



Alternate Drugs in Pain Management

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Disclosure information

No conflicts to disclose.

Katrina Harper, PharmD, MBA, BCPS, DPLA

Senior clinical manager, center of pharmacy practice excellence

katrina.harper@vizientinc.com



Learning Objectives

1. List common alternative medication used for pain management
2. Discuss side effect and drug interactions of alternative drugs
3. Discuss cannabis/cannabidiol's effect on anesthesia
4. Summarize cannabis/cannabidiol anesthetic considerations

Alternative analgesics

	Side Effects	Drug Interactions	Anesthetic considerations
Ginger (Anti-inflammatory; Anti-emetic)	Diarrhea, heartburn, mouth or throat irritation	NSAIDs and warfarin	Increased bleeding risk; DC 2 weeks pre-op
Turmeric (Analgesic, anti- inflammatory, etc.)	GI distress nausea, dizziness	The ability to inhibit microsomal enzyme P450 causes the prolonged duration of many drugs like fentanyl, midazolam, warfarin, theophylline, bupivacaine, ropivacaine, and lignocaine. May result in increased stomach acid if taken with antacid drugs such as H-2 blockers or PPIs.	DC 2 weeks pre-op

Common herbs and supplements

	Side Effects	Drug Interactions	Anesthetic considerations
Echinacea (Immunity)	GI disturbances, headache, dizziness	Immunosuppressants, hepatotoxic drugs (anabolic steroids, amiodarone, methotrexate and ketoconazole)	Avoid known hepatotoxic drugs; DC 2 weeks pre-op
Ephedra (CNS stimulant; Weight loss)	Palpitations, HTN, tachycardia, stroke, seizures; MI, fatal arrhythmias, acute hepatitis, psychosis	Sympathomimetic drugs/ adrenergic drugs (epinephrine, norepinephrine, dopamine, etc.)	Caution with other sympathomimetics; arrhythmias with volatile general anesthetic agents; DC 24 hours pre-op
Garlic (Treatment of hypertension, Hyperlipidemia)	Nausea, hypotension	Potentiate the anti-platelet effects of aspirin, heparin, and NSAIDs	Increased bleeding risk; DC 7 days pre-op
Ginkgo biloba (Memory; Neuroprotective)	GI upset, headaches	NSAIDs, aspirin, and warfarin	Increased bleeding risk; DC 36 hours pre-op

Common herbs and supplements

	Side Effects	Drug Interactions	Anesthetic considerations
Ginseng (Mood enhancer)	Hypoglycemia, irritability, insomnia, GI disturbances; gynaecomastia vaginal bleeding	NSAIDS, warfarin and monoamine oxidase inhibitors [MAOIs: selegiline (Emsam), isocarboxazid (Marplan), phenelzine (Nardil), and tranylcypromine (Parnate)]	Caution with other sympathomimetics; Blood glucose monitoring intra-operatively; increased bleeding risk; DC 7 days pre-op
Valerian (Sedative)	Tremor, headache, hepatic dysfunction, cardiac disturbances	Prolong the effects of Isoflurane, Sevoflurane, Desflurane, Propofol, Etomidate, Methohexital, Thiopental and midazolam	Reduce anesthetic requirements; DC 2 weeks pre-op; Benzodiazepine-like withdrawal; Dose tapering may be a more prudent strategy
Vitamin E	High doses of vitamin E (≥ 400 IU/day) might increase the risk of bleeding	Aspirin and warfarin	Increased bleeding risk; DC 2 weeks pre-op

	Side Effects	Drug Interactions	Anesthetic considerations
St. John's Wort (Antidepressant)	GI upset, fatigue, dizziness, dry mouth, confusion, headache, photosensitivity	Selective serotonin reuptake inhibitor (SSRIs) and MAOIs; Potent inducer of hepatic cytochrome P450 CYP3A4 isoform. Hence, it may significantly increase the metabolism of many concomitantly administered drugs such as alfentanil, midazolam, and lidocaine; Induces the P450 2C9 isoform that results in the reduction in effect of warfarin, NSAIDs, cyclosporine, digoxin, oral contraceptives, indinavir, and theophylline.	May prolong the effects of anesthesia; Serotonergic crisis; DC 5 days pre-op

Alternative analgesics



Medical marijuana

What is medical marijuana?

