TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER™
School *of* Medicine

SEX DIFFERENCES AND THE ENDOCANNABINOID SYSTEM IN PAIN

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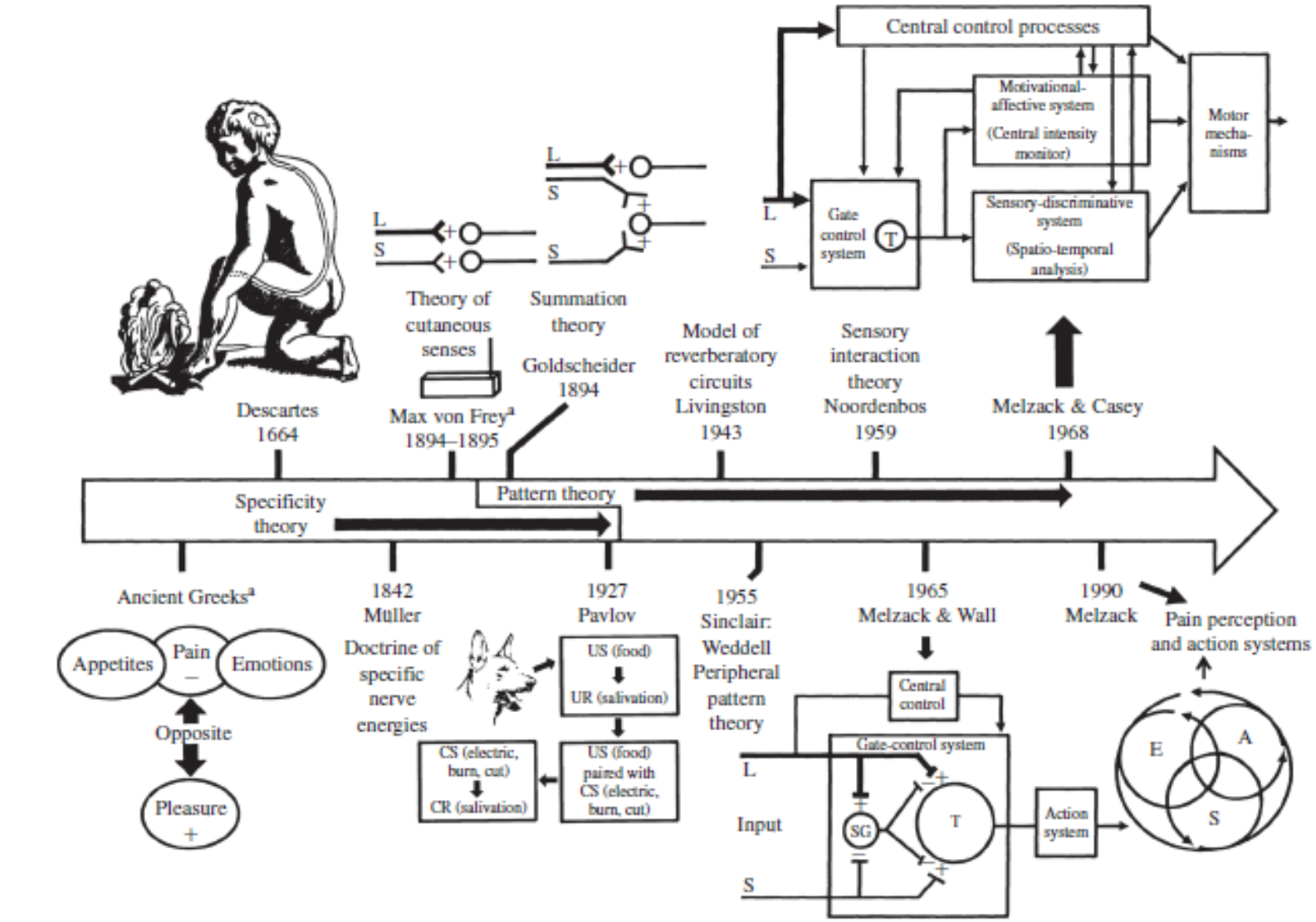
DEPARTMENT OF PHARMACOLOGY & NEUROSCIENCE

Evolution of Pain Theories



Guindon and Hohmann (2009) Chapter 33 Pain: mechanisms and measurement In: Handbook of Neuroscience for the Behavioral Sciences. Editors: Gary G. Berntson and John T. Cacioppo; John H Wiley & Sons.

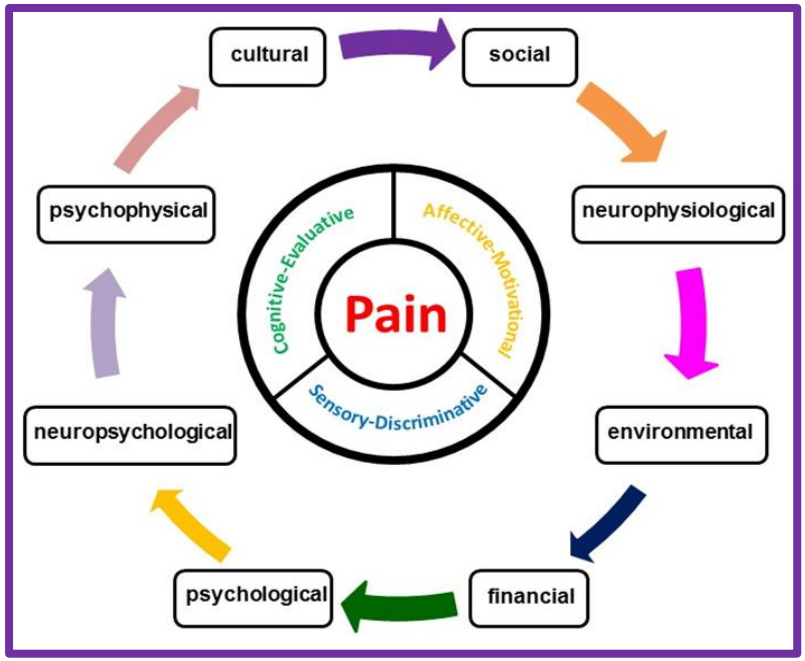
Defining Pain

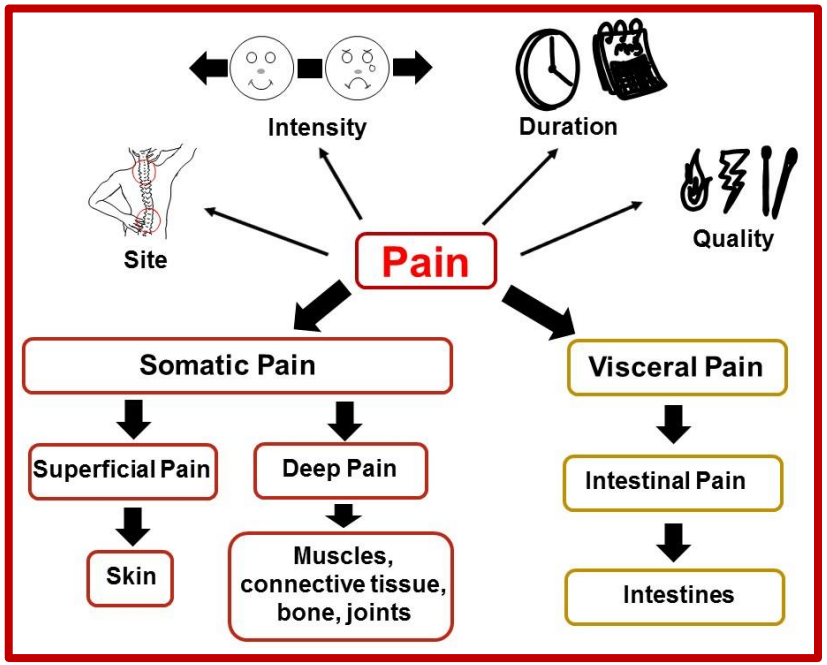
IASP
International Association for the Study of Pain

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

Raja S. N. et al., 2020

Pain

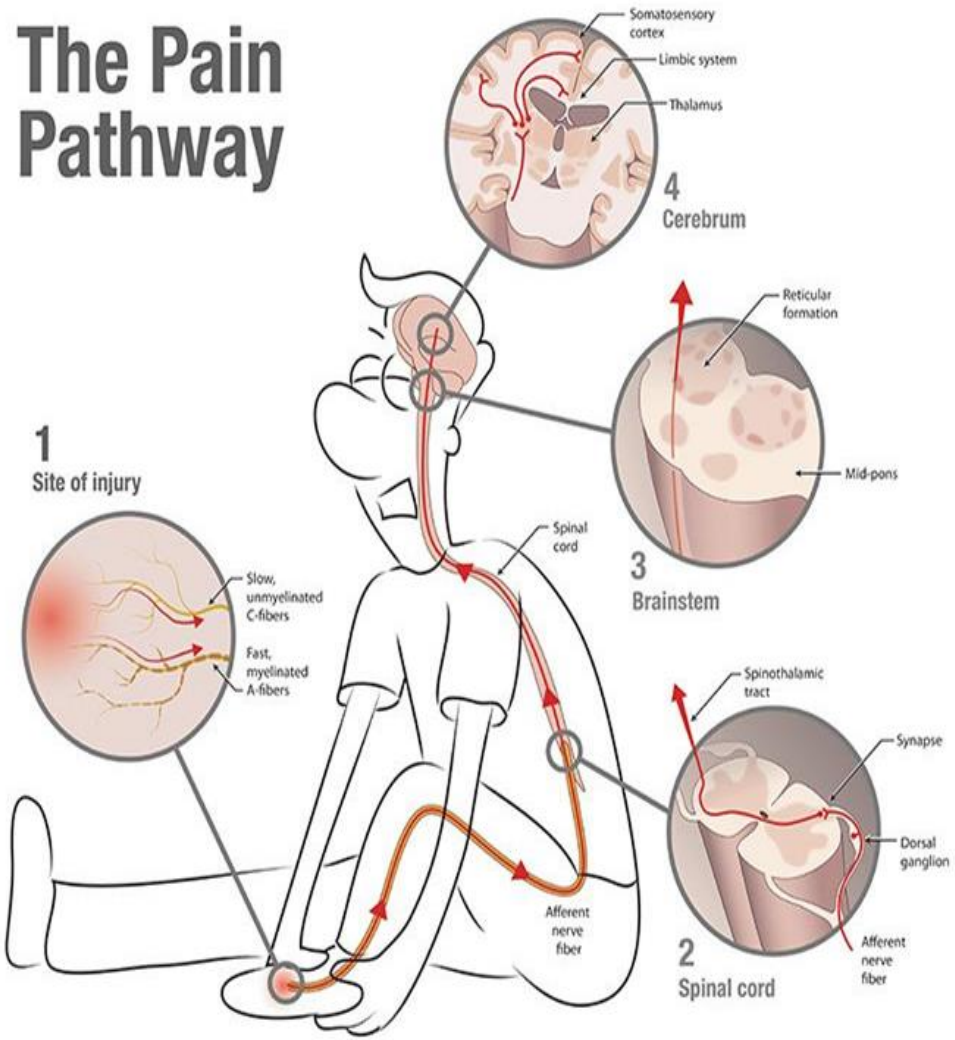


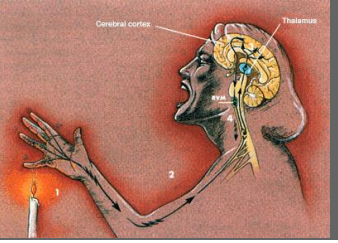


Blanton, Bergeson, Morgan & Guindon (2019) Ethanol and Pain Interactions
In: The Neuroscience of Alcohol: Mechanisms and Treatment, Elsevier.

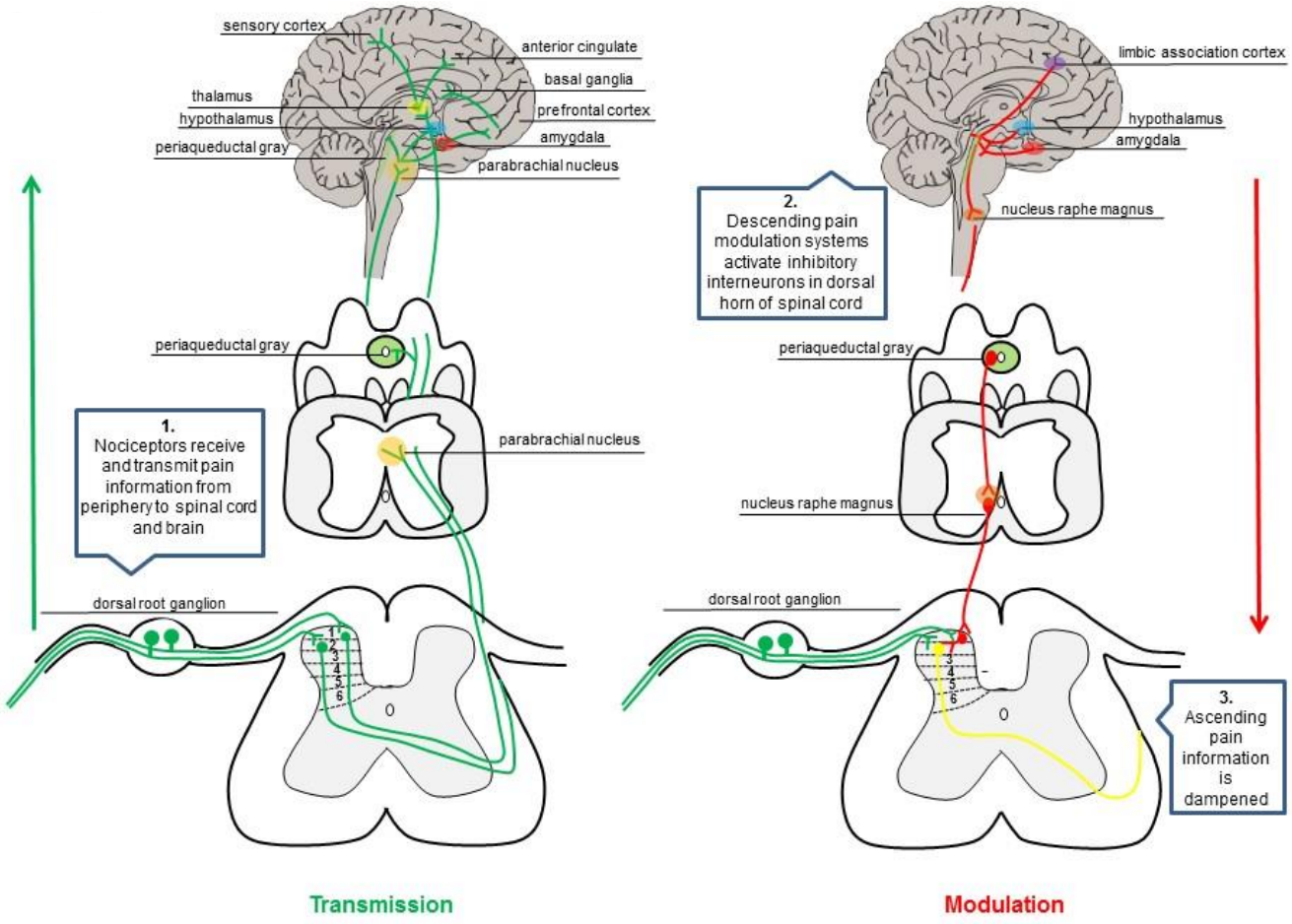
Nociception

Sensory transduction of information about potential or actual tissue damage





Pain transmission and modulation



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

Evaluation of Pain

McGill Pain Questionnaire

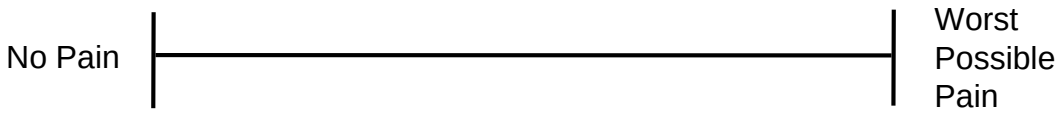
102 Words divided in 3 categories: sensory – affective – cognitive/evaluative

