PAINWEEK

3's Company: COX-2 Inhibitors, Medicinal Marijuana, and Opioid Prescribing

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Disclosure

- Nothing to disclose

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Learning Objectives

- Evaluate treatment safety and efficacy of COX-2 inhibitors for the management of chronic pain
- Explain how to interpret current literature regarding the benefits and burdens of medicinal versus recreational cannabis
- Appropriately apply the CDC guidelines for prescribing opioids for chronic pain

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The Facts

- Prevalence of chronic pain in US adult population ~11.2%
- There is an opioid epidemic
  - 1991-2014: 165,000 people died from opioid overdose in the US
- There is focus on the need for nonopioid medications to treat pain
- NSAID's may be reasonable consideration as alternatives
- Marijuana is trendy and becoming more accepted and available for medicinal purposes
- Opioids are good analgesics for some people
- Opioid medications are a major target of the media and the government in attempt to control the epidemic

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I'm going to attempt to iron this out for you!

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Cox-2 Inhibitors: Good, Bad, or Ugly?

NSAIDs

- In 2012, more than 98 million NSAID prescriptions were filled
- More than 23 million Americans use NSAIDs daily
- Utilization is likely to increase with aging of America
- Shift away from opioids will likely increase NSAID use
- 5%-7% of hospital admissions are related to adverse effects of drugs → NSAIDs are responsible for 11%-12% of these
- NSAID-induced GI complications result in >100,000 hospitalizations and >16,500 deaths annually

PainWeek http://www.nsaidalliance.com/wp-content/uploads/2014/10/NSAID-Alliance-NSAID-Fact-Sheet.pdf

COX Enzymes

COX-1

- Expressed in most tissues, variably
- "Housekeeping" enzyme
  - Regulates normal cellular processes
  - Gastric cytoprotection
  - Vascular homeostasis
  - Platelet aggregation
  - Kidney function
- Stimulated by hormones or growth factors

COX-2

- Expressed constitutively in the brain, kidney, bone, and female reproductive system
- Expressed at other sites during states of inflammation

PainWeek UpToDate, 2017, "Overview of selective COX-2 inhibitors"

NSAIDS and Gastrointestinal Toxicity (cont'd)

- Gastric damage
  - GI mucosa uses COX-1 to generate mucosal-protective PGs
  - Aspirin doses as low as 10 mg/day inhibit gastric PG generation considerably and can damage the stomach
  - After stopping low-dose aspirin, human stomach requires 5-8 days to recover its COX-1 activity and synthesize protective PGs (very slow turnover of gastric COX-1)
- Duodenal damage
  - ASA 325 mg qod increases risk of duodenal ulcers

PainWeek UpToDate, 2017, "Pathogenesis of gastroduodenal toxicity"

Risk of Gastrointestinal Complications

- COX-2 inhibitors are associated with a reduced risk of GI bleeding compared to nonselective NSAIDs
  - Relative risk 0.6 (95% CI 0.4-0.9)
  - But greater risk as compared to placebo
- Any potential GI sparing effect with selective COX-2 inhibitors is eliminated when taken concurrently with low-dose aspirin therapy for prevention of CV disease

PainWeek UpToDate, 2017, "Primary prevention of gastroduodenal toxicity"

NSAIDs and Cardiovascular Disease

- NSAIDs have been associated with increased risk of:
  - Myocardial infarction
  - Stroke
  - Heart failure
  - Atrial fibrillation
  - Cardiovascular death

Risk in patients without known CV disease:
1-2 excess events or less per 1000 person-years

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Risk of Acute MI in "The Real World" (cont'd)

- Cohort of 446,763 individuals, with 61,460 AMIs
- Taking any dose of NSAID for 1 week, 1 month or >1 month was associated with increased risk of AMI

NSAID	Odds Ratio (95% CI)
Celecoxib	1.24 (0.91-1.82)
Ibuprofen	1.48 (1.00-2.26)
Diclofenac	1.50 (1.06-2.04)
Naproxen	1.53 (1.07-2.33)
Rofecoxib	1.58 (1.07-2.17)

