Prescribing Opioids for Pain in Serious Illness

Allen Hutcheson MD

Southwestern Vermont Medical Center

2023 Spring Palliative Care Virtual Series

True or False

- **The effectiveness of opioid medications for treating chronic cancer pain has been demonstrated by well-designed studies.**

True or False

- **Patients with cancer-related pain are required to sign informed consent prior to the first opioid prescription under Vermont's 2019 opioid prescribing rule.**

Choose A or B

Which is a better statement to use when discussing pain management strategy with a patient?

A “I would really like you to take this medication. I want to help you,”

B “You really need to take this medication. We have ordered it for you, because we all care about you.”

Learning Objectives

- Choose an opioid to treat pain in seriously ill patients based on current guidelines and risk profiles.
- Follow Vermont regulations when prescribing opioids for cancer pain or palliative care.
- Use an empathic communication technique when treating seriously ill patients with complex pain.

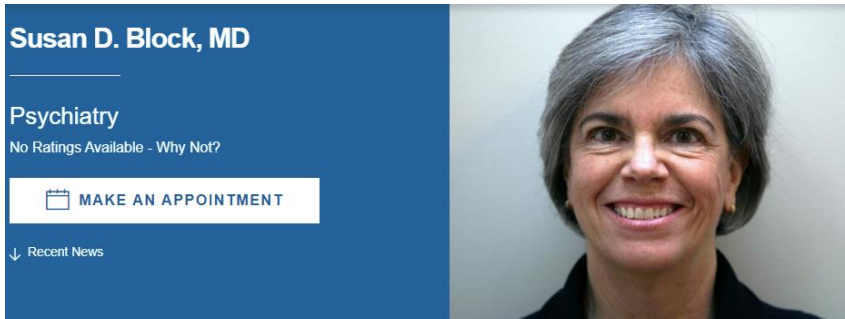
Fascinating topics not covered

- Pain pathophysiology
- Multimodal pain management
- Opioid pharmacology
- Diagnosis and treatment of opioid use disorder
- Pain management in patients with tolerance or opioid use disorder
- Management of opioid withdrawal
- Opioid non-pain treatment

- *Serious illness is a health condition that carries a high risk of mortality and either negatively impacts a person's daily functioning or quality of life or excessively strains his or her caregivers.*

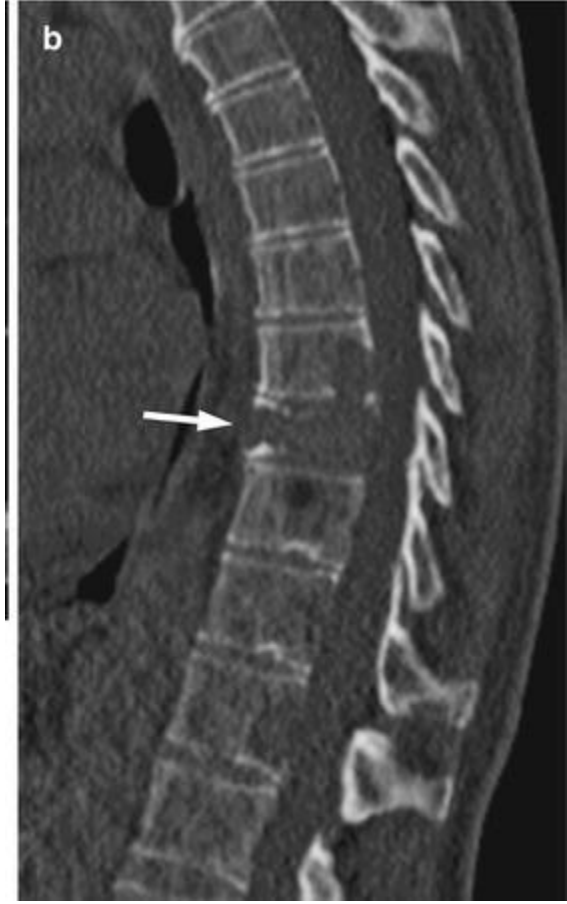
Title: Deputy Director, NIA
Office(s): Office of the Director (OD)
Email Address: amy.kelley2@nih.gov

While numerous approaches to identifying this population have been explored, so far they tend to be better at identifying patients who are closer to death, after multiple hospitalizations or significant functional decline. We need more inclusive approaches that allow patient identification to occur earlier on the illness continuum. At the same time, inclusion criteria need to be narrow enough that it is realistic for busy clinicians to focus enhanced attention of this population.



