STATEMENT OF DISCLOSURE

- I have no conflicts of interest
OBJECTIVES

- Identify the risks associated with herbal supplement use pre-transplant
- Identify major drug interactions with herbal supplements
- Explain the risks of marijuana use post-transplant
ALTERNATIVE MEDICINE

- Form of medical therapy used as a substitute for conventional medicine
  - Naturopathic medicine
  - Homeopathic medicine
  - Chinese medicine
  - Aromatherapy
  - Massage therapy
- Use of a special diet or herbal remedy to cure or alleviate the symptoms of a condition
HISTORY OF HERBAL THERAPY

- Ancient middle-eastern civilizations used herbal therapy extensively
  - Herbal gardens were created to grow medicinal plants for medical schools

- Early colonial days relied on herbal therapy to provide medical care in the home

- Herbal therapy re-emerged in the U.S. in the 1960s

- The Office of Alternative Medicines by the National Institutes of Health was established in 1992
REGULATIONS

- Dietary Supplement Health and Education Act (DSHEA) of 1994
  - Defines dietary supplements as “a product to supplement the diet”
  - Considered food, not drugs
  - No requirements for safety & efficacy testing

- Food and Drug Administration (FDA)
  - Included in the “supplement” category, not classified as a drug
  - Manufacturers exempt from approval by FDA
  - No protocol for standardization of these herbal supplements

- Lack of standard regulations and good manufacturing practice (GMP) leads to products available of variable quality and content

DIETARY SUPPLEMENTS

Vitamins
Minerals
Herbs
Amino acids
Enzymes
Organ tissues
Metabolites
FORMULATIONS

- Extracts
- Concentrates
- Tablets
- Capsules
- Gelcaps
- Liquids
- Powders
- Oils

There are >20,000 nutraceuticals available in the United States.

Approximately 36% of the population use nutraceuticals in conjunction with prescription drugs.

Majority of patients report utilizing these products to “cure” chronic conditions.

Misconception that these products are “natural” so they must be safe.

Only 12% of supplement users seek care from a physician or licensed complementary and alternative medicine provider.

HERBAL THERAPY & DIETARY SUPPLEMENTS

- 70% of patients failed to disclose their herbal supplement use

**Rationale:**
- Thoughts that physicians are not knowledgeable about herbal supplements
- Patient’s fear admitting to providers their use of non-standard therapy
- Thoughts that herbal supplement use is unrelated to their medical care
- Herbal supplements not considered medications that require reporting

Providers should seek out a history of herbal supplement use!
<table>
<thead>
<tr>
<th>TOP 10 BEST SELLING HERBAL PRODUCTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cranberry</td>
</tr>
<tr>
<td>Saw palmetto</td>
</tr>
<tr>
<td>Soy</td>
</tr>
<tr>
<td>Garlic</td>
</tr>
<tr>
<td>Gingko</td>
</tr>
<tr>
<td>Echinacea</td>
</tr>
<tr>
<td>Milk Thistle</td>
</tr>
<tr>
<td>Black cohosh</td>
</tr>
<tr>
<td>St. John’s Wort</td>
</tr>
<tr>
<td>Ginseng</td>
</tr>
</tbody>
</table>

PERI-OPERATIVE USE
SURGICAL CONCERNS

- Applicable to both organ donors and recipients

- Decreased platelet aggregation or inhibition of clotting $\rightarrow$ Bleeding

- Central nervous system (CNS) depression $\rightarrow$ Potentiation of anesthesia

- American Society of Anesthesiologists recommends that patients discontinue use of herbal supplements 2-3 weeks before surgery

