MHIF FEATURED STUDY:

NanoCor

Currently Enrolling

EPIC message to *Research MHIF Patient Referral*

CONDITION:	PI:	RESEARCH CONTACTS:	SPONSOR:
Non-Ischemic Cardiomyopathy	Jay Traverse, MD Kasia Hryniewicz, MD	Jake Jensen – Jacob.Jensen@allina.com | 612-863-3818 Kari Thomas - Kari.M.Thomas@allina.com | 612-863-7493	AskBio

DESCRIPTION: an early phase, non-randomized study evaluating the safety of a single antegrade epicardial coronary artery infusion of NAN-101 in up to 12 subjects with non-ischemic cardiomyopathy and NYHA class III symptoms.

NAN-101 is a gene therapy product composed of a novel adeno-associated virus designed to target cardiomyocytes and deliver it's payload of I-1c transgene. This genetic material provides code for an upstream inhibitor of the SERC2a pathway, which has been identified as a primary pathogenic mechanism in heart failure. The goal is to improve calcium cycling within the heart

Preclinical studies have shown that constitutively activating I-1 within the failing rat heart improved not only contractility, but also reversed adverse remodeling by directly decreasing fibrosis and cardiac hypertrophy.

CRITERIA LIST/ QUALIFICATIONS:

Inclusion:

- Chronic non-ischemic cardiomyopathy
- LVEF of 30% or less
- NYHA III

Exclusion:

- Ischemic cardiomyopathy
- Restrictive cardiomyopathy/ infiltrative cardiomyopathy
- Renal failure

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Creating a world without heart and vascular disease

Supplement Soup: Sifting Through Herbal Medicines, THC/CBD & Cardiac Medications

Paige Skelton, PharmD, BCCP

Monday February 1st, 2021

MHI Grand Rounds

1

Disclosure

- I have no financial interest or affiliation with the manufacturer of any marketed products discussed herein.

2

Objectives

- Locate resources on the AKN to evaluate herbal supplements
- Discuss Abbott Northwestern Hospital's "Non-Essential Medication" policy
- Assess common herbal supplements and evaluate their safety with common cardiovascular disease (CVD) medications
- Summarize common drug-drug interactions with THC/CBD products

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Background[1-3]

- ~40-60% of U.S. adults with chronic disease(s) use dietary supplements
- Among patients taking prescription medications, ~20-25% also use herbal supplements
- **Herbal dietary supplements** = supplements containing whole plant or plant extracts that are consumed as powder, capsule, tablet or liquid formulations

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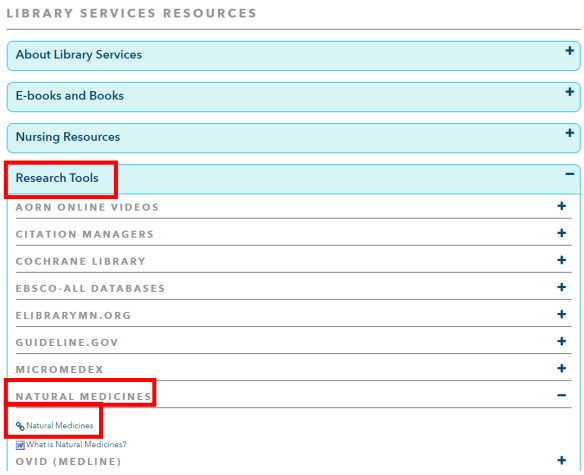
Natural Medicines

5

Natural Medicines



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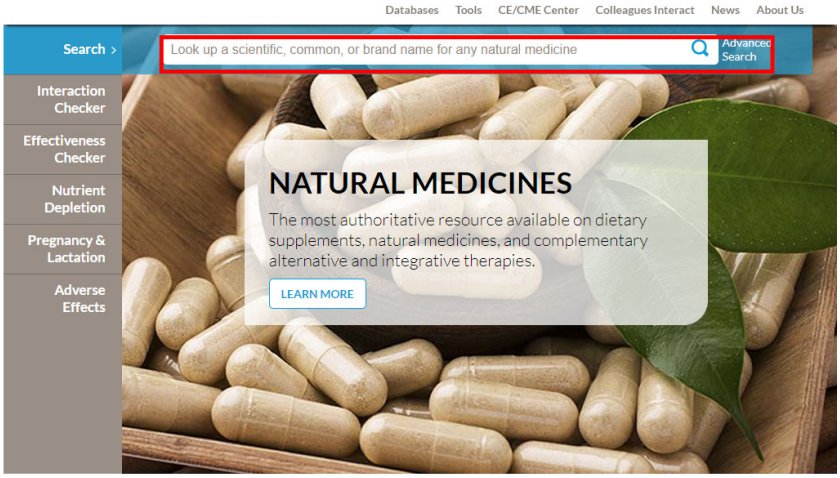
Natural Medicines



