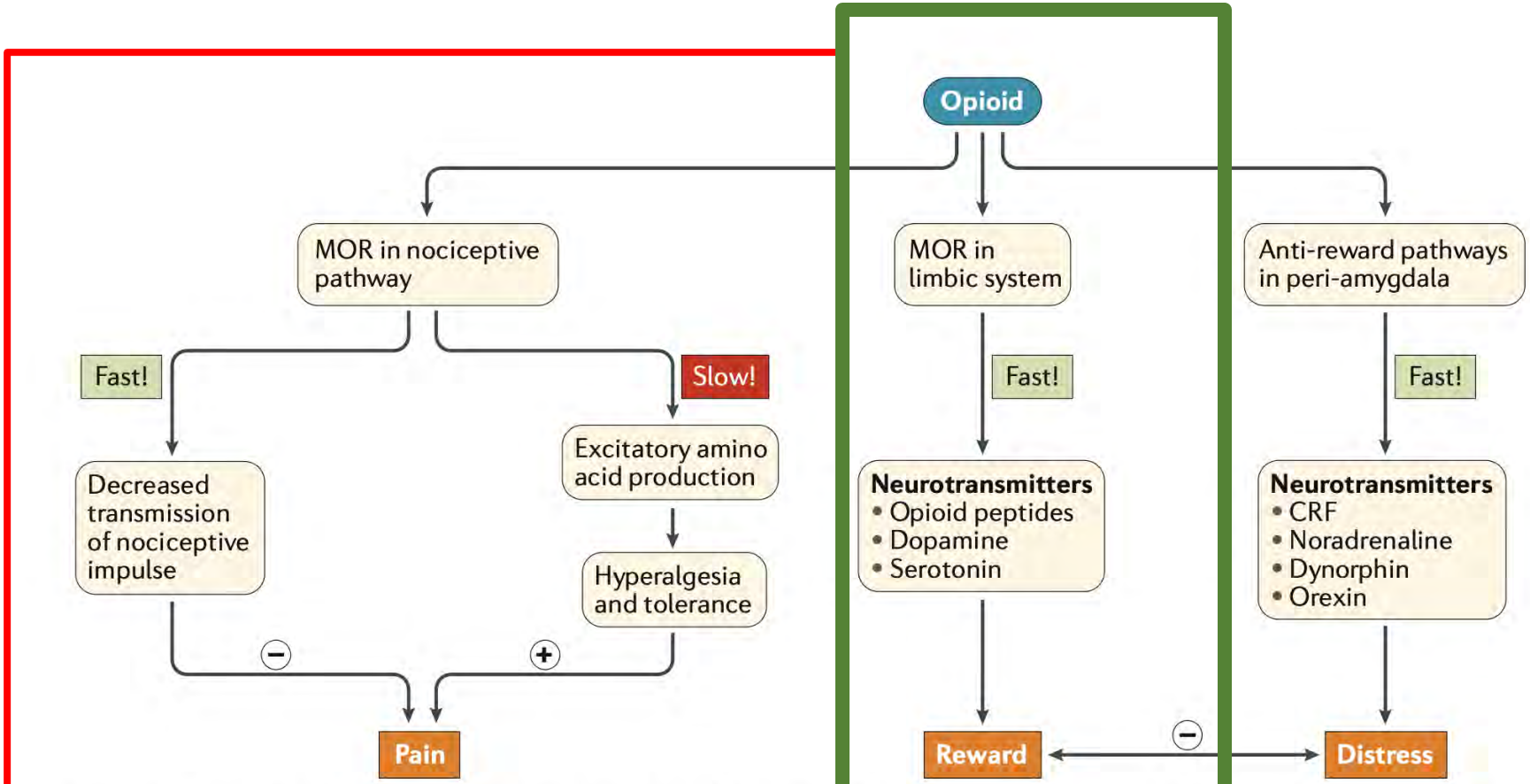


Fig. 2 | **Conceptual model of opioid effects on nociceptive and non-nociceptive pathways.** Opioid stimulation of the μ-opioid receptor (MOR) in the nociceptive pathway results in a rapid decrease in the transmission of nociceptive impulse on pain. Over time, however, the slow release of excitatory amino acids results in the development of tolerance and hyperalgesia. Opioid stimulation of MOR in the limbic pathway results in the fast release of neurotransmitters (including dopamine, opioid peptides and serotonin) that cause reward and/or pleasure. Over time, and as a consequence of the absence of opioids, anti-reward pathways become active, resulting in the release of neurotransmitters such as corticotropin-releasing factor (CRF), noradrenaline and dynorphin, which cause dysphoria and/or distress.

