FUNCTIONAL MEDICINE
Continuing Education

Medical Cannabis and the Treatment of Pain: Holy Grail or Total Fail?

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Disclosures

- Lindsey Elmore does not report any actual or potential conflicts of interest in relation to this continuing pharmacy education course.

Objectives

- Describe the history of medical cannabis and the recent changes to the legal status of CBD.
- Assess current literature for various medical cannabis products' safety and efficacy in the treatment of acute and chronic pain.
- Using a specific patient case, develop a medical cannabis treatment plan for patient with pain.

Background

- *Cannabis sativa* is one of the most used illicit drugs in the world
- Estimated use by 200,000,000 people in the last 12 months
- 66% of the US population supports legalization
- First legalized in the US in California in 1996
- Now 34 states plus DC, PR, and Guam permit medical use; 10 states support recreational use
- State regulations are in direct conflict with federal statutes
- New FDA labeling mandates confuse the clinician further

Active Substances

- Cannabis, like all herbs, is a polypharmaceutical substance
- The cannabis-derived cannabinoids of most therapeutic interest are THC and cannabidiol (CBD)
- Minor cannabinoids include cannabigerol, cannabichromene, and tetrahydrocannabivarin (a short-chain C19 homolog of THC)
- As many as 420 other constituents occur in the plant

Chronic Pain

- A debilitating medical condition that may be either difficult to treat or refractory to pharmacotherapy
- Defined as lasting more than 3-6 months after injury or insult
- May be musculoskeletal, inflammatory, mechanical or compressive, or neuropathic
- May limit mobility, lead to hormonal imbalances, neuropsychiatric disorders or poor quality of life

Treatment is Multifactorial

- Pharmacologic
  - Opioids
  - Anticonvulsants (gabapentin, pre-gabalin)
  - Antidepressants (amitriptyline, venlafaxine, duloxetine)
  - Topical agents (capsaicin)
- Non-pharmacologic
  - Massage
  - Acupuncture
  - Physical therapy/pet therapy
  - Meditation

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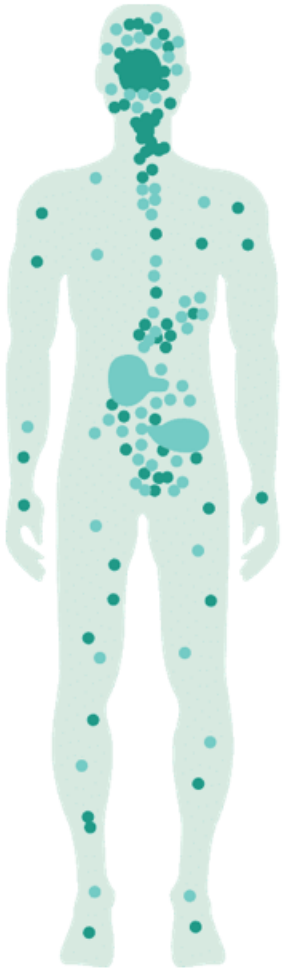
Chronic Pain and Cannabis

- Chronic pain is the most frequently cited medical condition, with interest in both reducing opioid requirements and in substituting for opioid therapy
- National Academy of Sciences, Engineering, and Medicine suggests that there is conclusive evidence that cannabis or cannabinoids are effective for the treatment of chronic pain
- States with medical cannabis laws have lower mortality rates from opioids

Manzanares J, et al. *Curr Neuropharmacol*. 2006;4(3):239–257.
Bachhuber MA, et al. JAMA Intern Med. 2014 Oct; 174(10):1668-73.

The Endocannabinoid System



CB1

CB1 Receptors target:

- Motor activity
- Thinking
- Motor co-ordination
- Appetite
- Short term memory
- Pain perception
- Immune cells

CB2

CB2 Receptors are much broader than CB1 and influence most of the body

- Gut
- Kidneys
- Pancreas
- Adipose tissue
- Skeletal muscle
- Bone
- Eye
- Tumours
- Reproductive system
- Immune system
- Respiratory tract
- Skin
- CNS
- Cardiovascular system
- Liver

Analgesic effects of medical cannabis?

