Are Cannabinoids Analgesics?

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Pain: Essential Concepts

- Definitions
- Categories of Painful Conditions
- Pain Mechanisms and Pathways

Definitions

- Pain
  - Acute
  - Chronic
- Nociceptive Pain
- Neuropathic Pain
- Central Pain

What is Pain

- IASP Definition[1]
  - An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.
- Acute[2]
  - pain of sudden onset that resolves spontaneously, with healing of an injury or an illness, of short duration (usually within weeks to months)
- Chronic[2]
  - Pain that persists or recurs over months to years, associated with a chronic illness or condition or continues after apparent healing has occurred.

1. https://www.iasp-pain.org/Education/Content.aspx?ItemNumber=1698
2. Adapted from https://my.clevelandclinic.org/health/articles/12051-acute-vs-chronic-pain

Nociceptive Pain

- Pain that arises from actual or threatened damage to non-neural tissue and is due to the activation of nociceptors
  - Examples: trauma, bone metastasis, infection, sunburn

Neuropathic Pain

- Pain caused by a lesion or disease of the somatosensory nervous system.
  - Examples: diabetic neuropathy, postherpetic neuralgia, trigeminal neuralgia, sciatica

Central Pain

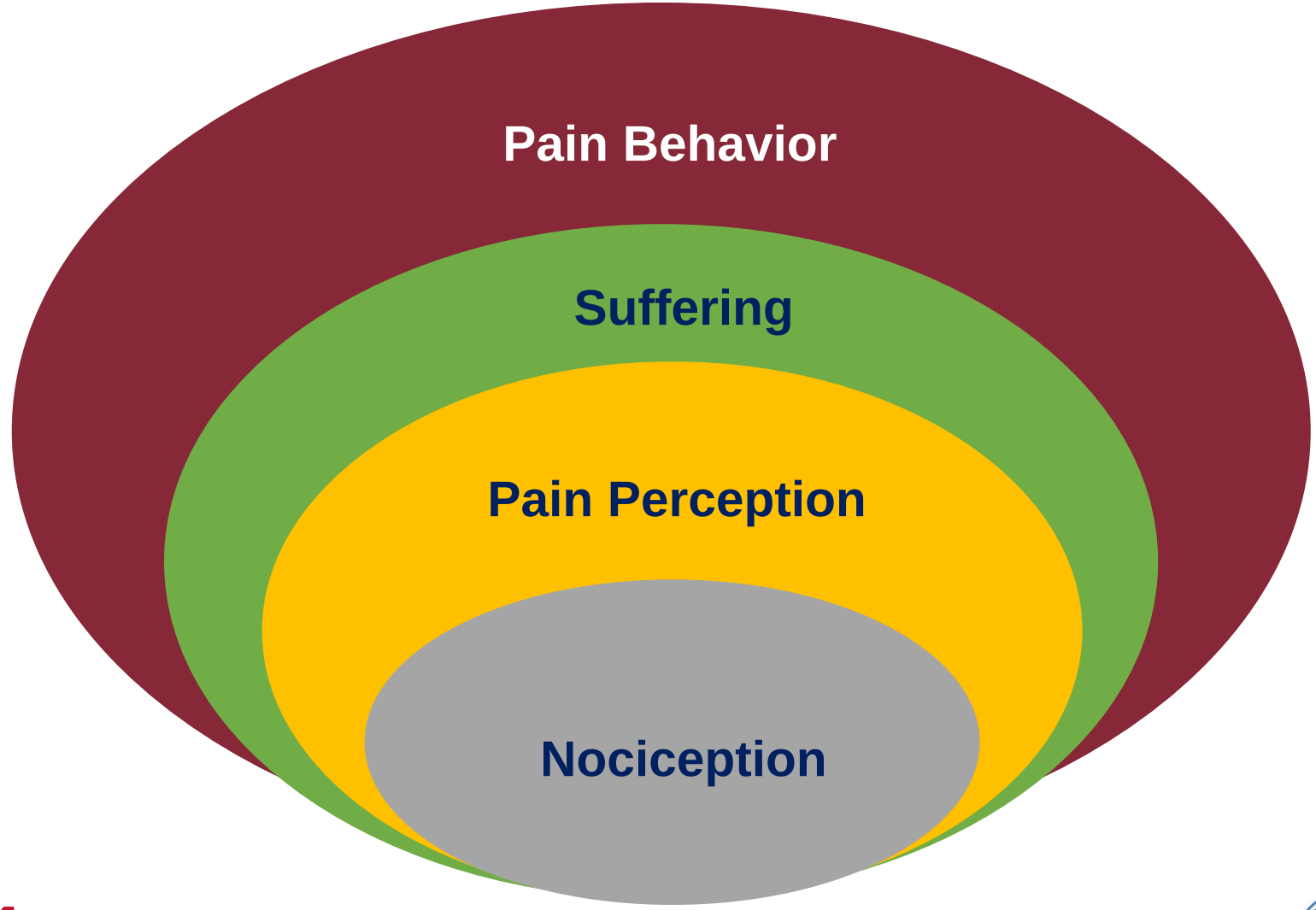
- Central pain syndrome is a neurological condition caused by damage to or dysfunction of the central nervous system (CNS), which includes the brain, brainstem, and spinal cord.
  - Examples: stroke, multiple sclerosis, tumors, epilepsy, brain or spinal cord trauma, Parkinson's disease.

