

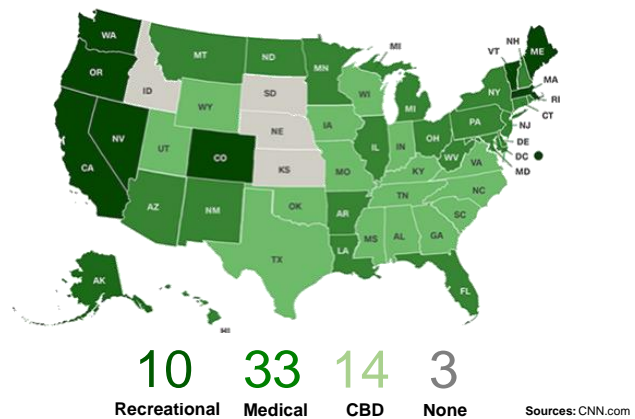
Sex Differences in the Effects of Cannabis

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States Where Cannabis is Legal



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Medical Cannabis

20 common qualifying conditions

- Addiction
- Alzheimer's disease
- Amyotrophic lateral sclerosis
- Anxiety
- Cancer
- Chemo-associated nausea vomiting, anorexia
- Chronic Pain
- Depression
- Epilepsy
- Glaucoma
- HIV associated anorexia, cachexia
- Huntington's disease
- IBS
- Multiple Sclerosis
- Parkinson's disease
- PTSD
- Schizophrenia and other psychoses
- Sleep Disorders
- TBI
- Tourette syndrome

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Cannabis Use in Women

- **Growing female demographic** of medical cannabis users for **pain**



Ste-Marie et al., 2016; Ryan-Ibarra et al., 2015; Aggarwal et al., 2009

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Cannabis Use in Women



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Factors contributing to epi findings

- **Growing female demographic** of medical cannabis users for **pain**
- Cultural / societal factors



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Factors contributing to epi findings

- **Growing female demographic** of medical cannabis users for **pain**
- Cultural / societal factors
- Sex-dependent differences in **therapeutic effectiveness** of cannabinoids?



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Sex Differences in Antinociception

Preclinical Evidence

- Cannabinoids are **2-3X more potent** in female rats
- Effect in **acute** and **chronic** pain models



Tseng et al., 2001; Craft et al., 2012; Craft et al., 2013

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Sex Differences in Antinociception

Preclinical Evidence

- Cannabinoids are **2-3X more potent** in female rats



Tseng et al., 2001; Craft et al., 2012; Craft et al., 2013

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Sex Differences in Abuse Liability

Preclinical Evidence

- Females **acquire** CB self-ad faster



Fattore et al., 2007 and 2010

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Sex Differences in Abuse Liability

Preclinical Evidence

- Females **acquire** CB self-ad faster
- Females maintain **higher rates** of self-ad



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Sex Differences in Abuse Liability

Preclinical Evidence

- Females **acquire** CB self-ad faster
- Females maintain **higher rates** of self-ad
- Females are slower to **extinguish**



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Sex Differences in Abuse Liability

Preclinical Evidence

- Females **acquire** CB self-ad faster
- Females maintain **higher rates** of self-ad
- Females are slower to **extinguish**
- Females **reinstat**e at a faster rate



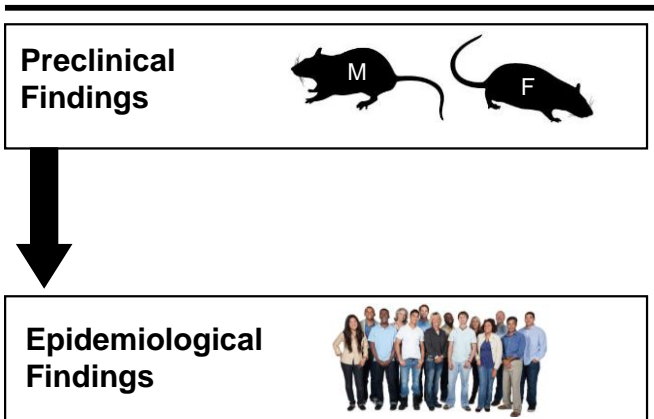
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Do
Preclinical Findings
Translate to Humans?