- CB receptor agonists:
  - Have antinociceptive and anti-hyperalgesic effects for both acute and chronic pain
  - Modulate nociceptive thresholds by regulating neuronal activity, and relieve pain by acting on non-nervous tissues
  - Exert analgesic effects on wind-up effect
- CB_1 receptors also present in mast cells; may lead to anti-inflammatory effects
- Both CB_1 and CB_2, are upregulated in models of chronic pain

Manzanares J, et al. *Curr Neuropharmacol*. 2006;4(3):239–257.

Role of Functional Medicine

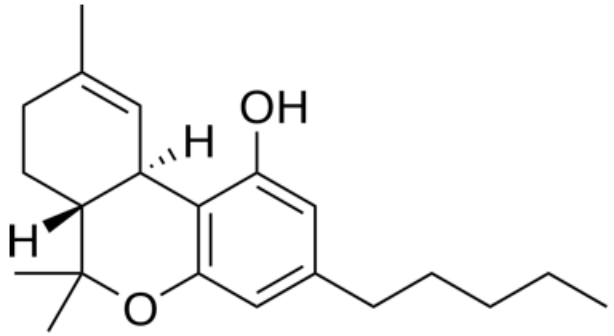
- Chronic pain may also be relieved with conventional functional medicine approaches such as
  - Elimination Diet
  - Physical Exercise
  - Mindful Eating
  - Sleep hygiene
  - Stress management

One Review to Demonstrate the Problem

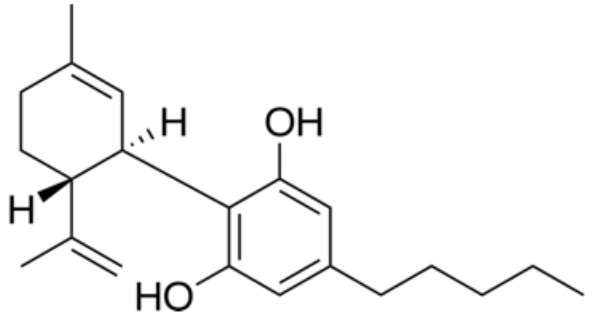
Systematic Review

- 28 studies, 2454 participants
- Formulations of cannabis include:
  - Nabiximols (13 studies)
  - Nabilone (5 studies)
  - Smoked THC (4 studies)
  - THC oromucosal spray (3 studies)
  - Ajuvenic acid (1 study)
  - Oral THC (1 study)

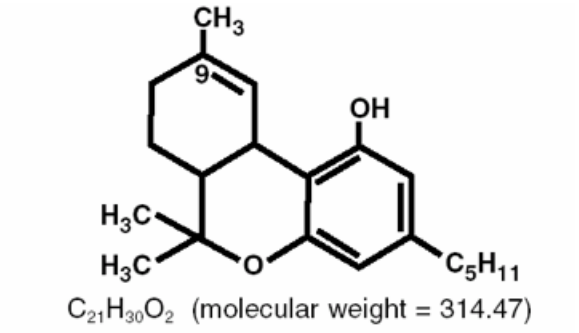
Compounds and Drugs



THC/Nabiximols

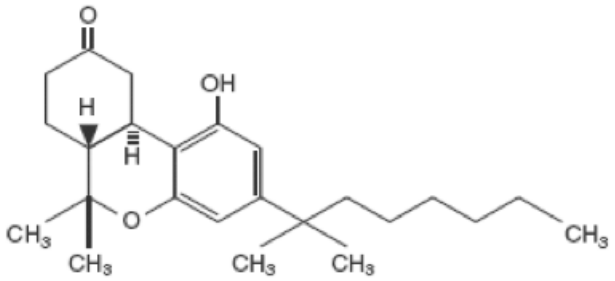


CBD

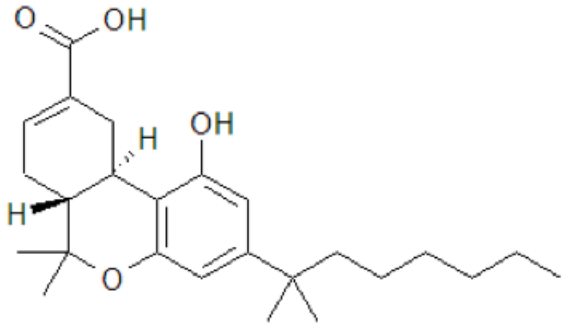


$C_{21}H_{30}O_2$ (molecular weight = 314.47)