<table>
<thead>
<tr>
<th>Herbal</th>
<th>Indication</th>
<th>Perioperative considerations</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Garlic (Allium sativum)</td>
<td>Vasodilatory effect ↓cholesterol</td>
<td>↑ bleeding risk through platelet dysfunction &amp; ↑ fibrinolytic activity</td>
<td>D/C 7 days prior to surgery</td>
</tr>
<tr>
<td>Ginger (Zingiber officinale)</td>
<td>N/V, motion sickness, vertigo</td>
<td>Potent inhibitor of thromboxane; ↑ bleeding risk</td>
<td>D/C 14 days prior to surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Avoid w/ use of antiplatelets, anticoagulants &amp; NSAIDs</td>
</tr>
<tr>
<td>Gingko biloba</td>
<td>Antioxidant, circulatory stimulant, dementia</td>
<td>Inhibits platelet activating factor; ↑ bleeding risk; gingko toxin</td>
<td>D/C 2 days prior to surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Avoid w/ use of antiplatelets, anticoagulants &amp; NSAIDs</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Avoid with anticonvulsants</td>
</tr>
</tbody>
</table>

## BLEEDING RISK

<table>
<thead>
<tr>
<th>Herbal</th>
<th>Indication</th>
<th>Perioperative considerations</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| Ginseng  | Mood enhancer, Immunomodulation, Hypoglycemic activity | Irreversible platelet inhibition → ↑bleeding  
↓blood glucose  
↑blood pressure | D/C 7 days prior to surgery  
Avoid w/ use of antiplatelets, anticoagulants & NSAIDs |
| Turmeric | Anti-infective, analgesic, anti-inflammatory and anti-oxidant effects | Antiplatelet effects                           | D/C 14 days prior to surgery                         |

Natural Medicines Database
**DRUG-DRUG INTERACTIONS**

<table>
<thead>
<tr>
<th>Herbal</th>
<th>Indication</th>
<th>Perioperative considerations</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s Wort (Hypericum perforatum)</td>
<td>Antidepressant</td>
<td>Inducer of CYP3A4 &amp; 2C9</td>
<td>D/C 5 days prior to surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sedative effects</td>
<td>Drug interactions!</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Immunostimulatory properties</td>
<td>Potential for anaphylaxis</td>
<td>D/C 14 days prior to surgery</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Inhibits CYP3A4</td>
<td>Drug interactions!</td>
</tr>
</tbody>
</table>

# SEDATIVE EFFECTS

<table>
<thead>
<tr>
<th>Herbal</th>
<th>Indication</th>
<th>Perioperative Complications</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kava kava (Piper methysticum)</td>
<td>Anxiolytic/sedative</td>
<td>Potentiation of the effects of anesthesia/sedatives</td>
<td>D/C 24 hours prior to surgery</td>
</tr>
<tr>
<td>Valerian</td>
<td>Anxiolytic/sedative</td>
<td>Potentiation of the effects of anesthesia/sedatives</td>
<td>D/C 2 weeks prior to surgery</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Sedative</td>
<td>Potentiation of the effects of anesthesia/sedatives</td>
<td>No general consensus for when to D/C - recommend D/C 7-14 days prior to surgery</td>
</tr>
</tbody>
</table>

Natural Medicines Database
RECOMMENDATION

- Providers should seek out a history of herbal supplement use
- Patients utilizing herbal supplements can be referred to pharmacy for consult
- All herbal supplements should be held at least 2 weeks prior to surgery
POST-TRANSPLANT USE
POST-TRANSPLANT CONSIDERATIONS

- Modulation of the immune system through “boosting” of the immune system

- Drug-drug interactions through alterations in cytochrome P450 metabolism and P-glycoprotein (P-gp) transporter function