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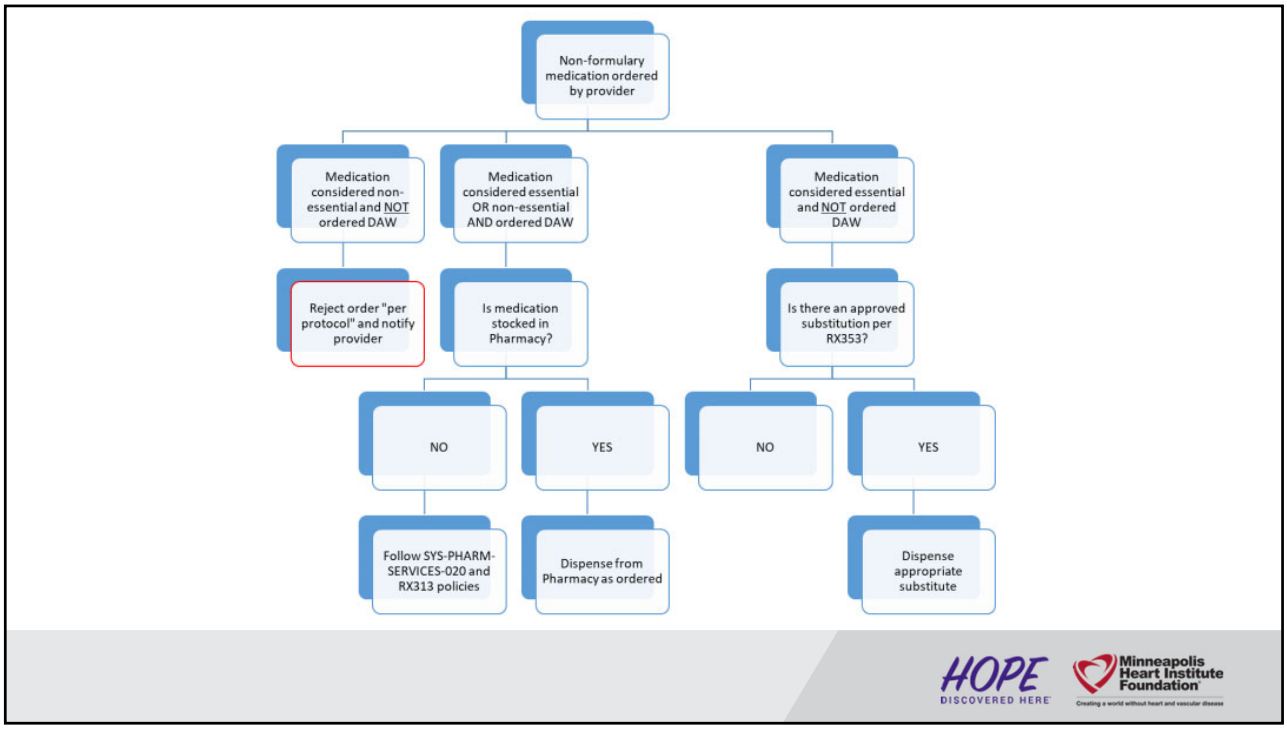
Non-Essential Medication Policy

RX489

- **Purpose:** provide guidance to health care providers about prescribing, dispensing, and administering non-formulary, complementary, and non-essential therapies
  - **Non-formulary** = a medication not included on the Allina Health medication formulary
  - **Complementary** = products designed for systemic or topical use that have not been approved by the FDA, and are not otherwise classified as pharmaceuticals. Examples: herbal remedies (derived from plants), extracts of animal origins, and dietary supplements.
  - **Non-essential** = A product that may or may not have FDA approval and is not required for the clinical care of the patient during the hospitalization, and will not cause harm to the patient if discontinued during the hospital stay.