Pain in Serious Illness

- **Cancer**

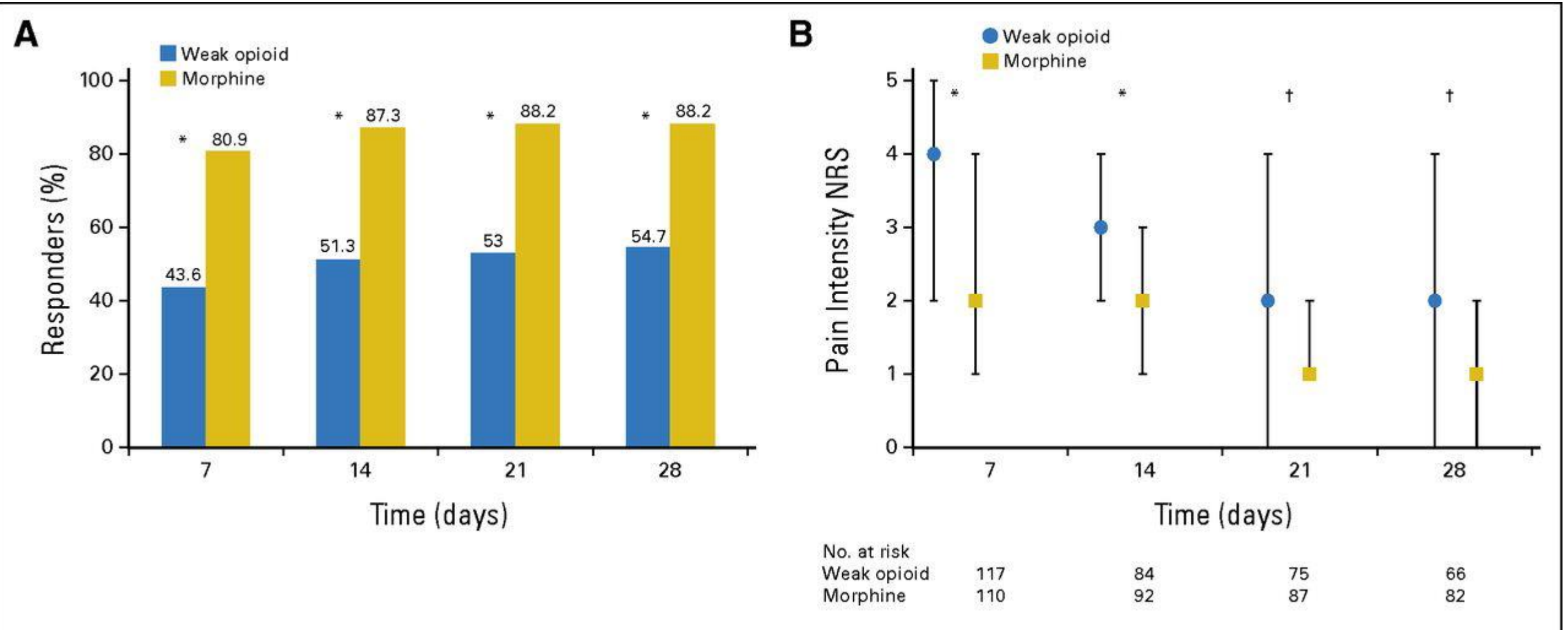


- Neurologic disease
- COPD:
  - chest and upper back pain 4-5 times more frequent than in controls.
- CHF
  - refractory angina or ischemia
- Renal or hepatic failure:
  - neuropathy, comorbidities, calciphylaxis.

Use of Opioids for Adults with Pain from Cancer or Cancer Treatment: JCO Feb 2023

- **RECOMMENDATIONS**
- Opioids should be offered to patients with moderate-to-severe pain related to cancer or active cancer treatment unless contraindicated.
- Opioids should be initiated PRN (as needed) at the lowest possible dose to achieve acceptable analgesia and patient goals, with early assessment and frequent titration.
- For patients with a substance use disorder, clinicians should collaborate with a palliative care, pain, and/or substance use disorder specialist to determine the optimal approach to pain management.
- Opioid adverse effects should be monitored, and strategies are provided for prevention and management.

Skip the **second** WHO ladder rung in cancer and serious illness: opioid+acetaminophen ("weak opioid")



Use of Opioids for Adults with Pain from Cancer or Cancer Treatment: Evidence Base

- Cites 16 RCT involving opioids for cancer pain
- Opioids vs opioids: 11
- Opioid vs non-opioid: 1
  - Pregabalin vs fentanyl for neuropathic syndrome x28 days. (57)
    - (pregabalin was superior)
- Opioid vs placebo: 2
  - transmucosal fentanyl (50): duration= 9 tablets
  - Transmucosal fentanyl spray (58): followup time= 60 minutes
- Meds to treat opioid SE (nausea, constipation): 2

A systematic review of randomized trials on the effectiveness of opioids for cancer pain

Pain Physician. 2012 Jul;15(3 Suppl):ES39-58.

- **Results:** The level of evidence for pain relief based on the USPSTF criteria was fair for transdermal fentanyl and poor for morphine, tramadol, oxycodone, methadone, and codeine.
- **Limitations:** Randomized trials in a cancer setting are difficult to perform and justify. There is a paucity of long-term trials and this review included a follow-up period of only 4 weeks.

- Cochrane Review 2016: Oral morphine for cancer pain
  - The quality of the evidence is generally poor. Studies are old, often small, and were largely carried out for registration purposes and therefore were only designed to show equivalence between different formulations.

- Which medication to start with?

- The literature on opioid comparative efficacy and effectiveness [71] precludes an evidence-based approach to opioid selection. Accordingly, recommendations continue to be based on clinical experience.

