Opioids

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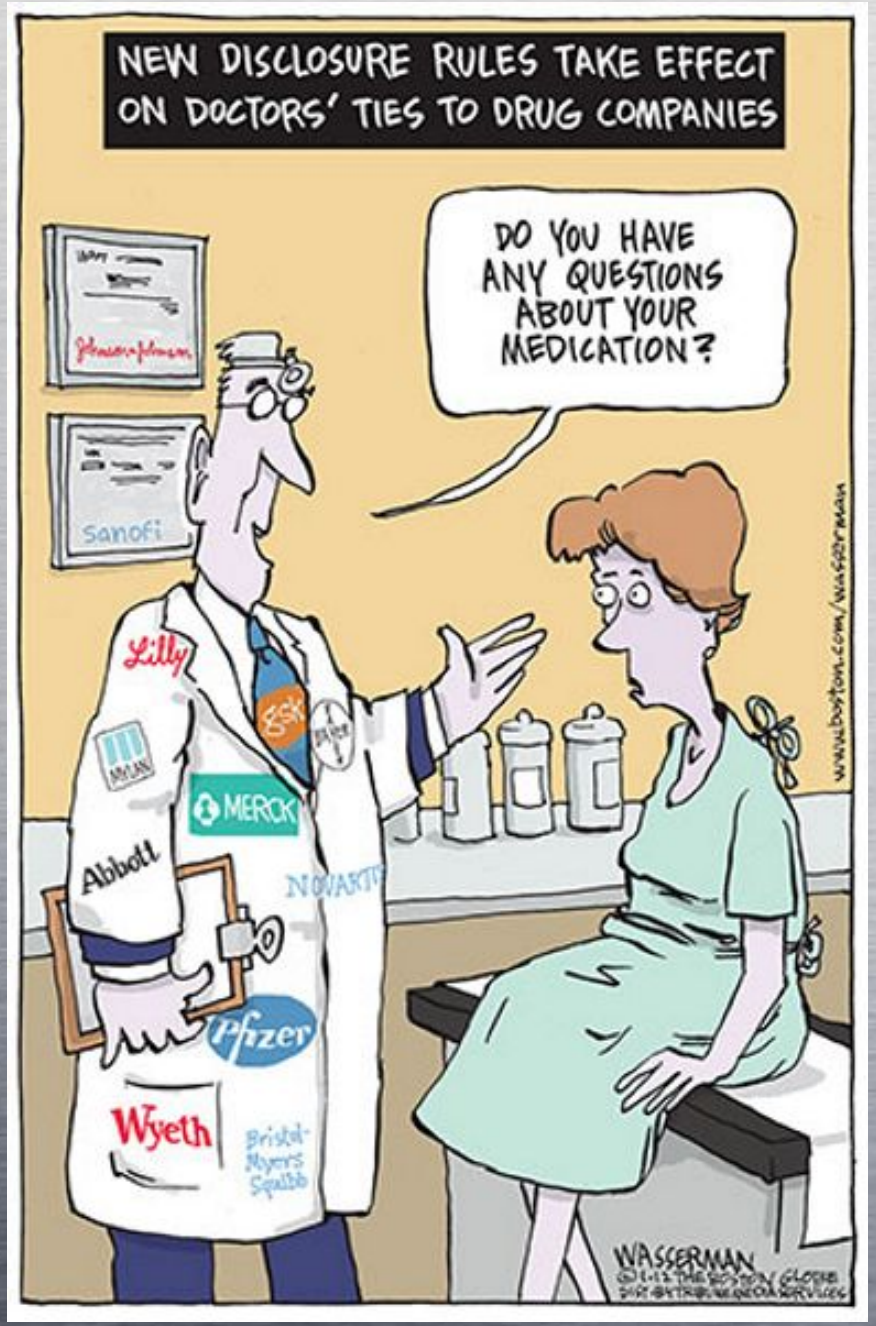
Knowledge that will change your wo



Disclosures

Dr. Bailey has no relevant financial conflicts of interest or disclosures.

Off Label use of medications will be clearly identified as such.