Dronabinol



Nabilone



Ajuvenic Acid

Systematic Review

- When compared to either placebo or comparator, pooled analysis shows a 30% or greater improvement in pain
- Most common side effects were dizziness, dry mouth, nausea, fatigue, somnolence, euphoria, confusion, loss of balance, and hallucinations

Whiting PF, et al. *JAMA* 2015;313:2456-73

Challenges

- This study review article illustrates that difficulty in cannabis for chronic pain
  - Lack of robust efficacy
  - Limited number of trial participants
  - Lack of standardization between cannabis products
    - No standard dose, ratio of THC to CBD, no evidence that one product that is currently available on the market can duplicate these findings

Also Challenging

- Much of the data related to cannabis and chronic pain uses an orally available product
- But the FDA has deemed all oral preparations of CBD as mislabeled except for FDA-approved medications
- Furthermore, all non-FDA products cannot make disease claims
- Plus, CBD products are considered substances authorized for investigation
- While patients are using THC and CBD by mouth, the role of the pharmacist in guiding this behavior is challenging at best

https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd

Preparations

Smoked Cannabis

- Difficult route to study, widely varying levels of THC and CBD
- RCT assessed smoked cannabis in patients with chronic neuropathic pain
  - Found a dose-response relationship between the potency of inhaled cannabis and pain amelioration
  - Statistically significant improvement in average daily pain scores between the highest potency and control group
- Presents a control problem

Beeham W, et al. Cannabinoids in the Older Person: A Literature Review. *Geriatrics* 2020, *5*(1), 2.

Mixed Cannabinoids

- Also difficult to study because no differentiation between natural or synthetic forms of combine THC and CBD
- No standardized ratio of THC to CBD
- May be administered orally or oromucosal spray

Mixed Cannabinoids

- 104 studies were eligible (n=9958 participants), including 47 RCTs and 57 observational studies
  - 48 neuropathic pain
  - 13 multiple sclerosis
  - 7 fibromyalgia, 6 visceral pain, 1 Rheumatoid arthritis
  - 29 mixed or other
- PERs for 30% reduction in pain were 29.0% (cannabinoids) vs 25.9% (placebo); NNB was 24. NS for 50% reduction in pain
- Δ pain intensity was -3 mm on a 100 mm VAS greater than placebo (95% CI -0.20 to -0.08)
- PERs for all-cause ADEs were 81.2% vs 66.2%; NNH: 6 (95% CI 5-8)
- No significant impacts on physical or emotional functioning

Stockings E. Pain. 2018 Oct;159(10):1932-1954

Nabilone Meta-Analysis

- Nabilone, a synthetic cannabinoid, is approved for treatment of severe nausea and vomiting associated with chemotherapy
- Eight RCTs, 2 prospective cohort trials, and 1 retrospective chart review
- Cancer pain, chronic noncancer pain, neuropathic pain, fibromyalgia, and pain associated with spasticity
- Nabilone adjunctive therapy and led to small but significant reductions in pain
- Most common ADEs were euphoria, drowsiness, and dizziness, rarely required drug discontinuation

Tsang CC, *Pharmacotherapy*. 2016;36(3):273–286.

Dronabinol

- Indicated for the treatment of anorexia in patients with AIDS and nausea and vomiting associated with cancer, but also used for pain.
- 240 patients with Multiple sclerosis and neuropathic pain randomized to 16-week placebo-controlled trial with a 32-week open label continuation and then long-term follow up.
- 100 patients continued therapy for up to 119 weeks.
- Pain intensity during 16-weeks dronabinol and placebo treatment was reduced by 1.92 and 1.81 points without significant difference in between (p = 0.676).
- The proportion of patients with ADEs was higher with dronabinol versus placebo (50.0 vs. 25.9%), but it decreased during long-term use of dronabinol (26%).
- No signs of drug abuse and only one possible case of dependency occurred.

Schimrigk S et al. *Eur Neurol*. 2017;78(5-6):320–329.