https://www.ninds.nih.gov/Disorders/All-Disorders/Central-Pain-Syndrome-Information-Page

Other Pain Types and Conditions

- Mixed nociceptive-neuropathic pain conditions
  - Spinal pain (neck, low back); cancer pain syndromes
- Other
  - Recurrent/chronic headache, fibromyalgia

The Complex Nature of Pain



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Adapted from: Loeser J, et al. *Bonica's Management of Pain.* 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins. 2001;241-254.

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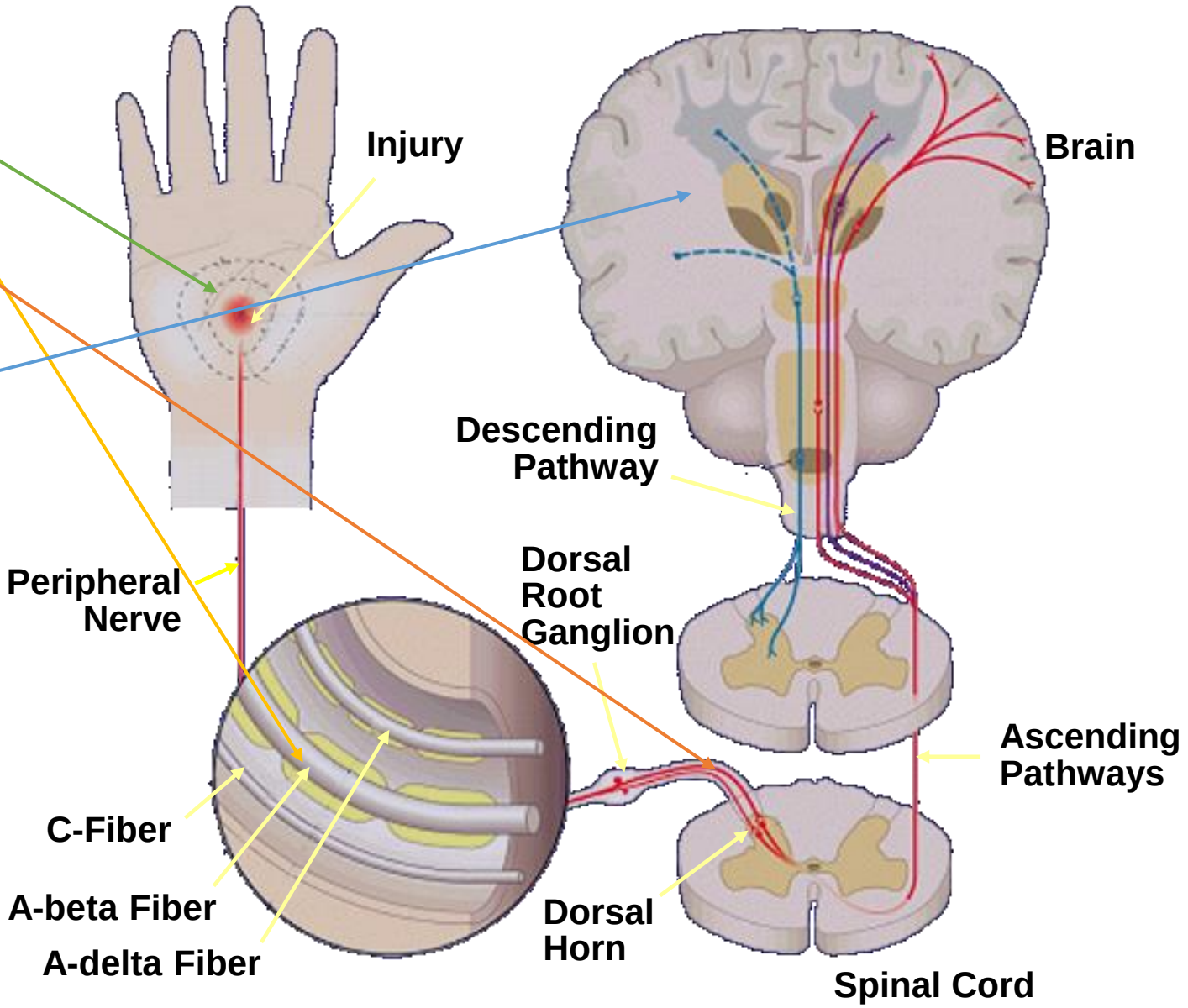
Nociceptive (acute) Pain Pathways

