SEX DIFFERENCES
AND THE ENDOCANNABINOID SYSTEM IN PAIN

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Evolution of Pain Theories

Defining Pain

“an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage”

Raja S. N. et al., 2020
Blanton, Bergeson, Morgan & Guindon (2019) Ethanol and Pain Interactions
In: The Neuroscience of Alcohol: Mechanisms and Treatment, Elsevier.
Nociception
Sensory transduction of information about potential or actual tissue damage

The Pain Pathway
Pain transmission and modulation

1. Nociceptors receive and transmit pain information from periphery to spinal cord and brain.

2. Descending pain modulation systems activate inhibitory interneurons in dorsal horn of spinal cord.

3. Ascending pain information is dampened.

Blanton, Bergeson, Morgan & Guindon (2019) Ethanol and Pain Interactions
In: The Neuroscience of Alcohol: Mechanisms and Treatment, Elsevier.
Evaluation of Pain

McGill Pain Questionnaire

102 Words divided in 3 categories: sensory – affective – cognitive/evaluative

<table>
<thead>
<tr>
<th>Pain Rating Index</th>
<th>Number of Words Chosen</th>
<th>Actual Pain intensity:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sum of ranking of each words chosen in all 20 subclasses</td>
<td>Sum the words chosen in all 20 subclasses</td>
<td>• No Pain (0)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Mild (1)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Discomforting (2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Distressing (3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Horrible (4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Excruciating (5)</td>
</tr>
</tbody>
</table>

Visual Analogue Scale

No Pain | Score | Worst Possible Pain

Mild | 0

Moderate | 1

Severe | 2

3

Verbal Rating Scale

No Pain | Score

Mild | 0

Moderate | 1

Severe | 2

3

Smile-Sad Faces Scale

0 | 1 | 2 | 3 | 4 | 5

NIH 2016 Sex As a Biological Variable Policy (SABV)

The 4 Cs of Studying Sex to Strengthen Science

**Consider**
Design studies that take sex into account, or explain why it isn't incorporated

**Collect**
Tabulate sex-based data

**Characterize**
Analyze sex-based data

**Communicate**
Report and publish sex-based data
Sex Differences in Pain - Preclinical Evidence (Mogil, 2020)

Sex differences in pain are increasingly being studied. Female bias towards pain sensitivity versus male bias towards analgesic effect.

Male bias: more likely to see effect in males versus females.
Sex Differences in Pain - Humans

Sex Differences in Pain (Sorge & Totsch, 2017)

- Greater prevalence of pain in women: musculoskeletal, abdominal and migraine
- Women have lower tolerance in experimental pain studies
- Differences in evaluation and modulation of pain
- Different neural representation of pain: brain areas activated/inhibited during pain differ between men and women in fMRI
- Many species exist: *Cannabis Sativa* (European plant), *Cannabis indica* (Indian plant) and *Cannabis ruderalis* (Siberia and central Asia plant)

- 460 known chemical constituents of cannabis

- 66 constituents have a cannabinoid structure

- $\Delta^9$-THC most important constituent: principal psychoactive component of cannabis
Di Marzo V (2006)

Cannabis research

- Wood et al. isolate cannabinoids from cannabis resin
- Todd et al. and Adams et al. elucidate and synthesize cannabinoids
- Cannabinoid pharmacology is thoroughly investigated
- Matsuda et al. clone the CB1 receptor
- Munro et al. clone the CB2 receptor

1838–1840: Sir W.B. O'Shaughnessy assesses the medicinal properties of cannabis
1932: Cahn elucidates the structure of cannabinol
1904: Gaoni and Mechoulam elucidate the structure of THC
1988: Howlett’s group identifies specific THC binding sites in the brain
1992: Mechoulam's group identifies the second endocannabinoid, 2-AG

Cannabinoid research

- New drugs
- Rimonabant (SR141716A)
- Rinaldi-Carmona et al. at Sanofi develop the first CB1 receptor antagonist
- Cravatt et al. clone the first endocannabinoid-degrading enzyme, FAAH
- Zygmunt et al. show that anandamide activates vanilloid receptors
- Sativex® approved for sale in Canada, regulatory approval filed to sell rimonabant in the USA; the Aberdeen group discovers an allosteric site on CB1 receptors

Endocannabinoid research

- 2003: Bisogno et al. clone the first endocannabinoid-biosynthesizing enzymes
- 2005: Cloning of new cannabinoid receptors; identification of other endocannabinoid enzymes; cloning of the endocannabinoid transporter; more endocannabinoid-based therapies

Di Marzo V (2006)
Cannabinoid receptors

CB$_1$

Matsuda et al 1990

CB$_2$

Munro et al 1993
Cannabinoid Receptor Type 1 (CB1)

- $G_i$ coupled GPCR, found throughout CNS & PNS
- Activation produces inhibitory effect through inhibition of cAMP formation, activation of potassium channels, and inhibition of calcium entry
- Expressed throughout pain pathway (brain, DRG and laminae of spinal cord, peripheral nerve endings)
- Activation of CB1 in the brain is responsible for psychotropic effects of cannabis
- Activation in rodents produces analgesia, hypothermia, and decrease in motor activity and coordination

$[^{18}\text{F}]-\text{MK-9470} – \text{Radiolabeled CB1 ligand}$
Cannabinoid Receptor Type 2 (CB2)

- CB2R found in peripheral tissues, immune cells, glia, etc.
- Inducible expression in CNS (injury, inflammation, neurodegenerative diseases)
- Activation not associated with classical cannabinoid (CB1R) associated side effects (catalepsy, hypothermia)
- Analgesic mechanisms still under investigation
- Being explored in clinical trials for osteoarthritic pain (ClinicalTrials.gov, NCT00447486) and GI pain associated with Chron’s (ClinicalTrials.gov, NCT03155945)