Joseph Arthur and Eduardo Bruera. Balancing opioid analgesia with the nonmedical opioid use in patients with cancer. Nature Reviews 2018

Harms of chronic opioid use

- Diversion
- Risk for persistent opioid dependence
- Development of opioid use disorder
- Non-Medical Use of Opioids
- Overdose
- Death-more than 40% of all opioid – related overdose deaths involve a prescription opioid

75% of heroin users report being introduced to heroin through prescription opioids

Harms of chronic opioid use

- Chronic opioid exposure may increase pain sensitivity----→Opioid induced hyperalgesia
- Endocrinopathies-
  - Binds opioid receptors in hypothalamus suppresses H-P-G axis
  - Increases osteoporosis (osteoblasts have mu-receptors, binding has inhibitory effect)

Harms of chronic opioid use

- Negative impact on immune system
  - Morphine inhibits T lymphocyte proliferation, NK cells,
- Some evidence may promote tumor progression

What do we know about the long-term use of opioid use in disease-free CS

Rates of long-term opioid use

- Canadian study of cancer survivors 24-70 years
- Evaluation of opioid use > 5 years among disease-free cancer survivors
  - N=7431
- CS had 22% higher overall opioid Rx rate

Even at 5 years out, disease-free cancer survivors have 22% higher opioid prescription rate compared to general population

Barbera L. *Factors associated with opioid use in long-term cancer survivors*. J Pain Symptom Manage 2019

Long-term opioid use beyond 5 years in CS n=7431

6.8% of cohort had persistent use beyond 5 yrs.

	RR [95% CI]
Depression	1.76 [1.36-2.29]
Chemotherapy exposure*	0.68 [0.52-0.88]
Surgery^	0.84[0.67-1.05]
Pre-diagnosis opioid use	1.78 [1.44-2.19]
Continuous use (diagnosis to index date)	46.13[34.75-61.24]

*paclitaxel, oxaliplatin, nab-paclitaxel, eribulin, docetaxel, etc.
^mastectomy, AND, abdominal perineal resection, total mesorectal excision, thoracotomy

Barbera L. *Factors associated with opioid use in long-term cancer survivors*. J Pain Symptom Manage 2019

Opioid use in military CS 2+ years n=106,732

	Rates [95% CI]
Persistent Opioid Use overall	8.3% [8.1-8.4]
Rate of abuse/dependence	2.9% [2.8-3.0]
Opioid related admissions	2.1% [2.0-2.2]

Persistent opioid use defined as filling 120+ days of opioids 2 years after curative treatment

Vitzthum LK. Predicting persistent opioid use, abuse, toxicity among cancer survivors. JNCI 2020

Risk factors for persistent opioid use in military CS

	OR [95% CI]
Current smoker versus never smoker	2.37 [2.21-2.52]
Depression	2.33 [2.24-2.42]
CCI 3 versus 0	1.71 [1.63-1.80]
Unemployed	1.71 [1.58-1.84]

Persistent opioid use defined as filling 120+ days of opioids 2 years after curative treatment

Vitzthum LK. Predicting persistent opioid use, abuse, toxicity among cancer survivors. JNCI 2020

OD rates in cancer patients

OD rates in cancer patients presenting to ED between 2006-2015

- Nationwide ED Sample
  - Largest ED database in US
    - 950 hospitals across 34 states
    - Represents 20% of US hospital-based ED visits.
- Total of 35,330 opioid-related ED visits for patients with cancer