PainWeek Bally M et al. BMJ 2017;357:j1909 | doi: 10.1136/bmj.j1909

So you have heart disease and your knees hurt…

- PRECISION trial – compared cardiovascular safety of celecoxib, ibuprofen, and naproxen
- 24,081 patients with osteoarthritis (90%) or rheumatoid arthritis (10%) and established CV disease or increased risk of developing CV disease were randomized to receive:
  - Celecoxib 100 mg twice daily
  - Ibuprofen 600 mg 3 times daily
  - Naproxen 375 mg twice daily
- Mean treatment duration was 20.3 months, and mean follow-up period was 34.1 months
- About half were taking low-dose ASA at baseline

PainWeek SE Nissen et al. NEJM 2016 Nov 13 (epub)

So you have heart disease and your knees hurt…

- Primary outcome event: CV death (including hemorrhagic death), nonfatal MI or nonfatal CVA
- 68.8% patients DC'ed study drug; 27.4% DC'ed during follow up

Celecoxib		Ibuprofen		Naproxen	
Intent to treat	On treatment	Intent to treat	On treatment	Intent to treat	On treatment
188 (2.3%)	134 (1.7%)	201 (2.5%)	155 (1.9%)	218 (2.7%)	44 (1.8%)

- Risk of GI events significantly lower with celecoxib than naproxen or ibuprofen
- Risk of renal events significantly lower with celecoxib than ibuprofen, but celecoxib not significantly less than naproxen

PainWeek SE Nissen et al. NEJM 2016 Nov 13 (epub)

So you have heart disease and your knees hurt…

- Limitations
  - Dosage of celecoxib was limited to 200 mg per day, lower than doses previously associated with CV toxicity
  - Ibuprofen and naproxen doses were allowed to be increased
  - Ibuprofen and naproxen (but not celecoxib) inhibit aspirin binding to platelet COX-1, thus the cardioprotective effects of aspirin may have been blunted in patients who were taking ibuprofen or naproxen
- Conclusion
  - Researchers state celecoxib is noninferior to ibuprofen and naproxen from a cardiovascular perspective
  - Others state the celecoxib dose is too low to support this conclusion

PainWeek SE Nissen et al. NEJM 2016 Nov 13 (epub)

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Medical Cannabis

So who's with me?

I would prescribe or recommend cannabis (medical marijuana) for a patient with a disease or symptom where cannabis has been shown to be helpful.

A. Absolutely, where do I sign?
B. Maybe, I need more convincing
C. Not in this lifetime

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Let's get that prescription pad out…

- Survey of 520 members of the Colorado Academy of Family Physicians (2013)
  - 19% believed physicians should recommend medical cannabis
  - 80% agreed it should be incorporated into medical school education
  - 82% agreed that it should be included in residency training
  - 92% agreed it should be a topic of CME for practicing MDs
  - Majority agreed that there are significant mental and physical health risks associated with marijuana

PAINWEEK Kondrad E, at al. Colorado family physicians' attitudes toward medical marijuana. *J Am Board Fam Med* 2013;26:52-60.

Cannabis

- "Cannabis" is the species name for the entire plant
- 3 generally accepted varieties:
  - *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*
- Can be given orally, sublingually, rectally, topically, or inhaled
- Crude product contains >460 active chemicals and >100 cannabinoids
  - δ-9-tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)

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National Highway Traffic Safety Administration. Cannabis/Marijuana (Δ-9-tetrahydrocannabinol, THC). http://www.nhtsa.gov/people/injury/research/job185drugs/cannabis.htm.
Smith, GL. Medical cannabis: basic science & clinical applications: what clinicians need to know and why. Beverly Farms, MA: OEM Press, 2016.