Pain Rating Index
Sum of ranking of each words chosen in all 20 subclasses

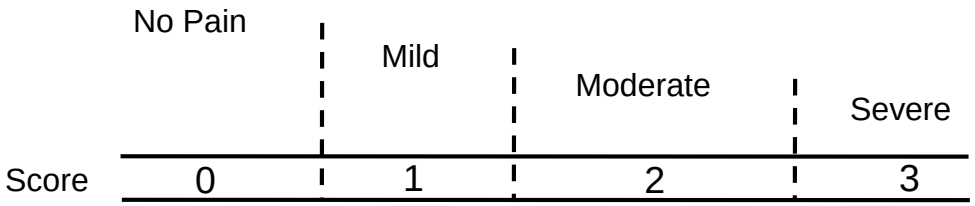
Number of Words Chosen
Sum the words chosen in all 20 subclasses

Actual Pain intensity:
- No Pain (0)
- Mild (1)
- Discomforting (2)
- Distressing (3)
- Horrible (4)
- Excruciating (5)

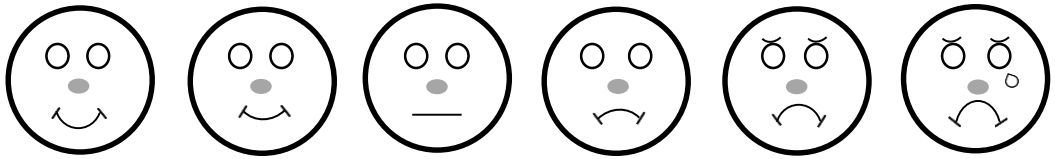
Visual Analogue Scale



Verbal Rating Scale

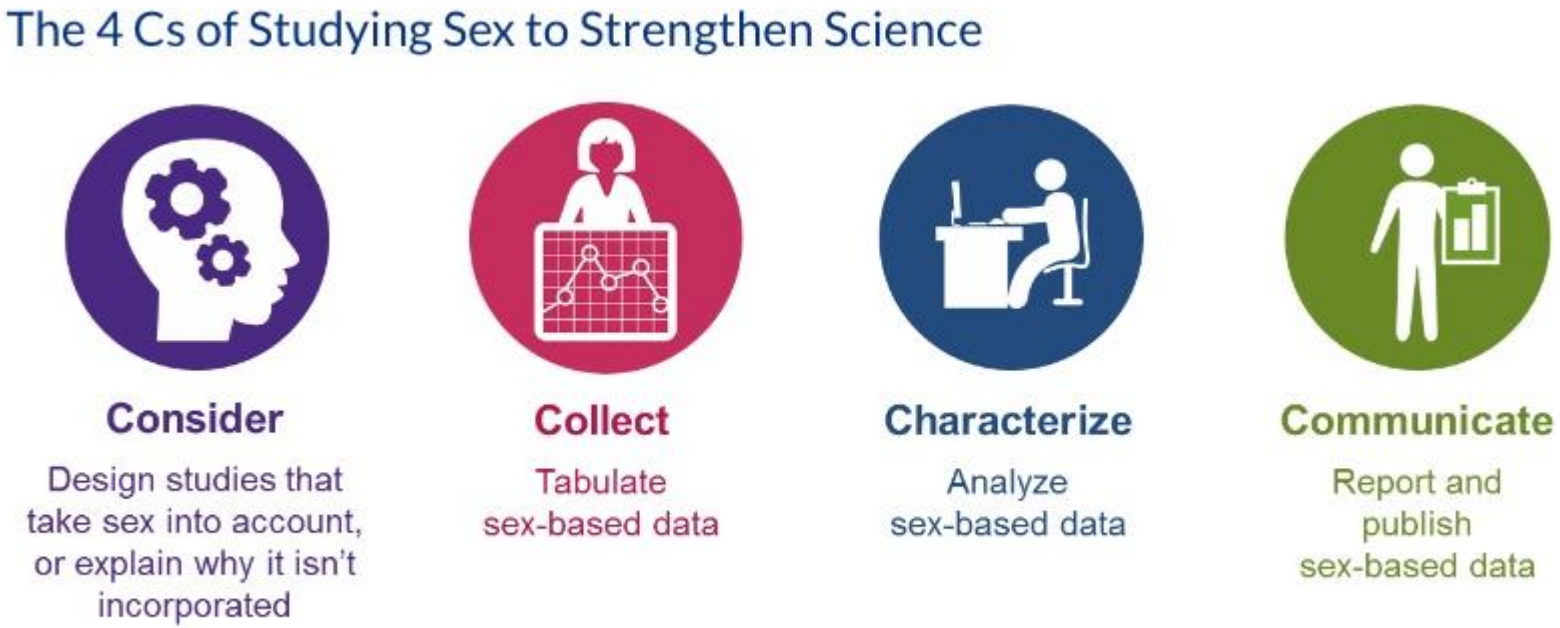


Smile-Sad Faces Scale



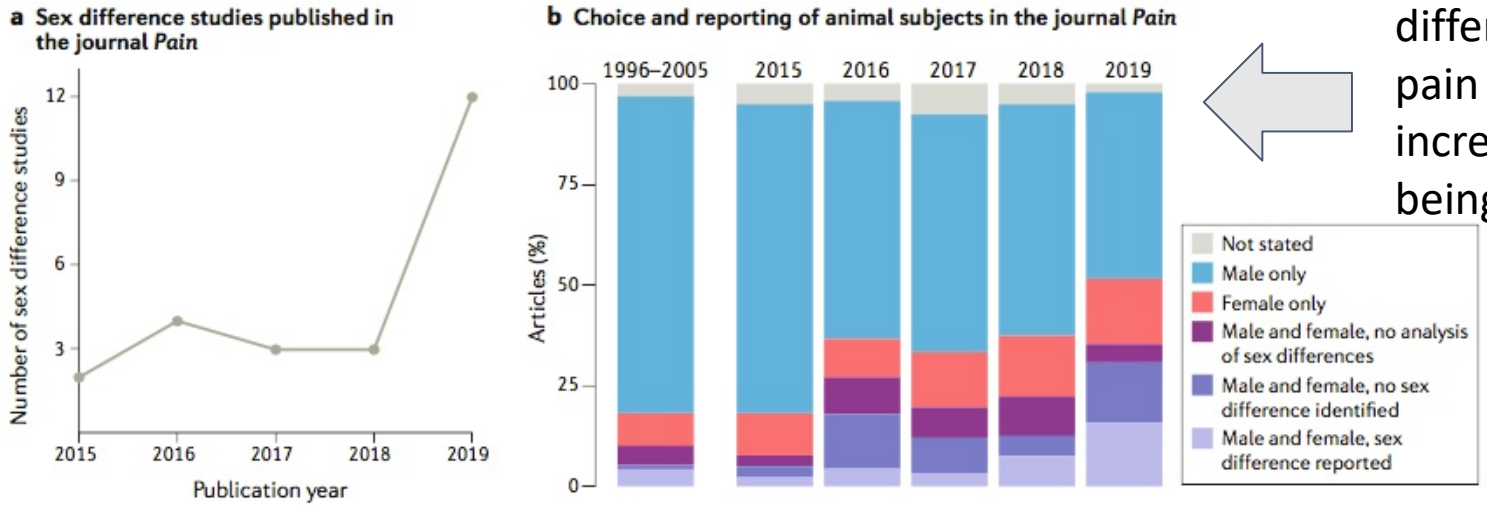
Blanton, Bergeson, Morgan & Guindon (2019) Ethanol and Pain Interactions
In: The Neuroscience of Alcohol: Mechanisms and Treatment, Elsevier.

NIH 2016 Sex As a Biological Variable Policy (SABV)



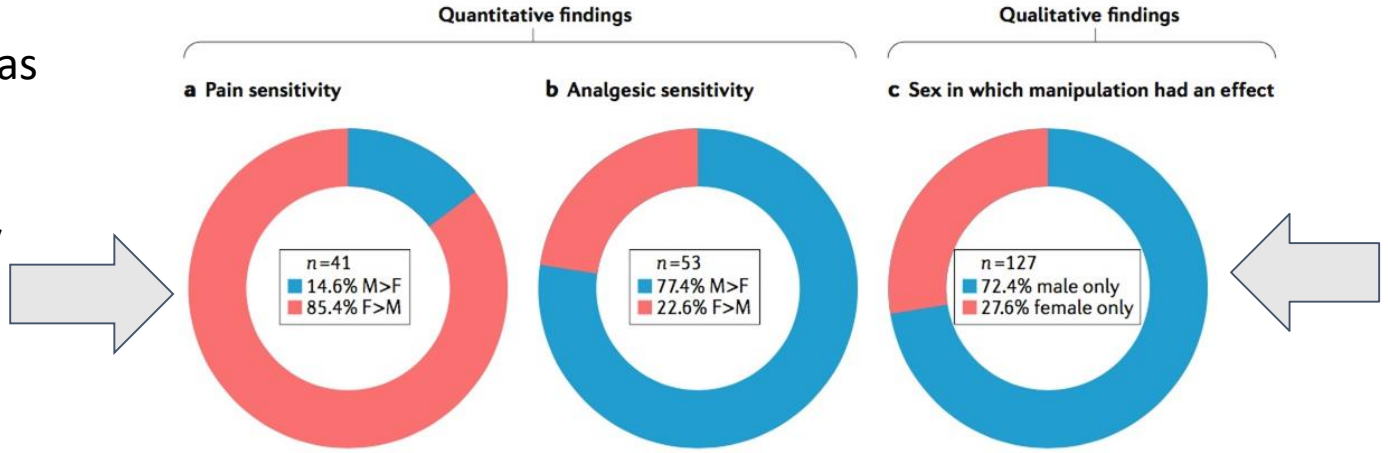
Sex Differences in Pain - Preclinical Evidence (Mogil, 2020)

Sex differences in pain are increasingly being studied



Female bias towards pain sensitivity

Male bias towards analgesic effect



Male bias: more likely to see effect in males versus females

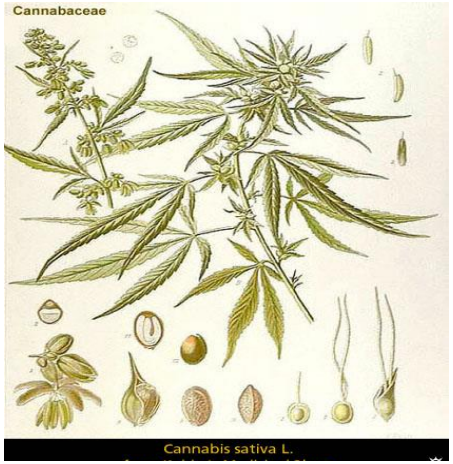
Fig. 1 | **Analysis of quantitative and qualitative sex differences in the pain literature.** The data shown are based on a search of the PubMed database on 1 August 2019 with the search terms 'sex difference AND pain AND (mouse OR rat)', which yielded 474 results (see Supplementary methods). Each article was opened and perused by the author for findings

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

Cannabis sativa

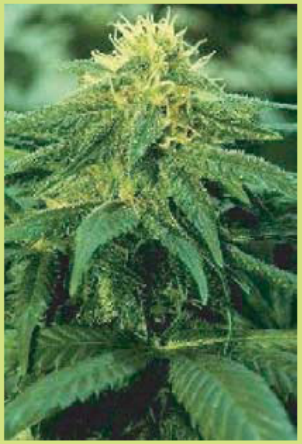


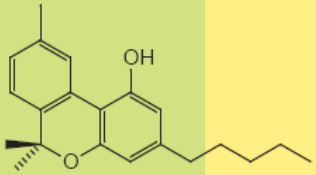
- Many species exist: *Cannabis Sativa* (European plant), *Cannabis indica* (Indian plant) and *Cannabis ruderalis* (Siberia and central Asia plant)

- 460 known chemical constituents of cannabis

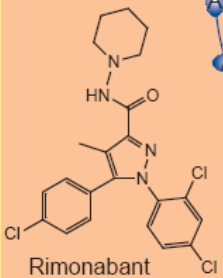
- 66 constituents have a cannabinoid structure

- Δ^9-THC most important constituent: principal psychoactive component of cannabis

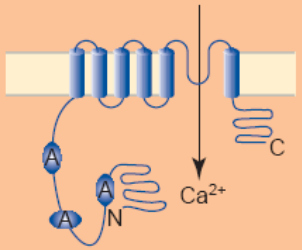




Cannabinol



Rimonabant
(SR141716A)