[^11C]-NE40 – Radiolabeled CB2 ligand

Endocannabinoid System

Cannabinoid Receptors
- CB₁ receptor
- CB₂ receptor

Endocannabinoids
- Anandamide (AEA)
- 2-Arachidonyleglycerol (2-AG)

Synthesis & Degradation Enzymes
- Phospholipase A₂
- Phospholipase C
- NAPE-PLD
- Fatty Acid Amide Hydrolase (FAAH)
- Diacylglycerol Lipase (DAGL)
- Monoacylglycerol Lipase (MAGL)
The Endocannabinoid System

Exogenous agonists

- Δ⁹-THC
- CP-55940
- WIN-55212-2
- HU-210

Endogenous agonists

- Anandamide
- 2-Arachidonylglycerol

Antagonists

- SR-141716A
- SR-144528
# Natural and Synthetic Cannabinoid Agonists

<table>
<thead>
<tr>
<th>Natural agonists</th>
<th>CB&lt;sub&gt;1&lt;/sub&gt;</th>
<th>CB&lt;sub&gt;2&lt;/sub&gt;</th>
</tr>
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<tbody>
<tr>
<td><strong>Δ&lt;sup&gt;9&lt;/sup&gt;-THC</strong></td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td><strong>Cannabidiol (no psycho-active properties)</strong></td>
<td>0</td>
<td>±</td>
</tr>
<tr>
<td><strong>Cannabinol (psycho-active properties)</strong></td>
<td>+</td>
<td>++</td>
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</table>

<table>
<thead>
<tr>
<th>Synthetic Agonists</th>
<th>CB&lt;sub&gt;1&lt;/sub&gt;</th>
<th>CB&lt;sub&gt;2&lt;/sub&gt;</th>
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</thead>
<tbody>
<tr>
<td><strong>Dronabinol (Marinol®)</strong></td>
<td>++</td>
<td>++</td>
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<tr>
<td><strong>Nabilone (Cesamet®)</strong></td>
<td>++</td>
<td>++</td>
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<tr>
<td><strong>Levonantradol</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>HU-210</strong></td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Win 55,212-2</strong></td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>CP-55940</strong></td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td><strong>Methanandamide</strong></td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>ACEA</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>0-1812</strong></td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td><strong>JWH-051</strong></td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td><strong>HU-308</strong></td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>AM1241</strong></td>
<td>+</td>
<td>+++</td>
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<tr>
<td><strong>JWH-133</strong></td>
<td>+</td>
<td>+++</td>
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<td><strong>L-759633</strong></td>
<td>+</td>
<td>+++</td>
</tr>
<tr>
<td><strong>GW405833 (L768242)</strong></td>
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<td>+++</td>
</tr>
<tr>
<td><strong>GW842166X</strong></td>
<td>+</td>
<td>+++</td>
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<tr>
<td><strong>AM1714</strong></td>
<td>+</td>
<td>+++</td>
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<tr>
<td><strong>JWH-015</strong></td>
<td>+</td>
<td>+++</td>
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</table>

<table>
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<tr>
<th>Antagonists/Inverse agonists</th>
<th>CB&lt;sub&gt;1&lt;/sub&gt;</th>
<th>CB&lt;sub&gt;2&lt;/sub&gt;</th>
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<tr>
<td><strong>SR141716A</strong></td>
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<td>0</td>
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<tr>
<td><strong>LY-320135</strong></td>
<td>++</td>
<td>0</td>
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<td><strong>AM251</strong></td>
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<td>0</td>
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<tr>
<td><strong>AM281</strong></td>
<td>++</td>
<td>0</td>
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<td><strong>SR144528</strong></td>
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<td>++</td>
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<tr>
<td><strong>AM630</strong></td>
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Cannabidiol, also known as CBD,
- Decreases seizures
- Pain relief
- Reduce inflammation
- Antidepressant
- Improve headaches/migraines/sleep
- Reduce stress
### Effects of cannabinoids on different physiological systems

<table>
<thead>
<tr>
<th>Systems</th>
<th>Effects</th>
</tr>
</thead>
</table>
| **Central nervous system** | - Euphoria—cannabinoid exhilaration  
                          - Increase sensory perception  
                          - Disruption of intellectual and psychomotor performance  
                          - Temporospatial disorientation  
                          - Ideation trouble  
                          - Memory trouble  
                          - Thermoregulation disorder  
                          - Psychotic trouble  
                          - **Analgesia**  
                          - Antiemetic properties  
                          - Appetite stimulant  
                          - Anticonvulsive properties |
| **Cardiovascular system** | - Tachycardia  
                          - Vasodilatation |
| **Respiratory system**   | - Bronchodilatation |
| **Ocular system**       | - Decrease of intra-ocular pressure (glaucoma) |
| **Other systems**       | - Effects on the immune functions  
                          - Effects on the reproductive system  
                          - Tolerance phenomenon after prolonged utilization |
States with Legalized Marijuana
American Nonsmokers' Rights Foundation
October 1, 2021

Laws are enacted; not yet necessarily in effect. CBD oil legislation is not reflected.