Clinical Effects of Cannabis

Symptom Relief	Disease Management
▪ Addiction	▪ Arthritis
▪ Anxiety, tension, stress	▪ ADHD, PTSD
▪ Depression	▪ Cancer treatments
▪ Digestive problems	▪ Gastrointestinal disorders
▪ Inflammation	▪ HIV/AIDS
▪ Nausea and vomiting	▪ Insomnia
▪ Pain	▪ Migraine
▪ Spasms and convulsions	▪ Movement disorders
	▪ Multiple sclerosis

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Smith, GL. Medical cannabis: basic science & clinical applications: what clinicians need to know and why. Beverly Farms, MA: OEM Press, 2016.

Systematic Review

Indication	Cannabinoids	Therapeutic Outcome
Chemotherapy Induced N/V	Nabilone, Dronabinol, Nabiximols, THC (vs placebo, traditional comparators)	All studies showed a greater benefit with cannabinoids than placebo or comparators; Did not achieve SS
Appetite stimulation in HIV/AIDS Infection	Dronabinol (3 studies vs megestrol; 1 study vs placebo)	May have ↑ appetite, % body fat; Did not achieve SS.
Chronic Pain	Nabiximols, THC (smoked, oral), Nabilone, THC oromucosal spray, Dronabinol, Vaporized cannabis	% of patients with ≥30% reduction in pain was greater than placebo (especially with neuropathic pain)

SS: Statistically significant

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Whiting PF, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015;313(24):2456-2473.

Systematic Review (cont'd)

Indication	Cannabinoids	Therapeutic Outcome
Spasticity due to MS or paraplegia	Nabiximols, Dronabinol, Nabilone, THC/CBD, Smoked THC	Cannabis improved spasticity but failed to reach SS. More patients had global improvement
Anxiety disorder	Cannabidiol vs placebo	Greater improvement in anxiety on visual analogue mood scale (SS)
Sleep disorder	Nabilone	Greater effect than placebo (SS)
Psychosis	Cannabidiol vs placebo	No difference in outcomes
Glaucoma	THC, Cannabidiol, Cannabidiol oromucosal spray	No difference when compared to placebo

SS: Statistically significant

PAINWEEK Whiting PF, et al. Cannabinoids for medical use: a systematic review and meta-analysis. *JAMA* 2015;313(24):2456-2473.

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- **Chronic pain**
  - Cross-sectional retrospective survey of 244 medical cannabis patients with chronic pain in Michigan
    - Medical cannabis use associated with 64% decrease in opioid use, decreased number and side effects of medications, and improved quality of life (45%)
- **Neuropathic pain**
  - Randomized, double-blind, placebo-controlled, crossover study of 16 patients with treatment-refractory painful diabetic neuropathy
    - Vaporized cannabis associated with a dose-dependent effect on spontaneous pain, with the high dose showing the strongest effect size

PAINWEEK Boehke KF, Litinas E, Clauw DJ. Medical cannabis use in associated with decreased opiate medication use in a retrospective cross-sectional survey of patients with chronic pain. J Pain. 2016;17(6):739-744.

Muscle Spasticity

- Commonly associated with painful spasms and sleep disturbances, and contributes to increased morbidity
- Largely studied in patients with multiple sclerosis
- Systematic review (*Koppel et al.)*
  - Nabiximols (THC:CBD extract) and orally administered THC are "probably effective" for reducing patient-reported spasticity scores
  - Oral cannabis extract is "established as effective" for reducing patient-reported spasticity scores

PAINWEEK Koppel BS, Brust JC, Fife T, et al. Systematic review: Efficacy and safety of medical marijuana in selected neurologic disorders: Report of the Guideline Development Subcommittee of the American Academy of Neurology. *Neurology.* 2014;82(17):1556–1563.