8


Non-formulary medication ordered by provider
Medication considered non-essential and NOT ordered DAW
Medication considered essential OR non-essential AND ordered DAW
Medication considered essential and NOT ordered DAW
Reject order "per protocol" and notify provider
Is medication stocked in Pharmacy?
Is there an approved substitution per RX353?
NO
YES
NO
YES
Follow SYS-PHARM-SERVICES-020 and RX313 policies
Dispense from Pharmacy as ordered
Dispense appropriate substitute
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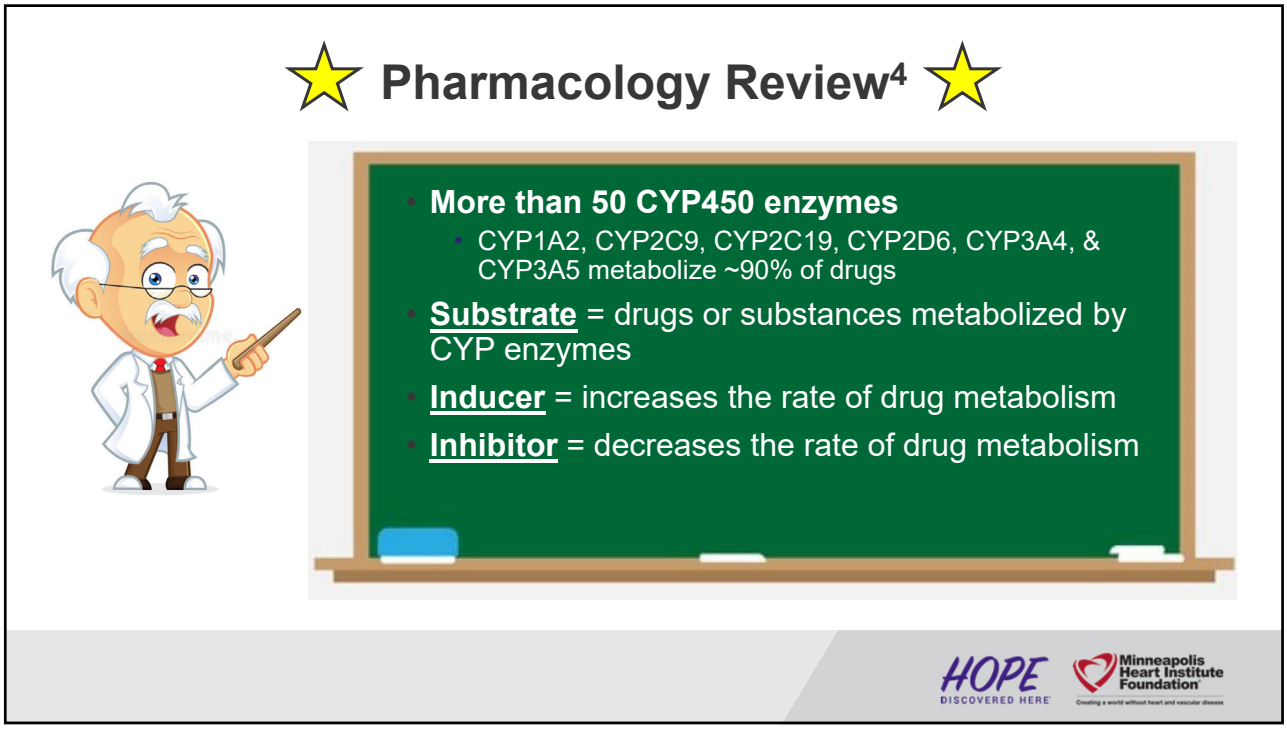
Pharmacology Review4
More than 50 CYP450 enzymes
CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP3A4, & CYP3A5 metabolize ~90% of drugs
Substrate = drugs or substances metabolized by CYP enzymes
Inducer = increases the rate of drug metabolism
Inhibitor = decreases the rate of drug metabolism
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CYP Inhibitors[5]