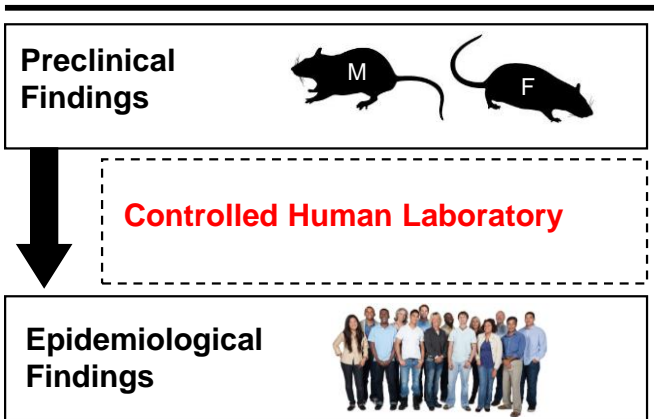
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Sex Differences in Cannabis Effects?



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Sex Differences in Cannabis Effects?



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Controlled Human Drug Administration Studies

•Analgesia

- Pain Threshold
- Pain Tolerance



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Controlled Human Drug Administration Studies

•Analgesia

- Pain Threshold
- Pain Tolerance

•Abuse liability

- Subjective responses
- Reinforcing effects



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Methods

Sex-dependent Cannabis Effects

- **Active** cannabis (THC) vs **placebo** (no THC)

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Methods

Sex-dependent Cannabis Effects

- **Active** cannabis (THC) vs **placebo** (no THC)
- Exclude psychiatric disorder, medications, drug use other than cannabis, pain
- **No cannabis smoking** before sessions

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Methods

Sex-dependent Cannabis Effects

- **Active** cannabis (THC) vs **placebo** (no THC)
- Exclude psychiatric disorder, medications, drug use other than cannabis, pain

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Methods

Sex-dependent Cannabis Effects

- **Active** cannabis (THC) vs **placebo** (no THC)
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- **No cannabis smoking** before sessions
- Cannabis smoked according to controlled inhalation procedures

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Methods

Sex-dependent Cannabis Effects

- **Active** cannabis (THC) vs **placebo** (no THC)
- Exclude psychiatric disorder, medications, drug use other than cannabis, pain
- **No cannabis smoking** before sessions
- Cannabis smoked according to controlled inhalation procedures



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Study #1

Sex-Dependent Effects of Cannabis Induced Analgesia

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Sex-dependent effects of cannabis

- 1) Analgesia
- 2) Abuse Liability

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Study #1 Design

2 sessions

2 dosing conditions

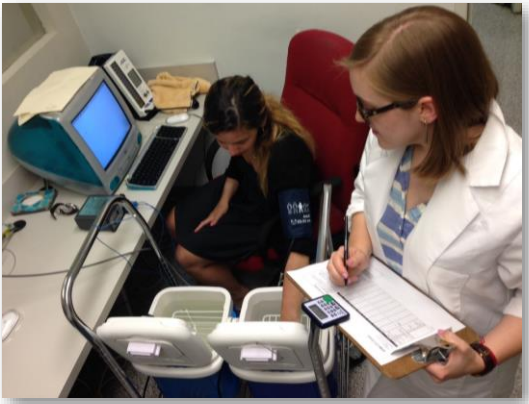
| SESSION | 1 | 2 |
|------------------|-----------------|---------------|
| Cannabis (% THC) | Inactive (0.0%) | Active (4-6%) |

Analgesic Effects -- Cold Pressor Test (CPT)

Subjective Effects -- Visual Analog Scales

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Cannabis Analgesia Cold Pressor Test (CPT)

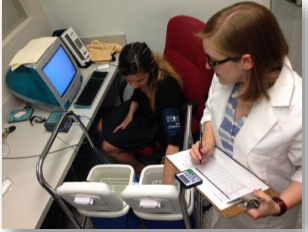


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Cannabis Analgesia Cold Pressor Test (CPT)

Pain Threshold
*Latency to **report** pain*

Pain Tolerance
*Latency to **withdraw** hand*



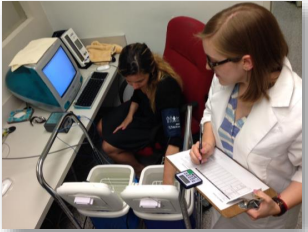
Cooper et al., 2013

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Cannabis Analgesia Cold Pressor Test (CPT)