Common Adverse Effects

- Nausea
- Fatigue/weakness
- Dry mouth
- Cough
- Dizziness or vasovagal symptoms
- Tachycardia
- Feelings of intoxication, disorientation, confusion
- Hallucinations, behavioral or mood changes
- Psychosis, euphoria/dysphoria, anxiety

PAINWEEK Koppel BS, et al. Systematic review: efficacy and safety of medical marijuana in selected neurologic disorders: report of the Guideline Development Subcommittee of the AAN. Neurology 2014;82(17):1556-63

Cannabinoid Hyperemesis Syndrome

- Characterized by chronic cannabis use, cyclic episodes of nausea and vomiting, and the learned behavior of hot bathing
- Typically seen in young adults with a long history of cannabis use
  - One study found an average duration of cannabis use prior to onset of recurrent vomiting = 6.3 ± 3.4 years
- 3 Phases
  - Pre-emetic/Prodromal - months/years, morning nausea, fear of vomiting, abdominal discomfort
  - Hyperemetic - Paroxysms of intense and persistent nausea and vomiting, numerous hot showers alleviate symptoms - becomes compulsive
  - Recovery - last for days, weeks, or months

PAINWEEK Galli JA, Sawaya RA, Friedenberg FK. *Curr Drug Abuse Rev.* 2011;4(4):241-9.

Don't go breaking my heart…

- Nationwide Inpatient Sample of patients age 18-55 years old discharged from hospitals in 2009 & 2010
  - Compared cardiovascular disease rates in patients reporting marijuana use vs nonreporters
  - After adjusting for confounders, marijuana use was independently associated with a **26%** increase in the risk of **stroke**, and a **10%** increase in the risk of developing **heart failure**
- Limited evidence of a statistical association between cannabis use and the triggering of acute MI

PAINWEEK https://www.acc.org/about-acc/press-releases/2017/03/09/14/05/marijuana-use-associated-with-increased-risk-of-stroke-heart-failure

Long-Term Use of Cannabis

- **Cognitive dysfunction**
  - Past exposure to marijuana significantly associated with worse verbal recall in middle age but doesn't appear to affect other domains of cognitive function. More evidence with earlier onset of use.
- **Pulmonary damage**
  - Conflicting data; many studies confounded by cigarette smoking
  - Occasional & low cumulative marijuana use was not associated with adverse effects on pulmonary function (≤ 7 joint-years of life exposure)
  - Chronic low-level use over 20 years associated with an increase in FEV_1; diminishes and may reverse in high-level users
  - Chronic use associated with bronchitis and airway infections
- **Periodontal disease**
  - Periodontal disease found in 55.6% of people with > 15 joint-years of marijuana use compared with only 13.5% who never used cannabis.

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Auer R, et al. *JAMA Intern Med* 2016;176(3):352-361; Fletcher MJ, et al. *JAMA Intern Med* 2016;176(3):352-361; Hill KP, et al. *JAMA* 2016;315(21):2338-2339. Danielsson AK, et al. *Journal of Affective Disorders* 2016;192:103-108.

Long-Term Use of Cannabis (cont'd)

- **Psychosis and schizophrenia**
  - 15-year follow-up of >50,000 Swedish males, if tried cannabis by age 18 → 2.4 times more likely to be diagnosed with schizophrenia
  - Pooled odds ratio of 1.4 (95% CI: 1.20, 1.65) of psychotic symptoms or psychotic disorder among ever-users; OR = 2.09 (95% CI: 1.54, 2.84) in regular users.
  - Risk doubles from ~7 in 1000 nonusers to 14 in 1000 for regular cannabis users
- **Affective disorders**
  - No documented longitudinal association between cannabis use and incidence of depression/anxiety
  - Associated with increased mania and hypomania in individuals with bipolar disorders
- **Cancer**
  - Cannabis contains at least 33 carcinogens and may be contaminated with pesticides.
  - Research is conflicting

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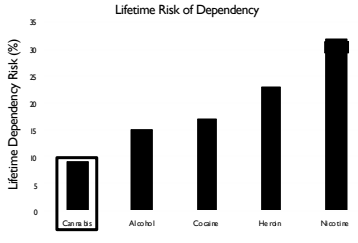
Auer R, et al. *JAMA Intern Med* 2016;176(3):352-361; Fletcher MJ, et al. *JAMA Intern Med* 2016;176(3):352-361; Hill KP, et al. *JAMA* 2016;315(21):2338-2339. Danielsson AK, et al. *Journal of Affective Disorders* 2016;192:103-108. Andréasson S, Engström A, Allebeck P, et al. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. Lancet. 1987;2:1483; Wright S, Metts J. Recreational cannabinoid use: the hazards behind the high. The Journal of Family Practice. 2016;65(11):770-779.