	Strong inhibitors	Moderate inhibitors	Weak inhibitors
CYP1A2	ciprofloxacin, fluvoxamine	**mexilietine**	acyclovir, allopurinol, **amiodarone**
CYP2B6			**clopidogrel**, voriconazole
CYP2C8	gemfibrozil	**clopidogrel,** trimethoprim, pioglitazone, rosiglitazone	
CYP2C9	fluconazole	**amiodarone, fenofibrate, fluvastatin, lovastatin,** paroxetine, sertraline, sulfamethoxazole	voriconazole
CYP2C19	fluconazole, fluoxetine		omeprazole (all PPIs), voriconazole
CYP2D6	bupropion, fluoxetine, paroxetine, **quinidine**	duloxetine, sertraline	**amiodarone**, celecoxib, citalopram, escitalopram, **labetalol**, **midodrine**, sertraline
CYP3A4	**conivaptan**, grapefruit juice, itraconazole, ketoconazole, voriconazole, clarithromycin	cyclosporine, **diltiazem,** tacrolimus, **verapamil**	**amiodarone**

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CYP Inducers[5]

	Strong inducers	Moderate inducers	Weak inducers
CYP1A2		phenytoin, rifampin, smoking	
CYP2B6	carbamazepine	rifampin	
CYP2C8		rifampin	
CYP2C9		rifampin	carbamazepine
CYP2C19	rifampin	phenytoin	
CYP3A4	carbamazepine, phenytoin, rifampin, St. John's wort	**bosentan,** pioglitazone	modafinil

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Common Herbal Supplements

13

Black Cohosh[6-9]

- **Scientific name:** *Actaea racemose*
- **Uses:**
  - Menopause – some evidence
  - Premenstrual syndrome (PMS), infertility, and osteoporosis – insufficient evidence
- **Side effects:** stomach upset, cramping, headache, rash, weight gain, and liver damage
- **Drug interactions:** reduced effectiveness of **amiodarone**, fexofenadine, glyburide, and many **statin medications**
  - **No major clinical drug interactions**

14

Coenzyme Q10[6]

- **Scientific name:** *Ubiquinone*
- **Uses:**
  - Coenzyme Q10 deficiency, mitochondrial myopathies – likely effective
- **Side effects:** appetite suppression, N/V/D, and heartburn
- **Drug interactions:** potential additive effects with **anti-hypertensives** and reduced anticoagulant effects of **warfarin**
  - **No major clinical drug interactions**

15

Cranberry[6,10,11]

- **Scientific name:** *Vaccinium macrocarpon*
- **Uses:**
  - Preventing urinary tract infections (UTIs) – best evidence
  - Benign prostatic hyperplasia (BPH) or kidney stones – insufficient evidence
- **Side effects:** dyspepsia and diarrhea (high doses)
- **Drug interactions:** increases [**warfarin**]/INR (anecdotal) – two human clinical trials did not show a significant effect on either outcome
  - **No major clinical drug interactions**

16

Curcumin[6,12-14]

- **Scientific name:** *Curcuma longa*
- **Uses:**
  - Allergic rhinitis, depression, hyperlipidemia, nonalcoholic fatty liver disease (NAFLD), osteoarthritis, and pruritus – possibly effective
- **Side effects:** stomach upset (flatulence, N/V/D), vertigo, and liver damage
- **Drug interactions:** decreased levels of many antidepressants and antipsychotics
  - Human clinical trials demonstrated no effect on CYP2C9, CYP3A4 & UGT
  - **No major clinical drug interactions**

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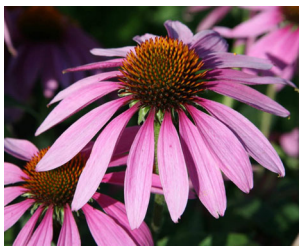
Echinacea[6,9,15-17]



- **Scientific name:** *Echinacea purpurea*
- **Uses:**
  - Common cold – possibly effective
- **Side effects:** stomach upset (N/V/D), heartburn, and rashes
- **Drug interactions:** exercise caution with antipsychotics and antidepressants metabolized by CYP1A2 and/or CYP3A4; increased clearance of **warfarin** (not clinically significant)
  - Human clinical trials showing no inhibitory or inductive effects on CYP2D6, CYP2C9, or P-gp
  - **No major clinical drug interactions**