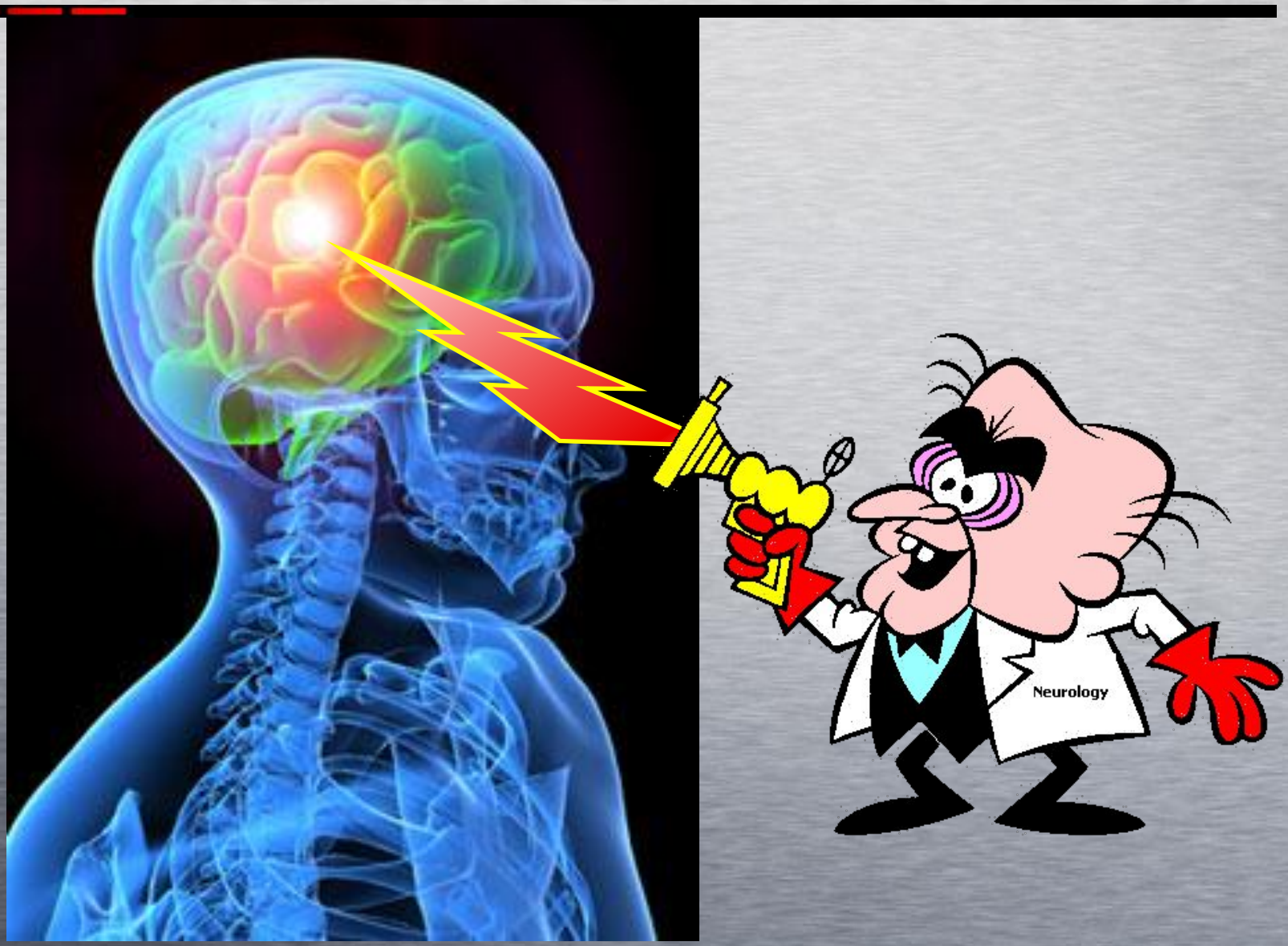
Objectives

- **Identify and better understand opioid taxonomy and nomenclature**
- **Know where and how opioids work**
- **Expand understanding of opioid kinetics and dynamics**
- **Know basic opioid dose conversion factors**
- **Better understand the uses and limitations of urine drug screening**
- **Introduce pharmacological management by reviewing non-opioid medications for pain management**
- **Discuss the importance of interdisciplinary pain management, including pain psychology and pain physical therapy**

Overview

- **Opioid Basics**
- **Opioid Effectiveness**
  - Acute
  - Chronic
- **When is the use of opioids appropriate?**
- **Evolving trends in pain management**
- **Prognostications**

Opioid Basics



Opioid Taxonomy

- **Opioids**
  - Synthetic
    - Fentanyl
    - Methadone
    - Tapentadol
    - Meperidine
  - Semisynthetic
    - Hydrocodone
    - Oxycodone
    - Hydromorphone
    - Oxymorphone
    - Buprenorphine

- **Opiates**
  - Natural
    - Morphine
    - Codeine
    - Endogenous

Opioid Nomenclature

- Narcotics – **an often misused term that has come to mean any illegal drug.**
- **By convention and common use, opioids are any drug that activates the bodys opioid receptors**
- **Legal definition includes opioids as well as cocaine and its derivatives**

Opioid Receptors

- Types
  - mu – subtypes 1-3
  - delta – analgesia, seizures at high doses
  - kappa – mu antagonist, dysphoria, ? addiction
  - epsilon – related to beta-endorphin
  - nociceptin – tolerance, but not analgesia
- Location
  - Brain
  - Spinal Cord
  - Digestive Tract
  - Peripheral

Duration of Action

- **Short-acting**
  - Morphine
  - Codeine
  - Hydrocodone
  - Oxycodone
  - Fentanyl
  - Oxymorphone
  - Hydromorphone
  - Tapentadol

- **Long-Acting**
  - Methadone
  - Levorphanol

- **ER-Formulations of short-acting drugs**

Advantage of one vs. the other?

Pure Opioid Agonists

Weak

- **Tramadol**
- **Codeine**
- **Propoxyphene**
- **Loperamide (Imodium)**
  - Peripheral Only

The terms ‘weak’ and ‘strong’ are rarely used in present-day nomenclature.

