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

- Summarize current literature supporting topical opioid administration for pain
- Describe the pharmacokinetic and pharmacodynamics properties of topical morphine
- Identify medical staff and patient/family education needs and implement strategy
- Discuss logistics of adding topical morphine to your health system formulary, establishing medication prescribing guidelines, development of an order set in EHR, and identifying a list of approved prescribers

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The Facts

- Prevalenc… …on 20.4%[1]
- From 1999… …om overdoses…
- NSAID's c… …K, stroke and heart…
- Smoking r… …ncreased risk of sub… …chitis

1. https://www.cdc.gov/mmwr/volumes/67/wr/mm6736a2.htm accessed 4.11.2019
2. https://www.cdc.gov/drugoverdose/epidemic/index.html accessed 4.11.2019
3. https://www.fda.gov/drugs/drugsafety/ucm461800.htm accessed 4.11.2019
4. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4827335/ accessed 4.11.2019
5. https://hackernoon.com/5-reasons-why-its-not-all-doom-gloom-6e0d4f0b6647 accessed 4.11.2019

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GI toxicity, acute MI and heart failure, oh my!

Cox-2 Inhibitors

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NSAIDs

- In 2012, more than 98 million NSAID prescriptions were filled
- More than 23 million Americans use over the counter NSAIDs daily
- Shifting away from opioids will likely increase NSAID use
- As more NSAIDs are taken over longer periods, adverse event risks increase

http://www.nsaidalliance.com/wp-content/uploads/2014/10/NSAID-Alliance-NSAID-Fact-Sheet.pdf accessed 4.12.2019

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NSAIDs (cont'd)

- 5%-7% of hospital admissions are related to adverse effects of drugs → NSAIDs are responsible for 11%-12% of these
- Significant dose and duration-dependent gastrointestinal, renal, and cardiovascular adverse events with selective and nonselective NSAIDs
- NSAID use is a major cause of GI ulcers
- NSAID-induced GI complications result in >100,000 hospitalizations and >16,500 deaths annually

http://www.nsaidalliance.com/wp-content/uploads/2014/10/NSAID-Alliance-NSAID-Fact-Sheet.pdf accessed 4.12.2019

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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

https://www.uptodate.com/contents/overview-of-selective-cox-2-inhibitors?search=Overview%20of%20selective%20COX-2%20inhibitors&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1 accessed 4.12.2019

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NSAIDS and Gastrointestinal Toxicity

- 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)

PG = prostaglandin
COX= cyclo-oxygenase

https://www.uptodate.com/contents/nsaids-including-aspirin-pathogenesis-of-gastroduodenal-toxicity?search=Pathogenesis%20of%20gastroduodenal%20toxicity&source=search_result&selectedTitle=1~107&usage_type=default&display_rank=1 accessed 4.12.2019

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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 cardiovascular disease

https://www.uptodate.com/contents/nsaids-including-aspirin-primary-prevention-of-gastrointestinal-toxicity?search=Primary%20prevention%20of%20gastrointestinal%20toxicity&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1 accessed 4.12.2019

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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"

- Objective – to characterize the determinants, time course, and risks of acute MI associated with use of NSAIDs
- Design – systematic review followed by a one stage Bayesian individual patient data meta-analysis
- Systematic Review – studies in general or geriatric population, documented acute MI as specific outcome, studied traditional and selective NSAIDs, allowed for time-dependent analysis, and minimized effects of confounding and misclassification bias

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

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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 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)

Not statistically significant

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Bally M et al. BMJ 2017;357:j1909 | doi: 10.1136/bmj.j1909
AMI = acute myocardial infarction

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

- All traditional NSAIDs including naproxen appear to be associated with an increased risk of AMI
- The risk with celecoxib does not seem to be greater than that with traditional NSAIDs
  - Onset of risk occurs in the first week
- Short term use for 8-30 days at a high daily dose was associated with the greatest harms, without obvious further increases in risk beyond the first 30 days
  - celecoxib > 200 mg
  - diclofenac > 100 mg
  - ibuprofen > 1200 mg
  - naproxen > 750 mg

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

Reviewing the current literature

Medical Cannabis

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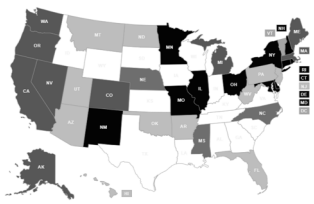
The United States of Marijuana?