New drugs

200
The therapeutic properties of cannabis are described in Chinese pharmacopoeia

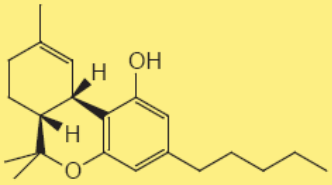
1838–1840
Sir W.B. O'Shaughnessy assesses methodically the medicinal properties of cannabis

1899
Wood *et al.* isolate cannabinol from cannabis resin

1932
Cahn elucidates part of the structure of cannabinol

1940
Todd *et al.* (and Adams *et al.* in the USA) fully elucidate and synthesize cannabinol

1964
Gaoni and Mechoulam elucidate the structure of THC



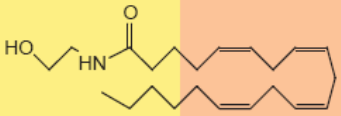
THC

1970–1990
Cannabinoid pharmacology is thoroughly investigated

1988
Howlett's group identifies specific THC binding sites in the brain

1990
Matsuda *et al.* clone the CB_1 receptor

1992
Mechoulam's group in collaboration with Pertwee's group identify the first endocannabinoid, anandamide

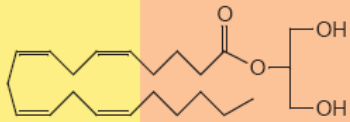


Anandamide

1993
Munro *et al.* clone the CB_2 receptor

1994
Rinaldi-Carmona *et al.* at Sanofi develop the first CB_1 receptor antagonist

1995
Mechoulam's group and Waku's group identify the second endocannabinoid, 2-AG



2-AG

1996
Cravatt *et al.* clone the first endocannabinoid-degrading enzyme, FAAH

1998
House of Lord's report on medical cannabis;
Di Marzo *et al.* propose the existence of interactions between endocannabinoids and vanilloid receptors

1999–2000
Zygmunt *et al.* and Smart *et al.* show that anandamide activates vanilloid receptors

2003
Bisogno *et al.* clone the first endocannabinoid-biosynthesizing enzymes

2005
Sativex ® approved for sale in Canada; regulatory approval is filed to sell rimonabant in the USA;
the Aberdeen group discovers an allosteric site on CB_1 receptors

????
Cloning of new cannabinoid receptors; identification of other endocannabinoid enzymes; cloning of the endocannabinoid transporter; more endocannabinoid-based therapies

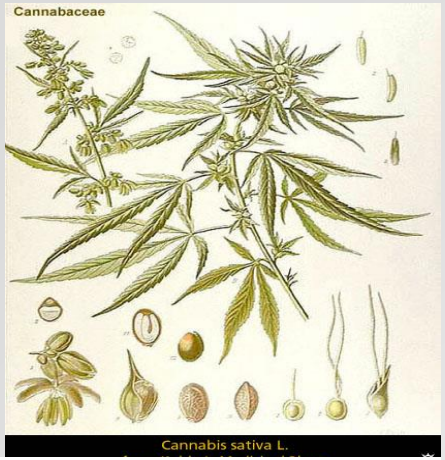
Cannabis research

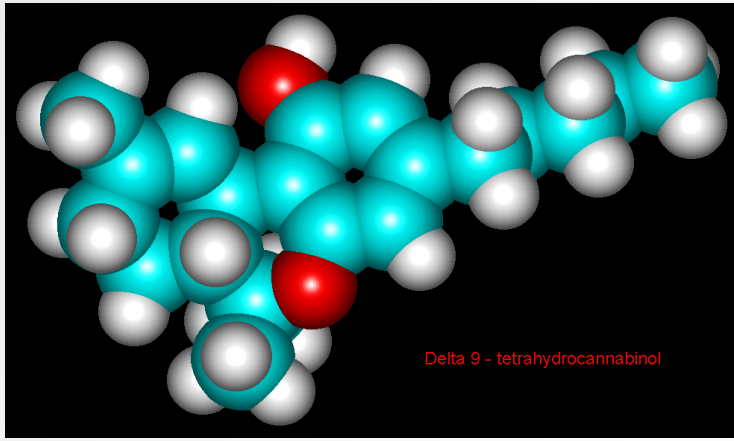
Cannabinoid research

Endocannabinoid research

Di Marzo V (2006)

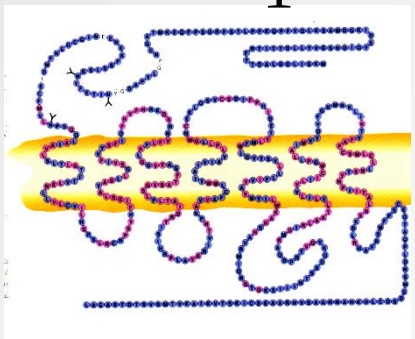
Cannabinoid receptors





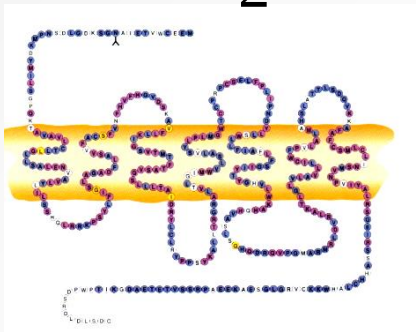
Cannabinoid receptors

CB_1



Matsuda et al 1990

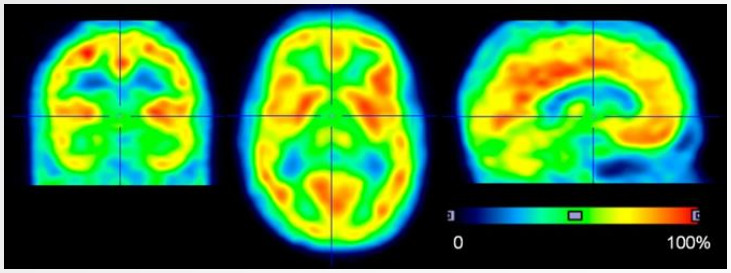
CB_2

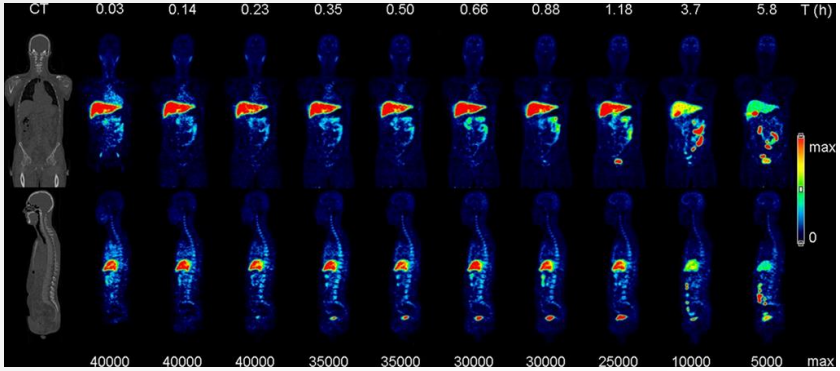


Munro et al 1993

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

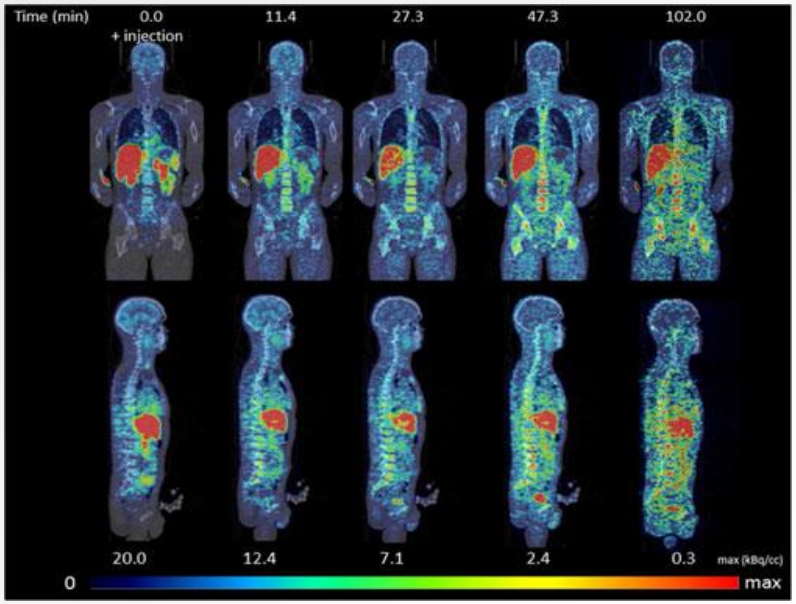




[^{18}F]-MK-9470 – Radiolabeled CB1 ligand

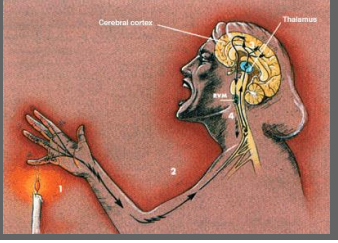
Cannabinoid Receptor Type 2 (CB2)

- 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)



[^{11}C]-NE40 – Radiolabeled **CB2** ligand

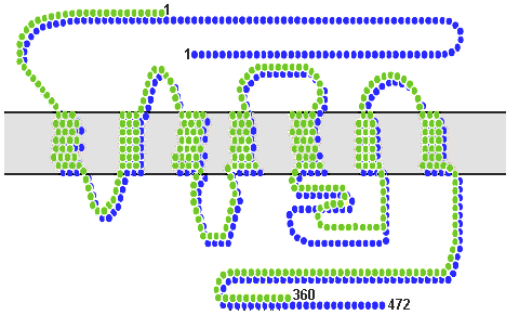
Ahmad R et al. 2013. *Mol Imaging Biol*.



Endocannabinoid System

Cannabinoid Receptors

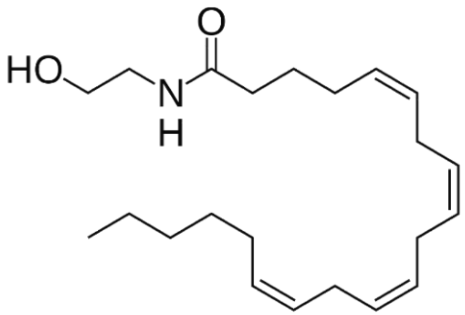
- CB_1 receptor
- CB_2 receptor



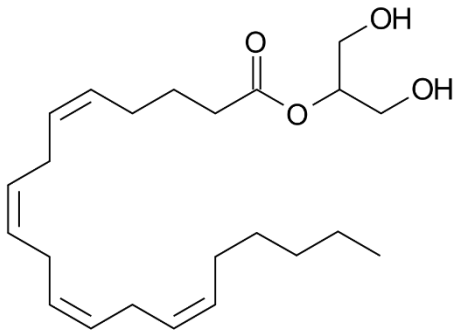
Struttura dei recettori CB1 e CB2

Endocannabinoids

- Anandamide (AEA)

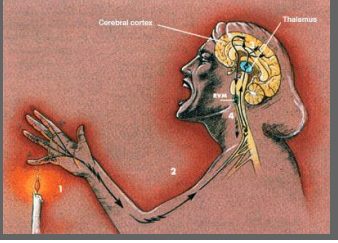


- 2-Arachidonylglycerol (2-AG)



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

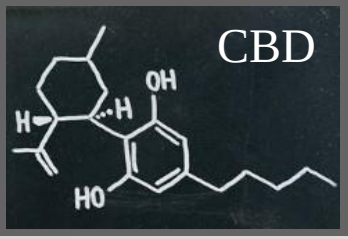
SR-141716A

SR-144528

Natural and Synthetic Cannabinoid Agonists

		CB_1	CB_2
Natural agonists	▪ Δ^9-THC	++	++
	▪ Cannabidiol (no psycho-active properties)	0	±
	▪ Cannabinol (psycho-active properties)	+	++
Synthetic Agonists	▪ Dronabinol (Marinol®)	++	++
	▪ Nabilone (Cesamet®)	++	++
	▪ Levonantradol	+	+
	▪ HU-210	+++	+++
	▪ Win 55,212-2	+++	+++
	▪ CP-55940	+++	+++
	▪ Methanandamide	++	+
	▪ ACEA	+++	+
	▪ 0-1812	+++	+
	▪ JWH-051	+	++
	▪ HU-308	+	+++
	▪ AM1241	+	+++
	▪ JWH-133	+	+++
	▪ L-759633	+	+++
	▪ GW405833 (L768242)	+	+++
	▪ GW842166X	+	+++
	▪ AM1714	+	+++
	▪ JWH-015	+	+++
Antagonists/Inverse agonists	▪ SR141716A	++	0
	▪ LY-320135	++	0
	▪ AM251	++	0
	▪ AM281	++	0
	▪ SR144528	0	++
	▪ AM630	0	++

Guindon, Beaulieu and Hohmann (2010) Chapter 6 in Pharmacology of Pain. Editors: P. Beaulieu, D. Lussier, F. Porreca, A.H. Dickenson; IASP Press.