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Garlic[6,18-20]

- **Scientific name:** *Allium sativum*
- **Uses:**
  - Atherosclerosis, diabetes, hyperlipidemia, hypertension, and nonalcoholic fatty liver disease (NAFLD) – possibly effective
- **Side effects:** abdominal pain, body odor, flatulence, malodorous breath, and nausea
- **Drug interactions:** decreased concentrations of drugs transported by P-gp (**colchicine**, **digoxin**, doxorubicin, **quinidine**, **rosuvastatin**, **tacrolimus**, **verapamil**) **– AVOID CONCOMITANT USE**
  - Human clinical trials showing no effects on CYP1A2, CYP2D6, or CYP3A4

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Ginkgo[6,18,21,22,23]

- **Scientific name:** *Ginkgo biloba*
- **Uses:**
  - Anxiety, dementia, premenstrual syndrome (PMS), schizophrenia, stroke, tardive dyskinesia, and vertigo – possibly effective
- **Side effects:** dizziness, gastrointestinal symptoms, and headache
- **Drug interactions:** caution with **antiplatelet** and/or **anticoagulant** medications (may inhibit platelet aggregation); increased risk of bleeding with **warfarin**
  - Human clinical trials showing no clinically important effects on CYP1A2, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A4

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Ginseng (American)[6,24-26]

- **Scientific name:** *Panax quinquefolius*
- **Uses:**
  - Diabetes & respiratory tract infections – possibly effective
- **Side effects:** headache, nervousness, trouble sleeping & stomach complaints
- **Drug interactions:** decreased effectiveness of **warfarin**; enhanced blood glucose lowering effects of **antidiabetics**; and potentially decreased effectiveness of **immunosuppressants**

21

Ginseng (Asian)[6,18,31-33]

- **Scientific name:** *Panax ginseng*
- **Uses:**
  - Cognitive function, erectile dysfunction, influenza, multiple sclerosis-related fatigue, and sexual arousal
- **Side effects:** insomnia
- **Drug interactions:** exercise caution with **anticoagulants** / **antiplatelets**, **antidiabetics**, insulin, **furosemide**, **immunosuppressants**, and **QT prolonging medications**
  - Human clinical trials showing no effect on CYP1A2, CYP2D6, CYP2E1 or P-gp
  - **Generally, avoid Asian ginseng with concomitant medication use**

22

Goldenseal[6,7,9]

- **Scientific name:** *Hydrastis canadensis*
- **Uses:**
  - Common cold, upper respiratory tract infections, nasal congestion, allergic rhinitis, gastritis, peptic ulcers, colitis, diarrhea, urinary tract infections (UTIs), and menorrhagia – some evidence
- **Side effects:** stomach upset, rash, bitter taste, and headache
- **Drug interactions:** lowered BP with **amlodipine**, increased risk of bleeding with **antiplatelets** / **anticoagulants**, increased risk of hypoglycemia with **antidiabetics**, increased **cyclosporine** & **tacrolimus** levels, increased **digoxin** levels, and decreased effectiveness of **losartan**
  - Shown to inhibit CYP2D6 and CYP3A4
  - **Avoid use in combination with most other medications!!!**

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Green Tea Extract[6,30-33]

- **Scientific name:** *Camellia sinensis*
- **Uses:**
  - Cognitive performance, mental alertness, stomach disorders, headaches, depression and obesity
  - FDA approved qualified health claim for use in prevention of prostate and breast cancer
- **Side effects:** gastrointestinal symptoms (higher doses)
- **Drug interactions:** increased [**simvastatin**], reduced plasma levels of **atorvastatin** / **rosuvastatin**, increased bleeding risk with **anticoagulants** / **antiplatelets**, and reduced [**nadolol**]
  - Human clinical trials showing no effect on CYP2D6 & CYP3A4
  - **Studies showing inhibition of OAT1A1, OAT1A2, and P-gp – AVOID USE!**

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Kava Kava[6,7,9,34-36]