Portenoy et al, *UpToDate*

Prescribing based on guidelines

- Underlying problem evaluation and treatment
- Risk evaluation
- Drug choice
- Starting dose
- Titration
- Monitoring
- Side effect management
- Tapering

Russell K. Portenoy, MD
Executive Director, MJHS Institute for Innovation in Palliative Care
Chief Medical Officer, MJHS Hospice and Palliative Care
Professor of Neurology and Family and Social Medicine, Albert Einstein College of Medicine

Cancer pain management with opioids: Optimizing analgesia

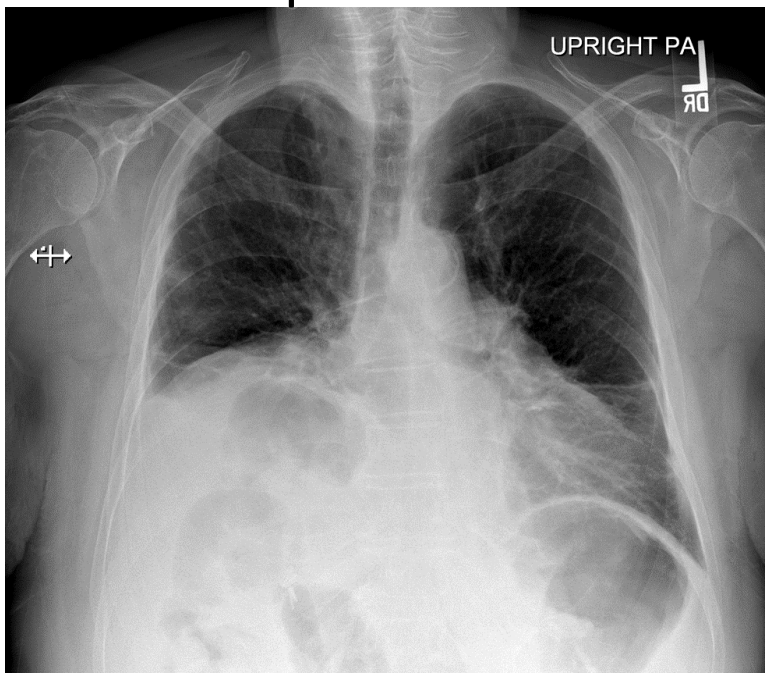
(*UpToDate*)

AUTHORS: Russell K Portenoy MD, Zankhana Mehta MD, Ebtesam Ahmed PharmD, MS

- Randomized trials and systematic reviews have failed to demonstrate the superiority of morphine over any other mu agonist(hydromorphone, oxycodone, oxymorphone, fentanyl, or methadone) in terms of efficacy or tolerability [2-9].
- Furthermore, there is very large intraindividual variation in the response to the different mu agonist drugs and no way to predict whether a patient will have a more favorable balance between analgesia and side effects when given morphine or one of the other drugs, unless a previous response to a specific drug helps to guide the choice of agent [2].

“The most important X-ray is the old X-ray.”

April 2023



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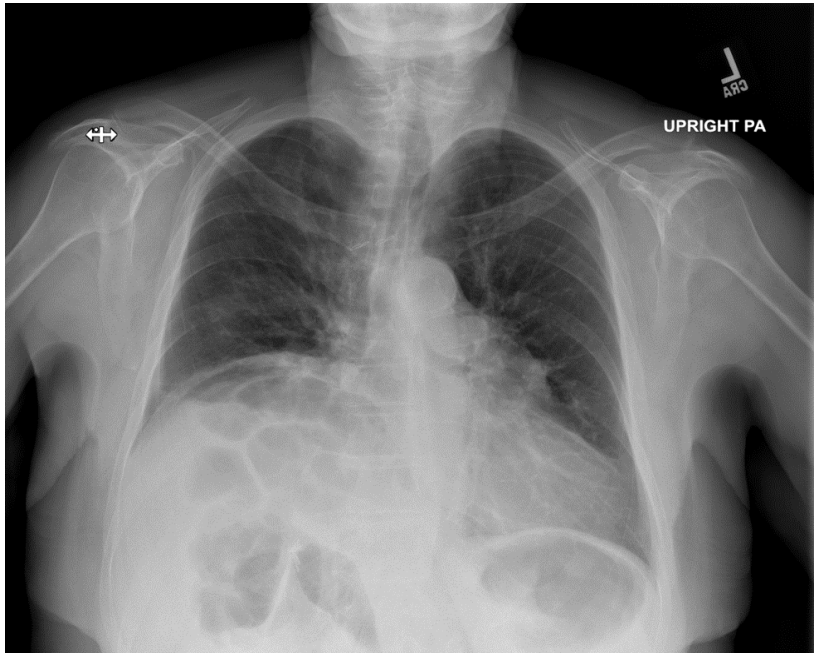


The most important **Opioid** is the old **Opioid**.