Definition

- The use of cannabis as medical therapy to treat disease or alleviate symptoms
- Medical cannabis
 - Cannabis sativa plant (dried leaves, flowers, stems, seeds)

Methods of use

- Smoking
- Vaporizing
- Topical
- Oral ingestion
 - Sprays
 - Oils
 - Capsules
 - Edibles



Cannabinoids

Chemical class of neuromodulators that function in the endocannabinoid system (ECS)

- Relax, Eat, Sleep, Forget and Protect
- May also play a role in ameliorating refractory nausea, muscle spasticity, seizures, pain, and inflammation

Cannabinoids are recognized in 3 groups

1. Endocannabinoids
2. Phytocannabinoids
 - δ -9-tetrahydrocannabinol (THC)
 - Cannabidiol (CBD)
3. Synthetic cannabinoids



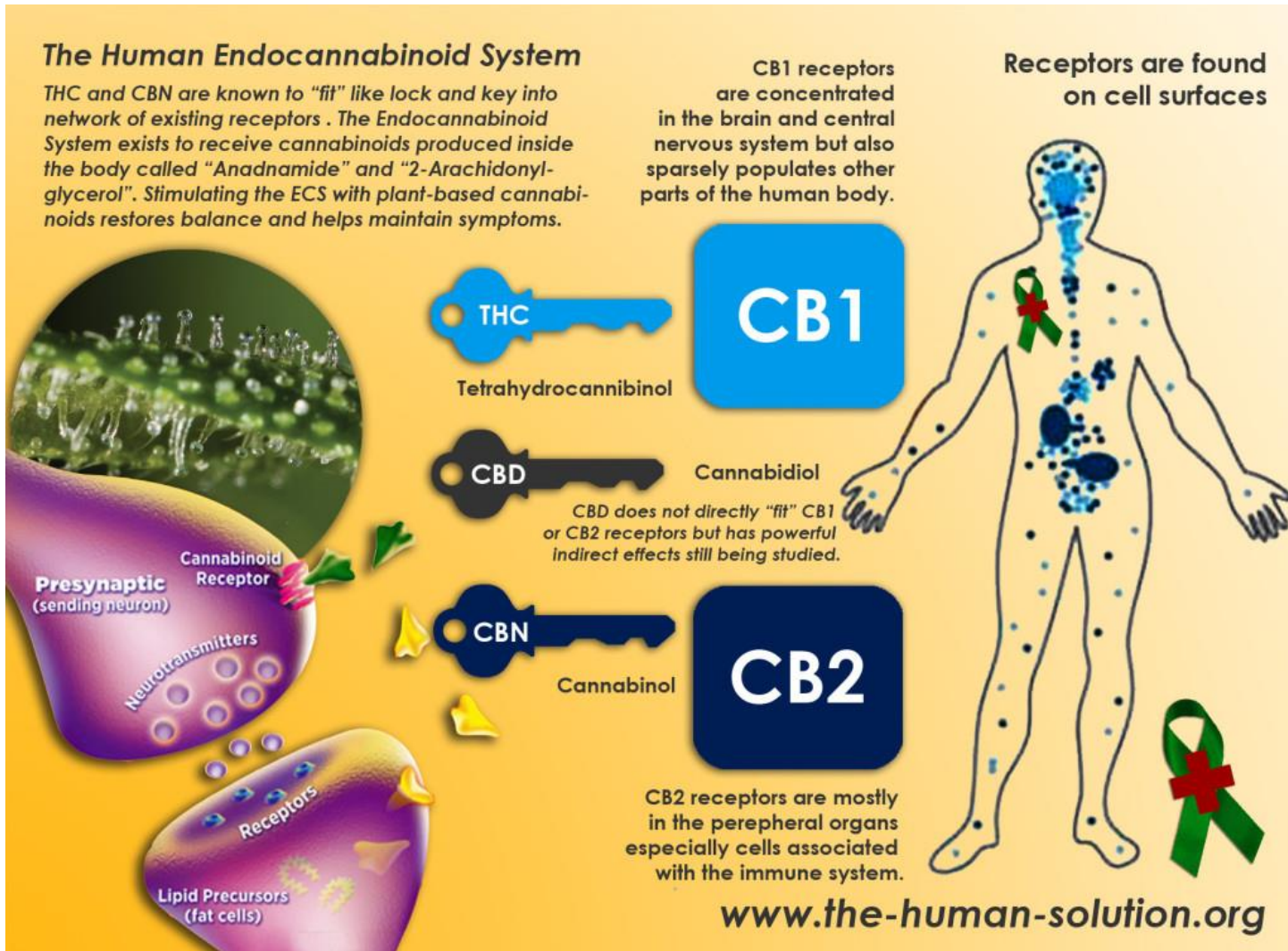
Endocannabinoid System

The Human Endocannabinoid System

THC and CBN are known to “fit” like lock and key into network of existing receptors. The Endocannabinoid System exists to receive cannabinoids produced inside the body called “Anandamide” and “2-Arachidonyl-glycerol”. Stimulating the ECS with plant-based cannabinoids restores balance and helps maintain symptoms.

CB1 receptors are concentrated in the brain and central nervous system but also sparsely populates other parts of the human body.

Receptors are found on cell surfaces