States with medical marijuana laws

States that have removed jail time for possessing small amounts of marijuana

States that have both a medical marijuana law and have removed jail time for possessing small amounts of marijuana

Marijuana is legal for adults and is taxed and regulated similarly to alcohol; state also has a medical marijuana law

Marijuana is legal for adults (no sales); medical marijuana law

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National Conference of State Legislatures. State medical marijuana laws. Available at www.ncls.org/research/health/state-medical-marijuana-laws.aspx.
Marijuana Policy Project. Available at http://www.mpp.org/states/ accessed 1-12-2016

Cannabis

- "Cannabis" is the genus name for the entire plant
- 3 generally accepted varieties:
  - *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*
- Can be administered 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.

Original Investigation

Cannabinoids for Medical Use
A Systematic Review and Meta-analysis

Penny F. Whiting, PhD; Robert F. Wolff, MD; Sohan Deshpande, MSc; Marcello Di Nisio, PhD; Steven Duffy, PgD; Adrian V. Hernandez, MD, PhD; J. Christiaan Keurentjes, MD, PhD; Shona Lang, PhD; Kate Misso, MSc; Steve Ryder, MSc; Simone Schmidlkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

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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, faporized cannabis	% of patients with ≥30% reduction in pain was greater than placebo (especially with neuropathic pain)

SS: Statistical significance

painweek 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
Sleep disorder	Nabilone	Greater effect than placebo
Psychosis	Cannabidiol vs placebo	No difference in outcomes
Glaucoma	THC, cannabidiol, cannabidiol oromucosal spray	No difference when compared to placebo

SS: Statistical significance

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

Pain

- **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

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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

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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.

Nausea and Vomiting

- Nabilone and dronabinol approved in 1985 for nausea and vomiting associated with cancer chemotherapy (CINV)
- No evidence to support use of cannabinoids over current firstline antiemetic therapies
- No good-quality randomized trials investigating plant-based cannabis, either inhaled or ingested orally, but abundance of anecdotal reports
- Consider as adjunctive therapy in refractory cases of CINV

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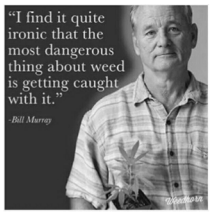
Safety of Cannabis

- Adverse effects
- Cardiovascular concerns
- Other long-term consequences
- Risk of addiction and dependence
- Contraindications/precautions



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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

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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

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
- **Pulmonary damage**
  - Conflicting data; many studies confounded by cigarette smoking
  - Occasional and 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;193:103-108.

Long-Term Use of Cannabis (cont'd)

- **Psychosis and schizophrenia**
  - 15-year follow-up of >50,000 Swedish males found that those who tried cannabis by age 18 were 2.4 times more likely to be diagnosed with schizophrenia
  - Meta-analysis reported a pooled odds ratio of 1.4 (95% CI: 1.20, 1.65) of psychotic symptoms or psychotic disorder among those who had ever used cannabis; OR = 2.09 (95% CI: 1.54, 2.84)
  - Risk of developing psychosis doubles from ~7 in 1000 nonusers to 14 in 1000 for regular cannabis users; important for patients with an affected 1st degree relative
- **Affective disorders**
  - No longitudinal association between cannabis use and incidence of depression/anxiety has been documented
  - Cannabis use associated with increased symptoms of mania and hypomania in individuals with bipolar disorders

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Auer R, et al. *JAMA Intern Med* 2016;176(2):252-261; Fletcher MJ, et al. *JAMA Intern Med* 2016;176(2):262-261; Kilf KP, et al. *JAMA* 2016;315(21):2328-2329.
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.

Long-Term Use of Cannabis (cont'd)

- Cancer
  - Cannabis contains at least 33 carcinogens and may be contaminated with pesticides
  - Research is conflicting
    - Some studies have suggested associations with cancers of the brain, testes, prostate, cervix, and rare pediatric cancers
    - Conflicting data regarding associations with head and neck squamous cell carcinoma, bladder cancer, and non-Hodgkin's lymphoma

Cannabidiol (CBD) may have an anti-neoplastic effect?