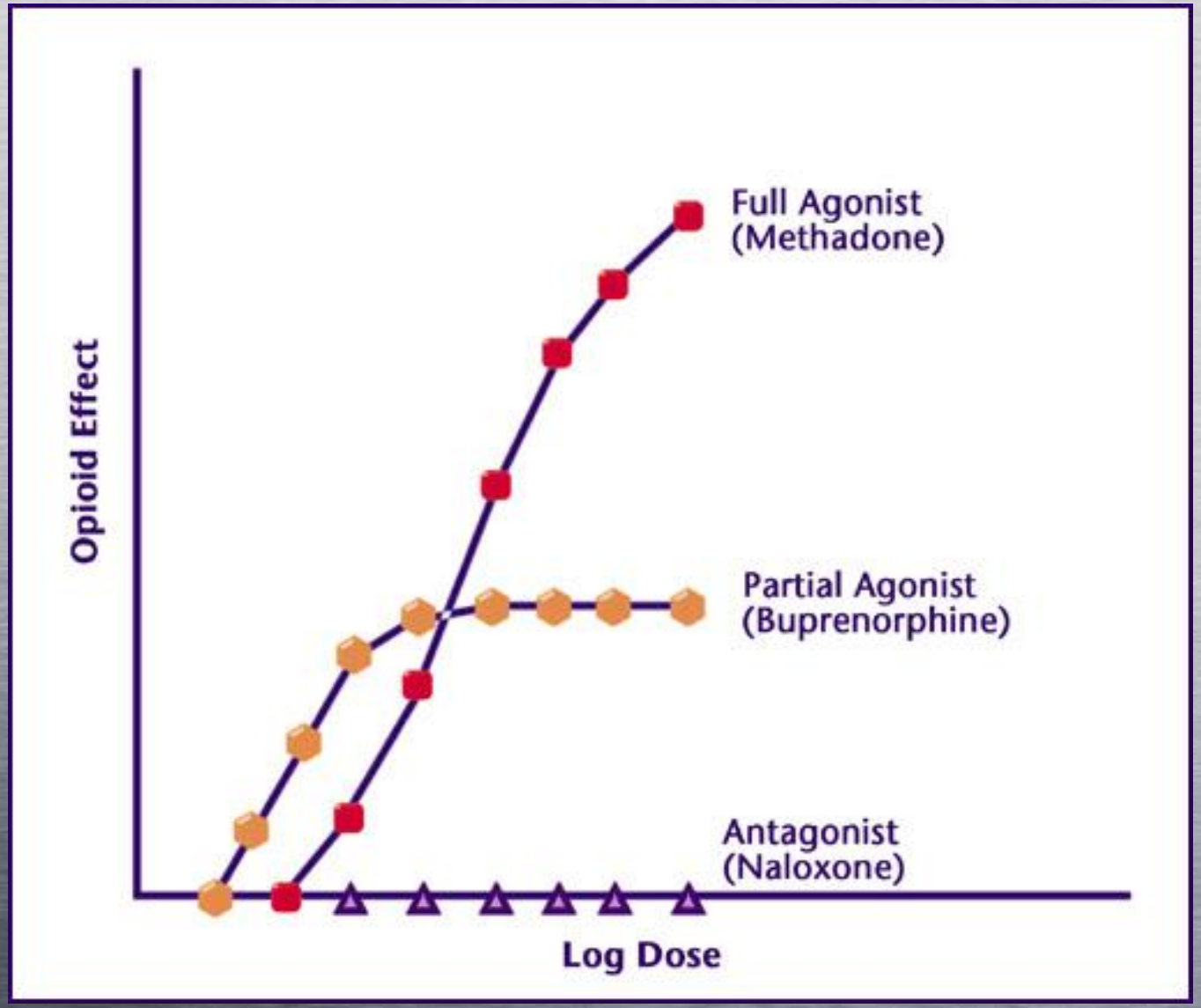
Strong

- **Morphine**
- **Hydromorphone**
- **Hydrocodone**
- **Methadone**
- **Oxycodone**
- **Oxymorphone**
- **Meperidine**
- **Tapentadol**
- **Fentanyl**

Opioid Partial Agonists

- **Butorphanol (Stadol)**
- **Nalbuphine (Nubain)**
- **Pentazocine (Talwin)**
- **Buprenorphine (Suboxone, Butrans)**

Ceiling Effect



Pure Opioid Antagonists

- **Central Acting**
  - Naloxone (Narcan)
  - Naltrexone (Trexan)
- **Peripheral Only**
  - Methylnaltrexone (Relistor)
  - Naloxegol (Movantik)

Multiple Receptors

- **Tapentadol**
  - Opioid
  - Noradrenergic reuptake inhibitor
- **Methadone**
  - Opioid
  - NMDA receptor antagonist
- **Tramadol**
  - Opioid
  - May be anti-inflammatory
  - May be anti-depressant (serotonin release)

Methadone

- Half-life for pain vs. toxicity
- Complex conversion from other opioids
- Volume of Distribution
- Elimination
- Drug Interactions
- Cardiac Toxicity
- 40mg tabs for inpatient or addiction only
- Medical / legal considerations
- Methadone Maintenance Clinics

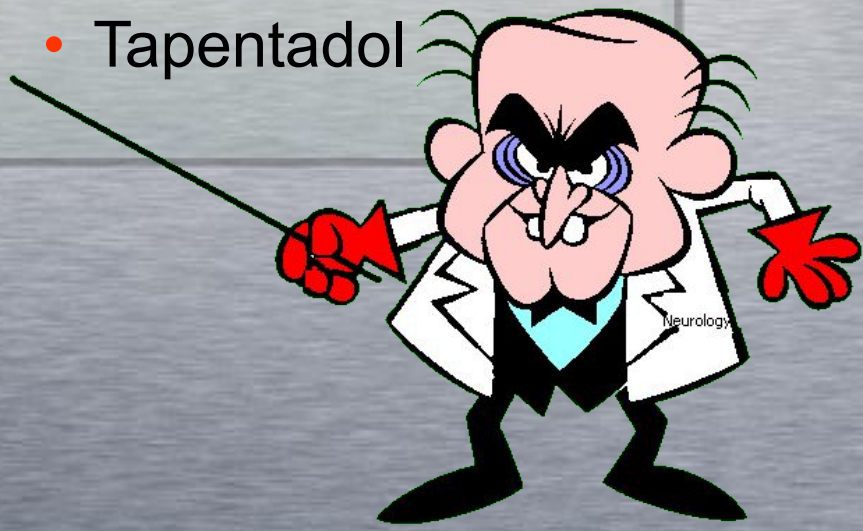
Less Familiar Formulations

- **Avinza (ER morphine)**
- **Butrans (transdermal buprenorphine)**
- **Exalgo (ER hydromorphone)**
- **Embeda (ER morphine + naltrexone)**
- **Kadian (ER morphine)**
- **Morphabond (ER morphine)**
- **Nucynta IR & ER (tapentadol)**
- **Opana IR & ER (oxymorphone)**
- **Short-acting Fentanyl Preparations**
- **Xartemis XR (ER oxycodone / ACP)**
- **Zohydro ER; Hysingla ER (ER hydrocodone)**