- **Scientific name:** *Piper methysticum*
- **Uses:**
  - Anxiety – possibly effective
- **Side effects:** stomach upset, headache, dizziness, drowsiness, enlarged pupils, dry mouth, and hepatotoxicity
- **Drug interactions:** increased drowsiness with CNS depressants and increased level of **anesthetics** & acetaminophen
  - Human clinical studies showing no effect on CYP1A2, CYP2D6, CYP3A4, or P-gp
  - Human clinical studies showing inhibition of CYP2E1
  - In vitro data suggesting inhibition of CYP2C9 & CYP2C19

25

Milk Thistle[6,8,9,16,37-39]

- **Scientific name:** *Silybum marianum*
- **Uses:**
  - Diabetes – possibly effective
  - Alcohol-related liver disease, allergic rhinitis, benign prostatic hyperplasia (BPH), hypercholesterolemia – insufficient evidence
- **Side effects:** abdominal bloating, dyspepsia, and nausea – generally well tolerated
- **Drug interactions:** reduces **losartan** metabolism, and decreases [**warfarin**], [phenytoin], and [diazepam]
  - Human clinical trials showing no inhibitory or inductive effects on CYP1A2, CYP2D6, CYP2E1, CYP3A4, or P-gp
  - **No major clinical drug interactions**

26

Saw palmetto[6,16,40]

- **Scientific name:** *Serenoa repens*
- **Uses:**
  - Reducing complications of transurethral resection of the prostate – some evidence
  - Benign prostatic hyperplasia (BPH) – possibly ineffective
- **Side effects:** stomach upset, dizziness, and headache
- **Drug interactions:** may prolong bleeding time with **anticoagulants** and **antiplatelets**
  - Human clinical trials showing no inhibitory or inductive effect on CYP1A2, CYP2D6, CYP2E1, or CYP3A4
  - **No major clinical drug interactions**

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St. John's Wort[6,17,41,42]

- **Scientific name:** *Hypericum perforatum*
- **Uses:**
  - Depression – likely effective
  - Menopausal symptoms – possibly effective
- **Side effects:** Stomach discomfort, dizziness, dry mouth, fatigue, headache, and restlessness – generally well tolerated
- **Drug interactions:** reduces effectiveness of **cyclosporine**, **tacrolimus**, **warfarin**, protease inhibitors, theophylline, **digoxin**, venlafaxine, and oral contraceptives
  - **AVOID CONCURRENT USE WITH OTC & PRESCRIPTION MEDICATIONS!!!**

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Valerian[6,7,43]

- **Scientific name:** *Valeriana officinalis*
- **Uses:**
  - Insomnia – possibly effective
- **Side effects:** dizziness, drowsiness, and mental slowness
  - Taper dose slowly to avoid withdrawal side-effects (tachycardia, anxiety, irritability, and insomnia)
- **Drug interactions:** additive sedative effects with CNS depressants, alprazolam, and alcohol
  - Human clinical trials showing no inhibitory or inductive effects on CYP1A2, CYP2D6, CYP2E1, or CYP3A4
  - **No major clinical drug interactions**

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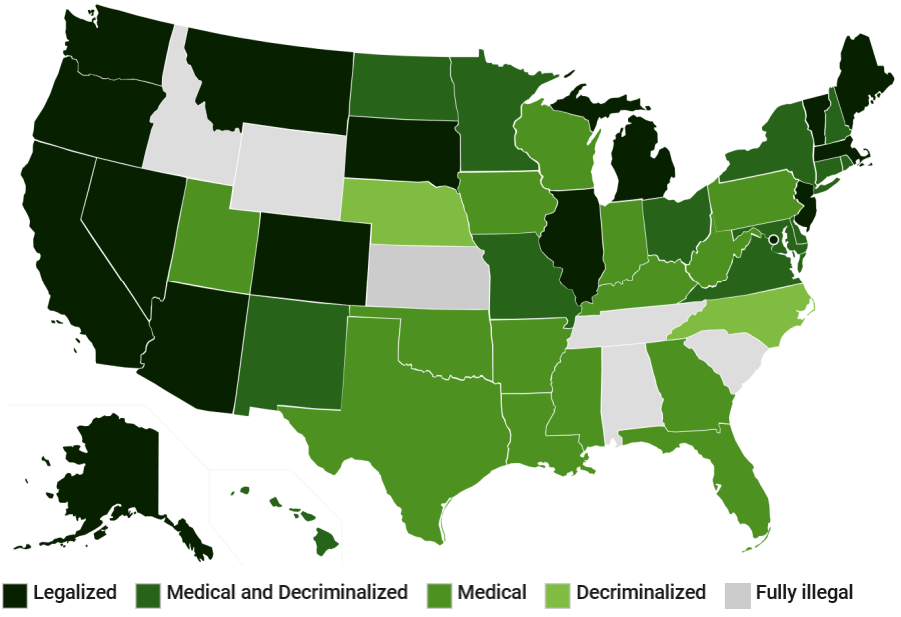