The diagram illustrates the human endocannabinoid system. On the left, a presynaptic neuron (sending neuron) is shown with neurotransmitters and cannabinoid receptors. Below it, a lipid precursor (fat cell) is shown with receptors. In the center, three cannabinoids are depicted as keys: THC (Tetrahydrocannabinol) in a light blue box, CBD (Cannabidiol) in a dark grey box, and CBN (Cannabinol) in a dark blue box. On the right, a human silhouette shows the distribution of these cannabinoids: THC and CBN are concentrated in the brain and central nervous system, while CBD is found in other parts of the body. A green ribbon with a red cross is shown on the human figure, symbolizing the endocannabinoid system's role in maintaining balance and health.

THC
Tetrahydrocannabinol

CB1

CBD
Cannabidiol

CBD does not directly “fit” CB1 or CB2 receptors but has powerful indirect effects still being studied.

CBN
Cannabinol

CB2

CB2 receptors are mostly in the peripheral organs especially cells associated with the immune system.

www.the-human-solution.org

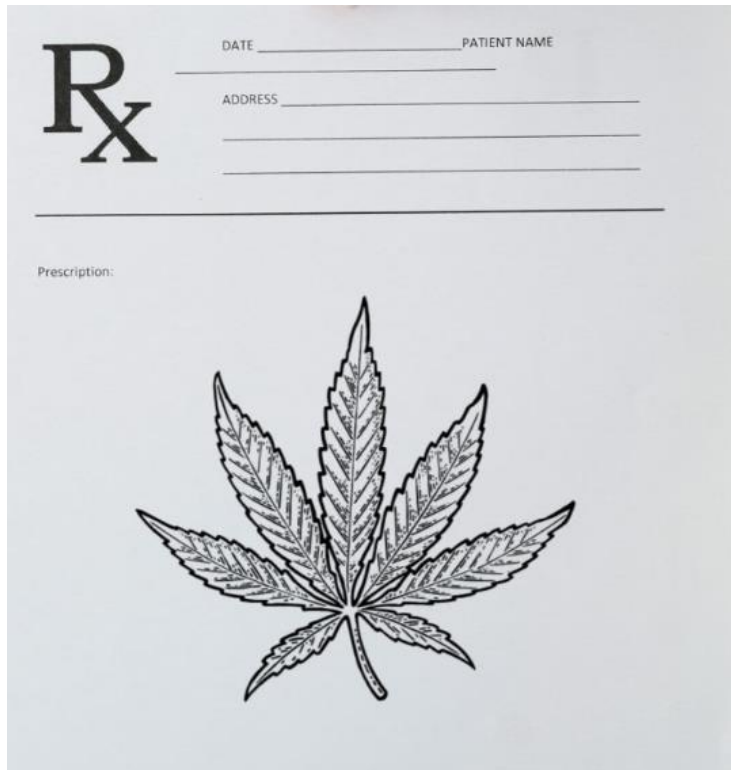
Cannabidiol Oil



- **Concentrated cannabis extract**
 - High CBD and low THC hemp, which makes it different from other medical marijuana products that usually have high concentrations of THC.
- **Sticky and viscous appearance**
- **Administered orally**
- **Preparation**
 - With whole cannabis plant, add a solvent, heat to recommended temperature, filter, and let cool
- **Solvents**
 - Petroleum Ether
 - Ethanol
 - Naphtha (butane/hexene)
 - Olive Oil (Organic)