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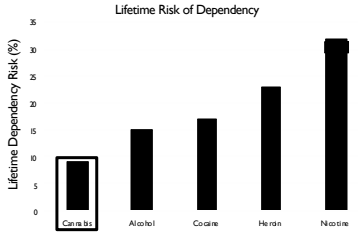
Wright S, Metts J. Recreational cannabinoid use: the hazards behind the high. *The Journal of Family Practice*. 2016;65(11):770-779.

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

Opioid Prescribing

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Sound Familiar?

MM 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 oxycodone 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
- 16,000 to 19,000 overdose deaths annually; $20 to $120 billion in related expenses
- 53% of people age ≥12 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 to opioids for these patients can be harmful
  - Patients can be safely monitored using a structured approach, which includes optimization of opioid therapy, management of adverse effects, and brief follow-up visits at regular intervals
  - Recommendations regarding the clinical use of opioids should 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)

- The approach should be individualized, based on a comprehensive clinical assessment that is conducted with dignity and respect and without value judgments or stigmatization of the patient
- This initial evaluation would include an appraisal of
  - Pain intensity, functional status, and quality of life
  - Known risk factors (history of or current substance use disorders; mood, stress, or anxiety disorders; medical comorbidity; and potential drug-drug interactions)
- Potential to redesign the electronic health record to facilitate such an assessment
- Incorporate the use of other clinical tools (eg, PDMPs) into this assessment
- Stratify those screening at highest risk for harm to more structured and higher intensity monitoring approaches

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

1. Sponsor research, development, and quality improvement initiatives
2. In the absence of definitive evidence, clinicians and health care systems should follow current guidelines by professional societies about which patients and which types of pain should be treated with opioids, and about how best to monitor patients and mitigate risk for harm
3. NIH or other federal agencies should sponsor conferences to promote harmonization of guidelines of professional organizations

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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 old with chronic pain outside of active cancer treatments, palliative care, and end-of-life
  - To improve communication about benefits and risks of opioids for chronic pain, improve safety and effectiveness of pain treatment, and reduce risks with long-term opioid therapy

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CDC Guidelines 2016 (cont'd)

- 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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CDC Response 2019

- Reaffirmed CDC's position regarding the 2016 guidelines
  - The CDC guideline is for primary care clinicians prescribing opioids outside of active cancer, palliative and end-of-life care
  - Clinical practice guidelines for sickle cell patients should be used for those patients

> The Guideline is not intended to deny any patients who suffer with chronic pain from opioid therapy as an option for pain management. Rather, the Guideline is intended to ensure that clinicians and patients consider all safe and effective treatment options for patients. Clinical decision-making should be based on the relationship between the clinician and patient, with an understanding of the patient's clinical situation, functioning, and life context, as well as a careful consideration of the benefits and risk of all treatment options, including opioid therapy. CDC encourages physicians to continue to use their clinical judgment and base treatment on what they know about their patients, including the use of opioids if determined to be the best course of treatment. Providers should communicate frequently with their patients to discuss both the benefits and risks of opioid therapy and revisit treatment plans for pain regularly to achieve the most positive outcomes for patients.
>
> http://freepdfhosting.com/0dc0977cdd.pdf accessed 4.15.2019

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Evidence Review

- Efficacy of short-term opioids has been established
- 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 RCTs were ≤6 weeks 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 and endocrine alterations

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Nonpharmacologic and Nonopioid Therapy

- Nonpharmacologic therapy (exercise, CBT) to reduce pain and improve function
- Nonopioids (NSAIDs, anticonvulsants, antidepressants, acetaminophen) should be used when benefits outweigh risks
- Nonpharmacologic and nonopioids should be used in combination
- Opioids should not be considered firstline or routine for chronic pain
- Long-term benefits of nonopioid therapies is also limited but risks in the short-term are also much lower
- If opioids are used, they should be combined with nonpharmacologic and nonopioid therapy

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Nonpharmacologic and Nonopioid Therapy (cont'd)

- Many systematic reviews in various pain syndromes
- Variable evidence supporting gabapentin, pregabalin, and duloxetine in diabetic peripheral neuropathy and fibromyalgia; TCAs and antidepressants in postherpetic neuralgia; NSAIDs for low back pain (LBP)
- Evidence supporting exercise in fibromyalgia, osteoarthritis, LBP
- Cognitive behavioral therapy seems to have positive lasting effects on mood, not as much on pain
- Improved data on many nonpharmacologic interventions is needed

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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 1 year follow-up
- In NC using PDMP with name-linked mortality data: 2,182,374 opioid analgesic patients
- Outcome: overdose deaths involving opioids in a 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 patient received benzodiazepines as well
  - Overdose rates were 10x higher with coprescribed 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.