State Law
Recreational and Medical Marijuana Use is Legal
Marijuana use is not Legal
Medical Marijuana Use, but not Recreational, is Legal
Note: In total, medical marijuana use is legal in 37 states.
Cannabidiol or CBD

- Decreases seizures
- Pain relief
- Reduce inflammation
- Antidepressant
- Improve headaches/migraines/sleep
- Reduce stress
Most commonly reported reason for use of cannabis for medical purposes is pain relief (Boehnke et al., 2019 Health Affairs)
Cannabinoids: Current and future options to treat chronic and chemotherapy-induced neuropathic pain

Cannabinoids: Current and Future Options to Treat Chronic and Chemotherapy-Induced Neuropathic Pain

Henry L. Blanton, Jennifer Brelsfoard, Nathan DeTurk, Kevin Pruitt, Madhusudhan Narasimhan, Daniel J. Morgan & Josée Guindon

Abstract

Increases in cancer diagnosis have tremendous negative impacts on patients and their families, and major societal and economic costs. The beneficial effect of chemotherapeutic agents on tumor suppression comes with major unwanted side effects such as weight and hair loss, nausea and vomiting, and neuropathic pain. Chemotherapy-induced peripheral neuropathy (CIPN), which can include both painful and non-painful symptoms, can persist 6 months or longer after the patient’s last chemotherapeutic treatment. These peripheral sensory and motor deficits are poorly treated by our current analgesics with limited effectiveness. Therefore, the development of novel treatment strategies is an important preclinical research focus and an urgent need for patients. Approaches to prevent CIPN have yielded disappointing results since these compounds may interfere with the anti-tumor properties of chemotherapeutic agents. Nevertheless, the first (serotonin noradrenaline reuptake inhibitors [SNRIs], anticonvulsants, tricyclic antidepressants) and second (5% lidocaine patches, 8% capsaicin patches and weak opioids such as tramadol) lines of treatment for CIPN have shown some efficacy. The clinical challenge of CIPN management in cancer patients and the need to target novel therapies with long-term efficacy in alleviating CIPN are an ongoing focus of research. The endogenous cannabinoid system has shown great promise and efficacy in alleviating CIPN in preclinical and clinical studies. In this review, we will discuss the mechanisms through which the platinum, taxane, and vinca alkaloid classes of chemotherapeutics may produce CIPN and the potential therapeutic effect of drugs targeting the endocannabinoid system in preclinical and clinical studies, in addition to cannabinoid compounds diffuse mechanisms of action in alleviation of CIPN.
## Cannabinoids and Chronic Pain: Clinical Studies