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Cooper et al., 2013

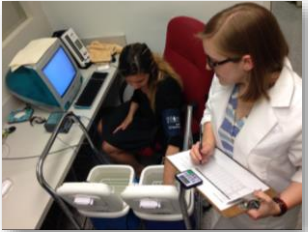
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Cannabis Analgesia Cold Pressor Test (CPT)

Pain Threshold
*Latency to **report** pain*

Pain Tolerance
*Latency to **withdraw** hand*

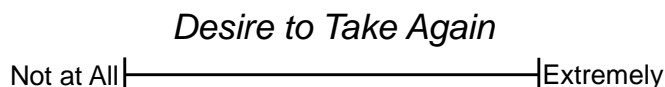
- Predictive validity
- Each person is his/her own control



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Cannabis Abuse Liability Visual Analog Scale (VAS)

Subject rated positive drug effects



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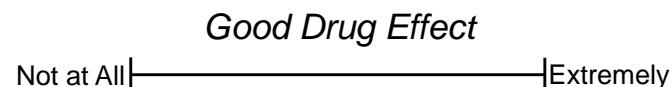
Demographics

| | Men (N = 21) | Women (N = 21) |
|---------------------|--------------|----------------|
| Age (years old) | 28 ± 6 | 28 ± 6 |
| Body Weight (kg) | 77.5 ± 13.7* | 67.7 ± 12.2 |
| CANNABIS USE | | |
| Days/Wk | 6.6 ± 0.8 | 6.4 ± 1.3 |
| Cannabis Cigs/Day | 7.2 ± 5.6 | 9.4 ± 8.5 |
| \$/Wk | 69.1 ± 56.1 | 78.4 ± 82.6 |
| Tobacco Use | | |
| Cigs/Day | 8.5 ± 7.1 | 7.8 ± 6.7 |

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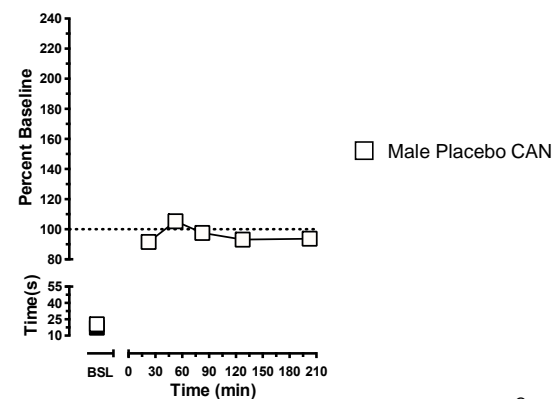
Cannabis Abuse Liability Visual Analog Scale (VAS)

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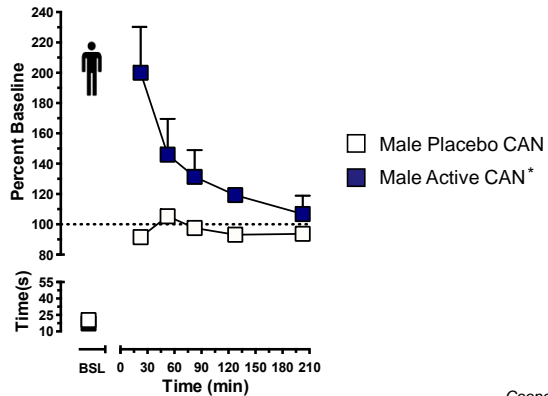
Cannabis Effects Pain Threshold



Cooper, Haney 2016

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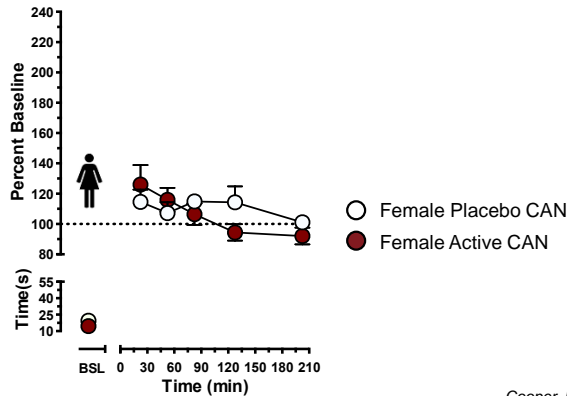
Cannabis Effects Pain Threshold