Risk of Addiction & Dependence



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Lopez-Quintero C, et al. Probability and predictors of transition from first use to dependence on nicotine, alcohol, cannabis, and cocaine: results of NESARC. *Drug Alcohol Depend* 2011;115(1-2):120-130.

Contraindications/Precautions

- Cannabis allergy
- Bipolar disorder
- Patients suffering from or at risk of developing schizophrenia
- Substance abuse (past or current)
- Pregnant and/or breastfeeding women
- Coronary heart disease

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Smith, GL. Medical cannabis: basic science & clinical applications: what clinicians need to know and why. Beverly Farms, MA: OEM Press, 2016.
Bultman L, Kingsley K. Medical Cannabis Primer for Healthcare Professionals. Minnesota Medical Solutions, 2014.

Our Responsibility as Healthcare Providers

- Be familiar with **state rules and regulations** regarding medical cannabis.
- Present a **balanced perspective**, identifying both the potential health benefits and risks associated with medical cannabis use if patients inquire.
- Frequently **reassess** our patients using medical cannabis for both efficacy and toxicity.

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Opioid Prescribing

A review of the CDC Guidelines for Chronic Pain in the United States - 2016

Sound Familiar?

- Mr. M is a 40 yo AA male who presents with chronic pain after having many surgeries since a car accident in 2007. He reports uncontrolled pain on his current analgesics – including acetaminophen, ibuprofen, and cyclobenzaprine. He reports being unable to work due to this severe pain and that his current regimen is just not working. He found the only time he was able to work was when he was on Oxycontin 10 mg twice daily. This was stopped when he went back to work, however, and he has since left work on disability.

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Sound Familiar? (cont'd)

- Mr. M is a 50 yo AA male admitted to the hospital with stage 4 lung cancer. He reports severe pain in his femur due to a boney metastasis. He reports being unable to walk around and finds working with physical therapy to be impossible. His current analgesic regimen includes acetaminophen, ibuprofen, and cyclobenzaprine but it is not enough. He tells you that his friend got good relief with Oxycontin when he had cancer. He is on disability from work and the current plan is to start chemotherapy and radiation.

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The Duel

Chronic Pain

- 25 to 39 million people experience daily chronic pain; $560-$630 billion annually
- 10 million people are disabled due to pain
- 40-70% of patients with chronic pain are not receiving proper medical treatment

Opioid Misuse/Abuse/Addiction

- 80% of all opioid prescriptions are written in the US
- Opioids involved in 47,600 overdose deaths in 2017; projected to cost more than $500 billion in related expenses through 2020
- 53% of people age 12 or older abusing analgesics report getting them from a friend or relative

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NIH Role of Opioids in the Treatment of Chronic Pain 2014

- Patients, providers, and advocates all agree :
  - There is a subset of patients for whom opioids are an effective treatment method for their chronic pain
  - Limiting or denying access for these patients can be harmful
  - Patients can be safely monitored using a structured approach,
  - **Avoid disruptive and potentially harmful changes in patients currently benefiting from this treatment**

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NIH Role of Opioids in the Treatment of Chronic Pain 2014 (cont'd)

- Looked at same data as CDC guideline and found:
  - Insufficient data to guide appropriate patient assessment, opioid selection, dosing strategies, or risk mitigation.
  - Need for high-quality research that focuses on establishing the appropriateness of long-term opioid treatment for the management of chronic pain.
- Recommendations

1. Sponsor research, development, and quality improvement
2. In the absence of definitive evidence, clinicians and health care systems should follow current guidelines by professional societies
3. NIH or other federal agencies should sponsor conferences