<table>
<thead>
<tr>
<th>Chronic pain conditions</th>
<th>Pain test before tx</th>
<th>Type of study</th>
<th>Study design</th>
<th>Time study</th>
<th>Drugs</th>
<th>Dose per day</th>
<th>Route</th>
<th>Patients (#)</th>
<th>Gender M/F</th>
<th>Ethnicity</th>
<th>Age</th>
<th>Reducton pain intensity</th>
<th>Pain test after tx</th>
<th>Side effects</th>
<th>Ref</th>
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</thead>
<tbody>
<tr>
<td>Neuropathic pain mixed etiology</td>
<td>VAS &gt;30/100</td>
<td>randomized double-blind placebo controlled</td>
<td>parallel</td>
<td>3 sessions of 6 hours; session interval 3 to 21 days</td>
<td>Δ9-THC or placebo</td>
<td>19.25 mg low dose 34.3 mg high dose</td>
<td>inhale using cigarette</td>
<td>38</td>
<td>20/18</td>
<td>33 C: 1 AA: 1 H: 3 O</td>
<td>46 (range 21-71)</td>
<td>Yes 50 %</td>
<td>VAS</td>
<td>Euphoria Mood changes Decline cognition [112]</td>
<td></td>
</tr>
<tr>
<td>Neuropathic pain mixed etiology</td>
<td>VAS &gt;40/100</td>
<td>randomized double-blind</td>
<td>4 period crossover Latin square</td>
<td>5 days (9 days washout)</td>
<td>Δ9-THC or placebo</td>
<td>1.875 to 7.05 mg of THC</td>
<td>gelatin capsules inhaled by pipe</td>
<td>23</td>
<td>11/12</td>
<td>NR</td>
<td>45.4 (±12.3)</td>
<td>Yes</td>
<td>NRS Daily</td>
<td>headache dry eye dizziness numbness cough burning sensation pain area [126]</td>
<td></td>
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<tr>
<td>Central and peripheral neuropathic pain mixed etiology</td>
<td>NPS &gt;40/100</td>
<td>randomized placebo-controlled</td>
<td>crossover</td>
<td>2 sessions; session interval 4 hours</td>
<td>Δ9-THC or placebo</td>
<td>45.9 mg low dose 56.3 mg high dose</td>
<td>vaporize using foltin puff</td>
<td>42</td>
<td>29/13</td>
<td>26 C: 7 H: 5 AA: 2 A: 2 O</td>
<td>46.4 (±13.6)</td>
<td>Yes 50 %</td>
<td>NPS</td>
<td>Hypotension [125]</td>
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<tr>
<td>Central and peripheral neuropathic pain mixed etiology</td>
<td>VAS &gt;30/100</td>
<td>randomized placebo-controlled</td>
<td>crossover</td>
<td>3 sessions of 6 hours; session interval 3 to 14 days</td>
<td>Δ9-THC or placebo</td>
<td>10.32 mg low dose 28 mg high dose</td>
<td>vaporized using volcano system</td>
<td>39</td>
<td>28/11</td>
<td>28 C: 5 AA: 3 H: 3 O</td>
<td>50 (±11)</td>
<td>Yes 50 %</td>
<td>VAS</td>
<td>Euphoria Sedation Confusion Nausea Hunger [127]</td>
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<tr>
<td>Central neuropathic pain MS associated</td>
<td>NRS &gt;40/100</td>
<td>randomized placebo-controlled</td>
<td>parallel</td>
<td>4 weeks</td>
<td>Δ9-THC formulation ECP002A</td>
<td>9 mg to 29 mg of Δ9-THC</td>
<td>oral</td>
<td>24</td>
<td>8/16</td>
<td>NR</td>
<td>54.3 (±8.9)</td>
<td>Yes after tx No daily diary</td>
<td>NRS VAS McGill 1QP</td>
<td>headache dizziness fatigue euphoric mood [122]</td>
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<tr>
<td>HIV-DSPN</td>
<td>VAS &gt;30/100</td>
<td>randomized double-blind</td>
<td>Parallel</td>
<td>12 days</td>
<td>Δ9-THC or placebo</td>
<td>96 mg Δ9-THC 3 sessions X 32 mg Δ9-THC per session</td>
<td>inhale using cigarette</td>
<td>55</td>
<td>22/5 Ed 26/2 Control</td>
<td>NR</td>
<td>50 (±6)</td>
<td>Yes ≥ 30 %</td>
<td>VAS Daily</td>
<td>NR [128]</td>
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<tr>
<td>HIV-DSPN</td>
<td>DDS &gt;5/20</td>
<td>randomized double-blind</td>
<td>Crossover</td>
<td>5 days (no washout)</td>
<td>Δ9-THC or placebo</td>
<td>titrating dose up and down 96 mg Δ9-THC 4 sessions X 24 mg Δ9-THC per session</td>
<td>inhale using cigarette</td>
<td>34</td>
<td>33/1</td>
<td>NR</td>
<td>49.1 (±6.9)</td>
<td>Yes</td>
<td>DDS</td>
<td>NR [129]</td>
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<td>Chemotherapy-induced neuropathy</td>
<td>NRS ≥ 4/10</td>
<td>randomized placebo-controlled</td>
<td>Crossover</td>
<td>4 weeks (2 weeks washout)</td>
<td>Nabiximols Sativex THC/CBD</td>
<td>8.1 to 32.4 mg of Δ9-THC 7.5 to 30 mg of CBD</td>
<td>oromucosal spray</td>
<td>18</td>
<td>3/15</td>
<td>NR</td>
<td>56 (±10.8)</td>
<td>No</td>
<td>NRS Daily</td>
<td>dizziness fatigue dry mouth nausea diarrhea [113]</td>
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<tr>
<td>Peripheral neuropathy</td>
<td>NRS ≥ 3/10</td>
<td>randomized placebo-controlled</td>
<td>parallel</td>
<td>15 weeks</td>
<td>Nabiximols Sativex THC/CBD</td>
<td>21.6 to 64.8 mg of Δ9-THC 10 to 60 mg of CBD</td>
<td>oromucosal spray</td>
<td>246</td>
<td>96/150</td>
<td>243 C: 2 AA</td>
<td>57.3 (±14.2)</td>
<td>No</td>
<td>NRS BPI-SF DAT</td>
<td>headache dizziness dry mouth nausea diarrhea [114]</td>
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<tr>
<td>Study</td>
<td>Population</td>
<td>Design</td>
<td>Duration</td>
<td>Treatment</td>
<td>Comparator</td>
<td>Primary Endpoint</td>
<td>Secondary Outcomes</td>
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<td><strong>Peripheral Neuropathic Pain</strong></td>
<td>NRS 7/10</td>
<td>Randomized double-blind placebo-controlled, parallel</td>
<td>5 weeks</td>
<td>Nabiximols Sativex THC:CBD 3.51 to 84.78 mg of Δ9-THC 3.25 to 78.5 mg of CBD</td>
<td>Oromucosal spray</td>
<td>125</td>
<td>51/74</td>
<td>121 C 4 O 52.4 (±15.8) Yes ≥ 30 % VAS NRS NPS PDI Dizziness fatigue dry mouth nausea diarrhea</td>
<td></td>
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<td><strong>Central Neuropathic Pain</strong></td>
<td>NRS ≥ 4/10</td>
<td>Randomized double-blind placebo-controlled, parallel</td>
<td>5 weeks</td>
<td>Nabiximols Sativex THC:CBD 21.6 to 129.6 mg of Δ9-THC 20 to 120 mg of CBD</td>
<td>Oromucosal spray</td>
<td>64</td>
<td>14/49</td>
<td>NR 49 (±8.4) Yes NRS daily dizziness headache dry mouth nausea diarrhea</td>
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<td><strong>Central Neuropathic Pain</strong></td>
<td>NRS ≥ 4/10</td>
<td>Randomized double-blind placebo-controlled, parallel</td>
<td>14 weeks</td>
<td>Nabiximols Sativex THC:CBD 23.76 to 32.4 mg of Δ9-THC 22 to 30 mg of CBD</td>
<td>Oromucosal spray</td>
<td>339</td>
<td>109/230</td>
<td>332 C 4 AA 2 A 48.97 (±10.47) No NRS dizziness fatigue dry mouth nausea diarrhea</td>
<td></td>
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<tr>
<td><strong>HIV-DSPN and Neuropathic Pain</strong></td>
<td>VAS &gt;30/100</td>
<td>Randomized double-blind placebo-controlled, crossover</td>
<td>2 weeks (washout)</td>
<td>Nabiximols Sativex THC:CBD 2.5 to 120 mg of Δ9-THC 2.5 to 120 mg of CBD</td>
<td>Oromucosal spray</td>
<td>20</td>
<td>10/10</td>
<td>NR 48 Yes &gt; 50 % VAS headache hypotension intoxication diarrhea</td>
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<tr>
<td><strong>Spinal Cord Injury</strong></td>
<td>NPS &gt;5/10</td>
<td>Randomized double-blind placebo-controlled, crossover</td>
<td>6 weeks (washout)</td>
<td>Dronabinol capsules 5 mg to 20 mg/day</td>
<td>Oral p.o.</td>
<td>7</td>
<td>5/2</td>
<td>6 C 1 AA 50.1 (±8.3) No NRS drowsiness fatigue dry mouth constipation</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td><strong>Central Neuropathic Pain</strong></td>
<td>NRS ≥ 3/10</td>
<td>Randomized double-blind placebo-controlled, crossover</td>
<td>6 weeks (washout)</td>
<td>Dronabinol 2.5 to 10 mg</td>
<td>Oral</td>
<td>24</td>
<td>10/14</td>
<td>NR 50 (23 to 55) Yes NRS dizziness tiredness myalgia dry mouth nausea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Central Neuropathic Pain</strong></td>
<td>NRS ≥ 4/10</td>
<td>Randomized double-blind placebo-controlled, parallel</td>
<td>16 weeks</td>
<td>Dronabinol 7.5 to 15.0 mg</td>
<td>Oral</td>
<td>240</td>
<td>65/175</td>
<td>NR 47.7 (±9.7) No NRS headache dizziness fatigue vertigo dry mouth nausea diarrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neuropathic Pain</strong></td>
<td>VAS &gt;70/100</td>
<td>Randomized double-blind placebo-controlled, crossover</td>
<td>14 weeks (2 weeks washout)</td>
<td>Nabulone or Dihydromedronine</td>
<td>Nabilone 2 mg</td>
<td>p.o.</td>
<td>96</td>
<td>46/50</td>
<td>NR 50.15 (±13.69) Yes VAS tiredness tingling headache</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>HIV-DSPN</strong></td>
<td>VAS &gt;70/100</td>
<td>Randomized double-blind placebo-controlled, parallel</td>
<td>9 weeks (4 weeks for titration)</td>
<td>Nabulone</td>
<td>2 mg</td>
<td>Oral</td>
<td>15</td>
<td>2/13</td>
<td>NR 45.5 (±10.84) Yes VAS dizziness drowsiness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Neuropathic Pain</strong></td>
<td>VAS &gt;70/100</td>
<td>Randomized double-blind placebo-controlled, crossover</td>
<td>5 weeks</td>
<td>1:1 Dimet hyd-A8- tetrahydrocannabinol-11oic acid (CT-5)</td>
<td>40 mg (10 mg per capsules)</td>
<td>Oral</td>
<td>21</td>
<td>13/8</td>
<td>NR 50.86 (±11.69) Yes VAS tiredness dry mouth</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