Cannabidiol also known as CBD

Cannabidiol or CBD

- **Decreases seizures**
- **Pain relief**
- **Reduce inflammation**
- **Antidepressant**
- **Improve headaches/migraines/sleep**
- **Reduce stress**

Effects of cannabinoids on different physiological systems

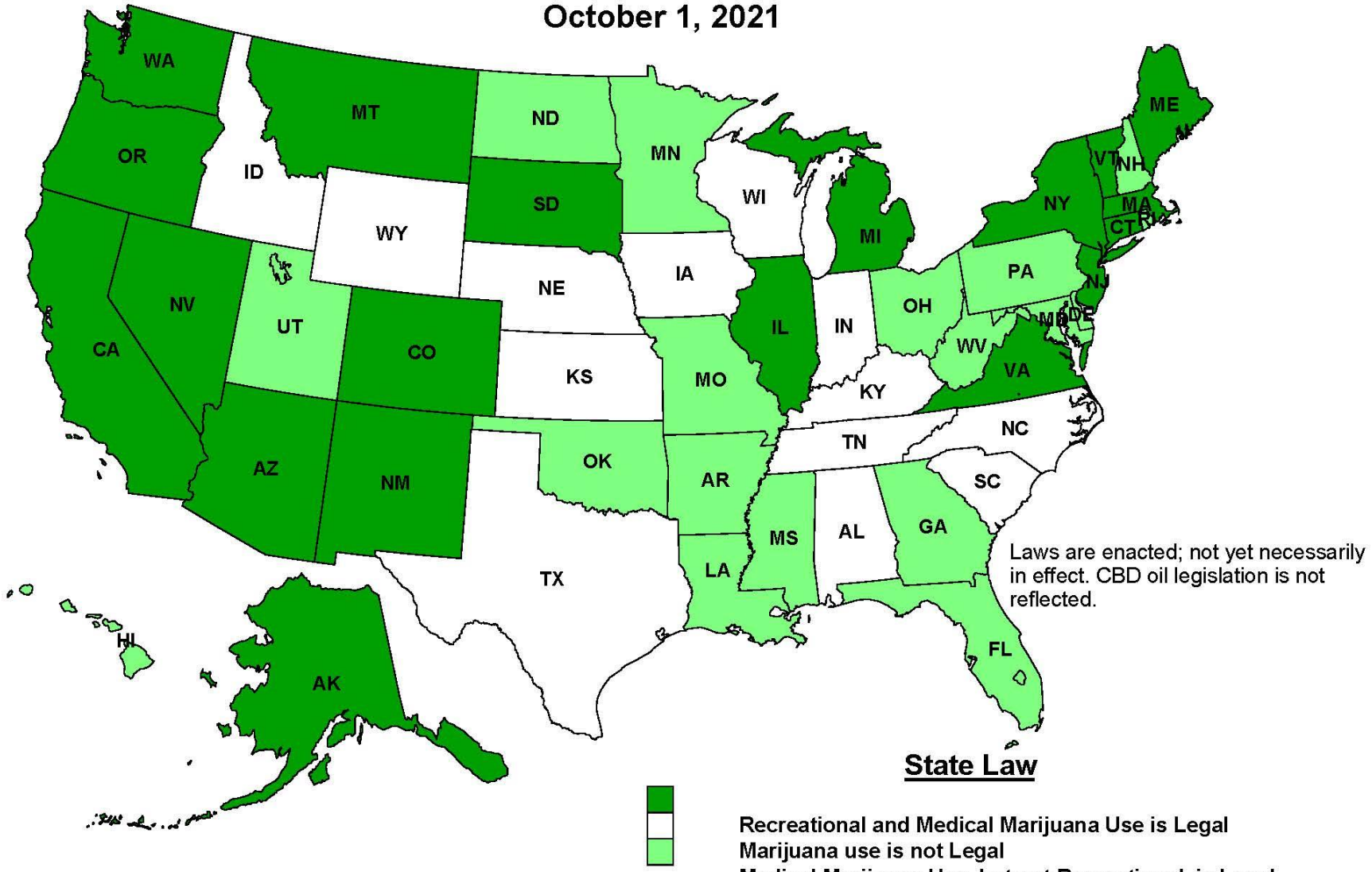
Systems	Effects
Central nervous system	• Euphoria—cannabinoid exhilaration • Increase sensory perception • Disruption of intellectual and psychomotor performance • Temporospatial disorientation • Ideation trouble • Memory trouble • Thermoregulation disorder • Psychotic trouble • Analgesia • Antiemetic 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

Guindon, Beaulieu and Hohmann (2010) Chapter 6 in Pharmacology of Pain. Editors: P. Beaulieu, D. Lussier, F. Porreca, A.H. Dickenson; IASP Press

States with Legalized Marijuana

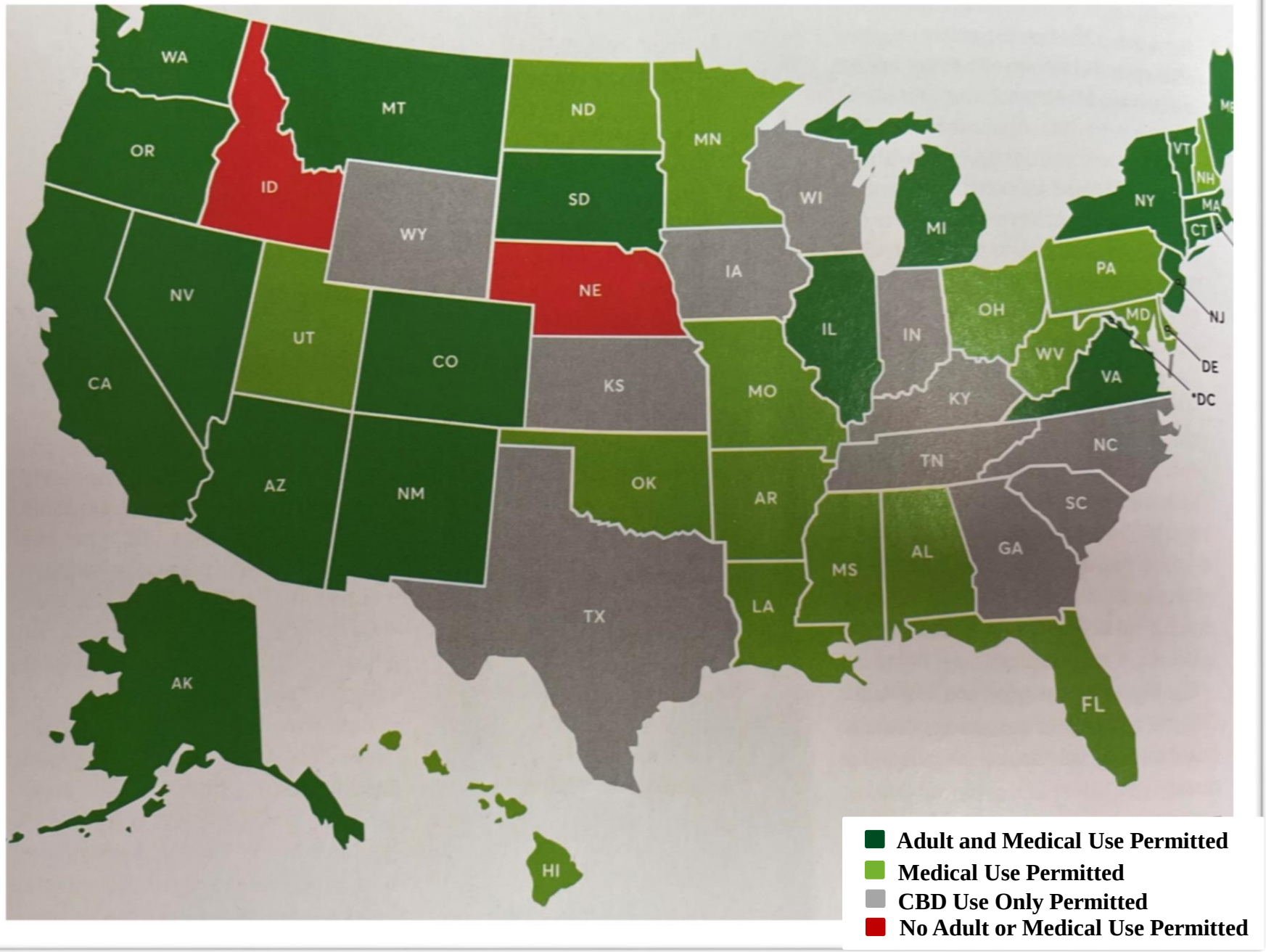
American Nonsmokers' Rights Foundation

October 1, 2021



Note: In total, medical marijuana use is legal in 37 states.

USA MAP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GA
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VA
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NY
MD
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AK
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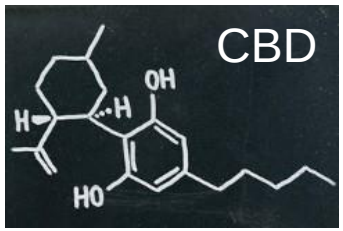
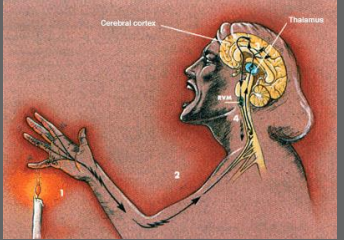
Adult and Medical Use Permitted
Medical Use Permitted
CBD Use Only Permitted
No Adult or Medical Use Permitted



Cannabidiol or CBD

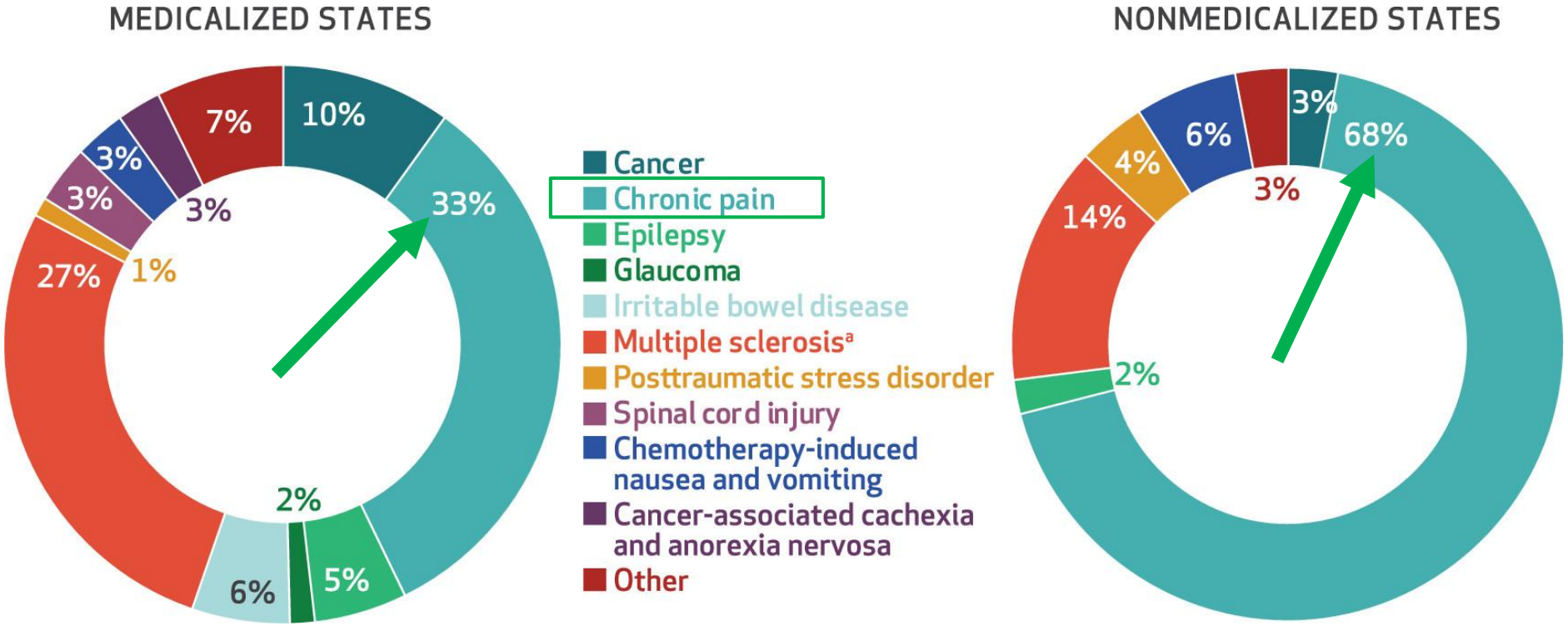
- **Decreases seizures**
- **Pain relief**
- **Reduce inflammation**
- **Antidepressant**
- **Improve headaches/migraines/sleep**
- **Reduce stress**



Cannabis and Pain

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

Drugs (2019) 79:969–995
https://doi.org/10.1007/s40265-019-01132-x

REVIEW ARTICLE

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

Henry L. Blanton[1] · Jennifer Brelsfoard[1] · Nathan DeTurk[3] · Kevin Pruitt[2] · Madhusudhanan Narasimhan[1] · Daniel J. Morgan[3] · Josée Guindon[1]

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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

Chronic pain conditions	Pain test before tx	Type of study	Study design	Time study	Drugs	Dose per day	Route	Patients (#)	Gender M/F	Ethnicity	Age	Reduction pain intensity	Pain test after tx	Side effects	Ref
Neuropathic pain mixed etiology	VAS >30/100	randomized double-blind placebo control	parallel	3 sessions of 6 hours; session interval 3 to 21 days	Δ9-THC or placebo	19.25 mg low dose 34.3 mg high dose	inhale using cigarette	38	20/18	33 C 1 AA 1 H 3 O	46 (range 21-71)	Yes 30 %	VAS	Euphoria Mood changes Decline cognition	[112]
Neuropathic pain mixed etiology	VAS >40/100	randomized double-blind	4 period crossover Latin square	5 days (9 days washout)	Δ9-THC or placebo	1.875 to 7.05 mg of THC	gelatin capsules inhaled by pipe	23	11/12	NR	45.4 (±12.3)	Yes	NRS Daily	headache dry eye dizziness numbness cough burning sensation pain area	[126]
Central and peripheral neuropathic pain mixed etiololy	NPS 40/100	randomized placebo-controlled	crossover	2 sessions; session interval 4 hours	Δ9-THC or placebo	45.9 mg low dose 56.3 mg high dosee	vaporize using foltin puff	42	29/13	26 C 7 H 5AA 2 A 2 O	46.4 (±13.6)	Yes 30 %	NPS	hypotension	[125]
Central and peripheral neuropathic pain mixed etiololy	VAS >30/100	randomized double-blind placebo-controlled	crossover	3 sessions of 6 hours; session interval 3 to 14 days	Δ9-THC or placebo	10.32 mg low dose 28 mg high dose	vaporized using volcano system	39	28/11	28 C 5 AA 3 H 3 O	50 (±11)	Yes 30 %	VAS	Euphoria Sedation Confusion Nausea Hunger	[127]
Central neuropathic pain MS associated	NRS	randomized double-blind placebo-controlled	parallel	4 weeks	Δ9-THC formulation ECP002A	9 mg to 29 mg of Δ9-THC	oral	24	8/16	NR	54.3 (±8.9)	Yes after tx No daily diary	NRS VAS McGill QP	headache dizziness fatigue euphoric mood	[122]
HIV-DSPN	VAS 30/100	randomized double-blind	Parallel	12 days	Δ9-THC or placebo	96 mg Δ9-THC 3sessions X 32 mg Δ9-THC per session	inhale using cigarette	55	22/5 Exp 26/2 Control	NR	50 (±6)	Yes ≥ 30 %	VAS Daily	NR	[128]
HIV-DSPN	DDS >5/20	randomized double-blind	Crossover	5 days (no washout)	Δ9-THC or placebo	Titrating dose up and down 96 mg THC 4 sessions X 24 mg Δ9-THC per session	inhale using cigarette	34	33/1	NR	49.1 (±6.9)	Yes	DDS	NR	[129]
Chemotherapy-induced neuropathy	NRS ≥ 4/10	randomized placebo-controlled	Crossover	4 weeks (2 weeks washout)	Nabiximols Sativex THC:CBD	8.1 to 32.4 mg of Δ9-THC 7.5 to 30 mg of CBD	oromucosal spray	18	3/15	NR	56 (±10.8)	No	NRS Daily	dizziness fatigue dry mouth nausea diarrhea	[113]
Peripheral neuropathy	NRS ≥ 3/10	randomized double-blind placebo-controlled	parallel	15 weeks	Nabiximols Sativex THC:CBD	21.6 to 64.8 mg of Δ9-THC 10 to 60 mg of CBD	oromucosal spray	246	96/150	243 C 2 AA	57.3 (±14.2)	No	NRS BPI-SF DAT	headache dizziness dry mouth nausea diarrhea	[114]