Jairam V Emergency department visits for opioid overdoses among patients with cancer. JNCI.2020

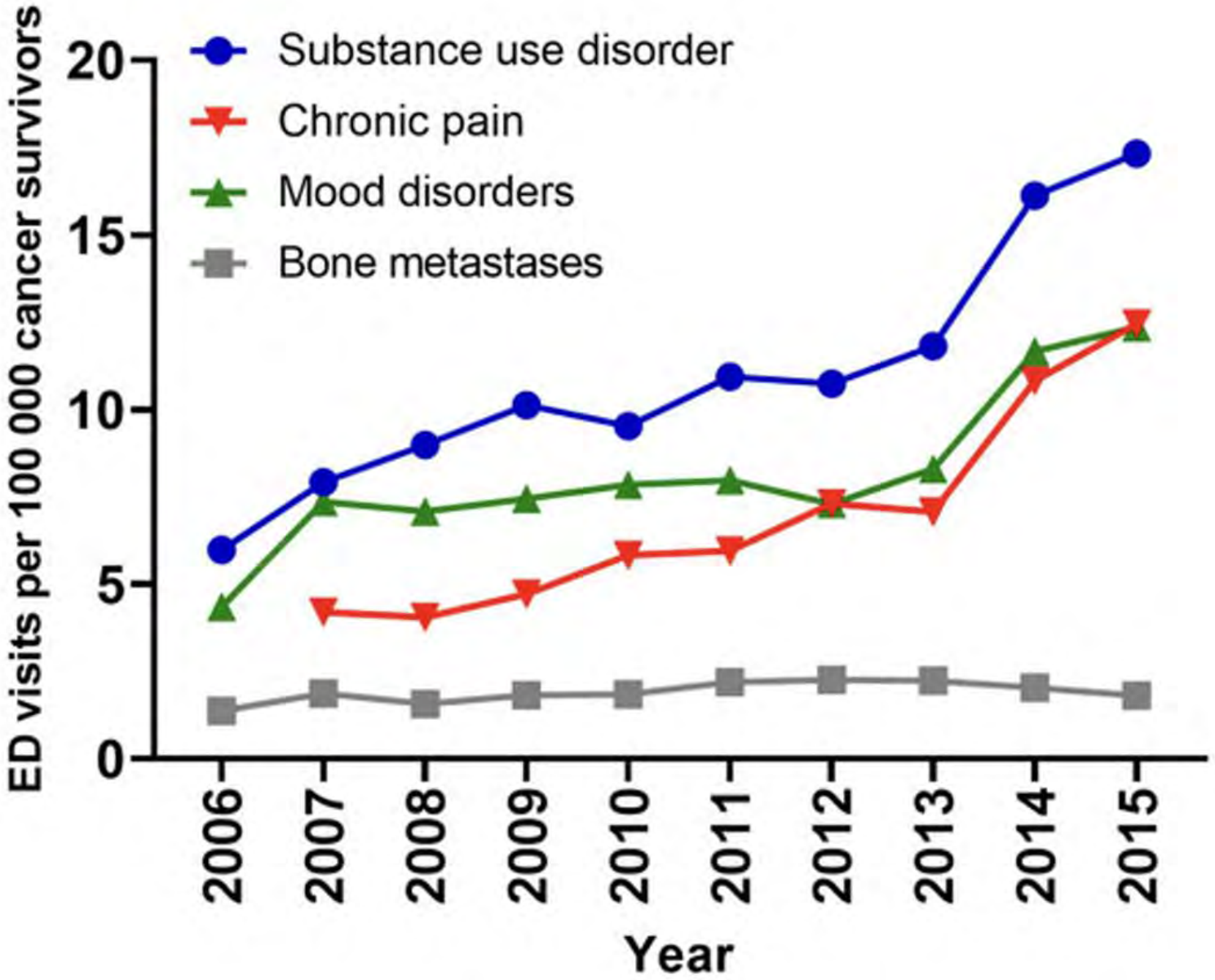
OD rates in cancer patients presenting to ED between 2006-2015