AA, African-American; A, asian; BPI-SF, brief pain inventory short form; C, caucasian; DAT, dynamic allodynia test; DDS, descriptor differential scale; H, hispanic; HIV-DSPN, human immunodeficiency virus distal sensory peripheral neuropathy; F, female; M, male; McGill QP, McGill pain questionnaire; Mixed etiology, include but are not exclusive to complex regional pain syndrome 1 (CRPS-1) and II (CRPS-II), spinal cord injury, diabetic neuropathy, post-herpetic neuralgia, radiculopathy, focal nerve lesion and others; NPS, neuropathic pain scale; NR, not reported; NRS, numerical rating scale; O, other; PDI, pain disability index; VAS, visual analogue scale.
Sex differences and the endocannabinoid system in pain

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b Department of Pharmacodynamics, College of Pharmacy, University of Florida, Gainesville, FL 32611, United States of America
Sex Differences in Brain Endocannabinoid System

Ant. Cingulate/PF Cortex
- CB1 mRNA: F > M (Xing et al., 2014)
- CB1 mRNA: M > F (Liu et al., 2020)
- CB1 density: M > F (Castelli et al., 2014)
- Increased CB1 efficacy with GDX (Farquhar et al., 2019)
- CB1-stimulated pERK: F > M (Rosas et al., 2018)
- Increased CB1 affinity with OVX (Castelli et al., 2014)

Hippocampus
- CB1 & CB2 mRNA: F > M (Xing et al., 2014)
- CB1 mRNA (dorsal): F > M (Liu et al., 2020)
- CB1 mRNA (CA1): F > M (Liu et al., 2020)
- CB1 density: M > F (Reich et al., 2009)
  - CP 55,950 efficacy: F > M (Farquhar et al., 2019)
  - Increased CB1 affinity with GDX (Farquhar et al., 2019)
  - Increased CB1 affinity with OVX (Riebe et al., 2010)

Midbrain
- CB1 density: M > F (Rodriguez de Fonseca et al., 1994)
- CB1 binding: F > M (Rodriguez de Fonseca et al., 1994)

Amygdala
- CB1 density: F > M (Riebe et al., 2010)
- CB1 density: M > F (Castelli et al., 2014)
- CB1 affinity: F > M (Riebe et al., 2010)
- CB1 mRNA: F > M (Xing et al., 2014)
- CB1 mRNA highest in estrous (Liu et al., 2020)
- Increased CB1 density with OVX (Castelli et al., 2014)

Cerebellum
- 2-AG levels: M > F (Bradshaw et al., 2006)
- CB1 mRNA: F > M (Xing et al., 2011)

Striatum
- CB1 affinity: F > M (Rodriguez de Fonseca et al., 1994)
- CB1 mRNA: M > F (Liu et al., 2020)

Limbic Forebrain
- CB1 affinity: F > M (Rodriguez de Fonseca et al., 1994)

Hypothalamus
- 2-AG levels: F > M (Bradshaw et al., 2006)
- CB1 density & binding: M > F (Riebe et al., 2010)
- CB1 & CB2 mRNA: F > M (Xing et al., 2014)

Pituitary
- 2-AG levels: F > M (Bradshaw et al., 2006)
- AEA levels: F > M (Gonzalez et al., 2000)

