



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

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Disclosure



Learning Objectives

- Evaluate treatment safety and efficacy of COX-2 Inhibitors for the management of chronic pain.
- Interpret current literature regarding the benefits and burdens of medicinal versus recreational cannabis.
- Appropriately apply the CDC guidelines for prescribing opioids for chronic pain.

The Facts

- Prevalence of chronic pain in U.S adult population ~11.2%
- There is an opioid epidemic
 - 1991-2014: 165,000 people died from opioid overdose in the U.S.
- There is focus on the need for non-opioid 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

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



PainWeek[®]

Cox-2 Inhibitors: Good, Bad or Ugly?

NSAIDs

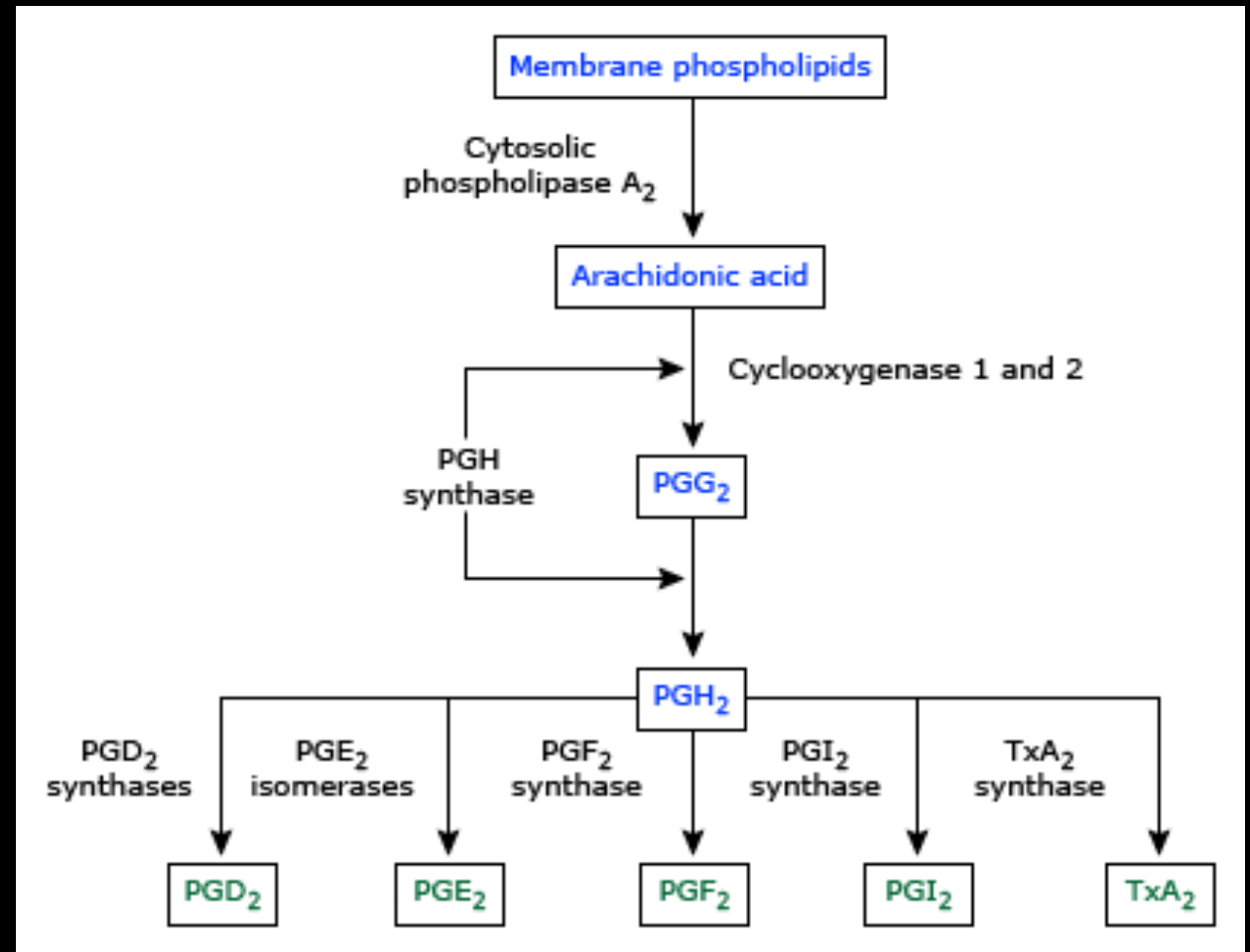
- In 2012, more than 98 million NSAID prescriptions were filled
- More than 23 million Americans use NSAIDs daily
- Utilization is likely to increase with aging of America
- Shift away from opioids will likely increase NSAID use

NSAIDs

- 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

Mechanism of Action

- NSAIDs inhibit COX or prostaglandin synthase (PGHS)
- Impairing the ultimate transformation of arachidonic acid to prostaglandins, prostacyclin, and thromboxanes