Cannabinoids and Chronic Pain: Clinical Studies

Neuropathic pain peripheral origin	NRS 7/10	randomized double-blind placebo control	parallel	5 weeks	Nabiximols Sativex THC:CBD	3.51 to 84.78 mg of Δ9-THC 3.25 to 78.5 mg of CBD	oromucosal spray	125	51/74	121 C 4 O	52.4 (±15.8)	Yes ≥ 30 %	VAS NRS NPS PDI	Dizziness fatigue dry mouth nausea	[115]
Central neuropathic pain MS associated	NRS	randomized double-blind placebo-controlled	parallel	5 weeks	Nabiximols Sativex THC:CBD	21.6 to 129.6 mg of Δ9-THC 20 to 120 mg of CBD	oromucosal spray	64	14/49	NR	49 (±8.4)	Yes	NRS daily	dizziness headache dry mouth nausea diarrhea	[118]
Central neuropathic pain MS associated	NRS ≥ 4/10	randomized double-blind placebo-controlled	parallel	14 weeks	Nabiximols Sativex THC:CBD	23.76 to 32.4 mg of Δ9-THC 22 to 30 mg of CBD	oromucosal spray	339	109/230	332 C 4 AA 2 A	48.97 (±10.47)	No	NRS	dizziness fatigue dry mouth nausea diarrhea	[121]
HIV-DSPN and neuropathic pain mixed etiology	VAS >30/100	randomized double-blind placebo-controlled	crossover	2 weeks (washout)	Nabiximols Sativex THC:CBD	2.5 to 120 mg of Δ9-THC 2.5 to 120 mg of CBD	oromucosal spray	20	10/10	NR	48	Yes > 50 %	VAS	headache hypotension intoxication diarrhea	[116]
Spinal cord injury	NPS >5/10	randomized double-blind	crossover		Dronabinol or control (diphenhydramine)	5 mg to 20 mg/day	capsules p.o.	7	5/2	6 C 1 AA	50.1 (±8.3)	No	NRS	drowsiness fatigue dry mouth constipation	[124]
Central neuropathic pain MS associated	NRS ≥ 3/10	randomized double-blind placebo-controlled	crossover	6 weeks (washout)	Dronabinol	2.5 to 10 mg	oral	24	10/14	NR	50 (23 to 55)	Yes	NRS	dizziness tiredness myalgia dry mouth nausea	[119]
Central neuropathic pain MS associated	NRS ≥ 4/10	randomized double-blind Placebo-controlled	parallel	16 weeks	Dronabinol	7.5 to 15.0 mg	oral	240	65/175	NR	47.7 (±9.7)	No	NRS	headache dizziness fatigue vertigo dry mouth nausea diarrhea	[123]
Neuropathic pain mixed etiology	VAS 70/100	randomized double-blind	crossover	14 weeks (2 weeks washout)	Nabilone or Dihydrocodeine	Nabilone 2 mg	p.o.	96	46/50	NR	50.15 (±13.69)	Yes	VAS	tiredness tingling headache	[117]
HIV-DSPN	VAS >70/100	randomized double-blind placebo-controlled	parallel	9 weeks (4 weeks for titration)	Nabilone	2 mg	oral	15	2/13	NR	45.5 (±10.84)	Yes	VAS	dizziness drowsiness	[120]
Neuropathic pain mixed etiology	VAS	randomized double-blind placebo-controlled	crossover	5 weeks	1',1'Dimethyl-Δ8-tetrahydrocannabinol-11oic acid (CT-3)	40 mg (10 mg per capsules)	oral	21	13/8	NR	50.86 (±11.69)	Yes	VAS	tiredness dry mouth	[53]

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 complexe 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

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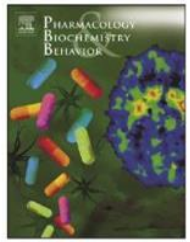

Review

Sex differences and the endocannabinoid system in pain

Henry L. Blanton [a,*], Robert C. Barnes [a], Melissa C. McHann [a], Joshua A. Bilbrey [b], Jenny L. Wilkerson [b], Josée Guindon [a,*]

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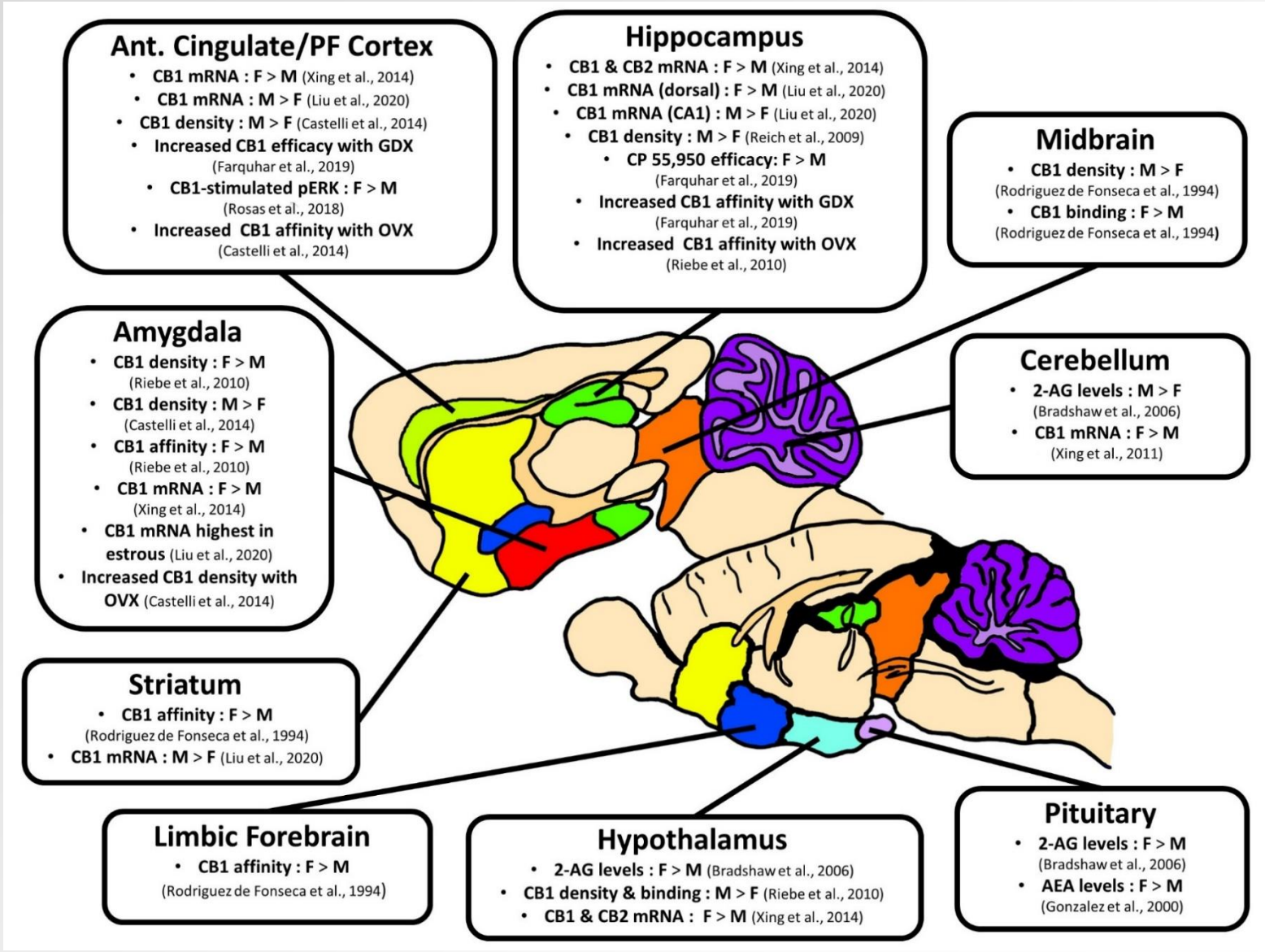
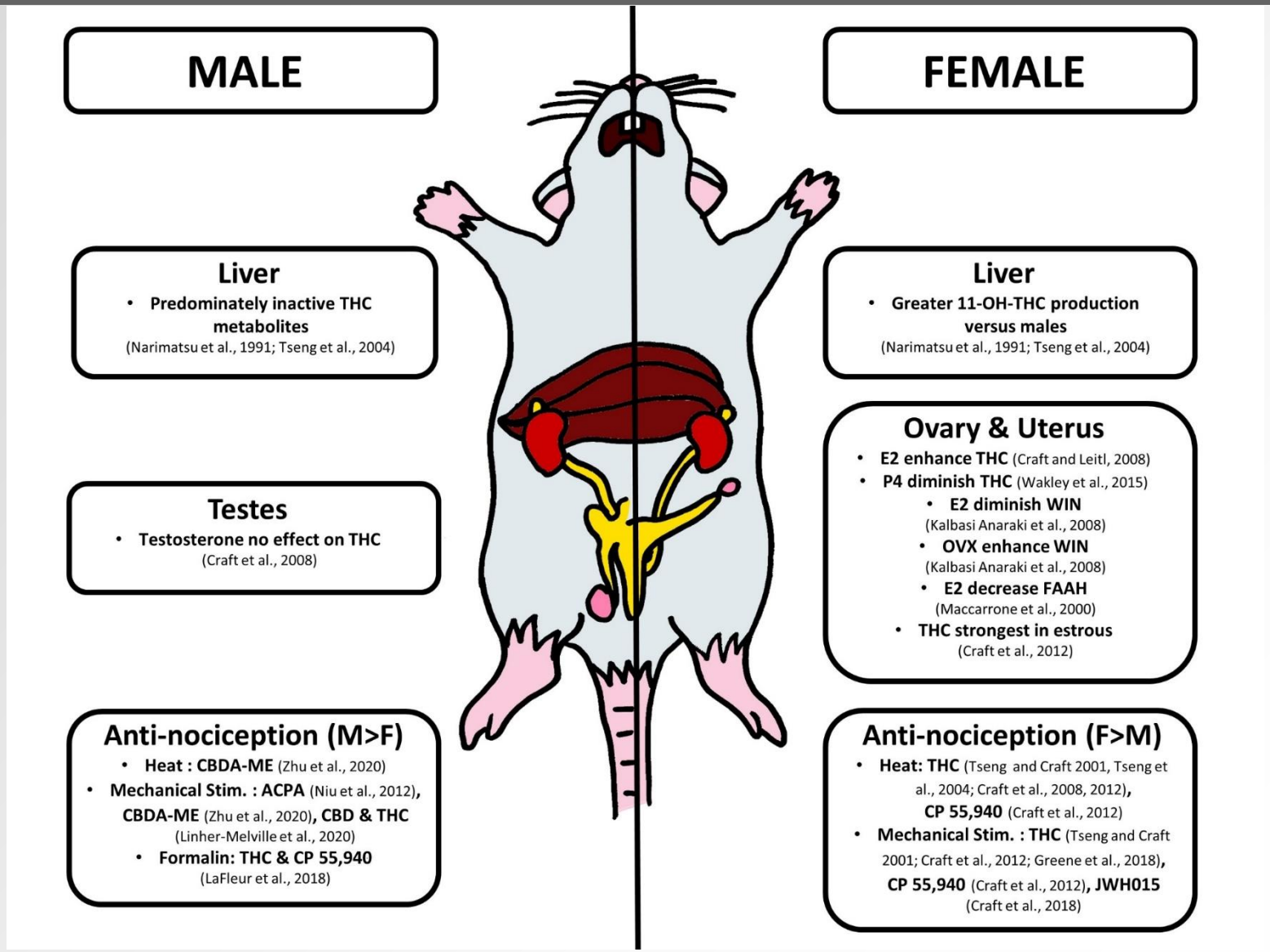
Sex Differences in Brain Endocannabinoid System



Blanton, Barnes, McHann, Bilbrey, Wilkerson and Guindon (**2021**) *Pharmacology, Biochemistry and Behavior 202:* 173107.

Mechanisms underlying Sex Differences in Cannabinoid Antinociception



Blanton, Barnes, McHann, Bilbrey, Wilkerson and Guindon (**2021**) *Pharmacology, Biochemistry and Behavior 202:* 173107.