- Direct toxic effects on the transplanted organ
<table>
<thead>
<tr>
<th>Herbal</th>
<th>Indication</th>
<th>Post-Transplant Concerns</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ginseng</td>
<td>Mood enhancer, Immunomodulation, Hypoglycemic activity</td>
<td>Stimulates the immune function by increasing T cell proliferation that may interfere with immunosuppressive therapy.</td>
<td>AVOID</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Immunostimulatory properties</td>
<td>Stimulates immune function through activation of complement pathway increasing activity of T cells potentially interfering immunosuppressive therapy</td>
<td>AVOID</td>
</tr>
<tr>
<td>Melatonin</td>
<td>Sedative</td>
<td>Stimulates immune function through secretion of cytokines potentially interfering immunosuppressive therapy</td>
<td>AVOID</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Case reports of autoimmune hepatitis</td>
<td></td>
</tr>
</tbody>
</table>
### DRUG-DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Herbal</th>
<th>Indication</th>
<th>Post-Transplant Concerns</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>St. John’s Wort (Hypericum perforatum)</td>
<td>Antidepressant</td>
<td>Inducer of CYP3A4 &amp; 2C9</td>
<td>AVOID Drug interactions!</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sedative effects</td>
<td>↓immunosuppression levels → rejection</td>
</tr>
<tr>
<td>Echinacea</td>
<td>Immunostimulatory properties</td>
<td>Inhibits CYP3A4</td>
<td>AVOID Drug interactions!</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑immunosuppression levels → toxicity</td>
</tr>
<tr>
<td>Turmeric</td>
<td>Anti-infective, analgesic, anti-inflammatory and anti-oxidant effects</td>
<td>Inhibits CYP3A4</td>
<td>AVOID</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>↑immunosuppression levels → toxicity</td>
</tr>
</tbody>
</table>

Natural Medicines Database
<table>
<thead>
<tr>
<th>Fruit Juice</th>
<th>Post-Transplant Concerns</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pomegranate</td>
<td>Case report of elevated tacrolimus levels in a heart transplant patient consuming 1-2 pomegranate popsicles per day (51g each)</td>
<td>CAUTION – may result in increased tacrolimus levels</td>
</tr>
<tr>
<td>Clementine</td>
<td>Case report of elevated tacrolimus levels in a renal transplant patient consuming &gt;1 kg/day of clementines; tacrolimus levels returned to normal with discontinuation</td>
<td>Recommend use in moderation</td>
</tr>
<tr>
<td>Grapefruit</td>
<td>Case report of elevated tacrolimus levels in a liver transplant patient consuming 250ml of grapefruit juice four times per day for 3 days</td>
<td>CAUTION – effect on tacrolimus level was delayed, peaking ~1 week after grapefruit ingestion</td>
</tr>
<tr>
<td>Cranberry</td>
<td>No significant difference in cyclosporine levels when 1 glass of cranberry juice consumed.</td>
<td>Recommend use in moderation</td>
</tr>
</tbody>
</table>

Fukatsu S et al. Drug Metabolism and Pharmacokinetics. 2006.
HEPATOTOXIC DIETARY SUPPLEMENTS

- Bee pollen
- Birch oil
- Blessed thistle
- Borage
- Butterbur
- Cascara Sagrada
- Celandine
- Chaparral
- DHEA
- Echinacea
- Ephedra
- Green tea
- Kava
- Mistletoe
- Periwinkle
- Sassafras
- Turmeric
- Valerian
- Vitamin E

HEPATOTOXIC DIETARY SUPPLEMENTS

- **Echinacea**
  - Used as an immunostimulant to fight a variety of infections
  - Multiple case reports of acute cholestatic hepatitis
  - Consumption of echinacea root extract 600mg-1500mg daily for 5-14 days

- **Green Tea**
  - Polyphenols are thought to be associated with the anti-oxidant properties of green tea
  - Data in animals showing acute tubular necrosis & hepatotoxicity with green tea supplement use

Natural Medicines Database
HEPATOTOXIC DIETARY SUPPLEMENTS

- Valerian
  - Used to manage insomnia and restlessness
  - Multiple case reports of hepatotoxicity with a variety of doses utilized
  - Long-term effect of valerian on liver function is unknown

- Vitamin E
  - Used for cancer prevention and wound healing
  - Immunostimulatory properties are undesirable post-transplant
  - Deleterious effects seen in patients taking more than 1000mg per day