CBD Alone

- Far less data than mixed cannabinoids or smoked cannabis, but with recent popularity of CBD isolates, research is expanding
- Great interest in CBD as a therapeutic agent because of anti-inflammatory and analgesic properties without the risk of psychiatric effects

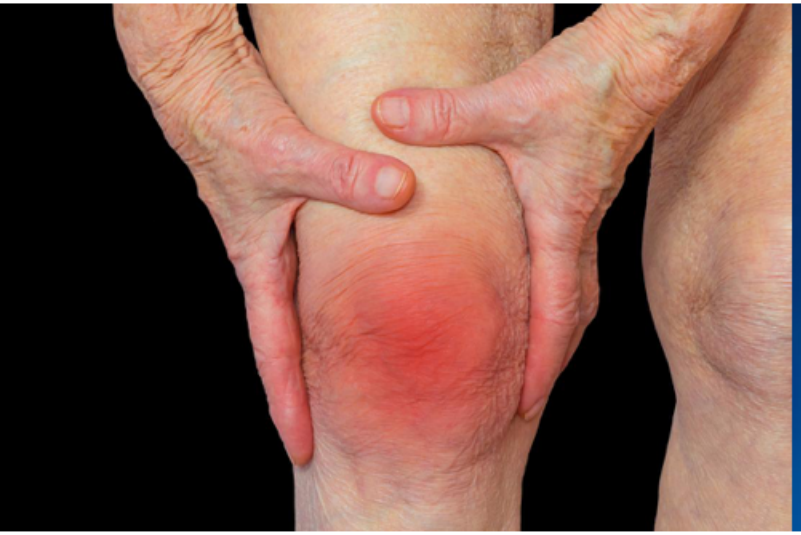
Animal Data, CBD, and Arthritis

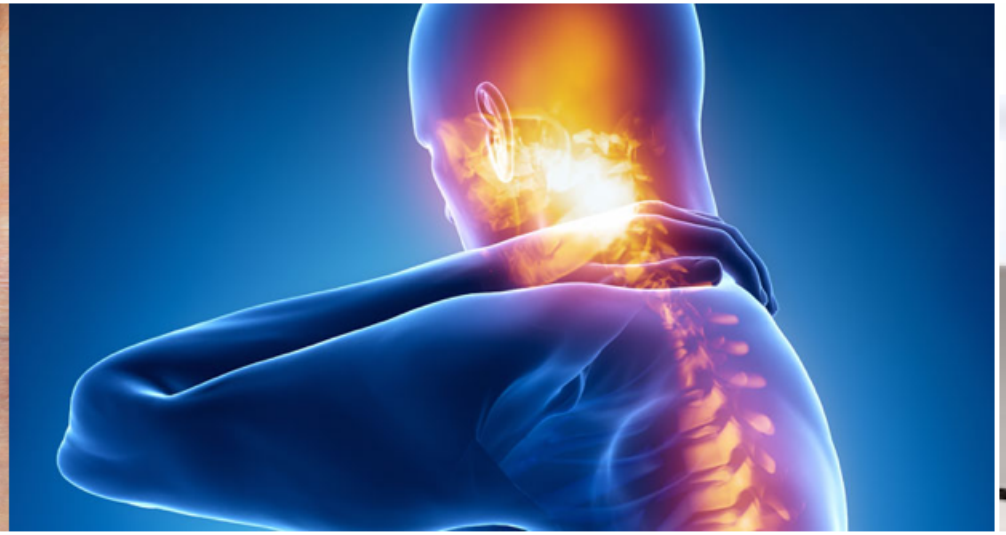
- Sprague-Dawley rats with Freud's Adjuvant-induced arthritis
- CBD gels (0.6, 3.1, 6.2 or 62.3 mg/day) were applied for 4 consecutive days after arthritis induction
- Transdermal CBD gel significantly reduced joint swelling, limb posture scores as a rating of spontaneous pain, immune cell infiltration and thickening of the synovial membrane in a dose-dependent manner up to 6.2 mg/day
- Immunohistochemical analysis of spinal cord and dorsal root ganglia revealed dose-dependent reductions of pro-inflammatory biomarkers.
- Exploratory behavior was not altered indicating limited effect on brain function.

Hammell DC, et al. *Eur J Pain*. 2016;20(6):936–948.
Malfait AM, et al. *Proc Natl Acad Sci U S A*. 2000;97(17):9561–9566.
Philpott HT, et al. *Pain*. 2017;158(12):2442–2451.

Questions?