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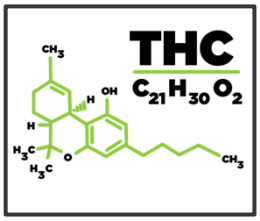
Qualifying Conditions in MN

- Chronic pain
- Cancer
- Glaucoma
- HIV/AIDS
- Tourette's
- ALS
- Seizures
- Severe & persistent spasms
- Inflammatory bowel disease (including Crohn's)
- Terminal illness with less than 1 year to live
- Intractable pain
- PTSD
- Autism
- Obstructive sleep apnea
- Alzheimer's

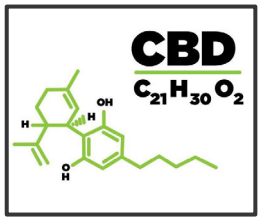
31

THC/CBD Background[44]

- THC and CBD are pharmacologically active cannabinoids in marijuana
  - THC is metabolized by CYP3A4 and CYP2C9 – potential INCREASE in [THC] with CYP3A4 and CYP2C9 inhibitors
  - CBD is metabolized by CYP3A4 – potential INCREASE in [CBD] with CYP3A4 and CYP2C19 inhibitors



Tetrahydrocannabinol

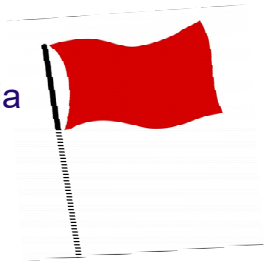


Cannabidiol

32

Five Things to Know…[44-48]

1) Cannabinoid levels can be increased by other medications
2) Cannabinoids can affect levels of other drugs
3) Smoking marijuana can increase clearance of some drugs
4) Additive effects can occur with other drugs
   1) Sympathomimetics – tachycardia, hypertension
   2) CNS depressants (alcohol, opioids) – drowsiness, ataxia
   3) Anticholinergics – tachycardia, confusion
5) There are potential "red flag" interactions



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Pharmacokinetic Interactions[44-50]

	THC	CBD
CYP3A4 inhibitors Clarithromycin, erythromycin, azole antifungals, HIV protease inhibitors, **diltiazem**, **verapamil**, **amiodarone**	✓ Ketoconazole ↑ [THC] nearly 2-fold ✓ Similar interaction possible with other 3A4 inhibitors, resulting in enhanced THC psychoactive effects	✓ Ketoconazole ↑ [CBD] nearly 2-fold ✓ Similar interaction possible with other 3A4 inhibitors, resulting in enhanced CBD effects, including somnolence and transaminase elevations
CYP3A4 inducers Rifamycins, efavirenz, St. John's wort, carbamazepine, phenytoin, phenobarbital	✓ Rifampin ↓ [THC] ~20% ✓ Similar interaction possible with other CYP3A4 inducers ✓ Clinical significance unclear	✓ Rifampin ↓ [CBD] ~60% ✓ Similar interaction possible with other CYP3A4 inducers ✓ Combined use may decrease effectiveness when used for seizure disorders

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Pharmacokinetic Interactions[44-50]

	THC	CBD
CYP3A4 inhibitors Clarithromycin, erythromycin, azole antifungals, HIV protease inhibitors, **diltiazem**, **verapamil**, **amiodarone**	✓ Ketoconazole ↑ [THC] nearly 2-fold ✓ Similar interaction possible with other 3A4 inhibitors, resulting in enhanced THC psychoactive effects	✓ Ketoconazole ↑ [CBD] nearly 2-fold ✓ Similar interaction possible with other 3A4 inhibitors, resulting in enhanced CBD effects, including somnolence and transaminase elevations
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Pharmacokinetic Interactions[44-50]