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CDC Guidelines 2016

- Intention
  - For **primary care providers** who are treating patients with **chronic pain** (lasting > 3 months or past time of normal tissue healing) in **outpatient settings**
  - For patients **18 years of age or older with chronic pain** outside of active cancer treatments, palliative care, and end of life
  - **To improve communication** about benefits and risks, **improve safety and effectiveness** of pain treatment, and **reduce long-term risks**
- Clinical decision-making should be based on clinician-patient relationship and an **overall understanding of the patient's functional status, clinical situation, and life context.**
- **Recommendations**, not prescriptive standards
- Clinicians should **consider the circumstances and unique needs of each patient** when providing care

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Evidence Review

- Efficacy of short-term opioids has been established (RCT <12 weeks duration)
  - High percentage of patient discontinued long-term use due to lack of efficacy and intolerable adverse effects
  - Difficult to extrapolate this data to long-term use
- Categories of key questions for clinical evidence review
  - Effectiveness and comparative effectiveness
  - Harms and adverse events
  - Dosing strategies
  - Risk assessment and risk mitigation strategies
  - Effect of opioid therapy for acute pain and long-term use

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Evidence Review (cont'd)

- Evidence for long-term use
  - Limited data outside of end of life care
  - No study looked at utilization > 1 year for chronic pain
    - Most placebo-controlled RCT's were 6 weeks or less in duration
  - Suggestive of dose-dependent effects on risks of opioid use
    - Including opioid-use disorder, overdose, and death
  - All evidence is either type 3 or type 4
  - Risk of misuse associated with history of substance use disorder, younger age, major depression, and use of psychotropic medications
  - Other risks: CV events, endocrinologic harms, road trauma
- Developed 12 recommendations

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Table 1. GRADE Ratings of the Evidence for the Key Clinical Questions[a]

Outcome	Studies	Limitations	Inconsistency	Imprecision	Type of Evidence[b]	Other Factors	Estimates of Effect or Findings
Effectiveness and Comparative Effectiveness (Key Question 1)							
Effectiveness of long-term opioid therapy vs placebo or no opioid therapy for long-term (≥1 y) outcomes							
Pain, function, and quality of life	None	NA	NA	NA	Insufficient	NA	No evidence.
Harms and Adverse Events (Key Question 2)							
Risks of opioids vs placebo or no opioids on opioid abuse, addiction, and related outcomes; overdose; and other harms							
Abuse or addiction	1 cohort study (n = 568 640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found long-term use of prescribed opioids was associated with an increased risk of abuse or dependence diagnosis vs no opioid use (adjusted OR range, 14.9-122.5, depending on dose).
Abuse or addiction	10 uncontrolled studies (n = 3780)	Very serious limitations	Very serious inconsistency	No imprecision	4	None identified	In primary care settings, prevalence of opioid abuse ranged from 0.6%-8%; prevalence of dependence, 3%-26%. In pain clinic settings, prevalence of misuse, 8%-16%, and addiction, 2%-14%. Prevalence of aberrant drug-related behaviors, 6%-37%.
Overdose	1 cohort study (n = 9940)	Serious limitations	Unknown (1 study)	Serious imprecision	3	None identified	Current opioid use associated with increased risk of any overdose events, adjusted HR, 5.2 (95% CI, 2.1-12), and serious overdose events, adjusted HR, 8.4 (95% CI, 2.5-28) vs current nonuse.
Fractures	1 cohort study (n = 2341) 1 case-control study (n = 21 739 case patients)	Serious limitations	No inconsistency	No imprecision	3	None identified	Opioid use associated with increased risk of fracture in 1 cohort study, adjusted HR, 1.28 (95% CI, 0.99-1.64), and 1 case-control study, adjusted OR, 1.27 (95% CI, 1.21-1.33).
Myocardial infarction	1 cohort study (n = 426 124) 1 case-control study (n = 11 693 case patients)	No limitations	No inconsistency	No imprecision	3	None identified	Current opioid use associated with increased risk of myocardial infarction vs nonuse, adjusted OR, 1.28 (95% CI, 1.19-1.37) and IRR, 2.66 (95% CI, 2.30-3.08).
Endocrinologic harms	1 cross-sectional study (n = 11 327)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	Long-term opioid use associated with increased risk for use of medications for erectile dysfunction or testosterone replacement vs nonuse, adjusted OR, 1.5 (95% CI, 1.1-1.9).
How do harms vary depending on the opioid dose used?							
Abuse or addiction	1 cohort study (n = 568 640)	Serious limitations	Unknown (1 study)	No imprecision	3	None identified	One retrospective cohort study found higher doses of long-term opioid therapy associated with increased risk of opioid abuse or dependence than lower doses. Compared with no opioid prescription, the adjusted ORs were 15 (95% CI, 10-21) for 1-36 MME/d, 29 (95% CI, 20-41) for 36-120 MME/d, and 122 (95% CI, 73-205) for ≥120 MME/d.