FDA Position on Sudden Discontinuation

- The FDA has received reports regarding serious withdrawal symptoms
  - Uncontrolled pain
  - Psychological distress
  - Suicide
- FDAs plan is to update the prescribing information regarding safe dose decreases in the outpatient setting

In general, for patients who are physically dependent on opioids, taper by an increment of no more than 10 percent to 25 percent every 2 to 4 weeks. It may be necessary to provide the patient with lower dosage strengths to accomplish a successful taper.

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FDA identifies harm reported from sudden discontinuation of opioid pain medicines and requires label changes to guide prescribers on gradual, individualized tapering 4.9.2019

Determining When to Initiate or Continue Opioids for Chronic Pain

1. Nonpharmacologic therapy and nonopioid pharmacologic therapy are preferred …opioid therapy only if expected benefits for both pain and function are anticipated to outweigh risks... If opioids are used…combined with nonpharmacologic therapy and nonopioid pharmacologic therapy, as appropriate
2. Before starting…establish treatment goals…realistic goals for pain and function…consider how therapy will be discontinued if benefits do not outweigh risks…Continue opioid therapy only if…clinically meaningful improvement in pain and function that outweighs risks to patient safety
3. Before starting and periodically…discuss with patients known risks and realistic benefits …and patient and clinician responsibilities...

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Opioid Selection, Dosage, Duration, Follow-Up, and Discontinuation

4. …Prescribe immediate-release opioids instead of extended-release/ long-acting opioids
5. …Prescribe the lowest effective dosage. …use caution…at any dosage…carefully reassess …benefits and risks when increasing dosage to ≥50 MME…avoid increasing dosage to ≥90 MME or carefully justify a decision to titrate dosage to ≥90 MME per day
6. …For acute pain …prescribe the lowest effective dose of immediate-release opioids and…no greater quantity than needed for the expected duration of pain... Three days or less will often be sufficient; >7 days will rarely be needed
7. …Evaluate benefits and harms…within 1-4 weeks of starting… or of dose escalation...and of continued therapy…every 3 months or more frequently. If benefits do not outweigh harms …optimize therapies and …taper opioids to lower dosages or to discontinue opioids

MME = morphine milligram equivalent

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Assessing Risk and Addressing Harms of Opioid Use

8. Before starting and periodically during continuation …evaluate risk factors for opioid-related harms…incorporate…strategies to mitigate risk, including considering offering naloxone when factors that increase risk for opioid overdose…are present
9. …Review the…state prescription drug monitoring program (PDMP) data…when starting opioid therapy for chronic pain and periodically during opioid therapy for chronic pain, …every prescription to every 3 months
10. …Use urine drug testing before starting opioid therapy and…at least annually … (category B, Type 4)
11. Avoid prescribing opioid pain medication and benzodiazepines concurrently ….
12. …Offer or arrange evidence-based treatment…for patients with opioid use disorder

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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 non-pharmacologic 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

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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?*

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https://www.painnewsnetwork.org/stories/2015/9/16/cdc-opioids-not-preferred-treatment-for-chronic-pain accessed 4.15.2019

What about this scenario?

RF is a 40 yo AA male who presents with chronic pain after having been treated for stage 2 lung cancer. He reports controlled pain on his current analgesics – including acetaminophen, ibuprofen, cyclobenzaprine, and oxycodone ER 30 mg PO Q12H and oxycodone IR 10 mg PO q6h PRN. His oncologist has deemed him to be in remission after lobectomy and chemo/radiation. He would like to continue on his current medications as his pain is tolerable, but his oncologist will no longer prescribe them for him since he will need frequent follow-up and monitoring and he will not need to be seen that often for his cancer follow-ups. He is still on disability post-treatment, but hopes to come off and get back to work soon.

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A Need for 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 agreements

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