Pain Syndromes





Neuropathic Pain

- Cochrane Database Review
- 16 studies between 2-26 weeks long with a total of 1750 participants
  - Oromucosal THC/CBD (10 studies)
  - Nabilone (2 studies)
  - Smoked cannabis (2 studies)
  - Dronabinol (2 studies)
- Most compared to placebo, one codeine
- Studies were primarily of moderate quality, but 9 ranked very high for risk of bias

Mücke M. *Cochrane Database Syst Rev.* 2018;3(3):CD012182.

Patient Characteristics

- Patients were between 34-61 years old, and the percentage of men ranged between 17% and 100%
- Neuropathic pain was associated with
  - Multiple sclerosis
  - Diabetic neuropathy
  - Plexus injury
  - HIV-neuropathy
  - Chemotherapy-induced polyneuropathy
  - Other various etiologies

Mücke M. *Cochrane Database Syst Rev.* 2018;3(3):CD012182.

Primary Outcomes

- Number of people achieving 50% or greater pain relief (21% for cannabis vs 17% for placebo; RD 0.05 (95% CI 0.00 to 0.09); NNB 20
- More participants withdrew due to adverse events with cannabis (10%) vs placebo (5%) (RD 0.04 (95% CI 0.02 to 0.07); NNH 25
- Not enough evidence to determine if cannabis increase frequency of serious ADEs vs placebo
- Low quality evidence

Mücke M. *Cochrane Database Syst Rev.* 2018;3(3):CD012182.

Secondary Outcomes

- Cannabis medicines increase
  - The number of people achieving pain relief of 30% or greater versus placebo (39% versus 33%; RD 0.09 (95% CI 0.03 to 0.15); NNB 11 (95% CI 7 to 33)
  - Nervous system adverse events compared with placebo (61% versus 29%; RD 0.38 (95% CI 0.18 to 0.58); NNH 3 (95% CI 2 to 6)
- Psychiatric disorders occurred in 17% of participants using cannabis-based medicines versus 5% using placebo (RD 0.10 (95% CI 0.06 to 0.15); NNTH 10 (95% CI 7 to 16)

Mücke M. *Cochrane Database Syst Rev.* 2018;3(3):CD012182.

Osteoarthritis

- OA was induced in male Wistar rats by intra-articular injection of 3 mg sodium monoiodoacetate.
- On day 14, joint mechanosensitivity was assessed and pain behavior was measured
- In end-stage OA, CBD dose-dependently decreased joint firing rate, and increased withdrawal threshold and weight bearing ($P < 0.0001$; $n = 8$).
- Acute, transient joint inflammation was reduced by local CBD ($P < 0.0001$; $n = 6$)
- Prophylactic administration prevented development of MIA-induced joint pain at later time points ($P < 0.0001$; $n = 8$), and was also found to be neuroprotective ($P < 0.05$; $n = 6$-8).
- Prophylactic CBD treatment prevented the later development of pain and nerve damage in these OA joints.

Philpott HT. *Pain*. 2017;158(12):2442–2451.

Rheumatoid Arthritis

- People who took oromucosal cannabis
  - rated their pain 0.7 points lower on a scale of 0 to 5 after 5 weeks treatment
  - rated their pain as 2.6 on a scale of 0 to 5 after 5 weeks
- People who took a placebo rated their pain as 3.3 on a scale of 0 to 5
- Total adverse events
  - 27 more people out of 100 experienced an adverse event after 4 weeks treatment with oromucosal cannabis (absolute difference 27%). These were most commonly dizziness (26%), light headedness (10%), dry mouth (13%), nausea (6%) and falls (6%); they completely resolved once treatment was ceased
  - 35 out of 100 people who took oromucosal cannabis suffered an adverse event
  - 8 out of 100 people who took a placebo suffered an adverse event

Richards BL et al. *Cochrane Database Syst Rev*. 2012;1(1):CD008921.

Inflammatory Bowel Disease

- IBD patients reported using cannabis to relieve symptoms of abdominal pain, nausea, diarrhea, anorexia, as well as to improve mood and quality of life
- In an anonymous questionnaire-based study, IBD patients reported that cannabis improved abdominal pain (83.9%), abdominal cramping (76.8%), joint pain (48.2%), and, to a lesser extent, diarrhea (28.6%)
- An estimated 9-18% of all IBD patients use cannabis

Picardo S. *Therap Adv Gastroenterol*. 2019;12:1756284819870977.