Comparison of Cannabinoid-Mediated Antinociception in Male and Female

Reference	Pain Model	Acute or Chronic	Species	Compound (s)	Dose & ROA	Acute and/or Repeated	Efficacy: Male v Female	Mediated By	Serum Analysis	Estrous Effect	Hormone
Blednov et al., 2003	Hotplate (Paw)	Acute	Mouse	WIN 55, 212-2	6 mg/kg; I.P.	Acute	M = F	GIRK 2; Male > Female	NT	NT	NT
Britch et al., 2017	Pressure (Paw), Heat (Tail Immersion)	Acute	Rat	CBD, THC	CBD (30 mg/kg) + THC (1.8 mg/kg); I.P.	Acute	M = F	NT	NT	No Effect	NT
Britch et al., 2020	Heat (Paw), Mech. Allodynia (Paw), Weight Bearing (paw)	Chronic - CFA (paw)	Rat	CBD,THC	CBD (1.25-10 mg/kg), THC (1-4 mg/kg); I.P.	Acute & Repeated	F>M; acute THC heat hyperalgesia	NT	Yes; TNF-α, IL-1β, IL-10, INFγ	NT	NT
Craft and Leitl, 2008	Pressure (Paw), Heat (Tail Immersion)	Acute	Rat	THC	5, 10 mg/kg; I.P.	Acute	F>M, E2 potentiate in Female	NT	NT	Yes; THC strongest in estrus	M & F Gonadectomy, Testosterone & Estradiol Replacement
Craft et al., 2012	Heat (Tail Immersion), Pressure (Paw)	Acute	Rat	CP 55,940,THC	CP 55,940 (0.05 - 1.6 mg/kg), THC (1.25 - 20 mg/kg); I.P.	Acute	CP 55,940 F>M; THC: F>M	CP55: CB1 - M & F; THC: CB1- Male, CB1 & CB2 - Female	Yes; Rimonabant	Yes; THC strongest in estrus	NT
Craft et al., 2013	Mech. Allodynia (Paw), Heat (Paw)	Chronic - CFA (paw)	Rat	THC	0.32 - 3.2 mg/kg I.P.; 0-500 µg I.PL.	Acute & Repeated	THC: F>M	IP: CB1 - M & F; I.PL.: CB1 & CB2 Female, CB1 only Male	NT	No Effect	NT
Craft et al., 2017	Pressure (Paw), Heat (Tail Immersion)	Acute	Rat	THC	THC: 3 mg/kg (Female), 5 mg/kg (Male), Proadifen: 25mg/kg, I.P.	Acute	F>M, E2 potentiate THC in male, T inhibit THC in female	Testosterone, Estradiol, and CYP450 (CYP2C family)	Yes; THC, 11-OH-THC, THC-COOH	NT	M & F Gonadectomy, Testosterone & Estradiol Replacement
Craft et al., 2018	Acute: Heat (Tail Immersion), Pressure (Paw), Inflammatory: Mech. Allodynia (Paw), Heat (Paw), Weight Bearing (paw)	Acute, Chronic - CFA (paw)	Rat	JWH015	5-40 mg/kg, I.P.	Acute	M=F, except mech. allodynia F>M (10 mg/kg)	CB1 & CB2	NT	NT	NT
Greene et al., 2018	Pressure (Paw), Heat (Tail Immersion)	Acute	Rat	CBD, THC	CBD: 10 mg/kg, THC: 3.6 mg/kg (Female), 9.3 mg/kg (Male); I.P.	Repeated	THC: F>M (acute), CBD: M>F (repeated - tail flick)	NT	Yes; CBD, CBN, THC, 11-OH-THC, THC-COOH	NT	NT
Javadi-Paydar et al., 2018	Heat (Tail Immersion)	Acute	Rat	CBD, THC	CBD: 12.5, 50 mg, THC: 1.5-25mg, Vaporized	Repeated (>1week washout between)	F>M	NT	Yes; THC	No Effect; THC equivalent between Diestrus & Estrus	NT
Kalbasi Anaraki et al., 2008	Heat (Tail Flick)	Acute	Mouse	WIN 55, 212-2	2, 4 mg/kg, I.P.	Acute	F only; OVX enhance analgesia, E2 inhibit, P4 no effect	CB1	NT	NT	F Only OVX, E2 & P4 Replacement
LaFleur et al., 2018	Inflammatory (Formalin-Paw)	Acute	Mouse	CP 55,940,THC	CP 55,940 (0.06 - 0.2 mg/kg), THC (1 - 6 mg/kg); I.P.	Acute & Repeated	CP 55,940: M>F; THC: M>F antinociception & rate of tolerance	NT	NT	NT	NT
Linher-Melville et al., 2020	Mech. Allodynia (Paw)	Chronic - Sciatic Nerve Cuff	Rat	CBD, THC	CBD: 0.41 mg/kg THC: 0.08 mg/kg, Combination: 0.2 mg/kg + 0.2 mg/kg; Oral	Repeated	M>F	NT	NT	NT	NT

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Comparison of Cannabinoid-Mediated Antinociception in Male and Female

Reference	Pain Model	Acute or Chronic	Species	Compound (s)	Dose & ROA	Acute and/or Repeated	Efficacy: Male v Female	Mediated By	Serum Analysis	Estrous Effect	Hormone
Marusich et al., 2015	Heat (Tail Flick)	Acute	Rat	THC	30 mg/kg, I.P.	Acute & Repeated	F>M (Acute); M=F (Chronic)	CB1	NT	Inconclusive	M & F Gonadectomy, Testosterone, Estradiol, & Progesterone Replacement
Mulpuri et al., 2018	Mech. Allodynia (Paw), Cold Allodynia (Paw)	Chronic - Cisplatin (systemic)	Rat	PrNMI	0-2 mg/kg I.P.; 0.25 mg/kg I.PL.; 3 mg/kg Oral	Acute & Repeated	M=F	CB1	NT	NT	NT
Niu et al., 2012	Mech. Allodynia (Masseter)	Chronic - CFA (masseter)	Rat	ACPA	10-300 µg I.M.	Acute & Repeated	M>F	CB1	NT	NT	M & F Gonadectomy, Testosterone, Estradiol Replacement
Romero et al., 2002	Heat (Tail Immersion)	Acute	Rat	CP 55,940	0.1-0.6 mg/kg, I.P.	Acute	M=F	CB1	NT	NT	NT
Tseng and Craft, 2001	Pressure (Paw), Heat (Tail Immersion)	Acute	Rat	CP 55,940, THC, 11-OH-THC	CP 55, 940 (0.1-0.56 mg/kg), THC (1-10 mg/kg), 11-OH-THC (0.3-10 mg/kg); I.P.	Acute	F>M	NT	NT	No Effect	NT
Tseng et al., 2004	Heat (Tail Immersion)	Acute	Rat	THC	10 mg/kg, I.P.	Acute	F>M	CYP 450 (Female)	THC, 11-OH-THC	NT	NT
Wakley et al., 2011	Pressure (Paw), Heat (Tail Immersion)	Acute	Rat	THC	100 µg, I.C.V.	Acute	F>M	NT	NT	Yes; F>M when in Late Proestrus	NT
Wakley et al., 2014	Pressure (Paw), Heat (Tail Immersion)	Acute	Rat	THC	5.4 mg/kg (Female), 7.6 mg/kg (Male), I.P.	Acute & Repeated	F>M	NT	NT	No Effect	NT
Wakley et al., 2015	Pressure (Paw), Heat (Tail Immersion)	Acute	Rat	THC	5.7 mg/kg (Female), 9.9 mg/kg (Male), I.P.		F>M antinociception & rate of tolerance; P4 inhibit THC	NT	NT	Inconclusive	M & F Gonadectomy, Testosterone, Estradiol, & Progesterone Replacement
Wiley et al., 2003	Heat (Tail Flick)	Acute	Rat	THC	1-300 mg/kg, I.P.	Acute	M=F	CB1	NT	NT	NT
Yuill et al., 2017	Inflammatory (Formalin-Paw)	Acute	Mouse	JWH 133	0.01 - 10 mg/kg (acute), 1 mg/kg repeated; I.P.	Acute & Repeated	M=F	CB2	NT	NT	NT
Zhu et al., 2020	Mech. Allodynia (Paw), Heat (Paw)	Chronic - Sciatic Nerve Cuff	Rat	CBDA-ME	0.01-4 µg/kg, I.P.	Repeated	M>F	NT	NT	NT	NT

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Sex differences and the endocannabinoid system in pain

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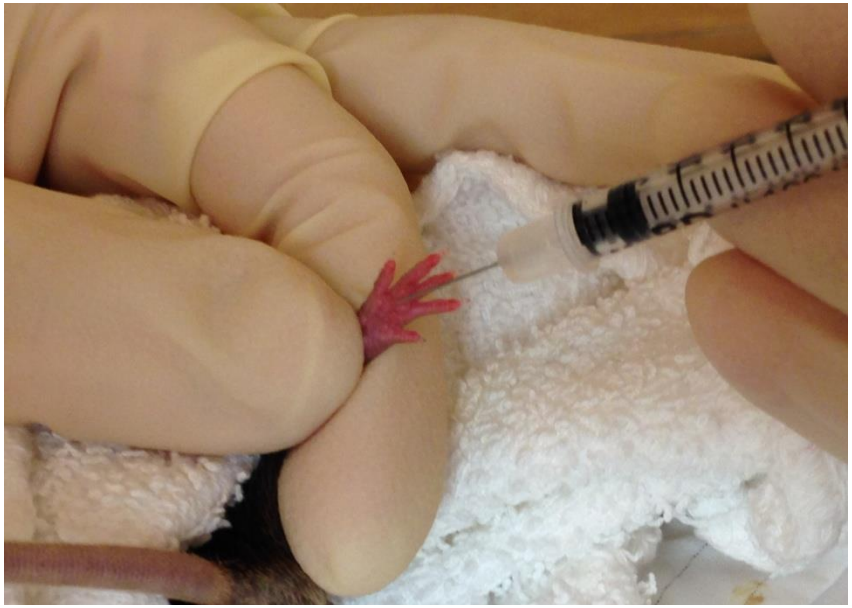
Major Findings

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

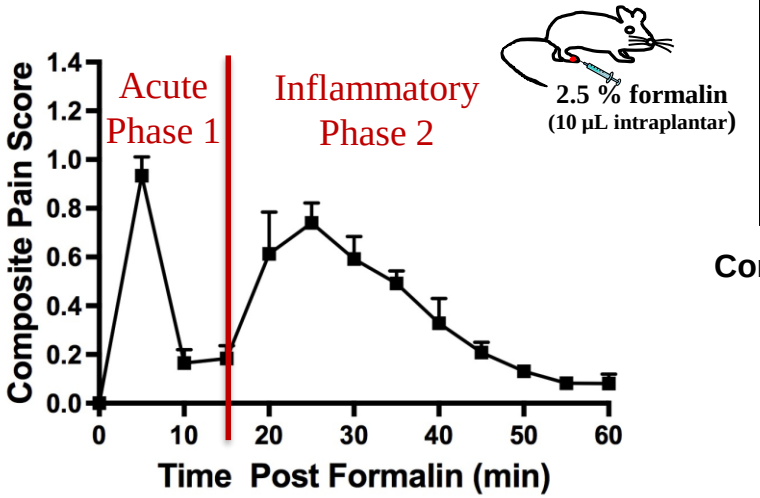
Limitations of Field

- 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



Injection 10 µL of Formalin 2.5 %

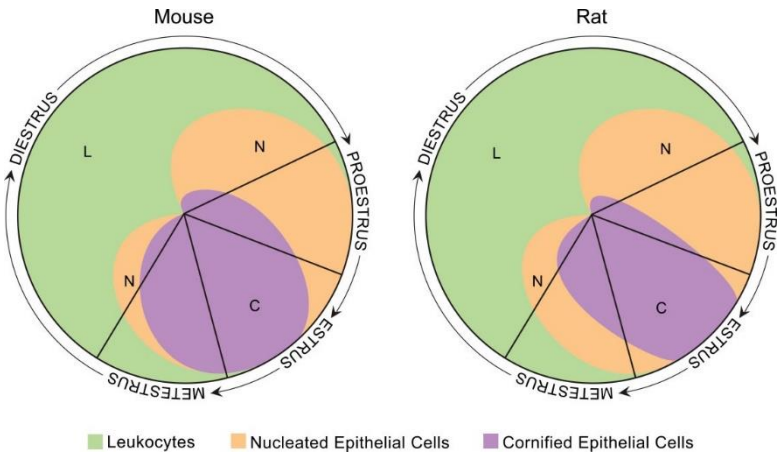


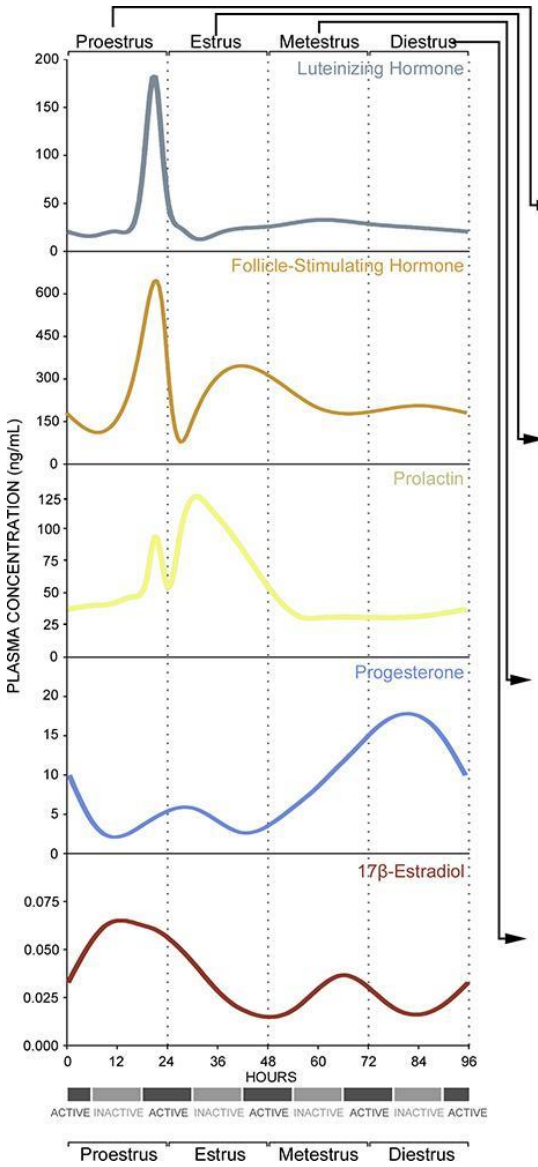
Behaviours*		Observations	Scoring system**
Normal behaviour		Injected paw can support the weight of the animal.	Time spent in this category ×0
Pain behaviour (1)		Injected paw has little or no weight on it.	×0
Pain behaviour (2)		Injected paw is elevated, not in contact with any surface.	×1
Pain behaviour (3)		Injected paw is licked, bitten or shaken.	×2

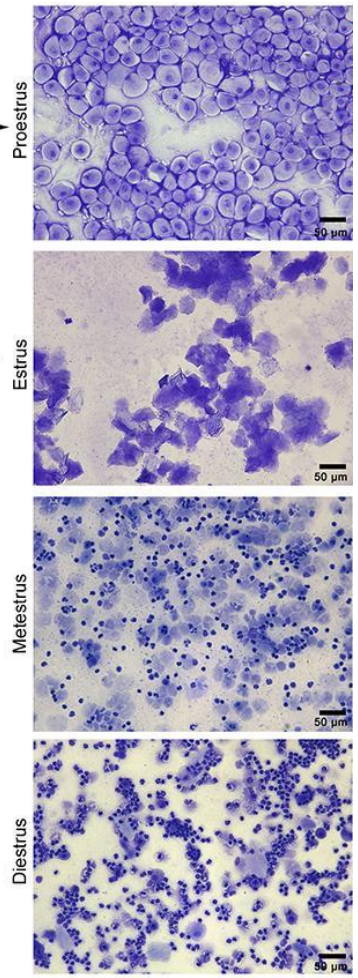
Composite Pain Score = ((Behavior 2 Time * 2) + Behavior 1 Time) / 300

Watson et al. (1997) *Pain* **70**:53-58.