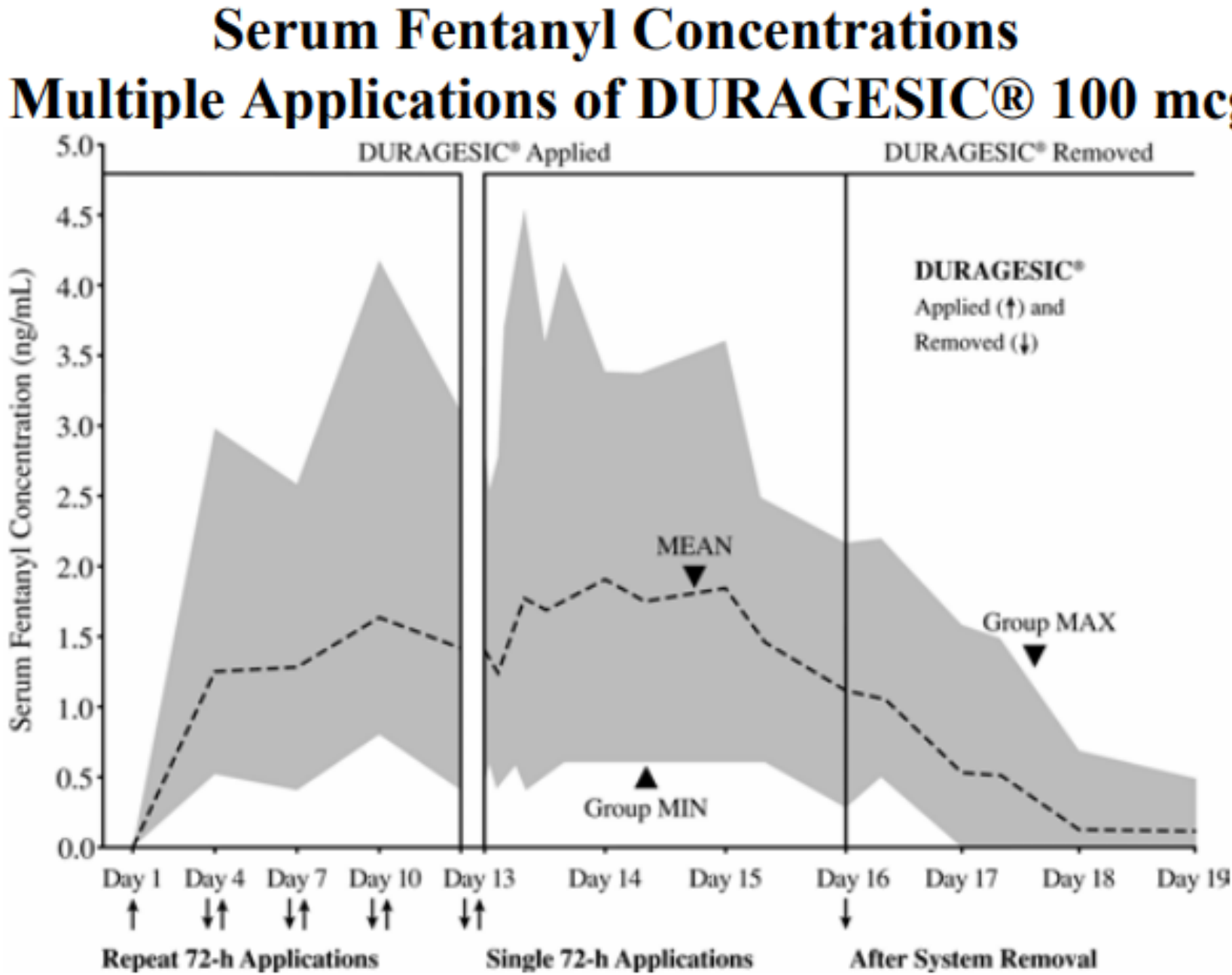
- For most patients with cancer pain who are relatively opioid naïve, we prefer a single-entity pure mu agonist at a low dose. Options include oral morphine (5 to 10 mg orally every three to four hours), oral oxycodone (2.5 to 5 mg orally every four hours), hydromorphone (1 to 2 mg orally every three to four hours), or transdermal fentanyl (12 mcg/hour every 72 hours).
- Methadone is another option. To start therapy in opioid-naïve patients, some palliative care clinicians prescribe a low fixed-dose regimen…

Portenoy et al, *UpToDate*

Fentanyl patch initiation: FDA prescribing info:

- 2.3 Initial Dosage
- Do not initiate treatment with DURAGESIC in opioid nontolerant patients [see Contraindications (4)]. The recommended starting dose when converting from other opioids to DURAGESIC is intended to minimize the potential for overdosing patients with the first dose. Discontinue all other around-the-clock opioid drugs when DURAGESIC therapy is initiated. While there are useful tables of opioid equivalents readily available, there is substantial inter-patient variability in the relative potency of different opioid drugs and products.

Fentanyl patch is slow…



Patients with kidney impairment: drugs to avoid

- Meperidine (Demerol) should not be used, since its active metabolite, normeperidine, accumulates with renal dysfunction and can cause serious central nervous system (CNS) toxicity.
- Morphine is metabolized in part to a potent opioid metabolite, morphine-6-glucuronide, and a metabolite, morphine-3-glucuronide, which is associated with neurotoxicity. These metabolites are renally excreted and there is concern that their accumulation in patients with renal insufficiency may lead to unanticipated changes in morphine potency or side effects [76].
- Oxycodone may be used among patients with kidney impairment but, like morphine, raises concerns about the impact of renally-excreted metabolites that may accumulate in this setting.
- Both codeine and tramadol can accumulate in patients with kidney impairment, enhancing both their effects and side effects.