Crohn's Disease

Author	Design	IBD	n=	Type	Safety	Results
Naftali	Retrospective Observational	CD	30	Oral or Inhaled Cannabis	Not reported	Improvement in disease activity (⩾4 point reduction in HBI score). A reduction in need for other medications
Naftali	Prospective Placebo Controlled Trial	CD	21	Cigarettes containing 115 mg THC twice daily	No difference	No difference in clinical remission. (CDAI score <150) Benefits in clinical response (decrease in CDAI of >100) and steroid use. Improvement in symptoms (sleep and appetite)
Naftali	Prospective Placebo Controlled Trial	CD	19	Oral CBD 10 mg twice daily	No difference	No beneficial effects in IBD. (Decrease in CDAI >70) Safe and well tolerated

Picardo S. *Therap Adv Gastroenterol*. 2019;12:1756284819870977.

Ulcerative Colitis/CD

Author	Design	IBD	n=	Type	Safety	Results
Irving	Double Blind placebo controlled, Parallel-group	UC	60	Oral capsule containing 50 mg CBD rich botanical extract taken twice daily	Higher mild-moderate adverse effects in treatment group (90% *versus* 48% in placebo)	Not effective in inducing remission. (Mayo score of ⩽2 with no sub score >1) Improved quality of life and global impression of change scores.
Lahat	Prospective Observational	CD and UC	13	50 g dry processed cigarettes per month	Not reported	Improvement in quality of life scores and disease activity indices (HBI)

Picardo S. *Therap Adv Gastroenterol*. 2019;12:1756284819870977.

Before Recommending

Selecting a Medical Cannabis Product

- Patient Preference
  - Many patients do not want the social stigma of smoking
  - Vaping is theorized to be a safer option, but jury is out
  - Candies, sodas, and edibles vary widely
  - Medications may put some patients at greater ease
  - THC versus CBD alone
- Duration of Action
  - Longer duration of action and onset of action with edible products versus smoked cannabis

Contraindications/Precautions

- Absolute Contraindications
  - Acute psychosis and other unstable psychiatric conditions
- Relative contraindications
  - Severe cardiovascular, immunological, liver, or kidney disease, especially in acute illness
  - Cannabis may exacerbate arrhythmia or a history of arrhythmias
  - Pregnancy or nursing
  - Parkinson's disease
  - Increased risk of *aspergillus* infection
- Lower doses recommended for patients with liver disease

Drug Interactions

- Little is known about clinically significant drug interactions
- THC and CBD are metabolized by CYP3A4 and CYP2C9
  - CYP3A4 inhibitors slightly increase THC levels.
  - CYP3A4 inducers slightly decrease THC and CBD levels.
- CBD, but not THC, is metabolized by CYP2C19

Yamaori et al 2012, Watanabe et al 2007
Stout and Cimino 2014

Drug Interactions

- THC is a CYP1A2 inducer
  - Theoretically, THC decreases concentrations of clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine
- CBD is a potent inhibitor of CYP3A4 and CYP2D6.
  - CBD may increase serum concentrations of macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil, antihistamines, haloperidol, antiretrovirals, and some statins (atorvastatin and simvastatin)
  - CYP2D6 metabolizes antidepressants, so CBD may increase serum concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids (including codeine and oxycodone)

Drug Interactions

- THC is known to increase warfarin levels
- Alcohol increases THC levels
- Smoked cannabis decreases theophylline levels
- Additive effects with medications that cause sedation

Side Effects

- Side effect profile depends on preparation
- CBD/THC effects
  - Drowsiness
  - Dry mouth, lightheadedness, and low blood pressure
  - Liver injury is possible, but uncommon
- THC specific effects
  - Paranoia
  - Anxiety
  - Red eye
  - Hunger
  - Memory impairment
  - Euphoria/"high"

Psychiatric Effects

- Although cannabis acts as an anxiolytic in low doses, high doses can be anxiogenic and can elicit panic reactions
- Chronic use may increase the risk of depression, although studies are mixed. A meta-analysis of 14 studies showed a weak risk (HR 1.17, 95% CI 1.05-1.30)
- Whether or not cannabis can cause psychosis is debated.
- Studies suggest that people at risk for schizophrenia run a higher risk of psychosis outcomes after cannabis use
- A study of cannabis use in 1237 people with schizophrenia, who had ever used cannabis, found no additive effect of cannabis use on cognitive dysfunction
- Smoking cannabis with a significant proportion of CBD may produce fewer psychotic symptoms