Mechanisms underlying Sex Differences in Cannabinoid Antinociception

## Comparison of Cannabinoid-Mediated Antinociception in Male and Female

<table>
<thead>
<tr>
<th>Reference</th>
<th>Pain Model</th>
<th>Acute or Chronic</th>
<th>Species</th>
<th>Compound(s)</th>
<th>Dose &amp; ROA</th>
<th>Acute and/or Repeated</th>
<th>Efficacy: Male v Female</th>
<th>Mediated By</th>
<th>Serum Analysis</th>
<th>Estrous Effect</th>
<th>Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blednov et al., 2003</td>
<td>Hotplate (Paw)</td>
<td>Acute</td>
<td>Mouse</td>
<td>WIN 55, 212-2</td>
<td>6 mg/kg; I.P.</td>
<td>Acute</td>
<td>M = F</td>
<td>GIRK 2; Male &gt; Female</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Britch et al., 2017</td>
<td>Pressure (Paw), Heat (Tail Immersion)</td>
<td>Acute</td>
<td>Rat</td>
<td>CBD, THC</td>
<td>CBD (30 mg/kg) + THC (1.8 mg/kg); I.P.</td>
<td>Acute</td>
<td>M = F</td>
<td>NT</td>
<td>NT</td>
<td>No Effect</td>
<td>NT</td>
</tr>
<tr>
<td>Britch et al., 2020</td>
<td>Heat (Paw), Mech. Allodynia (Paw), Weight Bearing (paw)</td>
<td>Chronic - CFA (paw)</td>
<td>Rat</td>
<td>CBD, THC</td>
<td>CBD (1.25-10 mg/kg), THC (1-4 mg/kg); I.P.</td>
<td>Acute &amp; Repeated</td>
<td>F=M; acute THC heat hyperalgesia</td>
<td>NT</td>
<td>Yes; TNF-α, IL-1β, IL-10, INFγ</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Craft and Leil, 2008</td>
<td>Pressure (Paw), Heat (Tail Immersion)</td>
<td>Acute</td>
<td>Rat</td>
<td>THC</td>
<td>5, 10 mg/kg; I.P.</td>
<td>Acute</td>
<td>F=M, E2 potentiate in Female</td>
<td>NT</td>
<td>Yes; THC strongest in estrus</td>
<td>M &amp; F Gonadectomy, Testosterone &amp; Estradiol Replacement</td>
<td></td>
</tr>
<tr>
<td>Craft et al., 2012</td>
<td>Heat (Tail Immersion), Pressure (Paw)</td>
<td>Acute</td>
<td>Rat</td>
<td>CP 55,940, THC</td>
<td>CP 55,940 (0.05 - 1.6 mg/kg), THC (1.25 - 20 mg/kg); I.P.</td>
<td>Acute</td>
<td>CP 55,940 F=M; THC: F=M</td>
<td>IP: CB1 - M &amp; F; THC: CB1 - Male, CB1 &amp; CB2 - Female</td>
<td>Yes; Rimonabant</td>
<td>Yes; THC strongest in estrus</td>
<td>NT</td>
</tr>
<tr>
<td>Craft et al., 2013</td>
<td>Mech. Allodynia (Paw), Heat (Paw)</td>
<td>Chronic - CFA (paw)</td>
<td>Rat</td>
<td>THC</td>
<td>0.32 - 3.2 mg/kg I.P.; 0-500 μg I.P.L.</td>
<td>Acute &amp; Repeated</td>
<td>THC: F=M</td>
<td>IP: CB1 - M &amp; F; THC: CB1 only Male</td>
<td>NT</td>
<td>Yes; THC strongest in estrus</td>
<td>NT</td>
</tr>
<tr>
<td>Craft et al., 2017</td>
<td>Pressure (Paw), Heat (Tail Immersion)</td>
<td>Acute</td>
<td>Rat</td>
<td>THC</td>
<td>THC: 3 mg/kg (Female), 5 mg/kg (Male), Procainen: 25mg/kg, I.P.</td>
<td>Acute</td>
<td>F=M, E2 potentiate THC in female, T inhibit THC in female</td>
<td>Testosteron, Estradiol, and CYP450 (CYP2C family)</td>
<td>Yes; THC, 11-OH-THC, THC-COOH</td>
<td>NT</td>
<td>M &amp; F Gonadectomy, Testosterone &amp; Estradiol Replacement</td>
</tr>
<tr>
<td>Craft et al., 2018</td>
<td>Acute: Heat (Tail Immersion), Pressure (Paw), Inflammatory: Mech. Allodynia (Paw), Heat (Paw), Weight Bearing (paw)</td>
<td>Acute, Chronic - CFA (paw)</td>
<td>Rat</td>
<td>JWh015</td>
<td>5-40 mg/kg, I.P.</td>
<td>Acute</td>
<td>M=F, except mech. allodynia F=M (10 mg/kg)</td>
<td>CB1 &amp; CB2</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Greene et al., 2018</td>
<td>Pressure (Paw), Heat (Tail Immersion)</td>
<td>Acute</td>
<td>Rat</td>
<td>CBD, THC</td>
<td>CBD: 10 mg/kg; THC: 3.6 mg/kg (Female), 3.3 mg/kg (Male); I.P.</td>
<td>Repeated</td>
<td>THC: F=M (acute), CBD: M=F (repeated - tail flick)</td>
<td>NT</td>
<td>Yes; CBD, CBN, THC, 11-OH-THC, THC-COOH</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Javadi-Paydar et al., 2018</td>
<td>Heat (Tail Immersion)</td>
<td>Acute</td>
<td>Rat</td>
<td>CBD, THC</td>
<td>CBD: 12.5, 50 mg, THC: 1.5-25mg, Vaporized</td>
<td>Repeated (&gt;1week washout between)</td>
<td>F=M</td>
<td>NT</td>
<td>Yes; THC</td>
<td>No Effect; THC equivalent between Diestrus &amp; Estrus</td>
<td>NT</td>
</tr>
<tr>
<td>Kalbasi Anaraki et al., 2008</td>
<td>Heat (Tail Flick)</td>
<td>Acute</td>
<td>Mouse</td>
<td>WIN 55, 212-2</td>
<td>2, 4 mg/kg, I.P.</td>
<td>Acute</td>
<td>F only; OVX enhance analgesia, E2 inhibit, P4 no effect</td>
<td>CB1</td>
<td>NT</td>
<td>NT</td>
<td>F Only OVX, E2 &amp; P4 Replacement</td>
</tr>
<tr>
<td>LaFleur et al., 2018</td>
<td>Inflammatory (Formalin-Paw)</td>
<td>Acute</td>
<td>Mouse</td>
<td>CP 55,940</td>
<td>CP 55,940 (0.06 - 0.2 mg/kg), THC (1 - 6 mg/kg); I.P.</td>
<td>Acute &amp; Repeated</td>
<td>CP 55,940: M=F; THC: M=F</td>
<td>antinociception &amp; rate of tolerance</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Linher-Melville et al., 2020</td>
<td>Mech. Allodynia (Paw)</td>
<td>Chronic - Sciatic Nerve Cuff</td>
<td>Rat</td>
<td>CBD, THC</td>
<td>CBD: 0.41 mg/kg THC: 0.08 mg/kg, Combination: 0.2 mg/kg + 0.2 mg/kg; Oral</td>
<td>Repeated</td>
<td>M=F</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
</tbody>
</table>
Comparison of Cannabinoid-Mediated Antinociception in Male and Female