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

NSAIDs and Gastrointestinal Toxicity

- The non-secretory cytoprotective effects of PG include:
 - Stimulation of glycoprotein (mucin) secretion by epithelial cells
 - Stimulation of bicarbonate secretion by epithelial cells
 - Stimulation of phospholipid secretion by epithelial cells
 - Enhancement of mucosal blood flow and oxygen delivery to epithelial cells via local vasodilation
 - Increased epithelial cell migration towards the luminal surface (restitution)
 - Enhanced epithelial cell proliferation

Primarily due to inhibition
of COX-I

NSAIDs and Gastrointestinal Toxicity

- Spectrum of gastroduodenal mucosal injury
 - Ranges from subtle alterations in gastric mucosal barrier function → microscopic damage to surface cells → gross injury visible through an endoscope or at the time of surgery for an ulcer complication
 - Aspirin-induced gastric injury is also associated with inhibition of vascular endothelial growth factor

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)
- Duodenal damage
 - ASA 325 mg qod increases risk of duodenal ulcers

NSAIDS and Gastrointestinal Toxicity

- NSAID use and H. pylori infection are independent and synergistic risk factors for uncomplicated and bleeding PUD
 - The risk of uncomplicated PUD is significantly higher among H. pylori positive compared with H. pylori negative NSAID users
 - Ulcers were common in H. pylori positive compared with H. pylori negative patients irrespective of NSAID use and in NSAID users compared with nonusers irrespective of H. pylori status

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

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

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

Risk of Acute MI in “The Real World”

- Cohort of 446,763 individuals, with 61,460 AMI's
- Taking any dose of NSAID for one week, one 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)

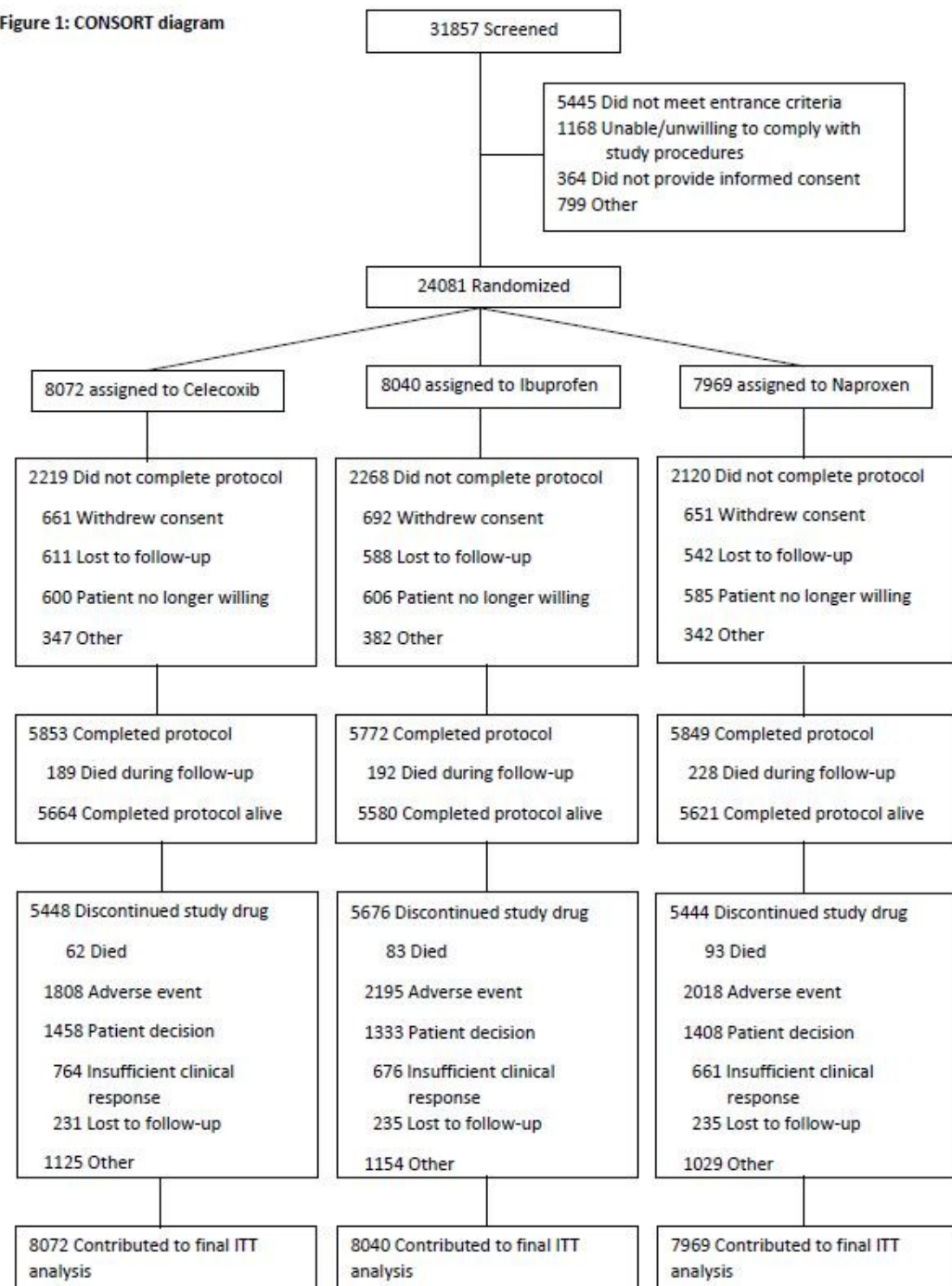
Risk of Acute MI in “The Real World”