(continued)

In A Close Relationship

Key Findings
24% of controls had dosages **>50 MME/d; 59% had doses above this level**
20- <50 MME/d, 50- <100 MME/d, ≥100 MME/d associated with **HR 1.88;4.63;7.18** vs 1- <20 mg MMEE/d
Steady increase in dose-dependent manner; rate of increased decreased after 200 mg MME/d; **concurrent benzo given in 61% of deaths**
20- <50 MME/d, 50- <100 MME/d, ≥100 MME/d associated with **HR 1.4, 3.7, 8.9** vs 1- <20 mg MMEE/d
20- <50 MME/d, 50- <100 MME/d, 100-199 MME/d associated with **OR 1.3,1.9,2.0** vs 1- <20 mg MMEE/d
>100 MME, ≥4 prescribers, ≥4 pharmacies (adjusted **OR 11.2, 6.5, 6.0**) - at least one factor present in 55% of deaths
Among patients on 50-100 MME/d, **overdose risk greatest with >1830 MME cumulatively over 6 months**
>40 MME has 12.2 greater odds of overdose vs lower or no opioid prescription
20- <50 MME/d, 50- <100 MME/d, ≥100 MME/d associated with **OR 1.5, 2.2, 4.1** vs 1- <20 mg MME/d

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Abrupt Cut-off or Gradual Shift?

- Prospective observational cohort with one year follow-up
- In NC using PDMP with name-linked mortality data – 2,182,374 opioid analgesic patients
- Outcome - overdose deaths involving opioids, primary or additive role
- 22.8% of residents were prescribed opioids, 629 overdose deaths – 50% had active opioid Rx at time of death
- Mortality rates increased gradually across a range of average daily milligrams or morphine equivalents
- 80% of opioid analgesic patients received benzodiazepines as well
  - Over-dose rates were 10x higher with co-prescribed benzos (7/10,000 person-years vs 0.7/10, 000 person years)

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Dasgupta N, et al. Pain Medicine 2016; 17:85-98.

CDC Recommendations

1. **Nonpharmacologic therapy/non-opioids** preferred. O**pioids if expected benefits are anticipated to outweigh risks**.
2. **Establish realistic treatment goals for pain/function. Consider how therapy will be discontinued if risks >> benefits**. Continue only if **clinically meaningful improvement.**
3. Discuss **with patients known risks and realistic benefits, patient and clinician responsibilities.**
4. **Immediate-release (IR) opioids** instead of extended-release
5. **Lowest effective dosage**, carefully reassess benefits/risks when increasing **dosage ≥ 50 MME.** Avoid increasing **≥90 MME**; carefully justify a decision to titrate **≥ 90 MME/day**