It should be noted that these recommendations are largely based upon pharmacokinetics and clinical experience; there is very little high-quality clinical evidence to support opioid choice in patients with kidney impairment [75].

“Only IV Dilaudid helps my pain”

Approximate dose conversions for commonly used opioids (refer to important notes below)					
Morphine		Hydromorphone (Dilaudid)		Oxycodone	Fentanyl transdermal*
IV (mg/day)	Oral (mg/day)	IV (mg/day)	Oral (mg/day)	Oral (mg/day)	Patch (mcg/hour)
5	15	0.75	3.5	10	NA
8.5	25	1.25	6.5	15	12
10	30	1.5	7.5	20	12
17	50	2.5	12.5	30	25
33	100	5	25	65	50
50	150	7.5	37.5	100	75
67	200	10	50	130	100
83	250	12.5	62.5	165	125

Patients with kidney impairment

- **Preferred drugs** — Preferred opioids in the setting of kidney impairment may be those whose metabolism does not pose an increased risk:
- Hydromorphone, for example, has active metabolites but these are produced in relatively low concentration (compared with morphine) and may be less likely to cause unanticipated effects in the setting of kidney impairment. Although this drug is often selected for this reason, it is important to recognize that accumulating metabolites can cause problems, particularly with higher doses [79-81].
- Fentanyl, buprenorphine, and methadone lack active metabolites and also are considered in the setting of kidney impairment on this basis. Although methadone is another option for patients with chronic kidney impairment, concerns about the risks associated with methadone, however, speak against the use of this drug in patients who may be metabolically unstable

Mixed-mechanism drugs: Tramadol and Tapentadol
Mu-agonist + SNRI

- A Cochrane review of four randomized trials of tapentadol compared with either placebo or an active control in 1029 adults with moderate to severe cancer pain concluded that there were insufficient data for pooling and statistical analysis of the four trials [55]. Overall, there was low quality evidence that tapentadol was no more or no less effective for pain relief than morphine or oxycodone, and there was no advantage of tapentadol in terms of serious adverse events.
- Similarly, a Cochrane review of 10 studies comparing tramadol with either placebo or an active control in 958 adults with moderate to severe cancer pain concluded that there was limited, very low-quality evidence from randomized trials that tramadol produces pain relief in some adults with pain due to cancer, and very low-quality evidence that it is not as effective as morphine [56].

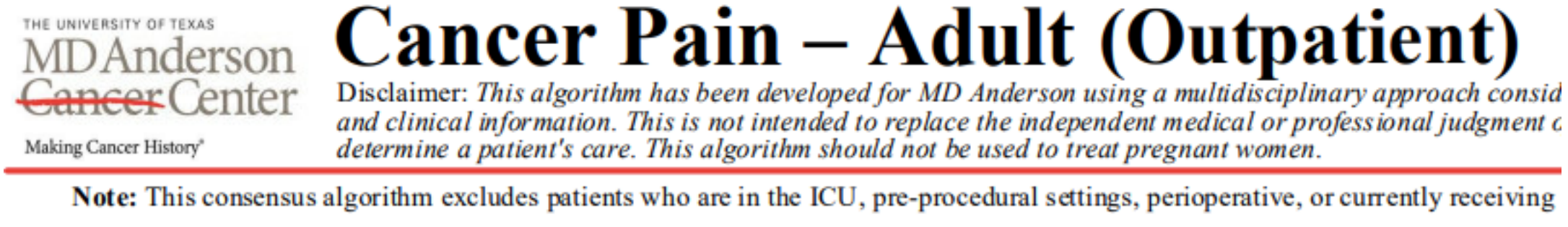
Mixed agonist-antagonist drugs

- Portenoy et al: Because it has the capacity to induce withdrawal in opioid-tolerant patients, we reserve the use of buprenorphine for individuals with new-onset, moderate or severe cancer pain, and limited or no prior opioid treatment. It may be particularly useful in those with kidney impairment or when the potential for respiratory depression is a concern. Beside buprenorphine, we generally suggest not using drugs of the mixed agonist-antagonist group (butorphanol, dezocine, pentazocine, and nalbuphine) for cancer pain management.
- Cochrane: five studies found that buprenorphine was superior to the comparison treatment. Three studies found no differences between buprenorphine and the comparison drug, while another three studies found treatment with buprenorphine to be inferior

Opioid Titration

- Start with the lowest standard dose
- Oxycodone 5, hydromorphone 2, morphine 7.5
- Assess response and side effects
- Increase if pain uncontrolled after 4 dose intervals (24-72h)
- Increase dose by 30-50% until pain adequately controlled or significant side effects.