- Using a Bayesian meta-analysis of individual patient data and studying real world settings, it is shown that 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 (celecoxib > 200 mg, diclofenac > 100 mg, ibuprofen > 1200 mg, and naproxen > 750 mg) is associated with the greatest harms, without obvious further increases in risk beyond the first 30 days.

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 three times daily
 - Naproxen 375 mg twice daily
- Mean treatment duration was 20.3 months, and the mean follow-up period was 34.1 months
- About half were taking low-dose ASA at baseline

Figure 1: CONSORT diagram



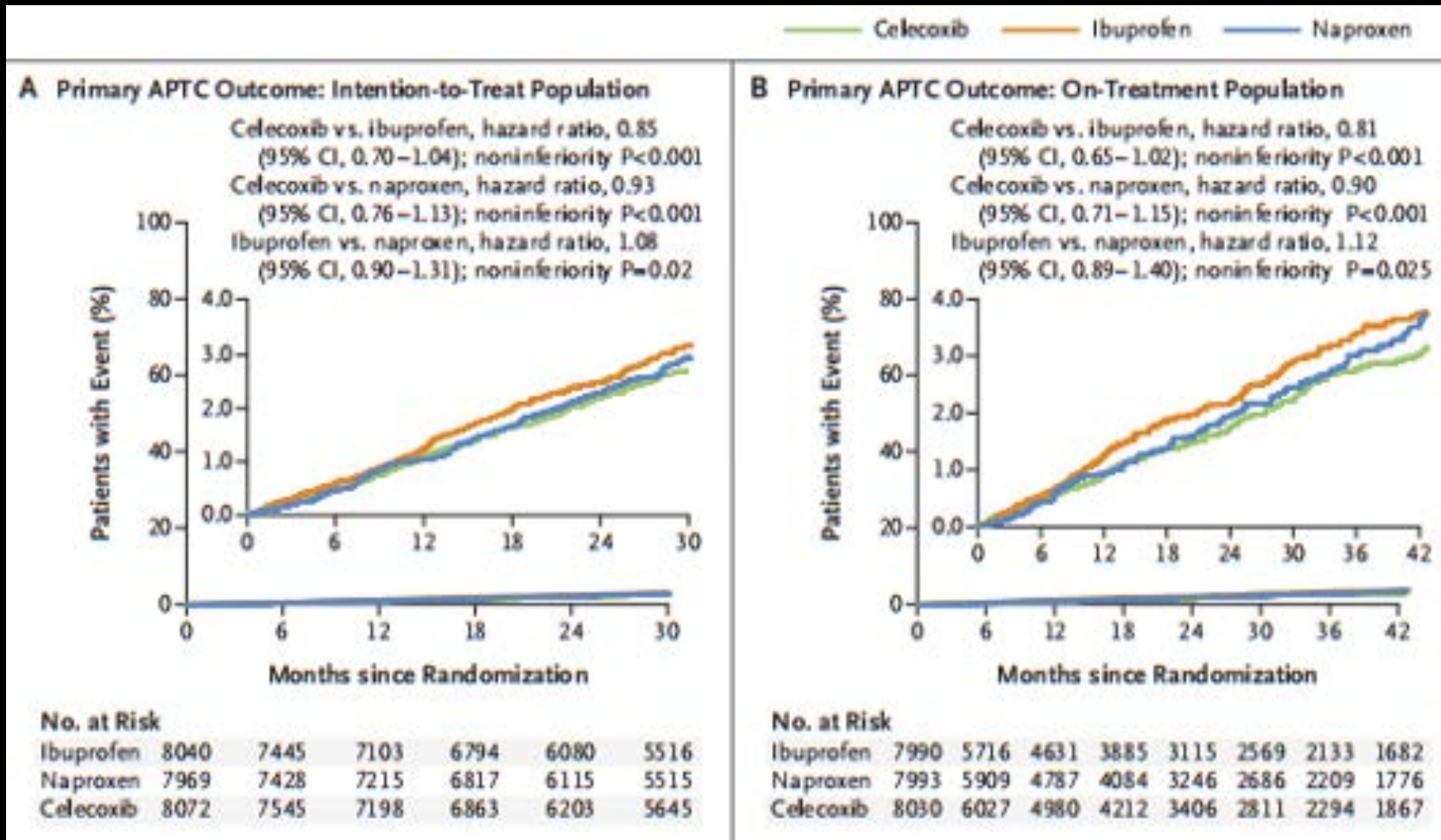
So you have heart disease and your knees hurt...