20 to 80% THC
depending on
strain

Increasing popularity



- **Most popular illicit drug in the United States**
- **Medical use - 10.5%**
- **26% of Americans have tried CBD in the last two years**
 - Higher rates for patients with conditions that seem to respond to CBD treatment.
 - A recent survey of arthritis patients, for example, found that more than 50% of respondents had tried CBD to treat joint pain.

Federal regulations

- **Many cannabis companies don't think of themselves as Pharma**
 - Quality assurance and quality control issues
- **FDA**
 - Warned companies about the marketing of unapproved cannabidiol products with unsubstantiated claims for therapeutic or medical uses that have not been approved by the FDA
 - Considering writing new CBD specific regulations
 - Created CBD working group
 - Held May 31st public meeting on CBD

Approved Medications

Nabilone (Cesamet[®])

- Indication
 - Prophylaxis and treatment of CINV
- Patient population
 - Approved in adults and geriatric
 - Off-label indication in adolescents and children
 - *Studied dosage regimen in a randomized trial comparing nabilone to prochlorperazine in pediatric patients aged 3.5 to 17.8 years*



Dronabinol (Marinol[®])

- Indications
 - Treatment of refractory CINV
 - Appetite stimulant in patient with anorexia due to AIDS or cancer
 - *Off-label indication for Intractable pruritus secondary to cholestatic liver disease*
- Patient population
 - Approved in adults and elderly
 - Not studied in adolescents and children



Approved medications



Epidiolex[®] (cannabidiol)

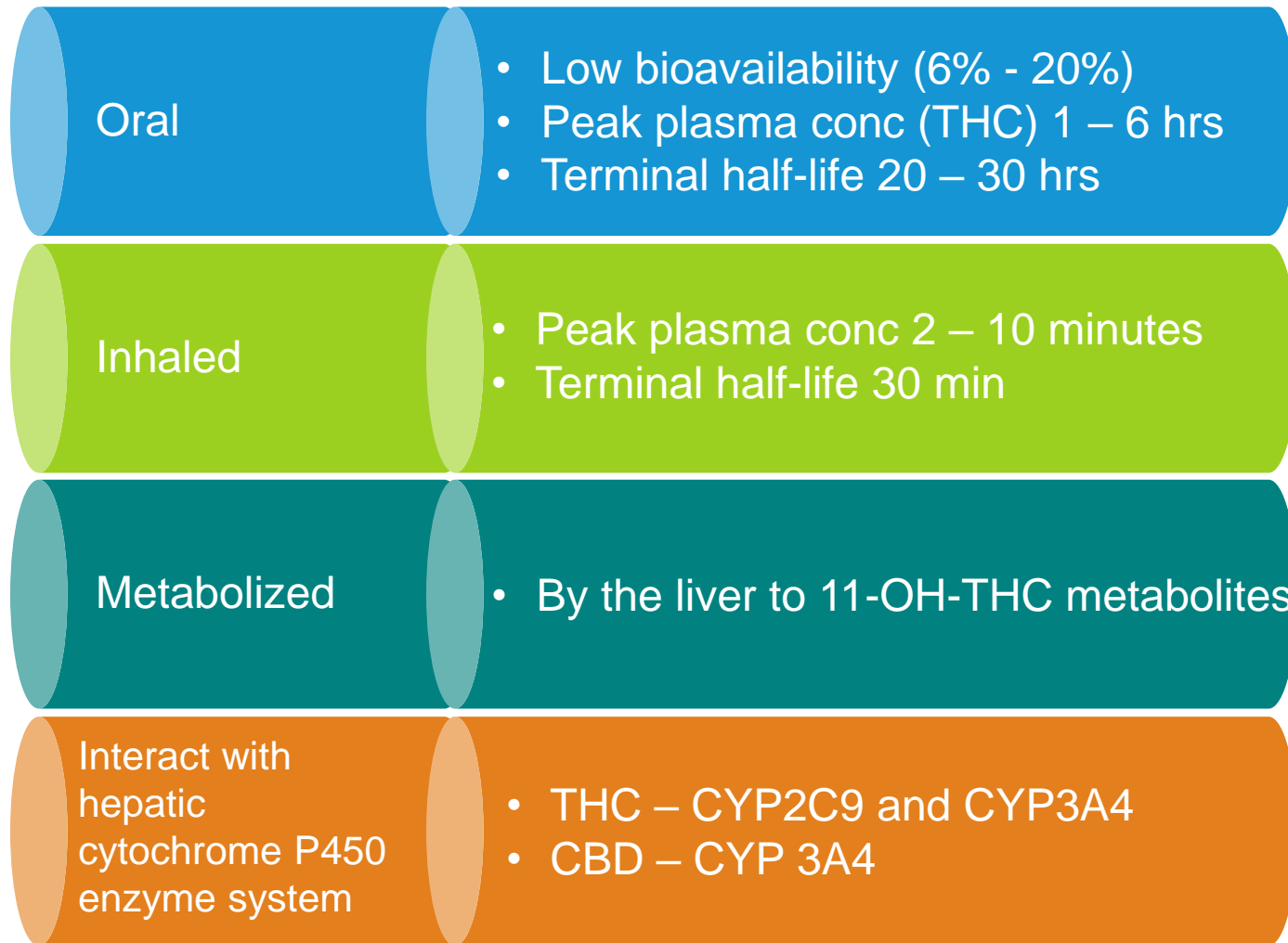
- First drug to be approved that is made directly from purified medicinal cannabis
- Treatment of two rare, serious childhood epilepsy syndromes:
 - Lennox-Gastaut syndrome
 - Dravet syndrome
- Approved June 2018 as Schedule V DEA controlled substance in patients 2 years of age and older.