Natural Medicines Database
HEPATOTOXIC DIETARY SUPPLEMENTS

- Turmeric
  - Multiple case reports of autoimmune hepatitis in patients taking turmeric dietary supplements
  - LFT abnormalities resolved with discontinuation of supplements

- Ramelteon/Melatonin
  - Case reports of autoimmune hepatitis
  - Immunostimulatory effects of melatonin through T-cell and B-cell modulation, potentiating autoimmune hepatitis

Lulefahr AL, et al. BMF Case Reports. 2018.
**NEPHROTOXIC DIETARY SUPPLEMENTS**

**Direct Nephrotoxicity**
- Chromium
- Creatine
- L-Lysine
- Yohimbe
- Willow Bark
- Cat's Claw
- Turmeric
- Ginger
- Green Tea

**Nephrolithiasis**
- Vitamin C
- Ephedra
- Cranberry

**Rhabdomyolysis**
- Wormwood Oil
- Creatine
- Licorice
- Red Yeast Rice

NEPHROTOXIC DIETARY SUPPLEMENTS

- Chromium
  - Used for weight loss, glucose control and hyperlipidemia
  - Multiple case reports of ATN related to chromium use
  - Amount consumed varied from 600mcg/day to 2400mcg/day for 2 weeks to 6 months

- Creatine
  - Used for muscle enhancement or “body building”
  - Two case reports of ATN & 5 cases of rhabdomyolysis following creatine use
  - One patient ingested 5g/day for 4 weeks and the second ingested 15g/day for 1 week followed by 2g/day for 12 weeks
  - After stopping creatine, serum creatinine normalized

NEPHROTOXIC DIETARY SUPPLEMENTS

- **L-Lysine**
  - Used to promote wound healing/treat oral ulcers/cold sores
  - Reported to cause Fanconi Syndrome and tubulointerstitial nephritis
  - Single case report of patient consuming 3000mg/day for 5 years

- **Ginger**
  - Theoretical risk based on known mechanisms
  - Used to treat inflammation and inhibit cyclooxygenase (COX)
  - Inhibition of prostaglandins leading to vasoconstriction & renal failure

NEPHROTOXIC DIETARY SUPPLEMENTS

- **Turmeric**
  - Theoretical risk based on known mechanisms
  - Used to treat inflammation and inhibit cyclooxygenase (COX)
  - Inhibition of prostaglandins leading to vasoconstriction & renal failure

- **Green Tea**
  - Polyphenols are thought to be associated with the anti-oxidant properties of green tea
  - Data in animals showing acute tubular necrosis & hepatotoxicity with green tea supplement use

NEPHROTOXIC DIETARY SUPPLEMENTS

- **Vitamin C**
  - Used to promote wound healing & prevent cancer and heart disease
  - Metabolized to oxalate leading nephrolithiasis secondary to oxaluria
  - Immunostimulatory properties are undesirable post-transplant
  - Seen in patients utilizing 60g/day of Vitamin C

- **Cranberry**
  - Used to acidify the urine and prevent urinary tract infections
  - Contains oxalate leading to nephrolithiasis secondary to oxaluria
  - Case reports of nephrolithiasis following administration of cranberry concentrate tablets and >1L of juice per day

NEPHROTOXIC DIETARY SUPPLEMENTS

- **Licorice**
  - Potent diuretic associated with severe hypokalemia
  - FDA Warning in October 2017 regarding risk of arrhythmia associated with black licorice use
  - Age 40 or older and consuming 2 ounces per day for at least two weeks

RESOURCES

- Natural Medicines

- National Center for Complementary and Integrative Health
  https://nccih.nih.gov/

"It appears to be a side effect of those herbal eye drops you've been using."
MARIJUANA USE
MARIJUANA