- Transduction
- Transmission
- Modulation
- Perception
- Interpretation
- Behavior



Peripheral Nociceptor Hyperexcitability and Sensitization

Mechanisms	Symptoms	Targets
Hyperexcitability		
Ectopic impulse generation; oscillations in dorsal root ganglion	Spontaneous pain (shooting)	Sodium channels, CB_2 receptors
Sensitization: Inflammation within nerves		
Cytokine release	Spontaneous pain	Cytokines, α3 glycine receptor (CBD)
Sensitization: Reduced activation threshold		
Reduced threshold to heat or cold	Heat allodynia or cold allodynia	TRPV1 receptor (anandamide)
Reduced threshold to mechanical stimuli	Static mechanical allodynia	ASIC receptor
Reduced threshold to histamine or norepinephrine	Sympathetically maintained pain	CB_1, CB_2 receptors, histamine and α receptors,

Adapted from: Baron R. Nature Clinical Practice Neurology. 2006;2(2):95-106.; Mendell JR, et al. N Engl J Med. 2003;348(13):1234-1255.; Woolf CJ, et. al. Lancet. 1999;353:1959-1964. TCA = Tricyclic antidepressant; TNF- α = tumor necrosis factor- α; NSAID = Nonsteroidal anti-inflammatory drug; ASIC = Acid-sensing ion channel; TRPV1 = Transient receptor potential vanilloid 1

Central Dorsal Horn Hyper-excitability

Mechanisms	Symptoms	Targets
Central sensitization, increased synaptic transmission		
Amplification of C-fiber input, gating of Aβ-fiber and Aδ-fiber input	Spontaneous pain (ongoing), dynamic mechanical allodynia, punctate mechanical hyperalgesia	CB_1, CB_2 receptors, μ, receptors, calcium channels (α2-δ), NMDA receptors, NK1 receptors, sodium channels, intracellular cascades
Intraspinal inhibitory interneurons decreased		
GABA-ergic or opioidergic interneurons decreased	Spontaneous pain (ongoing), dynamic mechanical allodynia, punctate mechanical hyperalgesia	$GABA_B$ receptors or μ receptors
Changes in supraspinal descending modulation		
Inhibitory control (5-HT, noradrenaline) decreased	Spontaneous pain (ongoing), dynamic mechanical allodynia, punctate mechanical hyperalgesia	5-HT receptors, α2 receptor, CB_1, CB_2 receptors