- 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%)

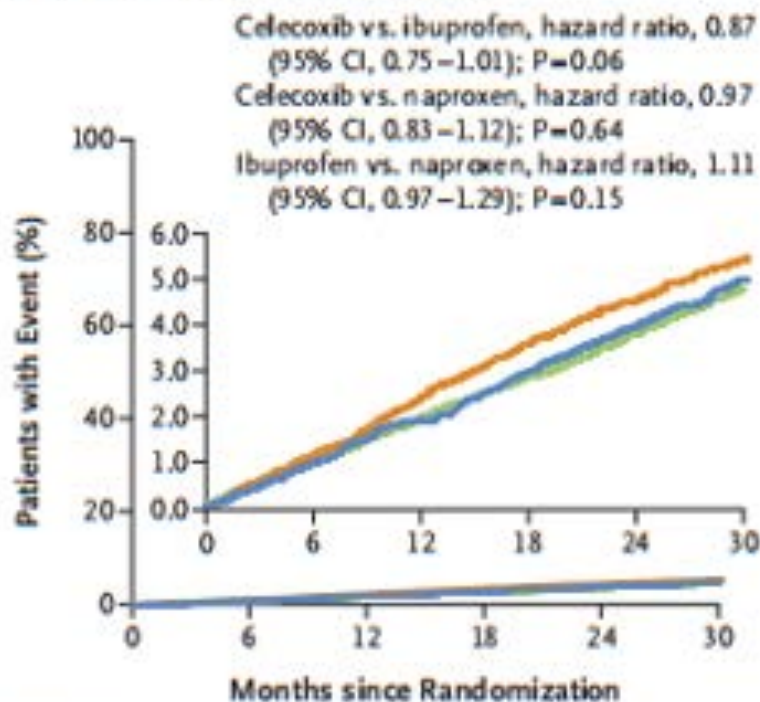
- Risk of GI events significantly lower with celecoxib than naproxen or ibuprofen
- Risk of renal events significantly lower with celecoxib than ibuprofen, but celecoxib not significantly less than naproxen

PRECISION Trial Results



PRECISION Trial Results

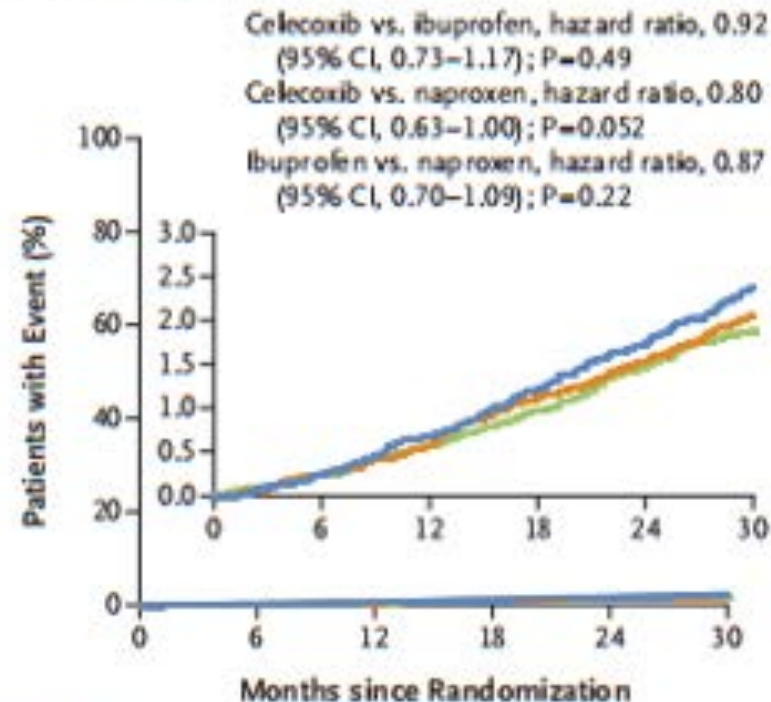
C Major Adverse Cardiovascular Events



No. at Risk

Ibuprofen	8040	7406	7022	6683	5951	5386
Naproxen	7969	7391	7065	6727	6009	5400
Celecoxib	8072	7507	7134	6780	6099	5524