Opioid Metabolism

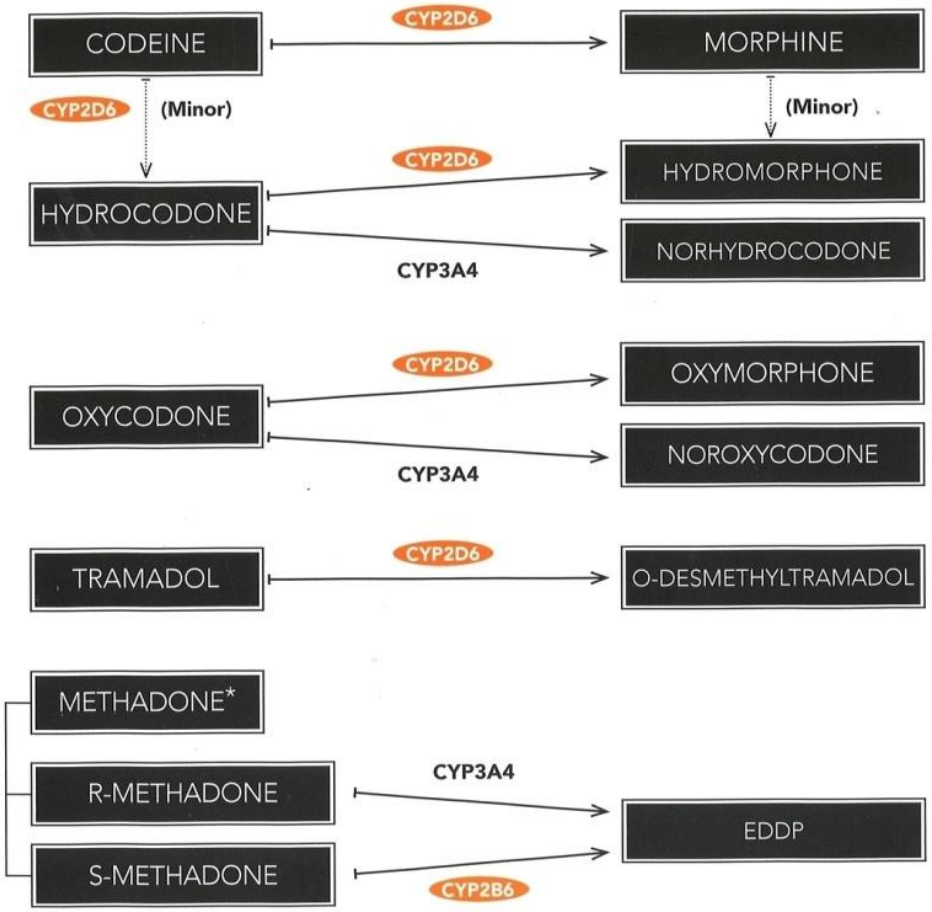
- **Pro-Drugs**
  - Hydrocodone
  - Codeine
  - Tramadol

- **Natively Active**
  - Morphine
  - Hydromorphone
  - Oxycodone
  - Tapentadol



Opioid Metabolism

PRIMARY OPIOID METABOLIC PATHWAYS[2,3]



*Lesser metabolic pathways for methadone also mediated by 2D6, 2C9, 2C19 to varying degrees

Major metabolic pathway

Minor metabolic pathway

= Tested by Millennium PGT

CYP = cytochrome P450

EDDP = 2-Ethylidene-1, 5-Dimethyl-3, 3-Diphenylpyrrolidine

PARENT DRUG	PRIMARY METABOLITES
CODEINE	Morphine, Hydrocodone (minor)
HYDROCODONE	Hydromorphone; Norhydrocodone
OXYCODONE	Oxymorphone, Noroxycodone
TRAMADOL	O-Desmethyltramadol
METHADONE (R- AND S-ISOMERS)	EDDP

(2) Adapted from Smith HS. Opioid Metabolism. *Mayo Clin Proc.* 2009; 84(7):613-624.
(3) Adapted from Trescot AM, et al. Opioid Pharmacology. *Pain Physician.* 2008;11(suppl):135S-153S.

Detection Times of Common Drugs

Amphetamines	• 48 hours
Barbiturates	• Short-acting (eg, secobarbital), 24 hours • Long-acting (eg, phenobarbital), 2–3 weeks
Benzodiazepines	• 3 days if therapeutic dose is ingested • Up to 4–6 weeks after extended dosage (≥ 1 year)
Cannabinoids	• Moderate smoker (4 times/week), 5 days • Heavy smoker (daily), 10 days • Retention time for chronic smokers may be 20–28 days
Cocaine	• 2–4 days, metabolized
Ethanol	• 2–4 hours
Methadone	• Approximately 30 days
Opiates	• 2 days
Phencyclidine	• Approximately 8 days • Up to 30 days in chronic users (mean value = 14 days)
Propoxyphene	• 6–48 hours

Gourlay DL, Heit HA. *Pain Med*. 2009;10 Suppl 2:S115-123.

SUBSTANCE FALSELY IDENTIFIED ON TEST	ACTUAL SUBSTANCE	TYPE OF STUDY	NOTES
Amphetamine and methamphetamine	Selegiline	Single case report[1,2]	L-stereoisomer only detected (D-stereoisomer present in illicit drugs)
Amphetamine and methamphetamine	Vicks Inhaler	Several case reports, controlled-exposure studies[1-3]	L-stereoisomer only detected; most positives noted with twice recommended dosage
Barbiturate	NSAIDs (ibuprofen, naproxen)	Controlled-exposure study of 60 subjects (510 specimens)[4]	0.4% false-positive rate
Benzodiazepine	Oxaprozin	Controlled-exposure study of 12 patients (36 specimens)[5]	100% false-positive rate, some cases lack controls
Cannabinoid	NSAIDs (ibuprofen, naproxen)	Controlled-exposure study of 60 subjects (510 specimens)[4]	0.4% false-positive rate
Opiate	Fluoroquinolone*	Controlled-exposure studies (8 subjects) and case series (9 subjects)[6]	Most levels detected were below new 1998 threshold (2000 ng/mL)
Opiate	Rifampin	3 case reports[7]	
Phencyclidine	Venlafaxine	1case report[8]	Confirmed by GC-MS (7200 mg intentionally ingested)
Phencyclidine	Dextromethorphan	1case report[9]	(500 mg ingested)

*Ofloxacin and levofloxacin most likely to cause false positive.

Opioid Effectiveness

- **Acute pain**
  - Opioids are among our most powerful analgesics and have been well demonstrated to be effective in acute pain.
- **Chronic pain**
  - More problematic
  - Side effects vs benefit

When are opioids appropriate?