Estrous Cycle







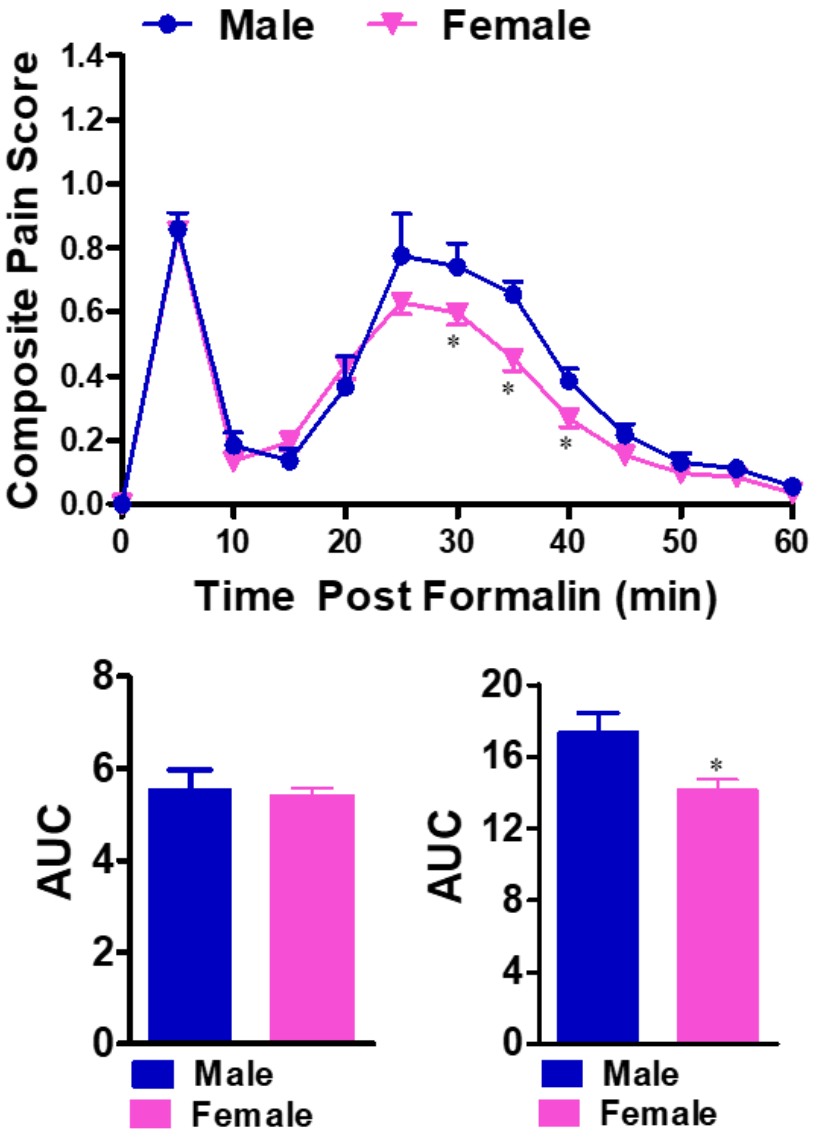
nucleated epithelial cells

cornified squamous epithelial cells

mix cell types (leucocytes, nucleated and/or cornified squamous epithelial cells)

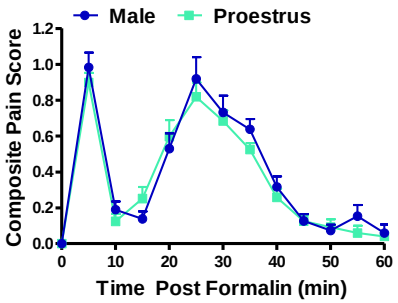
predominance of leukocytes

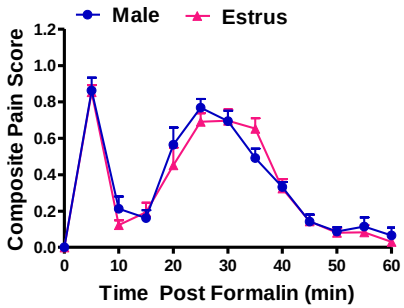
Sex differences in the formalin test

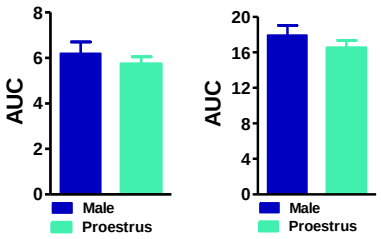


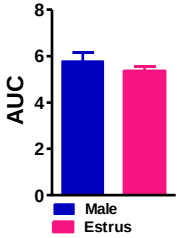
Blanton H et al., (**2021**) *In preparation*.

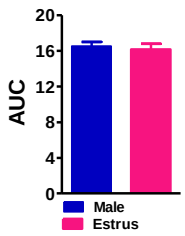
Male vs Female Estrous Cycle in Formalin







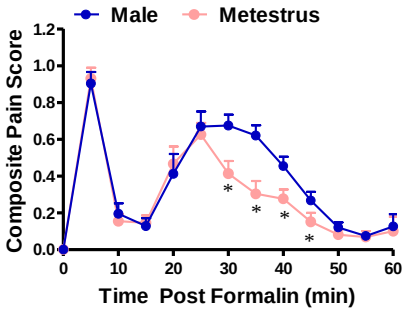




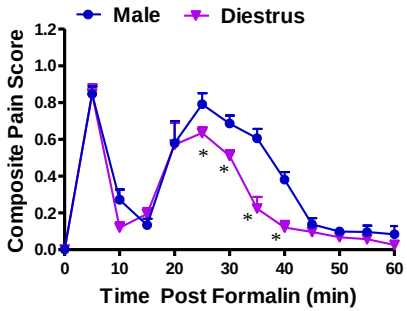
Proestrus

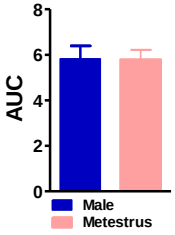
Estrus

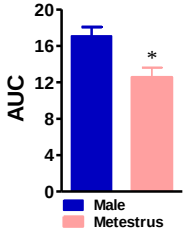
Metestrus

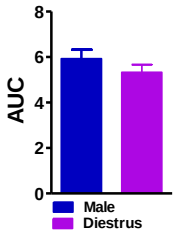


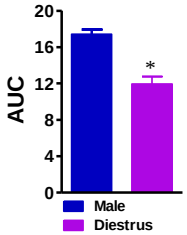
Diestrus





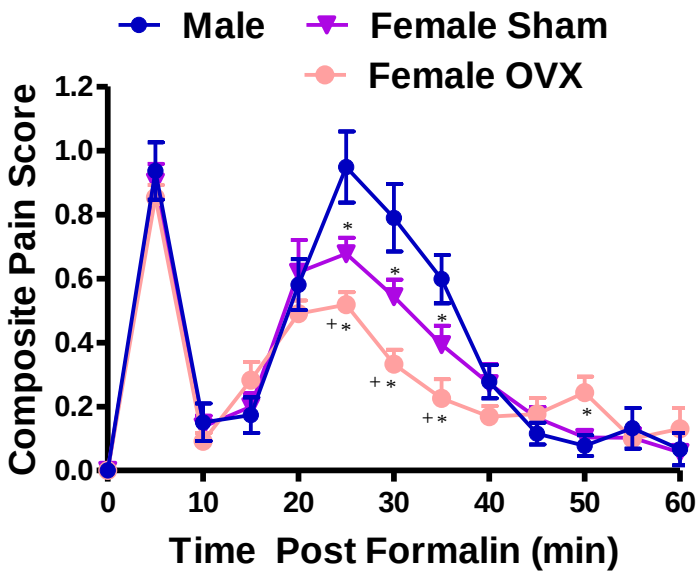


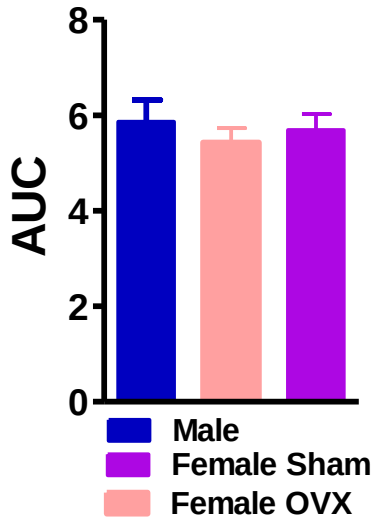


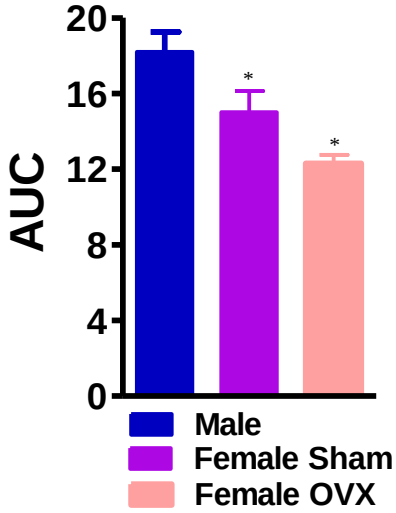


Blanton H et al., (**2021**) *In preparation.*

Male vs Female Estrous Cycle in Formalin

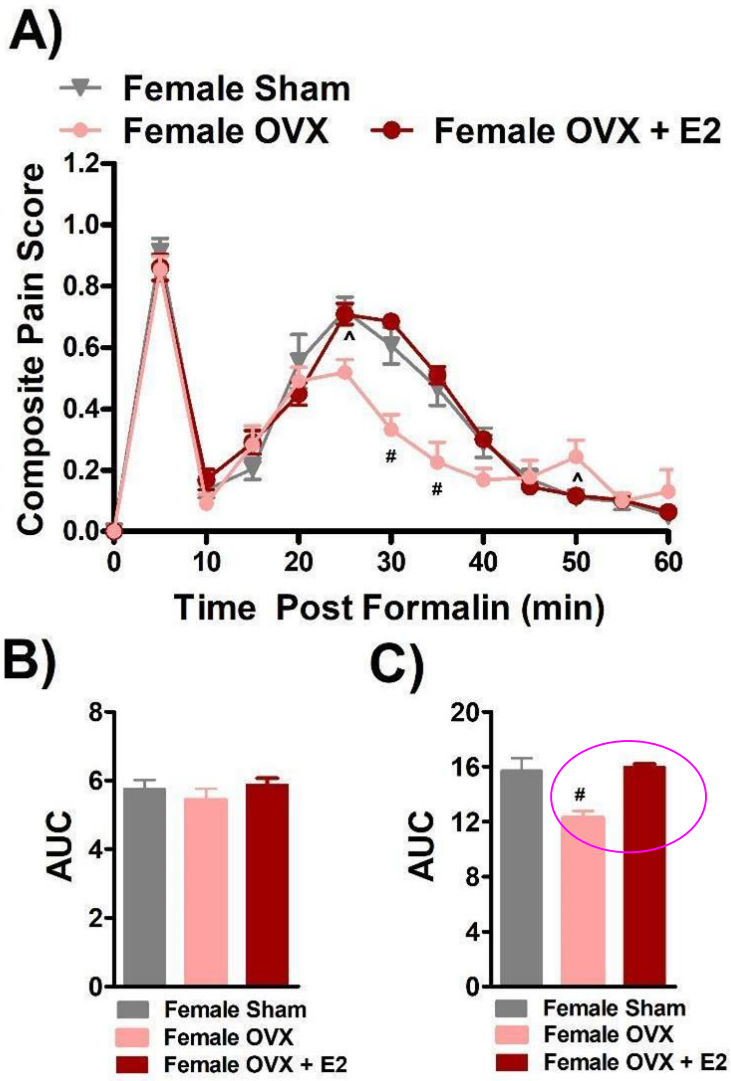






Blanton H et al., (**2021**) *In preparation*.

Estradiol increases inflammatory pain in ovariectomized females

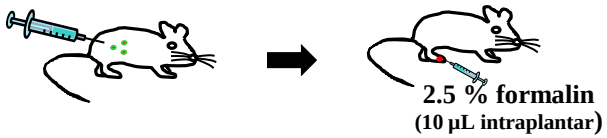


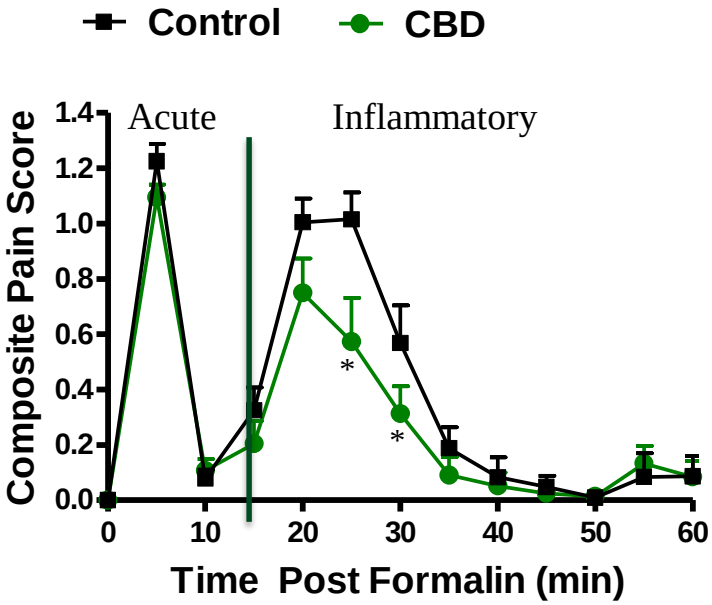
E2 increased pain

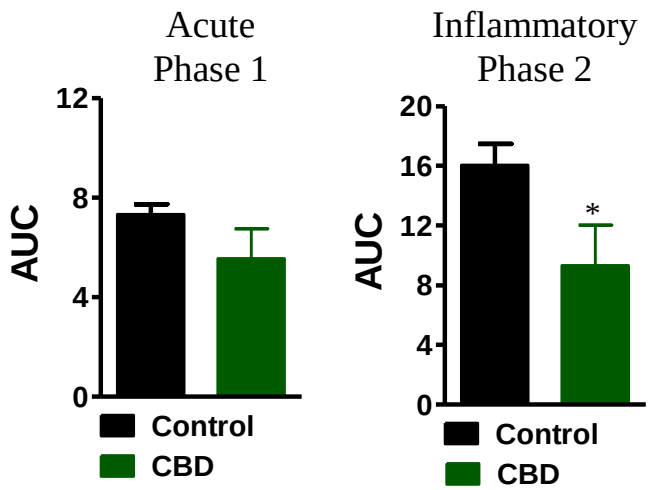
Blanton H et al., (**2021**) *In preparation*.