D Death from Any Cause

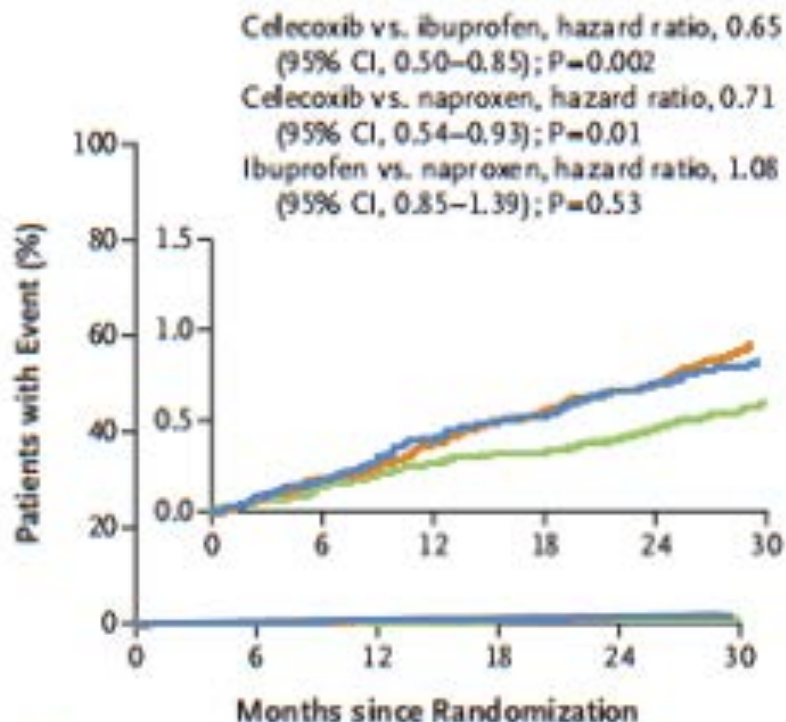


No. at Risk

Ibuprofen	8040	7476	7160	6871	6164	5509
Naproxen	7969	7450	7169	6883	6189	5602
Celecoxib	8072	7568	7253	6939	6289	5741

PRECISION Trial Results

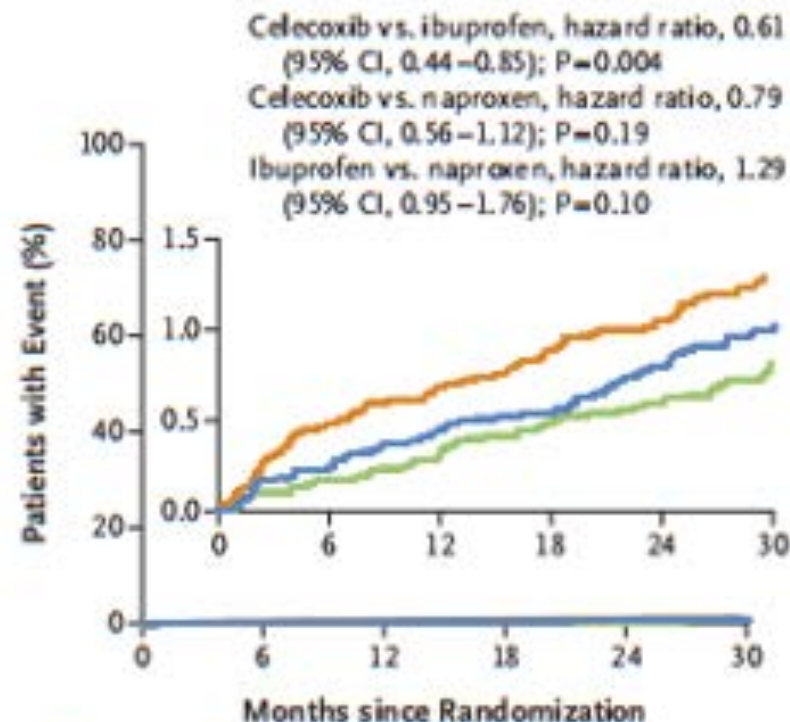
E Serious Gastrointestinal Events



No. at Risk

Ibuprofen	8040	7449	7109	6794	6079	5505
Naproxen	7969	7427	7113	6814	6099	5507
Celecoxib	8072	7549	7216	6896	6233	5674

F Renal Events



No. at Risk

Ibuprofen	8040	7440	7116	6820	6113	5552
Naproxen	7969	7433	7141	6852	6147	5556
Celecoxib	8072	7556	7234	6907	6256	5701

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

Wait a second...

- “The Risk of Major NSAID Toxicity with Celecoxib, Ibuprofen or Naproxen: A Secondary Analysis of the PRECISION Randomized Controlled Clinical Trial.”
 - Daniel H. Solomon, M. Elaine Husni, Peter A. Libby, Neville D. Yeomans, AM Lincoff, Thomas F. Luscher, Venu Menon, Danielle M. Brennan, Lisa M. Wisniewski, Steven E. Nissen, Jeffrey S. Borer.
 - Accepted manuscript: The American Journal of Medicine (2017), <http://dx.doi.org/doi:10.1016/j.amjmed.2017.06.028>

Results

- During follow-up, major toxicity sustained:
 - Celecoxib 4.1% subjects
 - Naproxen 4.8% subjects
 - Ibuprofen 5.3% subjects
- This translated into numbers needed to harm of:
 - 135 for naproxen compared with celecoxib
 - 82 for ibuprofen compared with celecoxib
- Among patients with symptomatic arthritis who had moderate to high risk of CV events, about 1 in 20 had a major toxicity over 1-2 years.
- Patients using naproxen or ibuprofen experienced significantly higher risk of major toxicity than those using celecoxib.

NSAIDs



PainWeek.

Medical Cannabis

So who's with me?