- **Acute pain – this is probably their strongest indication**
- **Chronic pain – only when all else fails and at minimal doses**
- **Pain related to active cancer as well as end-of-life are excluded from most prescribing limitations.**

Opioids

- **“For chronic back pain, systematic reviews find scant evidence of efficacy.**
- **Randomized controlled trials have high dropout rates, brief duration (four months or less), and highly selected patients.**
- **Opioids seem to have short term analgesic efficacy for chronic back pain, but benefits for function are less clear.**
- **The magnitude of pain relief across chronic non-cancer pain conditions is about 30%.**
- **Given the brevity of randomized controlled trials, the long term effectiveness and safety of opioids are unknown.**
- **Loss of long term efficacy could result from drug tolerance and emergence of hyperalgesia.”**

Opioids for low back pain BMJ 2015;350:g6380 doi: 10.1136/bmj.g6380

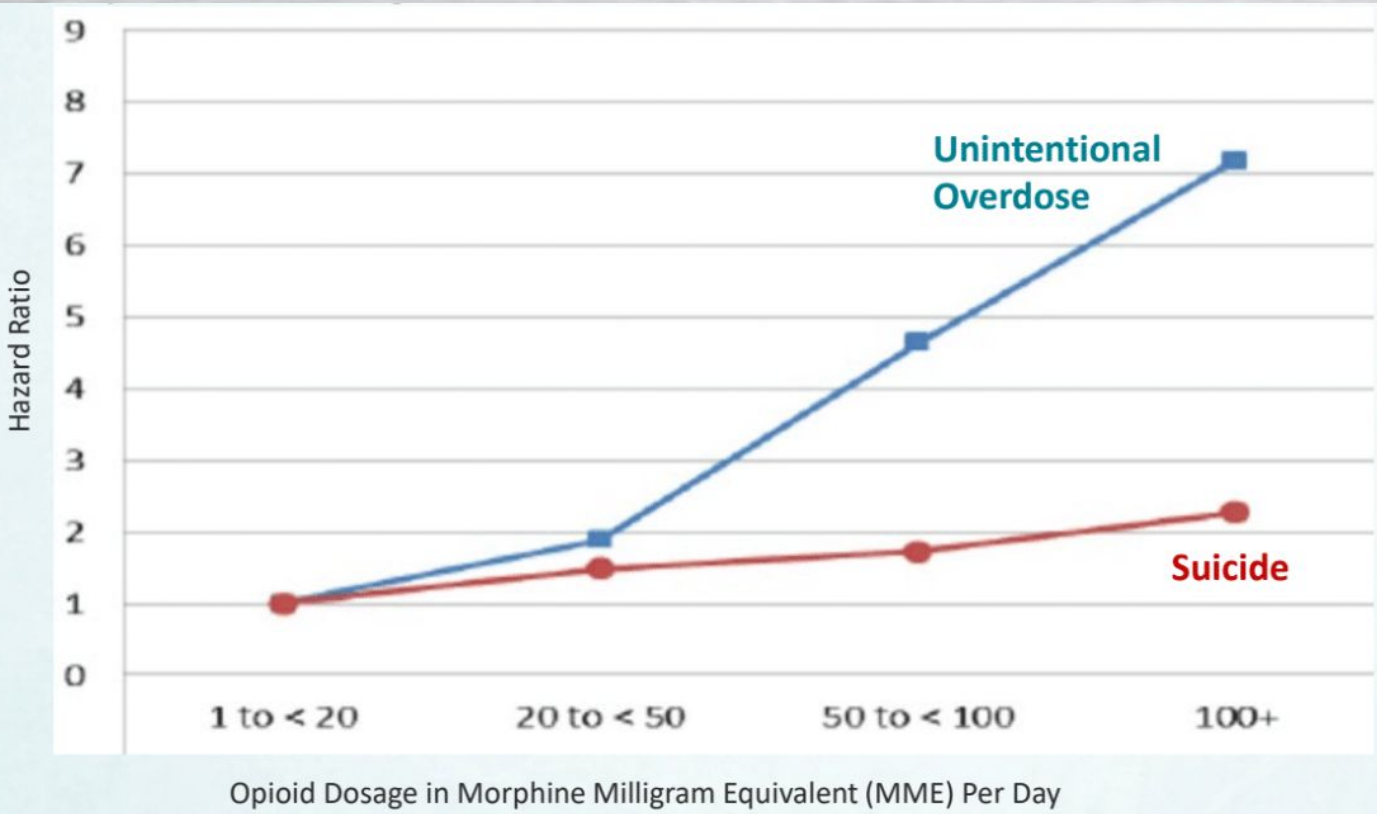
- “There is substantial, albeit not definitive, scientific evidence of the effectiveness of opioids in treating pain and of high variability in opioid dose requirements and side effects.
- The estimated risk of death from opioid treatment involving doses above 100 MMED is ~0.25%/year.
- Multiple large studies refute the concept that short-term use of opioids to treat acute pain predisposes to development of opioid use disorder.
- The prevalence of opioid use disorder associated with prescription opioids is likely <3%.”

Nadeau SE, Wu JK and Lawhern RA (2021) Opioids and Chronic Pain: An Analytic Review of the Clinical Evidence. *Front. Pain Res.* 2:721357. doi: 10.3389/fpain.2021.721357

- Morbidity, mortality, and financial costs of inadequate treatment of the 18 million Americans with moderate to severe chronic pain are high.
- Because of the absence of comparative effectiveness studies, there are no scientific grounds for considering alternative non-pharmacologic treatments as an adequate substitute for opioid therapy but these treatments might serve to augment opioid therapy, thereby reducing dosage.

Nadeau SE, Wu JK and Lawhern RA (2021) Opioids and Chronic Pain: An Analytic Review of the Clinical Evidence. *Front. Pain Res.* 2:721357. doi: 10.3389/fpain.2021.721357

Death Risks and MME



Multiple studies demonstrate **higher doses carry higher risk of opioid-related death**.