Lev-Ran et al 2014, Morrison et al 2015
Morgan and Curran 2008, Schubart et al 2011

Cannabis-Induced Hyperemesis

- Chronic cannabis use may be associated with Cannabinoid Hyperemesis Syndrome
  - Characterized by episodes of nausea and vomiting, abdominal pain, and sometimes polydipsia.
  - Obsessive hot-water bathing may be observed, as it alleviates symptoms.
  - The syndrome can lead to weight loss or acute renal failure from dehydration.
  - The etiology of CHS is thought to be activation of CB1 receptors that can reduce gastric emptying.

Special Populations

- No studies that assess specific effects on pain in elderly people
- Chronic Pain in Kidney Transplant
  - 7 patients mean age of 64.5 years, CBD dose from 50-150 mg BID for 3 weeks
  - Tacrolimus levels required measurement with appropriate dose adjustments; cyclosporin patients were stable
  - 2 patients had total pain improvement, 4 had a partial response, and 1 no change
  - ADEs were mild, but included nausea, dry mouth, dizziness, drowsiness, and episodes of heat

Cuñetti L, et al. *Transplant Proc*. 2018;50(2):461–464.

Adolescents

- Cannabis use in adolescence may increase psychotic symptoms later in life.
- A systematic review of the impacts of cannabis use during adolescence on various psychosis symptoms later in life was conducted.
- Authors concluded that “there is now sufficient evidence to warn young people that using cannabis could increase their risk of developing a psychotic illness later in life”

Moore et al 2007

True or False

- There is robust, well-controlled and validated evidence that CBD can help control chronic pain.

True or False

- There is robust, well-controlled and validated evidence that CBD can help control chronic pain.
  - False. It is difficult to conclude that CBD alone can help control pain, as most studies are conducted in combination with THC.

True or False

- There is consistency in which product to recommend for each disease state.

True or False

- There is consistency in which product to recommend for each disease state.
  - False, many times selection of a product comes down to patient preference.

Case

- BD presents to you with numbness, leg, spasms, and pain associated with Multiple Sclerosis.
- She is 37 yo with a family history of schizophrenia, depression and urinary urgency.
- She takes gabapentin, escitalopram, gabapentin, oxybutynin, and nitrofurantoin.
- Before starting medical cannabis, what would you consider?

Case

- Psychiatric history
  - Some experts contend that cannabis should not be used in patients with a history of psychosis
- Drug interactions
  - CBD strongly inhibits CYP 2D6, increased risk of SSRI syndrome with escitalopram

Case

- BD presents to you with numbness, leg, spasms, and pain associated with Multiple Sclerosis.
- She is 37 yo with a family history of schizophrenia, depression and urinary urgency.
- She takes gabapentin, escitalopram, gabapentin, oxybutynin, and nitrofurantoin.
- Which preparation of cannabis would you select?

Case

- How would you decide between:
  - Smoked cannabis
  - Vaporized cannabis
  - Oromucosal THC
  - Edible THC/CBD
  - CBD alone

Case

- BD presents to you with numbness, leg, spasms, and pain associated with Multiple Sclerosis.
- She is 37 yo with a family history of schizophrenia, depression and urinary urgency.
- She takes gabapentin, escitalopram, gabapentin, oxybutynin, and nitrofurantoin.
- What counseling points would you provide BD?

Case

- Edible preparations have a delayed onset of action, do not redose for at least 90 minutes
- Report mental status changes immediately
- Side effects: drowsiness, dizziness, GI upset, and if product contains THC, euphoria

Conclusion

- From a regulatory and research perspective, CBD and THC are a bit of the wild west
- Still, humans have been using marijuana as a medication for more than 5000 years
- While the risks appear low, the conflicting laws, regulatory status, and wide array of products make the pharmacist's job difficult

Conclusion

- If patients choose to use cannabis, here is some general advice:
  - Be sure that you are using in accordance to local laws
  - Be aware of the most common side effects: dizziness, sedation, dry mouth, hunger
  - If you are subjected to drug testing in the workplace, only choose products with CBD alone

Questions?

Let's Keep in Touch

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