- Extract of Cannabis sativa (Indian hemp) plant
- Classified as a Schedule 1 containing substances with high abuse potential
- Consists of 60 pharmacologically active cannabinoids
- Two most described cannabinoids are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD)


Figure 1: Chemical structure of cannabidiol.
MECHANISM OF ACTION

- Cannabinoid receptors are present in the brain and spinal cord

- CB1 receptors are primarily in the nervous system
  - Antagonism of these receptors leads to mental & behavioral effects
  - Alters perceptions & mood, affects memory and learning
  - Leads to impaired judgement

- CB2 receptors primarily in the periphery on cells in the immune system
  - Possible immunosuppressive activity of cannabis

- Inhibition of neurotransmitter release (acetylcholine & glutamate)

MECHANISM OF ACTION

- CBD does not have psychoactive effects & appears to block the effects of THC through antagonism at the CBD receptor
- Marijuana has become significantly more potent
- Newer forms of marijuana available with higher THC content

FORMULATIONS

- Natural Form
  - Consists of THC & CBD
  - Active component is THC which is sought after for psychoactive effects
  - Marijuana or “Medical Marijuana”
FORMULATIONS

- Synthetic Forms
  - Consist of THC
  - Two FDA-approved forms: Marinol (Dronabinol) & Cesamet (Nabilone)
  - Street Forms: K2, Spice, Joker, Black Mamba, Kush, and Kronic

Synthetic Cannabinoids. NIDA. 2018.
## FORMULATIONS

<table>
<thead>
<tr>
<th></th>
<th>Marinol (dronabinol)</th>
<th>Cesamet (nabilone)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Schedule</strong></td>
<td>CIII substance</td>
<td>CII substance</td>
</tr>
<tr>
<td><strong>Indication</strong></td>
<td>Indicated for the treatment of:</td>
<td>Indicated for the treatment of:</td>
</tr>
<tr>
<td></td>
<td>- Anorexia in AIDS patients</td>
<td>- N/V associated with cancer chemotherapy</td>
</tr>
<tr>
<td></td>
<td>- N/V associated with cancer chemotherapy</td>
<td></td>
</tr>
<tr>
<td><strong>Dosing</strong></td>
<td>Initial dose: 2.5mg BID</td>
<td>Initial dose: 1-2mg BID, 1-3 hours prior to chemotherapy</td>
</tr>
<tr>
<td><strong>Adverse Effects</strong></td>
<td>May cause psychiatric and cognitive effects and impairment</td>
<td>May cause psychiatric and cognitive effects and impairment</td>
</tr>
<tr>
<td><strong>Dose adjustment</strong></td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td>May increase LFTs (≤1%)</td>
<td></td>
</tr>
<tr>
<td><strong>Drug Interactions</strong></td>
<td>Substrate of 2C9 &amp; 3A4 **Cyclosporine/Tacrolimus</td>
<td>None</td>
</tr>
</tbody>
</table>
FORMULATIONS

- Semi-Synthetic Forms
  - Combination of THC & CBD
  - Sativex (Nabiximols) – Not available in U.S.
FORMULATIONS

- Epidiolex (cannabidiol) was approved by the FDA in June 2018
- CBD oral solution for management of Lennox-Gastaut syndrome and Dravet syndrome
- Three randomized, controlled trials showed significantly greater reductions in seizure activity compared to placebo
- Mild increases in liver transaminases were noted but raising the possibility of more severe injury

[Source](https://www.thecannabist.co/2018/04/18/gw-pharmaceuticals-epidiolex-cbd-justin-grover/103667/)
### PHARMACOKINETICS - ABSORPTION