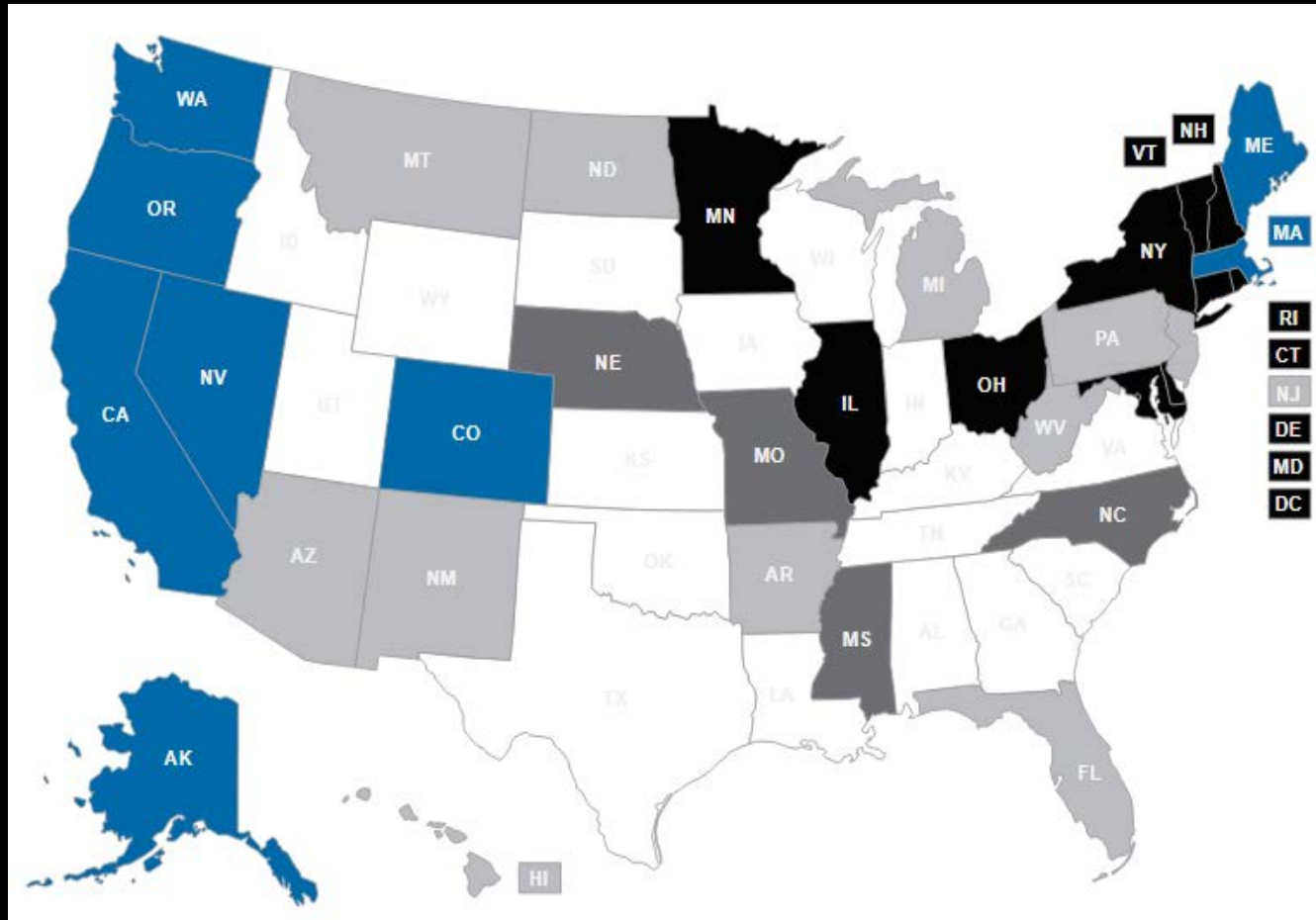
I would prescribe or recommend cannabis (medical marijuana) for a patient with a disease or symptom where cannabis has been shown to be helpful.

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

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

Current State of Affairs



Medical marijuana laws

Removed jail time for possessing small amounts of marijuana

Medical marijuana laws + removed jail time for possessing small amounts of marijuana

Medical marijuana laws + marijuana is legal for adults and is taxed and regulated similarly to alcohol

Legal in 29 U.S. states, the District of Columbia, Guam, and Puerto Rico

Cannabis

- “Cannabis” is the genus name for the entire plant.
- Three 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)



Clinical Effects of Cannabis

Symptom Relief

- Addiction
- Anxiety, tension, stress
- Depression
- Digestive problems
- Inflammation
- Nausea and vomiting
- Pain
- Spasms and Convulsions

Disease Management

- Arthritis
- ADHD, PTSD
- Cancer treatments
- Gastrointestinal Disorders
- HIV/AIDS
- Insomnia
- Migraine
- Movement disorders
- Multiple sclerosis

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 Schmidtkofer, MSc; Marie Westwood, PhD; Jos Kleijnen, MD, PhD