- Anticipate some high metabolizers
- Offer an ultra-low dose start in opiophobia



Long-acting opioids

- Consider prescribing a long-acting formulation if pill burden, frequent schedule, or night-time pain are concerns.
- No good data to support improved pain control in cancer or noncancer patients

- In-stock, covered by insurance, straightforward options are: morphine extended release and fentanyl transdermal.
- Relatively unobtainable: Oxycontin (oxycodone ER), Exalgo (hydromorphone ER)

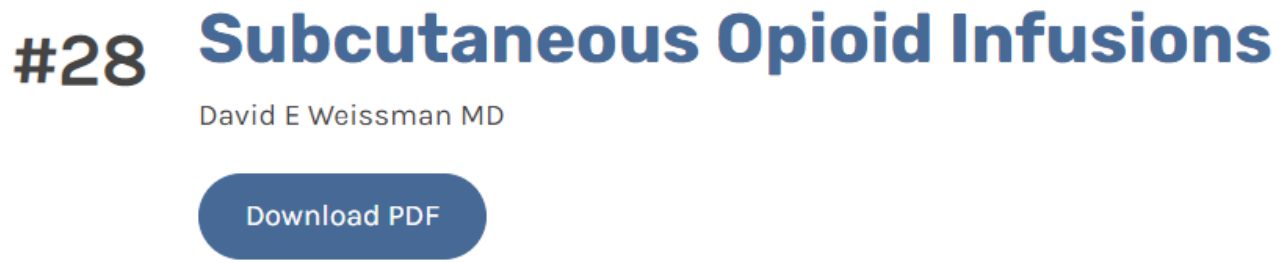
- Breakthrough short-acting medication
  - 5-15% of daily equivalent dose

Drug choice summary

- First line: oxycodone, hydromorphone, morphine
- Long-acting: MSContin or fentanyl transdermal
- Renal/ hepatic concerns: hydromorphone or fentanyl transdermal
- Oral administration concerns: fentanyl, liquid formulations

- Getting creative, and doing prior auths:
  - Methadone, oxycontin, buprenorphine, fentanyl transmucosal
- Rarely:
  - Oxymorphone, meperidine, levorphanol, tramadol

Other routes of administration: oral intensol, rectal, subcutaneous



- Though there are a limited number of commercially available drugs specifically manufactured for rectal administration, any pill can be given rectally.

- Morphine, hydromorphone (Dilaudid), fentanyl, and sufentanil can all be safely administered as SQ bolus doses or continuous SQ infusion.

Bowel Regimen

- Preventive and PRN meds for every patient
  - Regimen: Colace 300hs, Senna 2 daily, Miralax 17g qd prn
  - PAMORA: nalexagol (Movantik), naldemedine (Symproic)
    - For refractory cases; caution if bowel not intact

- Even if I have diarrhea?
  - Prescribe and hold
- I am already taking Metamucil.
  - Bulk-forming laxatives, which are considered safe in most cases of constipation, can be harmful to patients with OIC. The lack of peristaltic movement caused by opioids, accompanied by fiber-increased fecal bulk, can exacerbate abdominal pain, and in some cases, contribute to bowel obstruction.

Adverse effects

- Side effect assessment and treatment
  - Itching: antihistamines, paroxetine, gabapentin (clinical exp)
  - Nausea: metoclopramide, prochlorperazine, ondansetron
  - Myoclonus: benzodiazepine low dose
  - Somnolence: methylphenidate*, modafinil
  - Urinary retention: tamsulosin, catheterization
- Opioid dose reduction plus adjuvant
- Opioid rotation