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<th>Hormone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marusich et al., 2015</td>
<td>Heat (Tail Flick)</td>
<td>Acute</td>
<td>Rat</td>
<td>THC</td>
<td>30 mg/kg, I.P.</td>
<td>Acute &amp; Repeated</td>
<td>F&gt;M (Acute); M=F (Chronic)</td>
<td>CB1</td>
<td>NT</td>
<td>Inconclusive</td>
</tr>
<tr>
<td>Mulpuri et al., 2016</td>
<td>Mech. Allodynia (Paw), Cold Alloodynia (Paw)</td>
<td>Chronic - Cisplatin (systemic)</td>
<td>Rat</td>
<td>PrNMI</td>
<td>0-2 mg/kg I.P.; 0.25 mg/kg I.P.L.; 3 mg/kg Oral</td>
<td>Acute &amp; Repeated</td>
<td>M=F</td>
<td>CB1</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Niu et al., 2012</td>
<td>Mech. Allodynia (Masseter)</td>
<td>Chronic - CFA (masseter)</td>
<td>Rat</td>
<td>ACPA</td>
<td>10-300 μg I.M.</td>
<td>Acute &amp; Repeated</td>
<td>M&gt;F</td>
<td>CB1</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Romero et al., 2002</td>
<td>Heat (Tail Immersion)</td>
<td>Acute</td>
<td>Rat</td>
<td>CP 55,940</td>
<td>0.1-0.6 mg/kg, I.P.</td>
<td>Acute</td>
<td>M=F</td>
<td>CB1</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Tseng and Craft, 2001</td>
<td>Pressure (Paw), Heat (Tail Immersion)</td>
<td>Acute</td>
<td>Rat</td>
<td>CP 55,940, THC, 11-OH-THC</td>
<td>CP 55, 940 (0.1-0.56 mg/kg), THC (1-10 mg/kg), 11-OH-THC (0.3-10 mg/kg); I.P.</td>
<td>Acute</td>
<td>F&gt;M</td>
<td>NT</td>
<td>NT</td>
<td>No Effect</td>
</tr>
<tr>
<td>Tseng et al., 2004</td>
<td>Heat (Tail Immersion)</td>
<td>Acute</td>
<td>Rat</td>
<td>THC</td>
<td>10 mg/kg, I.P.</td>
<td>Acute</td>
<td>F&gt;M</td>
<td>CYP 450 (Female)</td>
<td>THC, 11-OH-THC</td>
<td>NT</td>
</tr>
<tr>
<td>Wakley et al., 2011</td>
<td>Pressure (Paw), Heat (Tail Immersion)</td>
<td>Acute</td>
<td>Rat</td>
<td>THC</td>
<td>100 μg, I.C.V.</td>
<td>Acute</td>
<td>F&gt;M</td>
<td>NT</td>
<td>NT</td>
<td>Yes; F&gt;M when in Late Prooestrus</td>
</tr>
<tr>
<td>Wakley et al., 2014</td>
<td>Pressure (Paw), Heat (Tail Immersion)</td>
<td>Acute</td>
<td>Rat</td>
<td>THC</td>
<td>5.4 mg/kg (Female), 7.6 mg/kg (Male), I.P.</td>
<td>Acute &amp; Repeated</td>
<td>F&gt;M</td>
<td>NT</td>
<td>NT</td>
<td>No Effect</td>
</tr>
<tr>
<td>Wakley et al., 2015</td>
<td>Pressure (Paw), Heat (Tail Immersion)</td>
<td>Acute</td>
<td>Rat</td>
<td>THC</td>
<td>5.7 mg/kg (Female), 9.9 mg/kg (Male), I.P.</td>
<td>F&gt;M antinociception &amp; rate of tolerance; P4 inhibit THC</td>
<td>NT</td>
<td>NT</td>
<td>Inconclusive</td>
<td>M &amp; F Gonadectomy, Testosterone, Estradiol, &amp; Progesterone Replacement</td>
</tr>
<tr>
<td>Wiley et al., 2003</td>
<td>Heat (Tail Flick)</td>
<td>Acute</td>
<td>Rat</td>
<td>THC</td>
<td>1-300 mg/kg, I.P.</td>
<td>Acute</td>
<td>M=F</td>
<td>CB1</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Yuill et al., 2017</td>
<td>Inflammatory (Formalin-Paw)</td>
<td>Acute</td>
<td>Mouse</td>
<td>JWH 133</td>
<td>0.01 - 10 mg/kg (acute), 1 mg/kg repeated; I.P.</td>
<td>Acute &amp; Repeated</td>
<td>M=F</td>
<td>CB2</td>
<td>NT</td>
<td>NT</td>
</tr>
<tr>
<td>Zhu et al., 2020</td>
<td>Mech. Alloodynia (Paw), Heat (Paw)</td>
<td>Chronic - Sciatic Nerve Cuff</td>
<td>Rat</td>
<td>CBDA-ME</td>
<td>0.01-4 μg/kg, I.P.</td>
<td>Repeated</td>
<td>M&gt;F</td>
<td>NT</td>
<td>NT</td>
<td>NT</td>
</tr>
</tbody>
</table>
Major Findings