Adapted from: Baron R. Nature Clinical Practice Neurology. 2006;2(2):95-106.; Mendell JR, et al. N Engl J Med. 2003;348(13):1234-1255.; Woolf CJ, et. al. Lancet. 1999;353:1959-1964.

NMDA = N-methyl-D-aspartic acid; NK-1 = neurokinin; $GABA_B$ = **Gamma-aminobutyric acid receptor – subtype B**; 5-HT = **5-hydroxytryptamine (serotonin) receptor; α2 = alpha 2 adrenergic receptor**

The Endocannabinoid System and Pain

- The endocannabinoid system is involved in pain signaling and modulation via endogenous cannabinoids (e.g. anandamide)acting at cannabinoid receptors (CB_1, CB_2) and regulating intermediary neurotransmitters and receptors involved in nociception and neuroinflammation.
- Involved in tissue healing in the face of inflammatory conditions, correlating clinically with prevention and treatment of inflammation-mediated pain.

The Endocannabinoid System and Pain

- Endogenous cannabinoids (anandamide, 2-AG) act at supraspinal, spinal and peripheral levels to mediate homeostatic acute pain modulating effects and perpetuate chronic pain states via:
  - CB_1 receptors, via G-protein coupled inhibition of adenylate cyclase mediated antinociception.
  - CB1 receptor activation in limbic brain areas that produce and influence affective/emotional responses to pain.
  - Vanilloid (TRPV1) receptors and other transient receptor potential (TRP) receptor types involved in pain signal processing.
  - CB_2, opioid, 5HT, and N-methyl-d-aspartate receptors and spinal noradrenergic pathways.
    - Localization of CB_2 receptors on immune cells (macrophages, lymphocytes, and mast cells in the periphery; astrocytes and microglia in the CNS) is essential to the roles of the CB_2 receptors in modulating pain states.

Summarized in: Fine PG, Rosenfeld MJ. Rambam Maimonides Med J, 2013;4(4):1-15

Exogenous Cannabinoids and Pain: Acute and Postoperative Pain

- The results from clinical studies with smoked cannabis, oral THC extract, cannabis extract, and nabilone (synthetic THC) in experimentally-induced acute pain in healthy human volunteers are limited and mixed and suggest a dose-dependent effect in some cases, with lower doses of THC having an analgesic effect and higher doses having a hyperalgesic effect.
- Clinical studies of certain cannabinoids (nabilone, oral THC, levonontradol, AZD1940, GW842166) for postoperative pain suggest a lack of efficacy.

Health Canada. INFORMATION FOR HEALTH CARE PROFESSIONALS Cannabis (marihuana, marijuana) and the cannabinoids, 2018: 79-82

Exogenous Cannabinoids and Pain: Chronic Pain

- A systematic review and meta-analysis of 28 RCTs (N = 2,454 participants) for chronic pain (including smoked cannabis, nabiximols, dronabinol) reported that there was moderate quality evidence of efficacy to support the use of cannabis & cannabinoids to treat chronic pain of various etiologies, mostly reducing central or peripheral neuropathic pain in individuals already receiving analgesic drugs[1]
  - National Academies of Science, Engineering and Medicine cites this systematic review as the most comprehensive
  - Incidence and severity of adverse effects were comparable to other conventional medical treatments for chronic pain
    - dizziness/lightheadedness, nausea, fatigue, somnolence, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, hallucinations, sedation, ataxia, a feeling of intoxication, xerostomia, dysgeusia, and hunger