- This may in part reflect the **prevalence of mental health comorbidities** in patients with chronic pain.

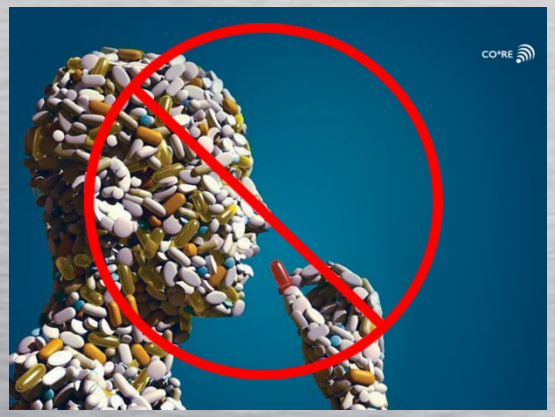
Bohnert AS et al. JAMA 2011 Apr 6 https://pubmed.ncbi.nlm.nih.gov/21467284/; Igen MA et al. Opioid Dose and Risk of Suicide. Pain. 2016 May https://pubmed.ncbi.nlm.nih.gov/26761386/

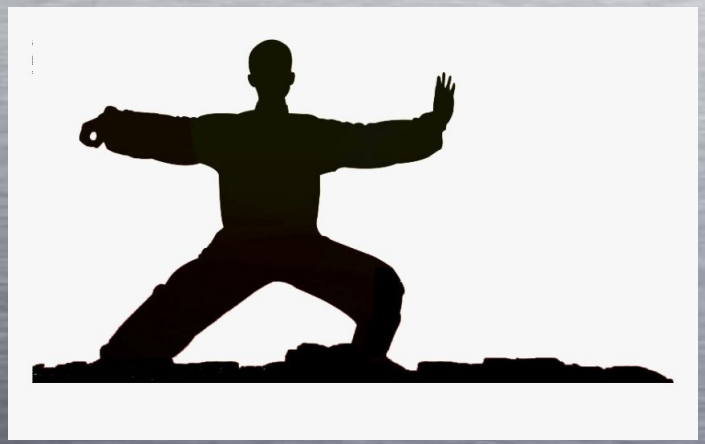
Opioid Dose Reductions

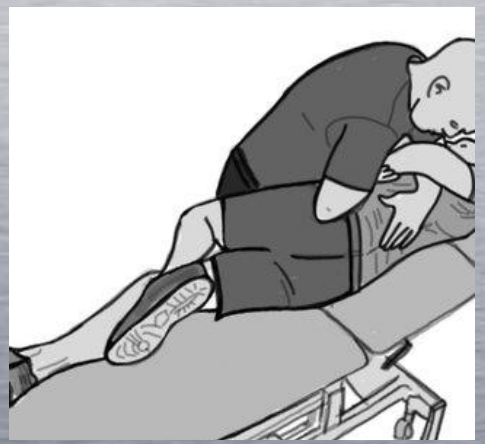
- Patients tapered from a stable, long-term, higher-dose opioid therapy are significantly more likely to incur an overdose or a mental health crisis within one year, compared with those who are not tapered, according to a retrospective cohort study.
- “Many factors have led to a major decrease in opioid prescribing over the past several years, and many patients who were taking stable doses of opioids for chronic pain have had their doses reduced or tapered,”

Agnoli A, Xing G, Tancredi DJ, Magnan E, Jerant A, Fenton JJ. Association of Dose Tapering With Overdose or Mental Health Crisis Among Patients Prescribed Long-term Opioids. JAMA. 2021 Aug 3;326(5):411-419. doi: 10.1001/jama.2021.11013. Erratum in: JAMA. 2022 Feb 15;327(7):688. Erratum in: JAMA. 2022 Feb 15;327(7):687. PMID: 34342618; PMCID: PMC8335575.