- 94.3% involved prescription opioids
- During study period for cancer patients:
  - 2-fold increase for opioid related visits
  - 1.3-fold increase in non-opioid related visits

Opioid Related ED Visits per in CS 100,000		
Year	2006	2015
Rate/100,000	2078	5324

Jairam V Emergency department visits for opioid overdoses among patients with cancer. JNCI.2020

Figure 3. Temporal trends in opioid-related emergency department visits among patients with cancer by comorbid risk factor, 2006–2015. Two-sided P_{trend} less than .001 for all risk factors. Temporal trends for chronic pain were analyzed beginning in 2007 to account for new diagnosis codes created on October 1, 2006.



Jairam V Emergency department visits for opioid overdoses among patients with cancer. JNCI.2020

Opioid safety behaviors among cancer patients

75% of individuals who abuse opioids obtain them from friends/family

Opioid safety at home

- Study by Silvestre and colleagues of 113 cancer patients presenting to ED of NCI-CCC

	%
Opioids were in plain sight	36%
Opioids were hidden but not locked	53%
Reported sharing their opioids*	5%
Reporting losing their opioids	8%
Had old opioids lying around	67%
Opioids were hidden and locked	15%

Silvestre J. et.al Frequency of unsafe storage, use, and disposal practices of opioids among cancer patients presenting to the ED. Palliative and Supportive Care 2017.

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Prevalence of OUD in CS

Opioid use disorder

- Diagnosis is based on DSM-V criteria
- Compilation of aberrant cognitive, physical, and behavioral symptoms
- Problematic pattern of opioid use leading to clinically significant impairment or distress

TABLE 1. ***DSM-5* Criteria for Opioid Use Disorder**

Category	*DSM-5* criteria
Impaired control	**1.** Larger amounts or longer period of opioid use than was intended **2.** Persistent unsuccessful efforts to decrease or control opioid use **3.** Excessive time spent obtaining, using, or recovering from use of opioids **4.** Craving, or a strong desire to use opioids
Social impairment	**5.** Failure recurre **6.** Persistent o opioid use c **7.** Reduced or recreational
Risky use	**8.** Recurrent o **9.** Continued c or psycholo opioid use
Pharmacologic properties[a]	**10.** Tolerance (the need to increase amounts to achieve intoxication or desired effect or a markedly diminished effect despite continued use of an opioid of the same dose) **11.** Withdrawal (cessation or reduction of opioid use or opioid antagonist use that resulted in at least 3 of the following symptoms: dysphoric mood; nausea or vomiting; muscle aches; lacrimation or rhinorrhea; pupillary dilation, piloerection, or sweating; diarrhea; yawning; fever; insomnia)

Must meet 2 criteria

OUD scale

2-3: mild

4-5: moderate

6+: severe

Don't consider if taking opioids under medical supervision

Risk factors for OUD

- Personal history of SUD (including tobacco use)
- Younger age: 90% of all addictions manifest by age 35*
- Psychiatric illness-depression, anxiety, PTSD, childhood adversity, antisocial personality disorder
- Family history of SUD

Starr TD. Substance abuse in cancer pain. Current Pain and Headache Report 2010.

Complex persistent opioid dependence (CPOD)

- Shares many features with OUD.

- Develops in the setting of opioid therapy that has not been effective
- Consider when tapering efforts are not effective

Ganguly A. et.al. Cancer pain and opioid use disorder. Psycho-oncology. 2022

Complex persistent opioid dependence

- May exhibit symptoms of *pseudoaddiction* –
  - "*iatrogenic, mimics behaviors and symptoms of addiction but due to inadequate pain control*"

Ganguly A. et.al. Cancer pain and opioid use disorder. Psycho-oncology. 2022

Nonmedical use of opioid: Use of Opioids

- Without a prescription,
- With a prescription but not as Rx
- Use primarily for the purposes of the experience
- Includes chemical coping -the use of opioids to treat psychological distress.

All addicts are chemical copers but not all chemical copers are addicts.

Arthur J. Balancing opioid analgesia with nonmedical opioid use in patients with cancer. Nature Reviewed Clinical Oncology 2019.