*clinical trials

Complications

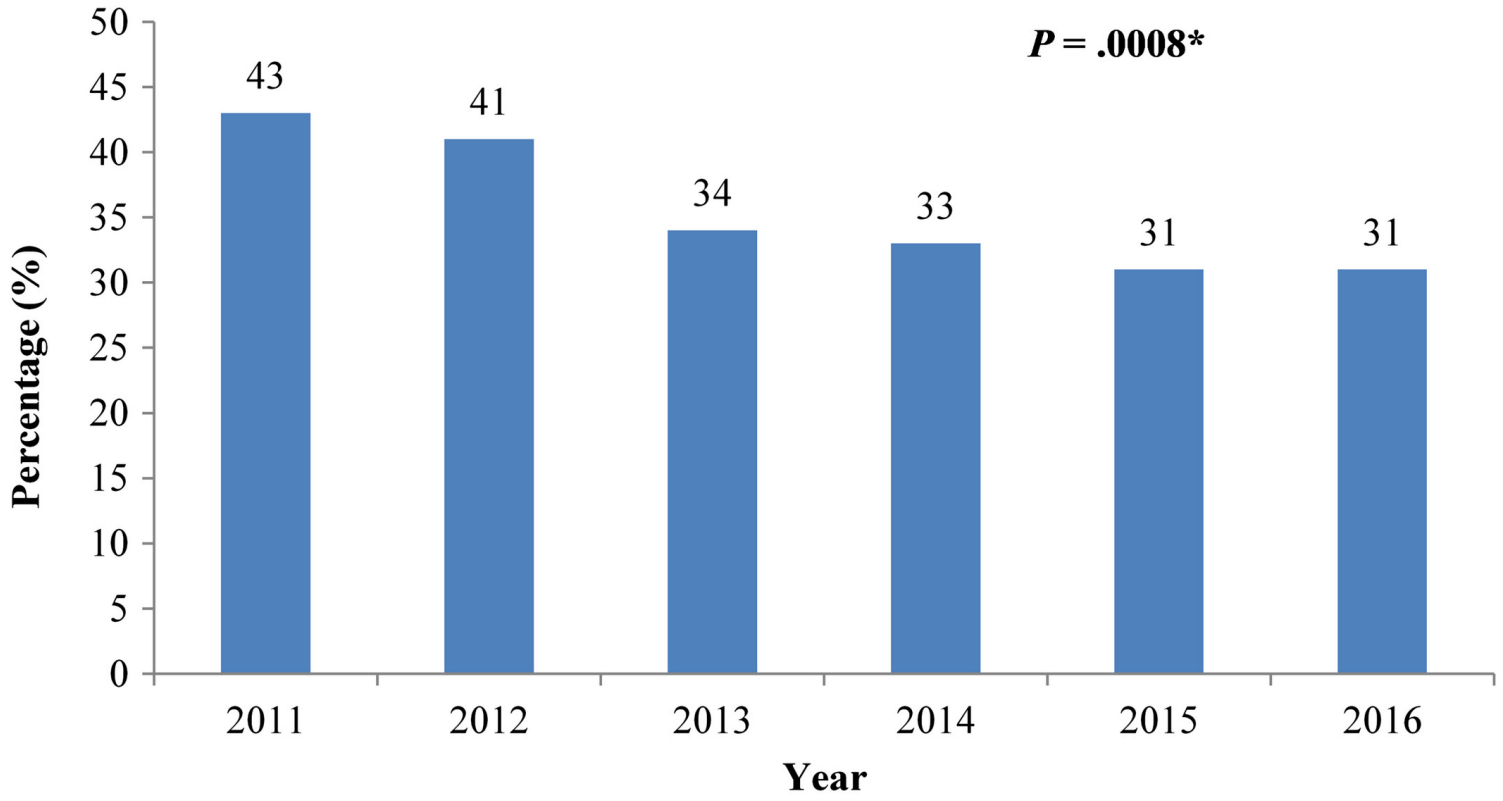
- Respiratory suppression
- Urinary retention
- Pneumonia or serious infection
- Sleep-disordered breathing
- Hypogonadism
- Opioid-induced hyperalgesia

Can I drive while taking pain meds?

- I counseled the patient regarding data on driving risk while using stable doses of opioids.

- Three simulated and one monitored driving test in noncancer patients on opioids, and one utilizing neurologic testing in cancer patients on or off opioids found no significant driving problems in patients on stable doses.
- One study showed at-fault drivers in fatal accidents were more likely to test positive for prescription opioids.
  - 5% vs 3%. They were prescription opioids but the study had no way to determine if they were prescribed. (alcohol was 29 vs 10% and both was 1 vs 0.3%) N=36,642

Opioids with benzodiazepines



*Significant trend over time using Cochran-Armitage Trend Test

Concurrent use of opioids with benzodiazepines or nonbenzodiazepine sedative hypnotics at the time of the initial palliative care consultation over a 6-year period (2011-2016).

Opioid misuse risk

- Risk Assessment
  - Personal or family history of alcohol or drug abuse
  - Psychiatric disorder
  - History of incarceration
  - MAT for substance use disorder
- Risk Reduction
  - Frequent prescription with small quantity
  - Signed opioid agreement
  - Periodic drug testing
  - Drug choice: fentanyl, methadone, buprenorphine
- Communicating constructively

Vermont Rule Governing the Prescribing of Opioids for Pain

- Section 4
- Universal precautions (prior to first prescription)
  - Consider non-opioids
  - Query VPMS
  - Discuss risks in detail
  - Provide DOH education sheet
  - Signed informed consent

- <u>Exemption</u>
  - Hospice-eligible patients

Vermont Rule Governing the Prescribing of Opioids for Pain

- Section 5
- Acute pain
  - First prescription dose limit: see charts
    - 50MME, 7 days for severe cancer pain
  - No long-acting forms
  - Communicate with primary care

- Exemptions
  - Hospice-eligible patients
  - Significant trauma
  - Complex surgery, Post-op complications
  - MAT
  - Not opioid naïve
    - Not more than 7 consecutive days in prior 30 days

Vermont Rule Governing the Prescribing of Opioids for Pain

- Section 6
- Chronic pain
  - Medical and physical evaluation
  - Document diagnoses
  - Misuse Risk assessment
  - Considered non-opioid alternatives
  - Trial of the opioid
  - Prior methadone buprenorphine or other contr sub?
  - Controlled substance agreement contract signed
  - Visit and eval at least every 90 days
  - MDD on prescription
  - Consultation if escalating dose or risk of misuse
  - Review contract yearly
  - In-person re-evaluation and assessment prior to exceeding 90MME