<table>
<thead>
<tr>
<th>Route</th>
<th>Absorption</th>
<th>Peak Concentration</th>
<th>Bioavailability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhalation/smoking</td>
<td>Rapid drug delivery to the brain</td>
<td>22 min</td>
<td>Varies, 2-56%</td>
</tr>
<tr>
<td>Oral</td>
<td>Slow</td>
<td>1-2hr but can be delayed to 8hr</td>
<td>10-20%</td>
</tr>
<tr>
<td>Sublingual</td>
<td>Fast</td>
<td>30 min</td>
<td>10-20%</td>
</tr>
<tr>
<td>Rectal</td>
<td>Fast</td>
<td>15min</td>
<td>20-40%</td>
</tr>
<tr>
<td>Transdermal</td>
<td>Slow</td>
<td>2hr; maintained for 48hr</td>
<td>10%</td>
</tr>
</tbody>
</table>

PHARMACOKINETICS - DISTRIBUTION

- Highly lipophilic which allows it to be easily taken up into the tissues

- THC and metabolites are formed with prolonged exposure, allowing for accumulation of these substances in tissues

- Half-life varies based on frequency of use
  - Infrequent users: 1.3 days
  - Frequent users: 5-13 days

- THC has a large volume of distribution (Vd) with slow elimination from the body

- Crosses the placenta & accumulates in breast milk

PHARMACOKINETICS - METABOLISM

- THC is metabolized in the liver by hydroxylation and oxidation by CYP450 enzymes
  - CYP2C9, 2C19, 3A4

- Certain metabolizing enzymes are decreased in cirrhosis
  - CYP1A and CYP3A are reduced
  - CYP2C, 2A and 2B are unaltered

- Equipotent active metabolite of THC is 11-OH-THC

- Possible extra-hepatic sites in the brain, intestine and lung

References:
PHARMACOKINETICS - ELIMINATION

- Rate of excretion varies based on gender
  - Women - clearance rate: 11.8 ±3 L/hr
  - Men - clearance rate: 14.9 ±3.7 L/hr

- 65% feces; 20% urine
A 'Catch-22' of medical marijuana and organ donation

Young Transplant Patient Has Tackled Marijuana Use Pre-Transplant

HUMAN ORGAN FOR TRANSPLANT

DENIED
USE PRE-TRANSPLANT

- Over 25 states have legalized medical marijuana with another 4 states legalizing recreational use.

- Marijuana use has been considered a relative contraindication to transplant listing in some centers.

- Transplant guidelines do not provide a recommendation regarding marijuana use pre-transplant.

- There are 7 states with current laws that prohibit transplant centers from denying transplant listing based solely on a patient's use of medical marijuana.
Current legislature includes the following statement regarding marijuana use and transplant listing:

“For the purposes of medical care, including organ transplants, a registered qualifying patient's authorized use of cannabis in accordance with this Act is considered the equivalent of the authorized use of any other medication used at the direction of a physician, and may not constitute the use of an illicit substance or otherwise disqualify a qualifying patient from needed medical care.”
CONCERNS POST-TRANSPLANT

1. Infection risk
2. Bleeding risk
3. Drug interactions
4. Cannabinoid Hyperemesis Syndrome
5. Impaired cognition
6. Cardiovascular effects
7. Abuse/Addiction potential
INFECTION

- Aspergillus species found in soil, air and vegetable matter, including tobacco

- Marijuana smoking may subject immunocompromised patients to serious & lethal opportunistic fungal infections

- Multiple case reports and at least 2 cases at BIDMC of invasive fungal infections related to smoking marijuana

Hamadeh R, et al. CHEST. 1988
INFECTION

- Use of a water pipe has been associated with severe infection
  - Case report of *Pseudomonas aeruginosa* necrotizing pneumonia secondary to water pipe usage

- Heating of cannabis buds is not sufficient for sterilization
  - Vaping does not reach high enough temperatures to kill fungal spores
  - Autoclaves have been used to sterilize marijuana
  - Temperatures as high as 150°C/300°F were utilized

Figure 1
(A) A water pipe or “bong” used by the patient. (B) Computed tomography (CT) thorax (coronal) image under lung tissue showing area of necrotizing pneumonia with apical pneumothorax.
BLEEDING

- Synthetic cannabinoids have been recently linked to serious, unexplained bleeding in numerous states.