- Females *generally* reported as more sensitive to cannabinoids versus males
- Ovariectomy and hormone replacement *may* influence cannabinoid-mediated antinociceptive effects

Limitations of Field

- majority of studies focused on THC; sex differences in metabolism
- focus on acute, rather than chronic pain models
- few studies looked at sex differences in cannabinoid tolerance
- few studies investigated individual roles of CB1 versus CB2 receptors in this process
Formalin test: Evaluation of nociceptive behavior

**Normalization and Observations**

<table>
<thead>
<tr>
<th>Normal behaviour</th>
<th>Observations</th>
<th>Scoring system**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Injected paw can support the weight of the animal.</td>
<td>× 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain behaviour (1)</th>
<th>Observations</th>
<th>Scoring system**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Injected paw has little or no weight on it.</td>
<td>× 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain behaviour (2)</th>
<th>Observations</th>
<th>Scoring system**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Injected paw is elevated, not in contact with any surface.</td>
<td>× 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pain behaviour (3)</th>
<th>Observations</th>
<th>Scoring system**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Injected paw is licked, bitten or shaken.</td>
<td>× 2</td>
</tr>
</tbody>
</table>

Composite Pain Score = \((\text{Behavior 2 Time} \times 2 + \text{Behavior 1 Time}) / 300\)

Estrous Cycle

- Nucleated epithelial cells
- Cornified squamous epithelial cells
- Mix cell types (leucocytes, nucleated and/or cornified squamous epithelial cells)
- Predominance of leukocytes
Sex differences in the formalin test

Male vs Female Estrous Cycle in Formalin

Male vs Female Estrous Cycle in Formalin

Estradiol increases inflammatory pain in ovariectomized females

CBD in the Formalin test in males

CBD 2.5 mg/kg

2.5 % formalin (10 µL intraplantar)

Composite Pain Score

Time Post Formalin (min)

Acute Phase 1

Inflammatory Phase 2

AUC

Control

CBD

*
Treatments of chemotherapy-induced peripheral neuropathy

**Current Treatments**

1st Line
- SNRI’s (Duloxetine)
- Pregabalin
- Gabapentin
- TCA’s

2nd Line
- Lidocaine Patch
- Capsaicin Patch
- Tramadol

3rd Line
- Strong Opioids
- Botox

**Current Clinical Trials**

- Acupuncture
- Amino Acids
- Anti-epileptics
- Cannabinoids
- Cryotherapy
- Dextromethorphan
- Electrostimulation
- Exercise, Yoga
- Minocycline
- Naloxone
- Neurofeedback
- Olesoxime
- Omega 3’s
- Vitamins

Chemotherapy-induced peripheral neuropathy

Neuropathy induced by platinum derived compounds (cisplatin, carboplatin, oxaliplatin)

Mechanical Allodynia

Cold Allodynia

Cisplatin (5 mg/kg ip) 1 X Week

Proestrus

Estrus

Metestrus

Diestrus
$\Delta^9$-THC ($\text{CB}_1/\text{CB}_2$ agonist) in males

Henderson-Redmond et al., (2020) Neuropharmacology
Neuropathic pain and estrous cycle

Mechanical Allodynia

A) **Female No cisplatin-Veh**  **Female Cisplatin-Veh**  **Male No cisplatin-Veh**  **Male Cisplatin-Veh**

B) **Threshold (g)**

C) **Time (sec)**

D) **Normal Cycle Order**  **P**  **E**  **M**  **D**

**Cisplatin**  **Saline**

**No Cisplatin Vehicle**  **Cisplatin Vehicle**

B) **Female No cisplatin-Veh**  **Female Cisplatin-Veh**  **Male No cisplatin-Veh**  **Male Cisplatin-Veh**

B) **Time (sec)**

D) **Number of days**

E) **Number of days**

F) **Cisplatin**  **Saline**

G) **No Cisplatin Vehicle**  **Cisplatin Vehicle**

H) **Normal Cycle Order**  **P**  **E**  **M**  **D**

• Sex differences has been demonstrated in preclinical and clinical studies
• Cannabinoids compounds have shown sex-differences between males and females
• Females develop tolerance faster than males to CB$_1$ (ACEA) and CB$_1$/CB$_2$ (CP55,940) agonists in the chemotherapy-induced pain
• CB$_2$ (JWH-133) agonist increases ovarian cancer tumor growth in females mice
More studies evaluating and investigating sex differences in preclinical and clinical studies are needed to better understand and improve treatment of pain.
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Questions

Thank you for your attention!