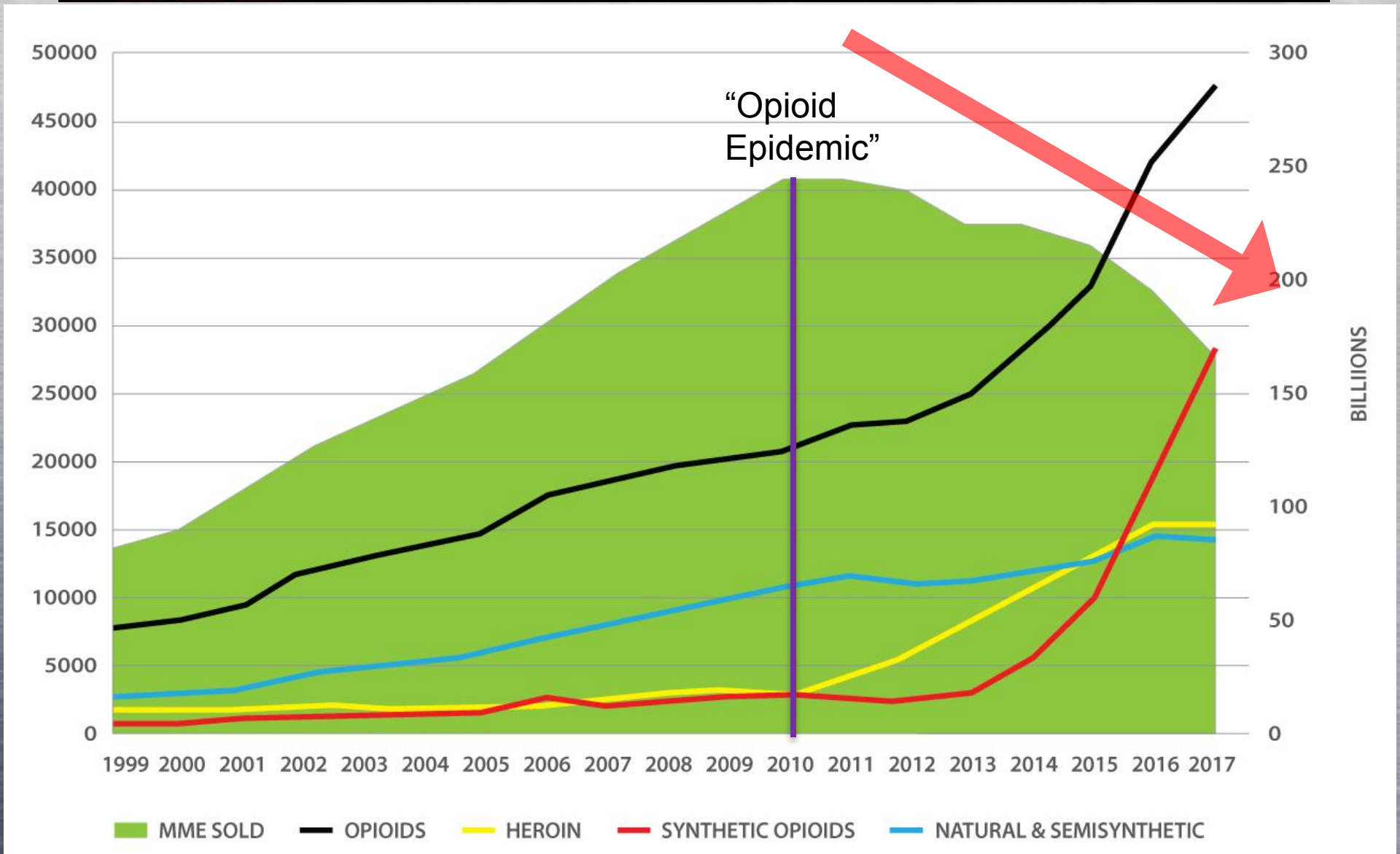
Pain Management Trends







Physician Response



Benzos and Opioids

- **This is an extremely ‘hot-button’ item in the area of medical-legal scrutiny. It is a metric that is being calculated on all of us.**
- **If one of your patients is on chronic opioids *please* do not start benzos.**
- **If all other treatment modalities fail and the patient requires benzos, please put that in your note.**
- **Otherwise, it is likely the patients opioids will be tapered and discontinued.**

CDC Guidelines / Revisions

- **Applies to additional clinicians**: While the 2016 guideline was intended only for primary care physicians, the 2022 version is intended to provide recommendations for physicians, nurse practitioners, physician assistants, and oral health practitioners

- **Promotes integrated pain management**: The draft states, “As clinicians may work within team-based care, the recommendations refer to and promote integrated pain management and collaborative working relationships with, for example, behavioral health specialists, such as social workers or psychologists, and pharmacists.” Further, the draft states that “medications should ideally be combined with nonpharmacologic therapy to provide greater benefits to patients in improving pain and function” and that multimodal therapies and multidisciplinary biopsychosocial rehabilitation-combining approaches can reduce long-term pain and disability.

CDC Guidelines / Revisions

- **Calls for improved payment of multimodal treatments**: The draft states that health systems and payers should work to ensure that multimodal pain treatments are available, accessible, and reimbursed. The CDC calls on public and private payers to support a broader array of nonpharmacologic interventions, stating that "reimbursement is often cited as a principal barrier to why these nonpharmacologic treatments are not more widely used."

- **Emphasis on joint decision making**: Unlike the 2016 guideline, the 2022 draft emphasizes the importance of the clinician and patient jointly determining treatment goals and how opioid effectiveness will be evaluated.

CDC Guidelines / Revisions

- **Removal of arbitrary dosage ceilings**: In a drastic departure from the 2016 guideline, the 2022 draft has removed recommendations related to arbitrary dosage ceilings. Mentions of specific dosages are now presented in a much more narrative form, alongside specific evidence and considerations, but without explicit warnings not to exceed certain dosages. The guideline does, however, caution clinicians to be aware of rules related to MME thresholds established on a state-by-state basis.

- **Explicitly voluntary** and not be used as mandatory limits: The draft says, "Of utmost importance, this clinical practice guideline provides voluntary clinical practice recommendations for clinicians that should not be used as inflexible standards of care. The clinical practice guideline recommendations are also not intended to be implemented as absolute limits of policy or practice across populations by organizations, healthcare systems, or government entities."

Adjuvant Agents

- Anticonvulsants
- Antidepressants
- Anxiolytics
- Muscle Relaxers
- Antiemetics
- Topical Agents

Opioids

- **Opioids for low back pain BMJ 2015;350:g6380 doi: 10.1136/bmj.g6380**

"For chronic back pain, systematic reviews find scant evidence of efficacy. Randomized controlled trials have high dropout rates, brief duration (four months or less), and highly selected patients. Opioids seem to have short term analgesic efficacy for chronic back pain, but benefits for function are less clear. The magnitude of pain relief across chronic non-cancer pain conditions is about 30%. Given the brevity of randomized controlled trials, the long term effectiveness and safety of opioids are unknown. Loss of long term efficacy could result from drug tolerance and emergence of hyperalgesia."

Anticonvulsants

- **Anticonvulsants in the treatment of low back pain and lumbar radicular pain: a systematic review and meta-analysis (CMAJ. 2018 Jul 3; 190(26): E786–E793)**
- **There is moderate- to high-quality evidence that anticonvulsants are ineffective for treatment of low back pain or lumbar radicular pain. There is high-quality evidence that gabapentinoids have a higher risk for adverse events.**

Gabapentin

- **A randomized controlled trial of gabapentin for chronic low back pain with and without a radiating component Pain. 2016 Jul; 157(7): 1499–1507.**
- **This randomized Phase II clinical trial in chronic non-specific low back pain did not detect analgesic effects for gabapentin compared to placebo. Adverse effects were higher than expected, given that gabapentin is often considered to have a benign side effect profile. Because of evidence that gabapentin is efficacious for neuropathic pain syndromes we also examined whether back pain with a radiating component into the legs was differentially responsive. Again there was no support for gabapentin analgesia. The secondary outcome of disability in everyday function due to back pain also indicated no difference between gabapentin and placebo.**

