**MHIF FEATURED STUDY: NanoCor**

**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 its 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

**CONDITION:** Non-Ischemic Cardiomyopathy  
**PI:** Jay Traverse, MD  
Kasia Hryniewicz, MD  
**RESEARCH CONTACTS:**  
Jake Jensen – Jacob.Jensen@allina.com | 612-863-3818  
Kari Thomas - Kari.M.Thomas@allina.com | 612-863-7493  
**SPONSOR:** AskBio
Supplement Soup: Sifting Through Herbal Medicines, THC/CBD & Cardiac Medications

Paige Skelton, PharmD, BCCP
Monday February 1st, 2021
MHI Grand Rounds

Disclosure

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

Background\(^1\text{-}^3\)

• ~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
Natural Medicines

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.
Pharmacology Review

- 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
### CYP Inhibitors

<table>
<thead>
<tr>
<th></th>
<th>Strong inhibitors</th>
<th>Moderate inhibitors</th>
<th>Weak inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td>ciprofloxacin, fluvoxamine</td>
<td>mexiletine</td>
<td>acyclovir, allopurinol, amiodarone</td>
</tr>
<tr>
<td>CYP2B6</td>
<td></td>
<td></td>
<td>clopidogrel, voriconazole</td>
</tr>
<tr>
<td>CYP2C8</td>
<td>gemfibrozil</td>
<td>clopidogrel, trimethoprim, pioglitazone, rosiglitazone</td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td>fluconazole</td>
<td>amiodarone, fenofibrate, fluvastatin, lovastatin, paroxetine, sertraline, sulfamethoxazole</td>
<td>voriconazole</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>fluconazole, fluoxetine</td>
<td></td>
<td>omeprazole (all PPIs), voriconazole</td>
</tr>
<tr>
<td>CYP2D6</td>
<td>buPROPion, fluoxetine, paroxetine, quinidine</td>
<td>duloxetine, sertraline</td>
<td>amiodarone, celecoxib, citalopram, escitalopram, labetalol, midodrine, sertraline</td>
</tr>
<tr>
<td>CYP3A4</td>
<td>conivaptan, grapefruit juice, itraconazole, ketoconazole, voriconazole, clarithromycin</td>
<td>cyclosporine, diltiazem, tacrolimus, verapamil</td>
<td>amiodarone</td>
</tr>
</tbody>
</table>

### CYP Inducers

<table>
<thead>
<tr>
<th></th>
<th>Strong inducers</th>
<th>Moderate inducers</th>
<th>Weak inducers</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYP1A2</td>
<td></td>
<td>phenytoin, rifampin, smoking</td>
<td></td>
</tr>
<tr>
<td>CYP2B6</td>
<td>carbamazepine</td>
<td>rifampin</td>
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<tr>
<td>CYP2C8</td>
<td></td>
<td>rifampin</td>
<td></td>
</tr>
<tr>
<td>CYP2C9</td>
<td></td>
<td>rifampin</td>
<td>car bamazepine</td>
</tr>
<tr>
<td>CYP2C19</td>
<td>rifampin</td>
<td>phenytoin</td>
<td></td>
</tr>
<tr>
<td>CYP3A4</td>
<td>carbamazepine, phenytoin, rifampin, St. John’s wort</td>
<td><strong>bosentan</strong>, pioglitazone</td>
<td>modafinil</td>
</tr>
</tbody>
</table>
Common Herbal Supplements

Black Cohosh\textsuperscript{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
Coenzyme Q10

- **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

Cranberry

- **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
Curcumin\textsuperscript{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**

Echinacea\textsuperscript{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**
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

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
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*

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
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 amloidipine, 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!!!
**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

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**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**
Saw palmetto\textsuperscript{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**

St. John’s Wort\textsuperscript{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!!!**
Valerian\textsuperscript{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**
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

THC/CBD Background

- 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
Five Things to Know…

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
   - Sympathomimetics – tachycardia, hypertension
   - CNS depressants (alcohol, opioids) – drowsiness, ataxia
   - Anticholinergics – tachycardia, confusion
5) There are potential “red flag” interactions

Pharmacokinetic Interactions

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

<table>
<thead>
<tr>
<th>CYP3A4 inhibitors</th>
<th>THC</th>
<th>CBD</th>
</tr>
</thead>
</table>
| 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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<tr>
<th>CYP3A4 inducers</th>
<th>THC</th>
<th>CBD</th>
</tr>
</thead>
</table>
| 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 |

## Pharmacokinetic Interactions

<table>
<thead>
<tr>
<th>CYP3A4 substrates</th>
<th>THC</th>
<th>CBD</th>
</tr>
</thead>
</table>
| 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 |

<table>
<thead>
<tr>
<th>CYP2C9 inhibitors</th>
<th>THC</th>
<th>CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfamethoxazole, <strong>amiodarone</strong>, metronidazole, fluconazole, voriconazole, valproic acid</td>
<td>✓ May ↑ THC levels, thus enhancing psychoactive effects</td>
<td>✓ No effects anticipated of CYP2C9 inhibitors or inducers based on current knowledge</td>
</tr>
</tbody>
</table>
## Pharmacokinetic Interactions

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

### 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
- CBD may compromise antiplatelet activity of clopidogrel
- Interactions with other 2C19 substrates possible – monitor for toxicity
- CBD↑ levels of clobazam 6-fold
Pharmacodynamic Interactions\textsuperscript{44-50}

<table>
<thead>
<tr>
<th></th>
<th>THC</th>
<th>CBD</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS depressants</td>
<td>Additive cognitive and psychomotor impairment</td>
<td>Additive cognitive and psychomotor impairment</td>
</tr>
<tr>
<td>Alcohol, opioids,</td>
<td></td>
<td></td>
</tr>
<tr>
<td>benzodiazepines,</td>
<td></td>
<td></td>
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<tr>
<td>tricyclic antidepressants</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sympathomimetics</td>
<td>Additive tachycardia,</td>
<td>No interaction anticipated</td>
</tr>
<tr>
<td>Amphetamines, cocaine,</td>
<td>hypertension and fluid retention</td>
<td></td>
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<tr>
<td>noradrenergic and</td>
<td></td>
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<tr>
<td>anticholinergic agents</td>
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</tbody>
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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
References


References


Questions?

- Email: Paige.skelton@allina.com
- EPIC in-basket message
- EPIC secure chat