Sativex (nabiximols)

- Phase III
- Cancer pain
- Multiple sclerosis spasticity



Cannabis Pharmacokinetics



Cannabis Pharmacodynamics

CNS depressant and alcohol	<ul style="list-style-type: none">• Enhanced sedative, respiratory, psychomotor effects
Sympathomimetics	<ul style="list-style-type: none">• Additive tachycardic effects
Anticholinergic agents	<ul style="list-style-type: none">• Additive tachycardic effects, possible increased blood pressure
Other possible interactions	<ul style="list-style-type: none">• Disulfiram/fluoxetine (hypomania), opioid antagonists (variable clinical findings), warfarin (INR elevation)
Induces CYP 1A2 (smoked formulation)	<ul style="list-style-type: none">• Increased substrate metabolism (e.g. theophylline)• Percentage double when combined with tobacco smoking

Marijuana Side Effects

General

- Dizziness
- Drowsiness
- Short-term memory loss
- Euphoria
- Dry mouth
- Blurred Vision
- Dry eyes
- Reddening of the conjunctiva
- Mydriasis
- Photophobia
- Weight Gain
- Vomiting

Serious

- Severe anxiety
- Psychosis
- Respiratory Depression
- Altered central nervous system responsiveness
- Increased heart rate
- Vasodilation

Adverse Health Effects of Marijuana Use

New England Journal of Medicine;
June 5, 2014; Nora Volkow M.D.

Drug effects of short-term use

- Impaired short-term memory
- Impaired coordination
- Altered judgment
- Paranoia
- Psychosis

Effects of long-term or heavy use

- Addiction
- Altered brain development
- Poor educational outcome
- Increased risk of chronic psychosis disorders in person predisposed to condition
- Symptoms of bronchitis
- Cognitive impairment
- Less life satisfaction and achievement

Effect is strongly associated with initial marijuana use in early adolescence

Drug interactions

Table. DDI Substrates: What to Look For

Enzyme	Drug Affected
UGT1A9	Propofol, fenofibrate and diflunisal
UGT2B7	Emfibrozil, lamotrigine, morphine and lorazepam
CYP2C8 and CYP2C9	Phenytoin, warfarin
CYP1A2	Theophylline, caffeine
CYP2B6	Bupropion, efavirenz
CYP3A4	Erythromycin, verapamil and ritonavir
CYP2C19	Clopidogrel, diazepam