1. Whiting PF et al. JAMA 2015 Jun 23-30;313(24):2456-73.

Medical cannabis for the reduction of opioid dosage in the treatment of noncancer chronic pain: a systematic review. Okusanya B, et al. BMC Sysstematic Reviews 2020;9:167-75

- Background: Medical cannabis (MC) is currently being used as an adjunct to opiates given its analgesic effects and potential to reduce opiate addiction. This review assessed if MC used in combination with opioids to treat noncancer chronic pain would reduce opioid dosage. Nine studies involving 7222 participants were included.
- Conclusions: While this review indicated the likelihood of reducing opioid dosage when used in combination with MC, we cannot make a causal inference. Although medical cannabis' recognized analgesic properties make it a viable option to achieve opioid dosage reduction, the evidence from this review cannot be relied upon to promote MC as an adjunct to opioids in treating non-cancer chronic pain. More so, the optimal MC dosage to achieve opioid dosage reduction remains unknown. Therefore, more research is needed to elucidate whether MC used in combination with opioids in the treatment of non-cancer chronic pain is associated with health consequences that are yet unknown. (Continued on next page)

Exogenous Cannabinoids and Pain: Chronic and Recurrent Conditions

- Neuropathic and Central Pain
  - A meta-analysis of randomized, double-blind, placebo-controlled trials of smoked/vaporized cannabis for neuropathic pain reported that inhaled cannabis resulted in short-term reductions in chronic neuropathic pain for one in every five to six patients treated (NNT = 5.6) with efficacy equivalent to gabapentin (NNT = 5.9)[1]
    - The meta-analysis could not draw any conclusions regarding the long-term efficacy or safety of inhaled cannabis for chronic neuropathic pain, as the original studies did not extend past a maximum two-week period.
  - Preclinical studies suggest potential efficacy of cannabidiol (CBD) but human RCTs are lacking[2]
  - Similar findings exist for prescription oral cannabinoids (nabilone, dronabinol, THC:CBD oral mucosal spray[a])

1. Andreae MH et al. J Pain 2015 Dec;16(12):1221-32.
2. Fine PG et al. Curr Pain Headache Rep 2014; 18 (10): 451-60.

a. Not available in the USA

Exogenous Cannabinoids and Pain:
Conditions and Evidence of Therapeutic Benefit

- Cancer Pain*
  - Prescription cannabinoids: The limited available placebo controlled clinical trials evidence with certain cannabinoids (dronabinol, THC:CBD spray [not available in the USA]) suggests a modest analgesic effect or no difference compared to placebo.
  - Studies with cannabis are largely uncontrolled and are difficult to interpret or inconclusive.

*mixed nociceptive/neuropathic pain syndromes attributable to cancer

Noyes et al. J Clin Pharmacol 1975;15:139-43.
Johnson et al. J Pain Symptom Manage 2010;39:167-79. 139
Lynch ME et al. J Pain Symptom Manage 2014;47:166-73.

Cannabis for Cancer Pain-RCTs 2010 to 2017

Reference	Number/Duration	Cannabis	Comparator	Primary Outcome	Secondary Outcome
Lichtman /2017	397/5 weeks Opioid tolerant	Nabiximols	Placebo	NRS wk3,5; NS P=0.085	Improved sleep p=0.027, improved PGIC, SGIG, PSQ
Johnson/2010	177/4 weeks Opioid tolerant	THC spray THC/CBD spray	Placebo	Change in NRS THC/CBD p=0.014 THC p=0.32	EORTC-QLQ-NS Increased nausea with THC/CBD Rescue doses-NS
Portenoy/2012	360/ 5 weeks Opioid tolerant	Nabiximols low, medium, high dose	Placebo	30% decrease in pain intensity p=0.32, better response with low dose	Improved sleep-low dose No difference PGIC, PAC-QOL Increased nausea with nabiximols
Cote /2016	56/4weeks HN cancer undergoing therapy	Nabilone	Placebo	EORTC QLQ** p=0.43	VAS pain, analgesic consumption, nausea, appetite, sleep-NS