CBD in the Formalin test in males

CBD
2.5 mg/kg







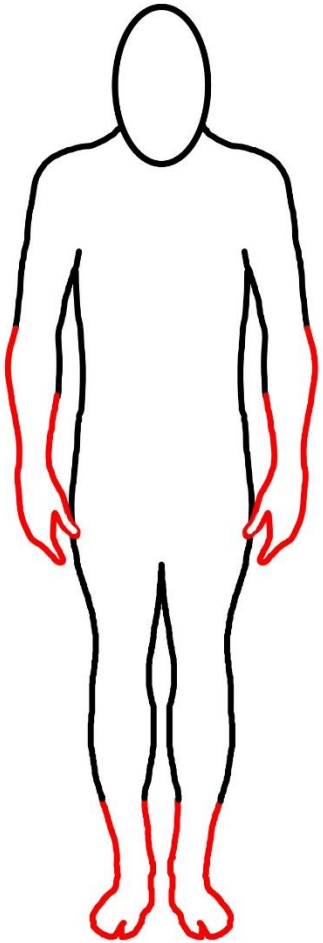
Treatments of chemotherapy-induced peripheral neuropathy

Current Treatments

1st Line
SNRI's (Duloxetine)
Pregabalin
Gabapentin
TCA's

2nd Line
Lidocaine Patch
Capsaicin Patch
Tramadol

3rd Line
Strong Opioids
Botox



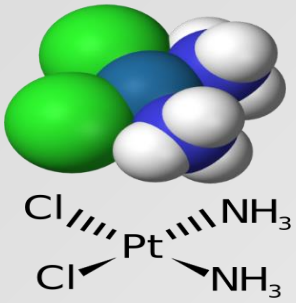
Current Clinical Trials

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

Blanton, Brelsfoard, DeTurk, Pruitt, Narasimhan, Morgan and Guindon (**2019**) *Drugs* 79: 969-995.

Chemotherapy-induced peripheral neuropathy

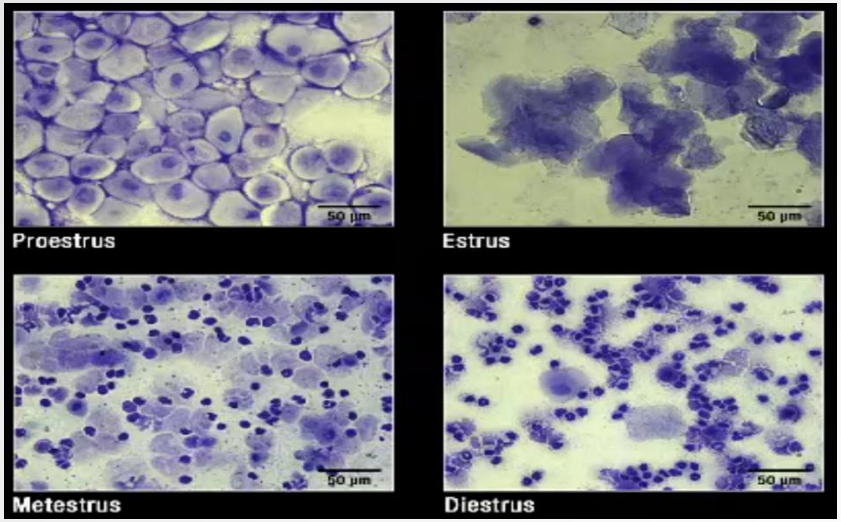
Neuropathy induced by platinum derived compounds
(**cisplatin**, carboplatin, oxaliplatin)



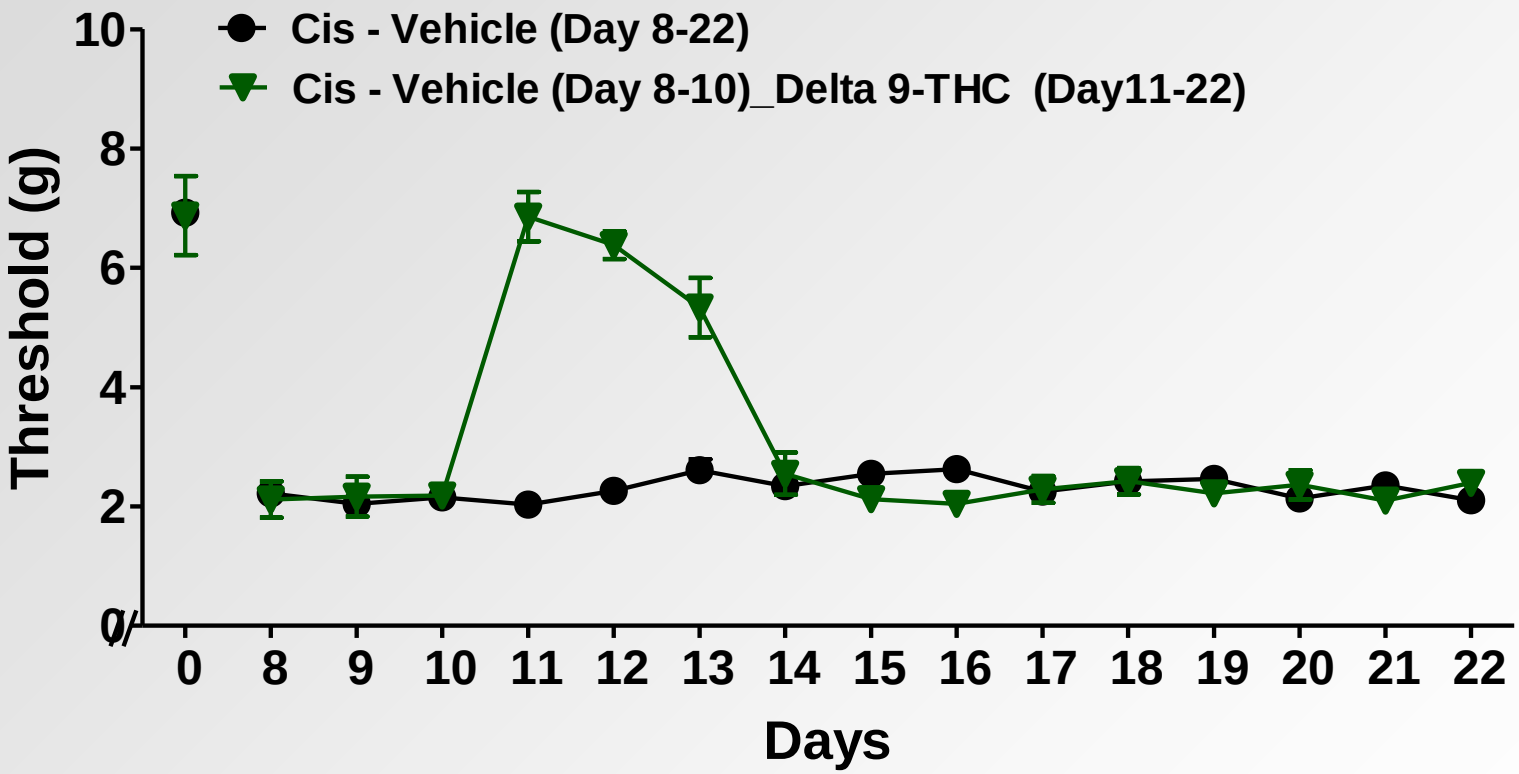
Cisplatin
(5 mg/kg ip)
1 X Week

Mechanical Allodynia

Cold Allodynia



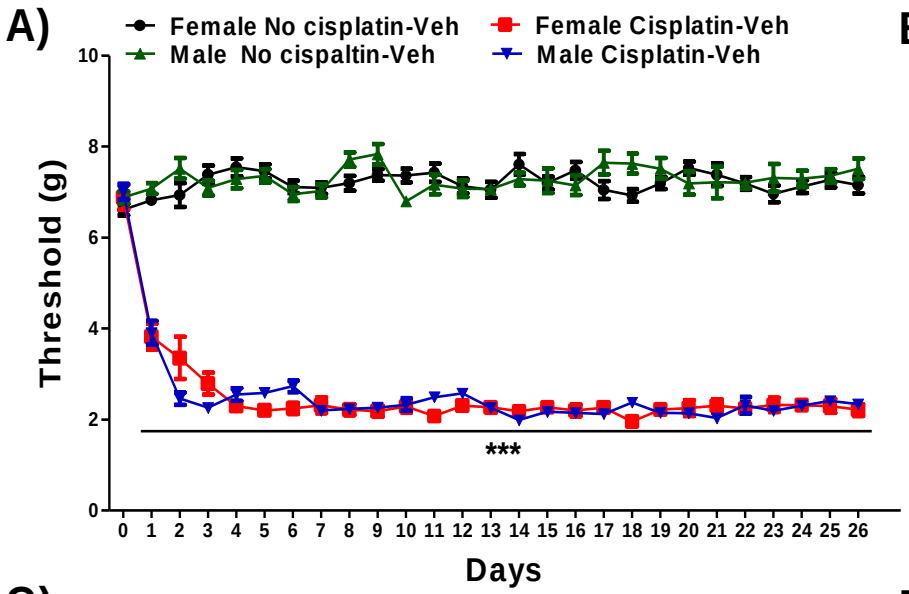
Δ^9-THC (CB_1/CB_2 agonist) in males



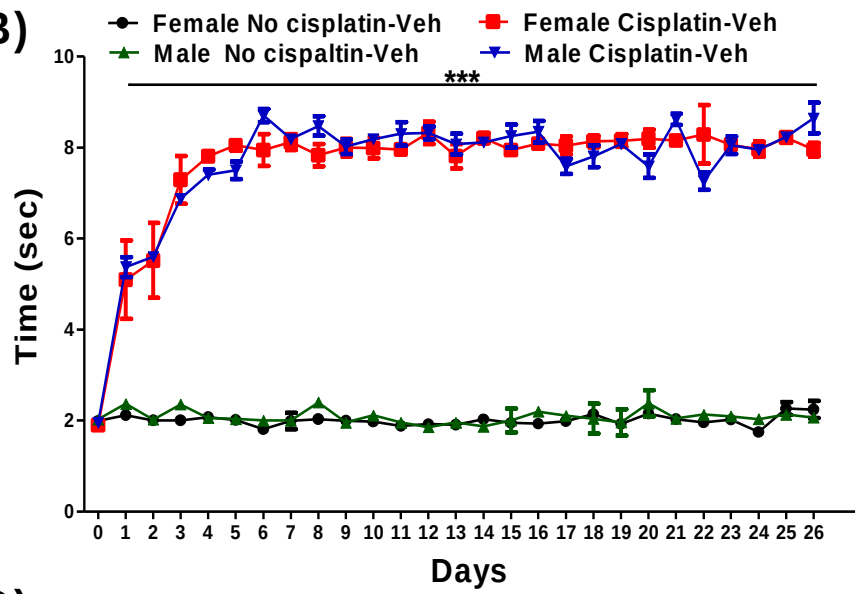
Henderson-Redmond et al., (2020) Neuropharmacology

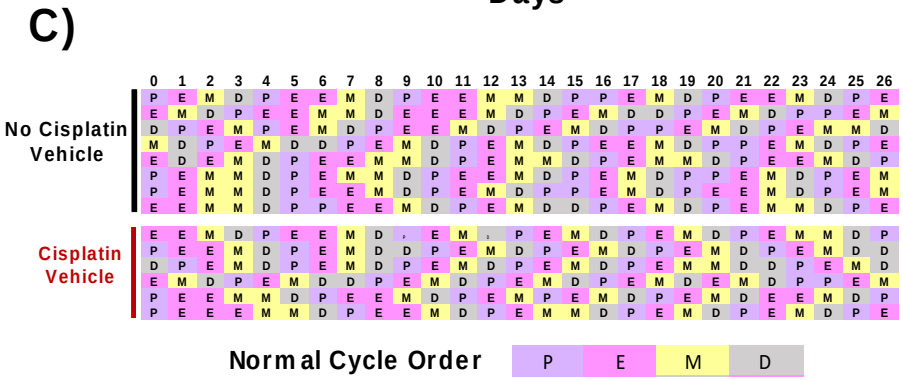
Neuropathic pain and estrous cycle

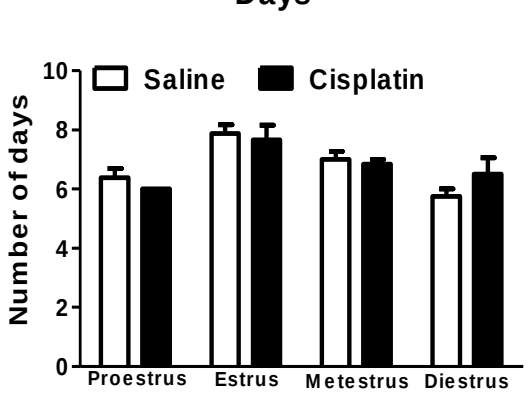
Mechanical Allodynia



Cold Allodynia







Blanton H et al., (**2021**) *In preparation*.

Summary

- 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

Conclusion

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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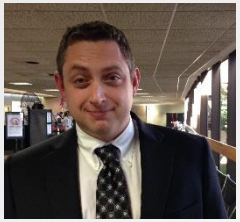

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Advancing Addiction Science

Questions

Thank you for your attention!