Cooper, Haney 2016

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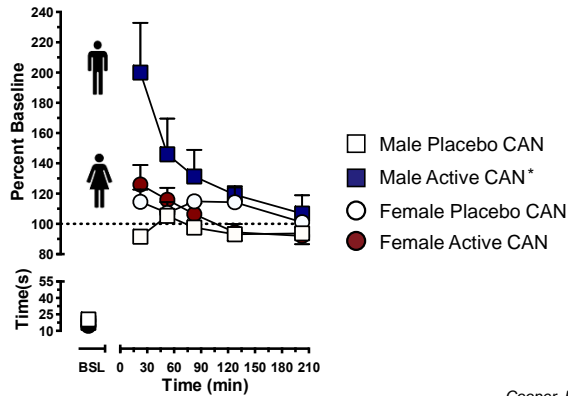
Cannabis Effects Pain Threshold



Cooper, Haney 2016

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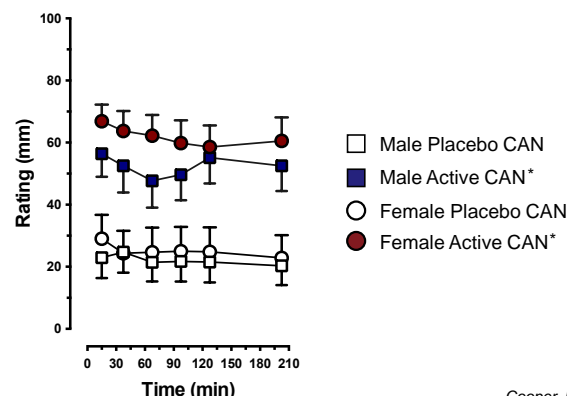
Cannabis Effects Pain Threshold



Cooper, Haney 2016

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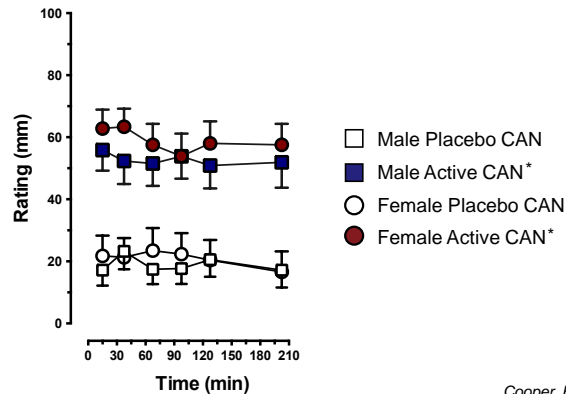
Positive Subjective Drug Effects Take Again



Cooper, Haney 2016

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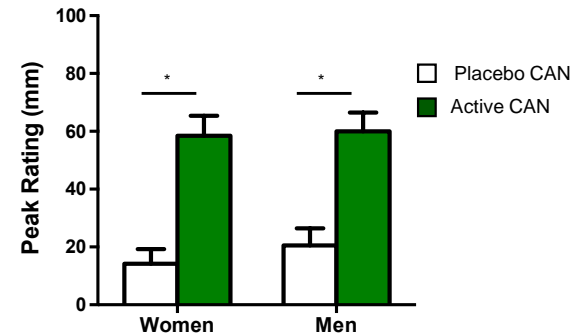
Positive Subjective Drug Effects Drug Liking



Cooper, Haney 2016

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Subjective Intoxication High



Cooper, Haney 2016

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Study #1 Summary

- Cannabis decreases pain response in males, **no effect** in females. **Tolerance?**

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Study #1 Summary

- Cannabis decreases pain response in males, **no effect** in females. **Tolerance?**
- Females endorse similar **subjective ratings** associated with abuse liability despite lack of analgesia.

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Study #1 Summary

- Cannabis decreases pain response in males, **no effect** in females. **Tolerance?**
- Females endorse similar **subjective ratings** associated with abuse liability despite lack of analgesia.
- Evidence for **sex** to play a significant role in cannabinoid effects.