GW Pharma completed 2 additional randomized trials of nabiximols-combined tetrahydrocannabinol (THC) plus cannabidiol (CBD) which failed to meet primary endpoints. *WWW.gwpharma.com/about-us/news/gw-pharmaceuticals-and-Otsuka-announced-results*,

**European Organization for Research and Treatment (EORTC) Quality of Life Questionnaire (QLQ)

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Cancer Pain Summary

- No long term studies typical of analgesic trials in cancer.
- Dose ceiling effect noted with nabiximols (CBD:THC)
- Dose-adverse effect noted with somnolence, dizziness, confusion, nausea, and hypotension which are generally mild and transient.
- Noted improvement in sleep in 2 studies.
- Interestingly there was no improvement in appetite ; nausea was a toxicity despite the fact that dronabinol (THC) is licensed as an antiemetic for chemotherapy.
- Trials were designed as "add-ons" to existing analgesics, most were opioid tolerant.

Exogenous Cannabinoids and Pain:
Conditions and Evidence of Therapeutic Benefit

- Headache/Migraine
  - Evidence of efficacy of cannabis/certain cannabinoids to treat headache and migraine is very limited and mixed.
  - Registry data from cannabis users suggest that migraine type headache is the most common type of headache for which cannabis use is sought to either abort or treat headache.
  - Headache is a common adverse effect associated with the use of cannabis or prescription cannabinoid medications, and one of the most frequently reported physical symptoms associated with cannabis withdrawal.

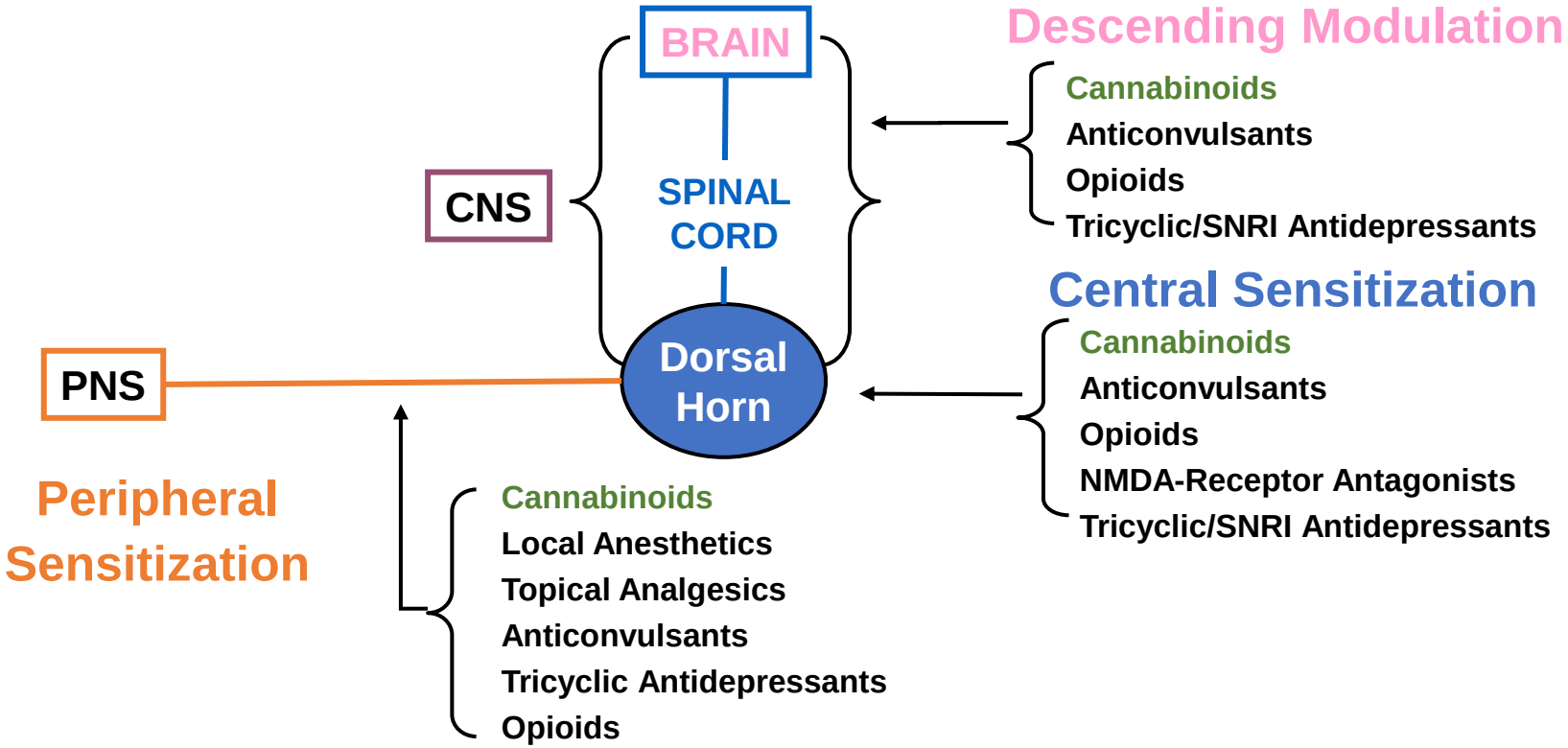
Rhyne et al. Pharmacotherapy 2016;36(5):505-10.
Lochte et al. Cannabis Cannabinoid Res 2017 Apr 1;2(1):61-71.
Baron et al. The Journal of Headache and Pain 2018;19:37-65.