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CDC Recommendations

6. For **acute pain → lowest effective IR dose**, **no greater quantity than needed** for expected duration. ≤ 3 **days** will often be sufficient**; rarely >7 days**
7. **Reassess within 1-4 weeks** of starting opioids, if dose escalation, & **at least every 3 months**. If benefits < harms, **taper** to lower dosages/to D/C.
8. **Evaluate risk factors** for opioid-related harms **before starting and periodically.** Incorporate risk mitigation strategies, including **naloxone.**
9. Review the **prescription drug monitoring program (PDMP) data** when starting opioid therapy for chronic pain and periodically.
10. **Urine drug testing** before starting opioids and at least annually.
11. **Avoid prescribing opioids and benzodiazepines** concurrently.
12. Offer/**arrange evidence-based treatment for patients with OUD.**

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What providers are saying
The Word on the Street

- AMA is largely supportive, but ***concerned about the evidence base*** *informing some of the recommendations;* ***conflicts with existing state laws and product labeling****; and* ***possible unintended consequences****…includes access and insurance coverage limitations for nonpharmacologic treatments, especially comprehensive care; and the potential effects of strict dosage and duration limits on patient care.*
  - Patrice A. Harris, MD, the AMA board chair-elect and chair of the AMA Task Force to Reduce Opioid Abuse
- *…[H]as the* ***potential to improve and save many, many lives****…success depends on* ***simultaneously addressing significant gaps*** *in the health care system…****reimbursement****, both for* ***chronic pain and for addiction treatment*** *and* ***few available care models…***
  - -Yngvild Olsen, MD, Institutes for Behavior Resources, INC
- *[T]here are few well-controlled clinical studies on opioid-prescribing methods for chronic pain…****appropriate access to opioids*** *could be negatively affected by federal guidelines based on* ***admittedly weak data****. It is important to note that the CDC guidelines are in this respect,* ***an iteration of well-accepted medical principles of drug prescribing****: to use the lowest effective dose for the shortest possible duration.*
  - William Renthal, MD, of the Department of Neurology at Brigham and Women's Hospital of Harvard Medical School, in JAMA Neurology

PAINWEEK https://wire.ama-assn.org/delivering-care/what-physicians-are-saying-about-new-cdc-opioid-guidelines

What Patients Are Saying

- In one survey, 95% of pain patients said that the CDC guideline discriminated against them, and 93% said that if published as is, the guideline would be harmful to pain patients.
- *I would caution the CDC that putting these dosage limits in here would cause problems for patients…These recommendations have severe ramifications.*
- *I have been on and off opiates for a few years. I do not have cravings for opiates. I am not addicted to opiates. I do think there has been a demonization of opiates among the medical community, as well as the CDC possibly and definitely the DEA, how do you decide which patients to continue, that really get benefits from this, and how do you decide which patients take them to get high?*

PAINWEEK https://www.painnewsnetwork.org/stories/2015/9/16/cdc-opioids-not-preferred-treatment-for-chronic-pain

The Attempt at Remediation

- CDC identified the following challenges that in the wake of the guideline:
  - Improper application of dosage ceilings and prescription duration guidance
  - Failure to appreciate the importance of patient involvement in decisions to taper or discontinue opioids
  - Barriers to diagnosis and treatment of opioid use disorder
  - Impeded access to recommended comprehensive, multimodal pain care
- Application of the Guideline without flexibility or full awareness of what the guideline contains by regulators and policymakers
- Clinicians should be allowed to individualize treatment based on the patient's history, and policies should allow such flexibility

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(*Pain Med* 2019;20[4]:724-735).

The Attempt at Remediation

- There are no shortcuts to safer opioid prescribing, appropriate and safe reduction, or discontinuation of opioid use
- Safest to start fewer patients on opioids, and not escalate to high dosages
- Maximize nonopioids
- Review the risks and benefits of opioid therapy with patients.
- For those already on opioids:
  - Closely monitor patients on higher doses for overdose risk
  - Offer and arrange medication-assisted treatment when opioid use disorder is identified

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(*Pain Med* 2019;20[4]:724-735).

A Need for Further Remediation?

- We need education and ongoing development and programming
- More studies are needed to determine dose limits, if they are indicated or beneficial
- Better support for those at risk or with addiction issues
- Need more patient-focused and individualized care
- Pain assessment and pain contracts!

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