Antidepressants

- **Efficacy and safety of antidepressants for the treatment of back pain and osteoarthritis: systematic review and meta-analysis (*BMJ* 2021; 372 doi: https://doi.org/10.1136/bmj.m4825 (Published 20 January 2021)**
- **Moderate certainty evidence shows that serotonin-noradrenaline reuptake inhibitors (SNRIs) offer a small, non-clinically relevant benefit for people with back pain and osteoarthritis**
- **SNRIs and tricyclic antidepressants might provide clinically important benefits for sciatica, but the certainty of evidence is low to very low**
- **Only SNRIs increased the risk of adverse events; however, the number of studies evaluating the safety of other antidepressant classes was small, trials were underpowered to detect harm, and the certainty of evidence ranged from low to very low**

Antidepressants

- **Moderate certainty evidence shows that the effect of SNRIs on pain and disability scores is small and not clinically important for back pain, but a clinically important effect cannot be excluded for osteoarthritis. TCAs and SNRIs might be effective for sciatica, but the certainty of evidence ranged from low to very low.**

Efficacy and safety of antidepressants for the treatment of back pain and osteoarthritis: systematic review and meta-analysis
BMJ 2021;372:m4825

Muscle Relaxants

- **Muscle Relaxants for Nonspecific Low Back Pain: A Systematic Review Within the Framework of the Cochrane Collaboration(** Spine: September 1, 2003 - Volume 28 - Issue 17 - p 1978-1992 doi: 10.1097/01.BRS.0000090503.38830.AD)
- **than analgesics or nonsteroidal anti-inflammatory drugs."**

- **"Muscle relaxants are effective in the management of nonspecific low back pain, but the adverse effects require that they be used with caution. Trials are needed that evaluate if muscle relaxants are more effective**

NSAIDS

- **In total, 65 trials (total number of patients = 11,237) were included in this review. Twenty-eight trials (42%) were considered high quality. Statistically significant effects were found in favour of NSAIDs compared to placebo, but at the cost of statistically significant more side effects. There is moderate evidence that NSAIDs are not more effective than paracetamol for acute low-back pain, but paracetamol had fewer side effects. There is moderate evidence that NSAIDs are not more effective than other drugs for acute low-back pain. There is strong evidence that various types of NSAIDs, including COX-2 NSAIDs, are equally effective for acute low-back pain. COX-2 NSAIDs had statistically significantly fewer side-effects than traditional NSAIDs.**
  - Roelofs PD, Deyo RA, Koes BW, Scholten RJ, van Tulder MW. Non-steroidal anti-inflammatory drugs for low back pain. Cochrane Database Syst Rev. 2008 Jan 23;(1):CD000396. doi: 10.1002/14651858.CD000396.pub3. PMID: 18253976.

Tylenol

- **Efficacy of paracetamol for acute low-back pain: a double-blind, randomised controlled trial** (July 23, 2014 DOI:https://doi.org/10.1016/S0140-6736(14)60805-)
- **"Our findings suggest that regular or as-needed dosing with paracetamol does not affect recovery time compared with placebo in low-back pain, and question the universal endorsement of paracetamol in this patient group."**

MULTIMODAL PAIN TREATMENT

- **“Of all approaches to the treatment of chronic pain, none has a stronger evidence basis for efficacy, cost-effectiveness, and lack of iatrogenic complications than interdisciplinary care.”**

- ***International Association for the Study of Pain, Vol. XX, Issue 7 December 2012***
- ***http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3656892/***

MULTIMODAL PAIN TREATMENT

- Most of the barriers to this well-documented, evidence-based form of pain management are related to money / reimbursement / availability.
- Some are related to how pain physicians are trained.
- We need a pain treatment Residency, as opposed to a fellowship following primary residency.

FUTURE GUIDELINES

- Opioids are imperfect options for all pain states and yet are the only treatment that works for many acute, subacute and chronic pain conditions; whenever possible, an equally efficacious therapy should be recommended, even if it costs more.
- Guidelines should strongly endorse evidence-based integrative therapies for chronic non-cancer pain, as first-line therapies when possible.
- Cognitive-behavioral therapy has strong support in the literature and should be recommended and covered by payers.

- Abuse-deterrent formulations that are FDA-approved should be made available to all patients who require extended-release (ER) opioids at equal cost to a generic ER formulation.
- The evidence that opioids cause birth defects is inconclusive and should be accompanied with guidance on the risks of unrelieved pain, and the use of alcohol and other pain medications, including nonsteroidal anti-inflammatory drugs, during pregnancy.
- Severe pain should be understood to persist in some people; those who are on opioids for more than 90 days are at increased risk for disability for reasons other than opioids; guidelines should not state or imply that opioids are the reason for the disability without supporting evidence.

- Guidelines should be directed toward public and private insurance payors as well as providers, indicating which therapies should be covered when opioids are ineffective or inadvisable.
- Urine drug and pharmacogenetic testing should be covered by all payors and used by prescribers.
- Guidelines should allow for personalized therapy, recognizing that not all mu-opioid agonists work the same way in all patients.

Webster, L., “Safeguarding Integrity in Opioid Clinical Practice”, Pain Medicine News, Aug 2015 | Vol: 13(8)

Prognostications

- More and more opioids must be viewed as a treatment of last resort – to be used only when all else fails.
- Non-opioid treatment is going to have to assume a much more prominent role in chronic pain management – and our patients are going to have to buy into this.
- Both patients and physicians are going to have to get past the 'pill for every symptom' mentality
- Patients are going to have to become more active participants in their own health care
- Our present strategies for dealing with the opioid crisis is not reducing opioid-related overdose deaths

Summary

- **Chronic pain is a widespread, and expensive medical problem.**
- **Because of skyrocketing opioid overdose deaths, many new regulations are in place.**
- **There are a growing number of requirements and regulations; particularly when writing ER/LA opioids.**
- **Patient participation in their own health care is going to become more and more necessary in the current 'opioids are last resort' mentality.**
- **The role of non-pharmacologic treatment is going to have to increase.**

Save the Pangolins!

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