- Over 94 people presented to the hospital with life-threatening coagulopathy secondary to brodifacoum.

- Brodifacoum is used in a commercial product used for killing rodents and pests.

- Synthetic cannabinoid product samples tested positive for brodifacoum.
DRUG-DRUG INTERACTIONS

- Exogenous cannabinoids are potent inhibitors of CYP3A and P-gp transporter

- CYP2C9, 3A4 and 2C19 inhibitors increase plasma concentration of THC & CBD

- Multiple case reports of elevated CNI levels
  - Tacrolimus level of 45.8ng/mL when previously at goal – patient using marijuana gummies
  - Cyclosporine level of 500ng/mL following marijuana brownie use

CANNABINOID HYPEREMESIS SYNDROME

- Cyclical vomiting without other identifiable cause seen in patients with chronic cannabis use

- Most commonly seen in patients with prolonged, high-dose cannabis use

- Most cases are refractory to usual antiemetic agents with patients reporting relief only from long, hot showers

- Concerning post-transplant if patients are unable to take immunosuppression consistently

IMPAIRED COGNITION

- Classified as a hallucinogen

- Impairs coordination, perception of time/surroundings, comprehension and cognition

- Develop psychotic symptoms including hallucinations, paranoia and delusions

- Post-transplant medication regimen consists of 15+ medications

- Patient must be able to make frequent dose adjustments, administer medications multiple times per day and ensure timing of administration is accurate
CARDIOVASCULAR EFFECTS

- Dose dependent tachycardia and increase cardiac workload
- Evidence suggest marijuana users are at a 5-fold increased risk of an acute cardiac event
- Increased risk of ischemia due to a reduction in blood flow to the brain
- Marijuana use can lead to vasodilation of peripheral blood vessels leading to orthostatic hypotension & syncope
**ABUSE/ADDICTION POTENTIAL**

- High potential for abuse, affecting the same reward system in the brain as alcohol and opioids

- Tolerance can develop over time, requiring an increase in the amount of cannabis to produce the same effect

- With discontinuation of use or between uses, withdrawal symptoms can occur including anxiety, depression, irritability and insomnia

- Withdrawal can occur within 1-3 days, peaks within 2-6 days and can last up to 4-14 days depending on frequency of use

CONCLUSION

- Marijuana consists of 60 pharmacologically active cannabinoids and is available as many formulations.

- Some centers consider marijuana use a relative contraindication to transplant listing.

- There is a potential for drug interactions with immunosuppression and marijuana may increase the risk for post-transplant complications, including infection.

- Patients utilizing marijuana should be educated on the risks of marijuana use pre- & post-transplant.
ST is scheduled for kidney donation in 3 weeks. When reviewing her medications, she reports taking gingko biloba and ginseng supplements daily at home. Which of the following is the correct recommendation in regards to herbal supplement use prior to surgery?

a) She should hold gingko biloba & ginseng 1 week prior to surgery

b) She does not need to hold gingko biloba & ginseng prior to surgery

c) She should hold gingko biloba & ginseng 2 weeks prior to surgery
MJ is s/p liver transplant 2 months prior and is maintained on tacrolimus, mycophenolate and prednisone. He is inquiring about turmeric supplements given their anti-infective and anti-oxidant properties and wants to know if they interact with his transplant medications. Which of the following is correct?

a) Turmeric is a CYP3A4 inducer, potential leading to a reduction in immunosuppression levels

b) Turmeric is a CYP3A4 inhibitor, leading to an increase in immunosuppression levels

c) Turmeric does not impact CYP3A4 and is safe to take post-transplant
QUESTION 3

Which of the following risks may be associated with marijuana use post-transplant?

a) Infection
b) Cardiovascular effects
c) Bleeding
d) A&B only
e) All of the above