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Study #2 Design

2 sessions
2 dosing conditions

| SESSION | 1 | 2 |
|------------------|-----------------|---------------|
| Cannabis (% THC) | Inactive (0.0%) | Active (5.6%) |

Reinforcing Effects -- Self-Administration
(\$1/ Puff)

Subjective Effects -- Visual Analog Scales

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Study #2

Sex-Dependent Effects of Cannabis Abuse Liability:

Reinforcing effects

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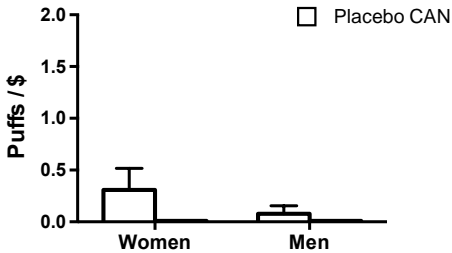
Demographics

| | Men (N = 13) | Women (N = 13) |
|---------------------|--------------|----------------|
| Age (years old) | 32 ± 7 | 28 ± 5 |
| Body Weight (kg) | 81.5 ± 13.2* | 63.8 ± 11.2 |
| CANNABIS USE | | |
| Days/Wk | 6.6 ± 0.9 | 6.7 ± 0.5 |
| Cannabis Cigs/Day | 8.0 ± 5.8 | 8.4 ± 7.6 |
| \$/Wk | 68.9 ± 42.1 | 99.7 ± 84.8 |
| Tobacco Use | 6/13 | 8/13 |

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Reinforcing effects

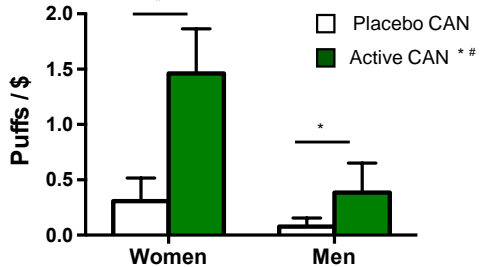
Puffs Purchased



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Reinforcing effects

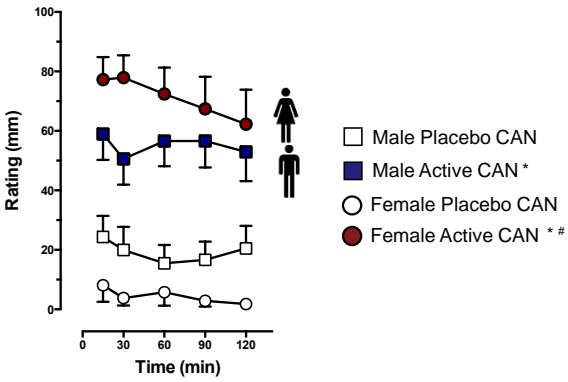
Puffs Purchased



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Positive Subjective Effects

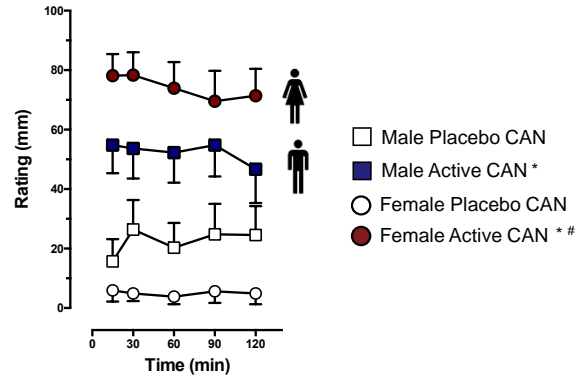
Good Effect



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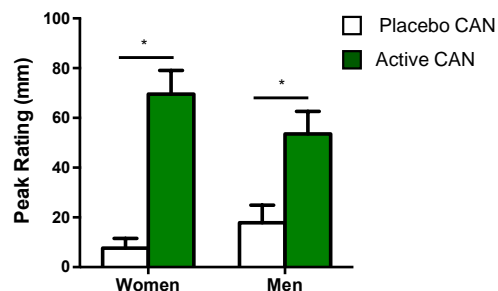
Positive Subjective Effects

Liking



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Subjective Intoxication High



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Study #2 Summary

- Females **self-administer** active cannabis more than males
- Females endorse higher **subjective ratings** associated with abuse liability

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Study #2 Summary

- Females **self-administer** active cannabis more than males

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Study #2 Summary

- Females **self-administer** active cannabis more than males
- Females endorse higher **subjective ratings** associated with abuse liability
- Consistent with **preclinical findings**

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Considerations

- **Dose** dependence?
- **Pharmacokinetics**?
- Menstrual cycle **phase**?
- **Generalizability** to cannabis initiates, lighter users, medical cannabis?

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Take Home Message

Controlled studies are integral to understand **sex dependent effects** of cannabis / cannabinoids for both **abuse liability** and potential **therapeutic effects**

Bridge the gap between **preclinical** evidence and **epidemiological findings**

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