Exemptions

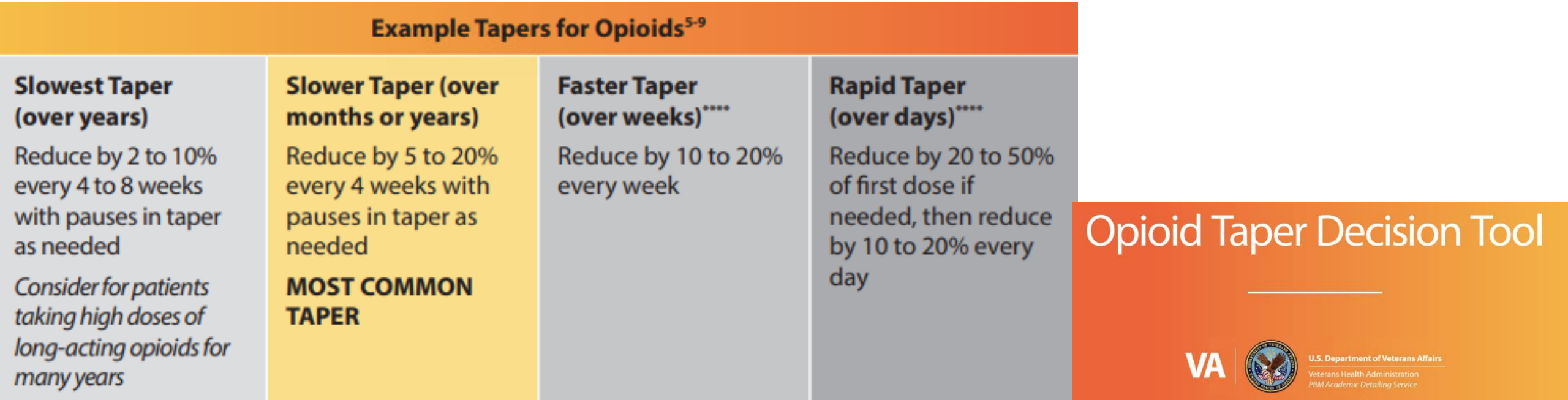
Cancer-related pain

Nursing home residents

Hospice-eligible patients

Tapering off opioids

- ASCO: Abruptly discontinuing opioids after long-term use has been shown to [correlate with] increase illicit substance use, emergency department visits, and deaths from overdose or suicide.[115-117] As a result, tapering opioid therapy must be conducted slowly, engaging patients throughout the process.[118]



"If it's any consolation, toward the end he was high as a kite."

Communication and pain: evidence review

Pain Med. 2018 Nov 1;19(11):2154-2165

- Matthias et al. [77] found that primary care physicians who demonstrated genuine concern for their patients' well-being were generally more highly regarded by patients, who in turn were more likely to accept a reduction or denial of opioid medications by their physicians.
- Two studies of patients with back pain found that patients were attentive to and valued clinicians who took them and their pain seriously [46,48].

Probing the Paradox of Patients' Satisfaction with Inadequate Pain Management

March 2002 Journal of Pain and Symptom Management

Table 3

Multiple Regression Analysis of Predictors of Satisfaction[a] with Pain Management: Overall and with Primary Care

	Overall		Primary Care Doctor	
Variable	Coeff.	*P*	Coeff.	*P*
Frequency that patient reported pain[b]	−1.93	0.000	−2.79	0.000
Pain went up, went down over last year[c]	2.62	0.124	0.97	0.611
Pain went down, stayed down over last year[d]	7.27	0.000	5.27	0.012
Patient told treating pain important goal[e]	5.32	0.000	5.28	0.000
Intensity of average pain during past three days[f]	−0.74	0.001	—	—
Belief that patients with pain cannot have good quality of life[g]	−0.81	0.007	—	—
Patient given instructions for managing pain at home[h]	—	—	3.67	0.010
Willingness to take opioid if prescribed and told not addicting[i]	—	—	1.78	0.020
Belief that people get addicted to pain medicine easily[g]	—	—	0.87	0.020
Belief that pain medicine cannot really control pain[g]	—	—	−0.88	0.012

28% in severe pain during the past three days but satisfied with pain management.

The Importance of Good Communication in Treating Patients' Pain

Anita Gupta, DO, PharmD

AMA J Ethics. 2015;17(3):265-267

- In accordance with the Golden Rule, we can take the following steps to improve communication:
- When entering the room of patients in pain, always tell them that you are there to help comfort them and to do your best to relieve their pain.
- Remain calm and show empathy.
- Express concerns for the patient's feelings.

Empathetic Listening

Honor the Patient Experience During Crisis

AMA | STEPSforward

The Importance of Good Communication in Treating Patients' Pain

Anita Gupta, DO, PharmD

AMA J Ethics. 2015;17(3):265-267

- Use "I" statements. For example, "I would really like you to take this medication. I want to help you," versus "You really need to take this medication. We have ordered it for you, because we all care about you." "You" statements often sound accusatory and can quickly alienate patients by provoking defensiveness and hostility. Use patient-centered interviewing and caring communication skills in daily practice.
- Even though it seems like a physical problem with a purely technical solution, treating the *patient* is an equally important part of treating *pain*.