DDI, drug-drug interactions. **Source:** Jacci Bainbridge, PharmD

Cannabinoids and anticoagulation

- **CBD oil was found to affect platelets and anticoagulants by suppressing their production and thereby potentially increasing bleeding tendencies.**
 - In vitro and in vivo studies are contradictory regarding prothrombic or antithrombotic effects
- **CBD can interact with warfarin and increase the risk of bleeding complications.**
 - CBD is metabolized through the hepatic P450 enzyme system, which warfarin also uses. Both share the same isoforms in their metabolism.
 - CBD can competitively compete with the metabolism of warfarin by occupying the same isoforms, thereby decreasing the degradation of warfarin.
- **Patients on warfarin who will be using cannabis should have their INR monitored to detect any interaction between both drugs.**

Cannabinoids and anesthesia

- A report in The Journal of the American Osteopathic Association looked at records from 250 people from Colorado undergoing an endoscopic procedure between 2015 and 2017. They were randomly chosen from a pool of 1,158 cases. In 2012, the state legalized recreational cannabis.
 - Out of 250 people, 25 were regular cannabis users. They received 19 colonoscopies, two esophagogastroduodenoscopies (EGDs), and four colonoscopy/EGDs. Of 225 non-users, 180 had colonoscopies, 27 EGDs, and 18 had colonoscopies/EGDs.
 - Those who smoked or ingested cannabis on a daily or weekly basis required (to achieve optimum sedation):
 - 14% more fentanyl
 - 20% more midazolam
 - 220% more propofol

Cannabinoids and anesthesia

- **Smoking marijuana regularly leads to the same risks of complications faced by patients who smoke cigarettes.**
 - Thus marijuana smokers are more likely than non-smokers to be on the ventilator longer, have a higher risk of developing pneumonia after surgery, and greater scarring of incisions.
- **Cannabis causes similar pulmonary complications to those of a tobacco smoker.**
 - Marijuana causes airway obstruction and increased anesthetic dosages needed to place laryngeal airways.
- **In elective procedures, inhaled (vaped or smoked) marijuana should be held preoperatively for a minimum of 72 hours.**
 - With THC and CBD being shown to be present for up to 30 days within the fat, its potential to affect the entire operative course in either chronic or acute smokers must be evaluated.

Anesthetic considerations

- 1. Keep abreast of local, state, and federal laws, as well as entity specific procedures and protocols**
- 2. If the patient is on dronabinol, nabilone, or cannabidiol, it appears safe to continue their preoperative dosage on the day of surgery and throughout their hospital course.**
 - If perioperative anxiolysis with benzodiazepines is required, the patient's level of sedation should be closely monitored.
- 3. If the patient is on a plant-derived cannabis product, obtain information from parents on dosing, mode of administration, product production, THC:CBD ratio, indication of use, symptom change with use, and compliance to medication.**
- 4. Acknowledge the possibility of withdrawal in chronic users, which could include anxiety, irritability, sweating, and insomnia.**

Anesthetic considerations

5. **If the patient is using marijuana recreationally, there may be increased airway irritability, edema, obstruction, chronic cough, bronchitis, emphysema, and bronchospasm.**
 - The perioperative period can be used to discuss risk reduction with patients using cannabis, whether it be medicinal or recreational.
6. **Monitor for medication interactions such as tachycardia or bradycardia, with the use of sympathomimetic drugs. Titrate sedative medications and opioids carefully to avoid excessive sedation.**
 - Because cannabis is mainly metabolized by CYP3A4 and CYP2C9 in the liver, drug interaction with other medications is possible and unpredictable. These include warfarin, clopidogrel, immunosuppressants, NSAIDs, celecoxib, fentanyl, oxycodone, codeine, tacrolimus, steroids, and antivirals among others.

Takeaways for Anesthesiologists

- **Conduct thorough medical and social histories that include herbs, supplements, cannabis products, and *essential oils***
- **Consider patients treated for serious and chronic debilitating conditions as possible users**
- **Screen patients for drug/drug and drug/disease interactions and counsel accordingly**
- **Discuss the contaminants including pesticides, mold, and fungi in some cannabis products, as well as contamination found in some herbs and supplements. These can be problematic to immunosuppressed patients, including in the recovery period.**

Questions?



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Katrina.Harper@vizientinc.com

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