NMUO in cancer patients

- Increases risk for adverse effects including substance use disorder, overdose, and death.
- Higher risk for dose escalation
- Among cancer patients, rate is estimated rate 18-20%

Ulker E. *Best practices in the management of nonmedical opioid use in patients with cancer-related pain*. The Oncologist 2020

Risk for long-term opioid use: could opioids promote cancer progression?

- Prostate cancer with high MOR expression linked to worse OS
  - VA study of 115 men with IV prostate cancer

Prostate Tumor MOR expression	HR shorter PFS	Shorter OS
High vs Low	1.65 [1.33-2.07]	1.55[1.20-1.99]

Zylla D. et.al. Opioid requirement, opioid receptor expression and clinical outcomes in patients with advanced prostate cancer. Cancer 2013.

Nelson Pain 2020

- SEER-Medicare database
- 2884 patients lobectomy for stage I NSCLC
- Persistent opioids use = ongoing refills 3-6 months after surgery; 27%

	5 –year overall survival
Without Persistent Opioid use	74.1% [71.2-76.7]
Persistent Opioid use	62.9% [58.5-67.0]

	Cancer-Specific survival
Without Persistent Opioid use	85.9% [83.5-87.9]
Persistent Opioid use	78.0% [73.8-81.6]

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Nelson D. Persistent opioid use is associated with worse survival after lobectomy for stage I NSCLC. Pain 2020

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Nelson Pain 2020

	Decreased overall survival
OME	**HR [95% CI]**
1st quartile (<300 OME)	1.27 [0.93-1.72]
2nd quartile (300-800 OME)	1.53 [1.14-2.03]
3rd quartile (800-1925 OME)	1.39 [1.04-1.83]
4th quartile (> 1925 OME)	2.50 [1.95-3.21]

Nelson D. Persistent opioid use is associated with worse survival after lobectomy for stage I NSCLC. Pain 2020

Strategies for managing chronic pain in cancer survivors

Case: complex persistent opioid use

- DS is 59 yo NHW male diagnosed with BRAF+IV melanoma of R UE.
- Dx in 2009 for which he received temozolimide, RT, AND.
- Given advanced stage at diagnosis he was on maintenance immunotherapy with ipilumumab 3/2013.
- He presented to CS 10/22 on the following medications:
  - Oxycodone 30 mg po Q4
  - Neurontin 600 mg po QHS
  - Morphine 90 TID
  - **Total 540 MME**

ASCO Opioid Recommendations

- *Clinicians may prescribe a trial of opioids in carefully selected cancer survivors with chronic pain who do not respond to more conservative management and who continue to experience pain-related distress or functional impairment.*

Paice JA. *Management of chronic pain in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guidelines.* JCO 2016.

Table 6. Risk Stratification and Adherence Monitoring

Action	Low Risk	Moderate Risk	High Risk
Risk stratification*	No history of alcohol abuse or drug abuse, no family history of alcohol or drug abuse No history of a major psychiatric disorder Older age No smoking Stable social support	Remote history of alcohol or drug abuse History of addiction with a sustained period of recovery and a strong system to help sustain recovery Questionable family history of alcohol or drug abuse History of major psychiatric disorder that has been managed effectively Younger age Smoking History of physical or sexual abuse Lack of social support Involvement with others engaging in drug abuse	Recent history, or multiple episodes, of alcohol or drug abuse History of addiction with limited or no system to sustain recovery Strong family history of alcohol or drug abuse History of major psychiatric disorder
Adherence monitoring and mitigation	At least annual adherence monitoring Monitoring should usually include: detailed interviewing about drug-related behavior questioning of family member and record review from other treating physicians check of prescription monitoring program urine drug screen	At least semiannual adherence monitoring (more frequent at higher levels of assessed risk) Monitoring should usually include: detailed interviewing about drug-related behavior questioning of family member and record review from other treating physicians check of prescription monitoring program urine drug screen	Adherence monitoring at least every 2-3 months and more frequent visits Monitoring should usually include: detailed interviewing about drug-related behavior questioning of family member and record review from other treating physicians check of prescription monitoring program urine drug screen pill counts
Respond to aberrant behaviors	Reconsideration of treatment to determine whether nonopioid therapies can be better used	Reconsideration of treatment to determine whether nonopioid therapies can be better	Reconsideration of treatment to determine whether nonopioid therapies can be better used Refills limited or not permitted Small frequent prescriptions No concurrent use of more than one opioid (eg, no prescription of a second short-acting drug for breakthrough pain in those prescribed a long-acting drug for daily use) Mandated consultation with addiction specialists/psychiatrist