	THC	CBD
CYP3A4 substrates PDE5 inhibitors (ie. **sildenafil**), **diltiazem**, **verapamil**, **cyclosporine**, **tacrolimus**, **sirolimus**, **simvastatin**, **atorvastatin**	✓ No effect of THC on CYP3A4 substrates anticipated based on current knowledge	✓ CBD ↑ [**tacrolimus**] 3-fold ✓ Interactions with other 3A4 substrates possible ✓ **Monitor for adverse effects and/or select alternatives agents when possible**
CYP2C9 inhibitors Sulfamethoxazole, **amiodarone**, metronidazole, fluconazole, voriconazole, valproic acid	✓ May ↑ THC levels, thus enhancing psychoactive effects	✓ No effects anticipated of CYP2C9 inhibitors or inducers based on current knowledge

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Pharmacokinetic Interactions[44-50]

	THC	CBD
CYP2C9 inducers Rifamycins, barbituates, carbamazepine	✓ May ↓ THC levels, attenuating psychoactive effects	
CYP2C9 substrates **Warfarin**, **rosuvastatin**, phenytoin	✓ **THC may ↑ levels → monitor for adverse reactions, dose reduction may be required** ✓ **Warfarin** - Cases of ↑ INR and bleeding with smoked marijuana	✓ **CBD may ↑ levels → monitor for adverse reactions, dose reduction may be required** ✓ **Warfarin** - Cases of ↑ INR and bleeding with smoked marijuana
CYP2C19 inhibitors Omeprazole, esomeprazole, fluconazole, fluoxetine, isoniazid	✓ No effects anticipated with 2C19 inhibitors based on currently available knowledge	

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Pharmacokinetic Interactions[44-50]

	THC	CBD
CYP2C19 inducers Barbiturates, St. John's wort, carbamazepine, rifamycins	✓ No effects anticipated with 2C19 inducers based on currently available knowledge	✓ Rifampin ↓ [CBD] ~60% ✓ Combined use may decrease effectiveness when used for seizure disorders
CYP2C19 substrates Aripiprazole, **clopidogrel**, citalopram, diazepam, clobazam	✓ No effects anticipated with 2C19 substrates based on currently available knowledge	✓ CBD ↑ levels of clobazam 6-fold ✓ Interactions with other 2C19 substrates possible – monitor for toxicity ✓ **CBD may compromise antiplatelet activity of clopidogrel**

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Pharmacodynamic Interactions[44-50]

	THC	CBD
CNS depressants Alcohol, opioids, benzodiazepines, tricyclic antidepressants	✓ Additive cognitive and psychomotor impairment	✓ Additive cognitive and psychomotor impairment
Sympathomimetics Amphetamines, cocaine, noradrenergic and anticholinergic agents	✓ Additive tachycardia, hypertension and fluid retention	✓ No interaction anticipated

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Summary

- Ensure accurate medication lists, including herbal supplements
- Assess for clinically significant interactions
  - Goldenseal and St. John's wort with overall high risk of drug interactions
- Encourage open dialogue on the use of THC/CBD products to assess potential pharmacokinetic and/or pharmacodynamic interactions

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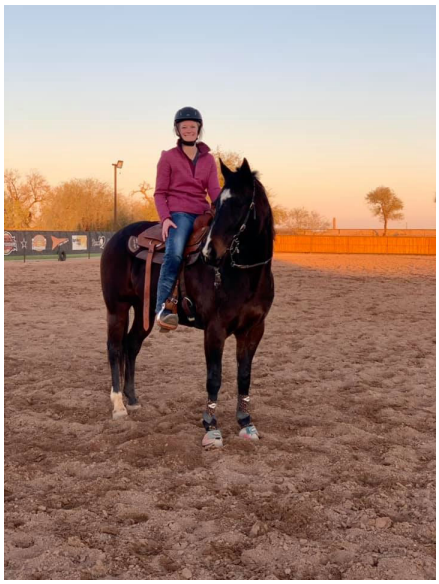

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