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 $\geq 30\%$ reduction in pain was greater than placebo (especially with neuropathic pain)

SS: Statistically significant

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

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

Muscle Spasticity

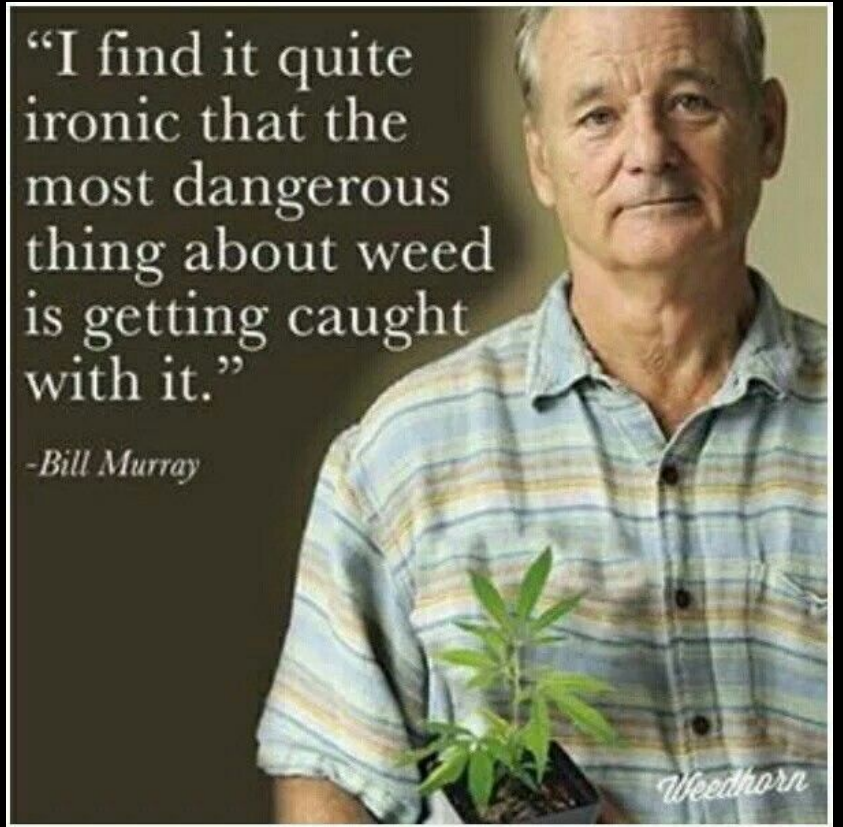
- Commonly associated with painful spasms and sleep disturbances, and contributes to increased morbidity
- Largely studied in patients with multiple sclerosis
- Systematic review (*Koppel et al.*)
 - Nabiximols (THC:CBD extract) and orally administered THC are “probably effective” for reducing patient-reported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

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 first-line 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

Safety of Cannabis

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



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



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

Cannabinoid Hyperemesis Syndrome

■ Three Phases

– Pre-emetic or Prodromal

- Can last for months or years
- Patients develop early morning nausea, a fear of vomiting, and abdominal discomfort

– Hyperemetic

- Paroxysms of intense and persistent nausea and vomiting, commonly described as overwhelming and incapacitating
- Patients take numerous hot showers throughout the day to alleviate symptoms (learned behavior); rapidly becomes a compulsive behavior

– Recovery

- Can last for days, weeks, or months
- Relative wellness and normal eating patterns
- Weight is regained and bathing returns to regular frequency

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. non-reporters
 - 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

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 FEV₁; 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.

Long-Term Use of Cannabis

■ 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 than those who had not.
- 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) in regular users.
- The risk of developing psychosis doubles from ~7 in 1000 non-users to 14 in 1000 for regular cannabis users; important for patients with an affected first-degree relative