*The level of risk conferred is indicated by the presence of one or more factors itemized in the corresponding risk categories.

How do we stratify risk?

- Risk stratification tools originally used in non-cancer patients have been validated in cancer patients
  - Screener for opioid assessment for pain patients (SOAPP)
  - Opioid Risk Tool

Screener for opioid assessment for patients with pain (SOAPP)

SOAPP- R -24 questions

Cuff off 18

sensitivity 81%

specificity 68%

SOAPP –SF

version 1 has 14 question

abbreviated SF with 5 questions:

sensitivity 86% specificity 67%

Opioid risk tool: risk for opioid misuse

Mark each box that applies	Female	Male
Family history of substance abuse		
Alcohol	1	3
Illegal drugs	2	3
Rx drugs	4	4
Personal history of substance abuse		
Alcohol	3	3
Illegal drugs	4	4
Rx drugs	5	5
Age between 16—45 years	1	1
History of preadolescent sexual abuse	3	0
Psychological disease		
ADD, OCD, bipolar, schizophrenia	2	2
Depression	1	1
Scoring totals		

4-7: Moderate Risk
8+: High Risk

Risk stratify DS using ORT

Mark each box that applies	Male
Family history of substance abuse	
Alcohol	3
Illegal drugs	3
Rx drugs	4
Personal history of substance abuse	
Alcohol	3
Illegal drugs	4
Rx drugs	5
Age between 16—45 years	1
History of preadolescent sexual abuse	0
Psychological disease	
ADD, OCD, bipolar, schizophrenia	2
Depression	1
Scoring totals	

45 yo at diagnosis

- Fhx ETOH use
- Personal hx ADD-not on meds

SCORE: 6

How should we be managing pain in CS

Table 2. Management of pain in cancer survivors

Assess pain, function, and risk of misuse

Develop a r… …ioids if feasibl…

Stratify risk…

Weigh the …

If prescribing opioids, use the lowest dose to achieve function goals

Employ universal precautions and monitor for aberrant use

Avoid the use of other sedating drugs, particularly benzodiazepines

Taper opioids gradually when feasible

Employ Universal precautions and monitoring for aberrant use

Paice JA. Pain in cancer survivors: how to manage. Curr Treat Options in Oncol 2019.

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Monitoring patients

- Performing periodic Urine tox screen –with confirmatory testing
- NCCN -Current Opioid Misuse Measure (COMM)
  - Self-administered questionnaire of 17 questions
    - Scored 0-68; >=13 cutoff
  - Assess 5 domains:
    - 1) Signs and symptoms suggestive of aberrant use
    - 2) Evidence of lying
    - 3) Medication misuse patterns
    - 4) Problems with appointments
    - 5) Problems with emotional regulation

Best practices: managing high-risk behaviors

- More frequent visits,
  - If needed: medication dispensing as often as once per day, pill counting
- Refer to pain psychologist, addiction specialist
- Using medication with lower diversion potential such as methadone, buprenorphine
- When opioids no longer needed –decrease 10% per month

Conclusions

- Disease-free cancer survivors experience chronic pain
- Growing proportion of disease-free CS remain on chronic opioids
- Risk versus benefit of long-term opioid use is unclear
- Risk stratifying patients should occur prior to initiation of opioid therapy
- Universal precautions should be employed
- CS should be educated on opioid safety
- Chronic pain management should ideally be multimodal with a multidisciplinary team approach

QUESTIONS?