Exogenous Cannabinoids and Pain:
Conditions and Evidence of Therapeutic Benefit

- OA, RA, muscle pain and fibromyalgia
  - The evidence from pre-clinical studies suggests
    - Stimulation of CB1 and CB2 receptors alleviates symptoms of osteoarthritis
    - THC and CBD alleviate symptoms of rheumatoid arthritis (RA).
  - Evidence from clinical studies is very limited, with a modest effect of THC:CBD mucosal spray for RA.
  - There are no well-controlled studies of cannabis for muscle pain or fibromyalgia syndrome, and the limited clinical evidence with dronabinol and nabilone suggests a modest effect on decreasing pain and anxiety, and improving sleep.

Richards et al. Cochrane Database Syst Rev 2012;1:1469-493
Walitt et al. Cochrane Database Syst Rev 2016;7:CD011694 (no page numbers)

The "Analgesic Formulary" of the Future



Scoping Review, 2000-2020*

- A search was performed in PubMed and Cochrane library for articles published in English between January 1, 2000 and May 8, 2020. The search terms used were related to cannabis and pain in adults. 34 studies identified; 30 were randomized controlled clinical trials (RCTs). Varying effects were identified from the RCTs, and as expected more promising effects from non-RCTs.
- Cannabis-based medications were found most effective as an adjuvant therapy in refractory multiple sclerosis, and weak evidence was found to support the treatment of cancer pain especially in advanced stages. Chronic rheumatic pain showed promising results.
- Adverse events of cannabis-based treatment were found to be more frequent with tetrahydrocannabinol herbal strains compared to other cannabis-derived products.

***Haleema R, et al. A Scoping Review on Clinical Trials of Pain Reduction With Cannabis Administration in Adults. J Clin Med Res 2020;12(6):344-351**

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Conclusions

- The endocannabinoid system plays an important homeostatic role in nociception and the experience of pain.
- There is a strong theoretical basis, supported by preclinical data, for exogenous cannabinoids in pain modulation and potential transformation of acute to chronic pain.
- RCTs are lacking in support of cannabis/cannabinoid use for most pain conditions.
- Current anecdotal and limited clinical trials evidence cannot inform a predictable risk-benefit analysis on an individual or population basis.

Additional References for Clinical Trials

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