■ Affective disorders

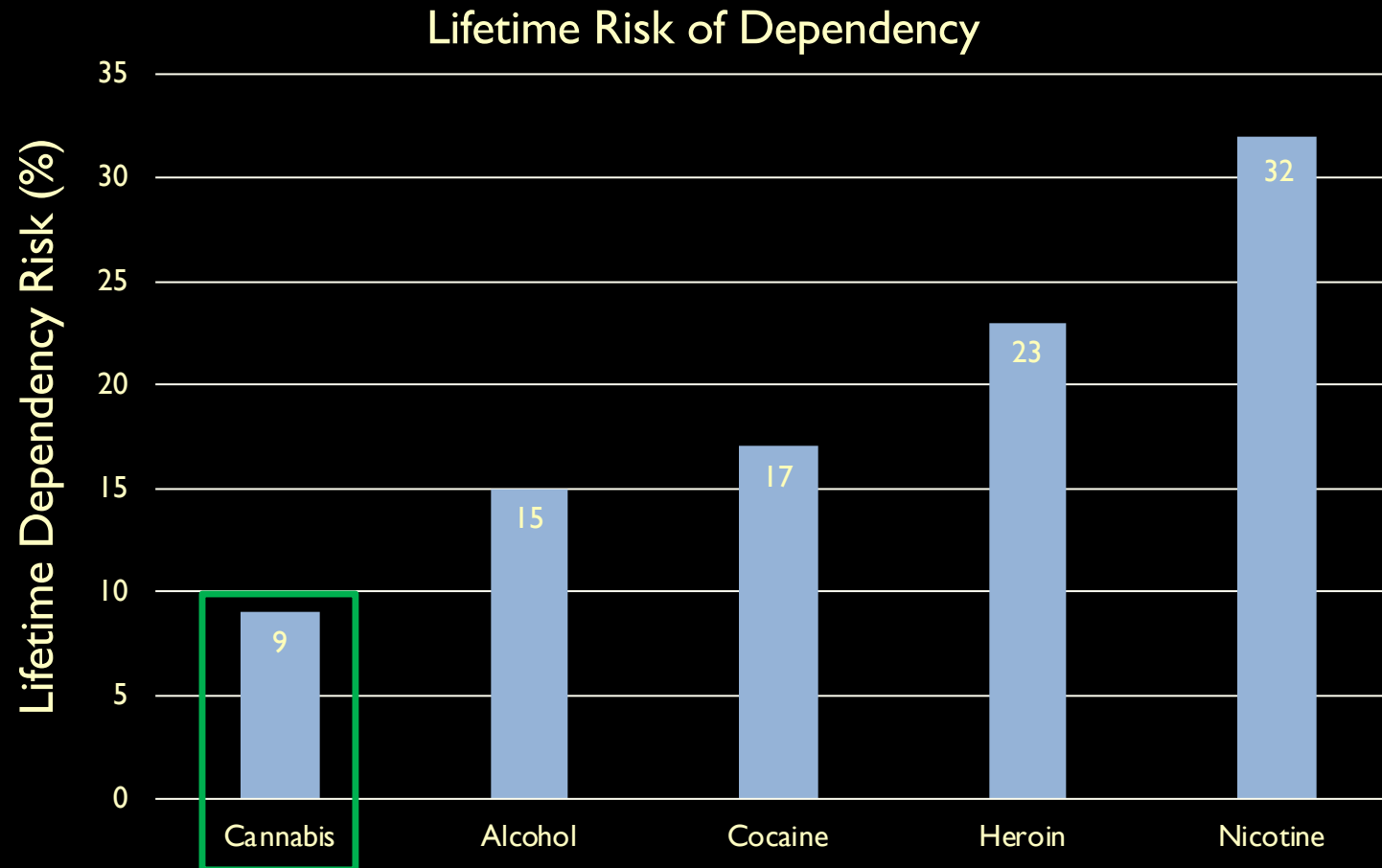
- No longitudinal association between cannabis use and incidence of depression/anxiety has been documented.
- Cannabis use associated with increased symptoms of mania and hypomania in individuals with bipolar disorders

Long-Term Use of Cannabis

■ 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 re: associations with head and neck squamous cell carcinoma, bladder cancer, and non-Hodgkin's lymphoma.
 - Cannabidiol (CBD) may have an anti-neoplastic effect?

Risk of Addiction & Dependence



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

Our Responsibility as Healthcare Providers⁵²

- 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.



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.

Sound Familiar?

- 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.

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 U.S.
- 16,000 to 19000 overdose deaths annually; \$20 to \$120 billion in related expenses
- 53% of people age 12 or older abusing analgesics report getting them from a friend or relative

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**

NIH Role of Opioids in the Treatment of Chronic Pain 2014

- 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** (e.g., PDMPs) into this assessment
- **Triage** those screening at highest risk for harm to more structured and higher intensity monitoring approaches

NIH Role of Opioids in the Treatment of Chronic Pain 2014

- 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 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

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 of opioids for chronic pain, **improve safety and effectiveness** of pain treatment, and **reduce risks with long-term** opioid therapy
- 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

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

Evidence Review

- 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

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 = 568640)	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 = 21739 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 = 426124) 1 case-control study (n = 11693 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 = 11327)	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 = 568640)	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)

Non-pharmacologic and Non-opioid 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 first-line** or routine for chronic pain
- Long-term benefits of non-opioid 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**

Non-pharmacologic and Non-opioid Therapy

- 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

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. I- <20 mg MME/d

Steady increase in dose-dependent manner; rate of increase 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. I- <20 mg MME/d

20- <50 MME/d, 50- <100 MME/d, 100-199 MME/d associated with **OR 1.3, 1.9, 2.0** vs. I- <20 mg MME/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. I- <20 mg MME/d

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 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
 - Over-dose rates were 10x higher with co-prescribed benzos (7/10,000 person-years vs 0.7/10, 000 person years)

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...**

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

4. ...**Prescribe immediate-release opioids** instead of extended-release/long-acting (ER/LA) 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 D/C opioids**.

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**.

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 Renthall, MD, of the Department of Neurology at Brigham and Women's Hospital of Harvard Medical School, in JAMA Neurology

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?*

What about this scenario?

- Mr. M 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.

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 contracts!



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

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