PRACTICAL APPROACH MEDICAL CANNABIS AND KIDNEY DISEASE

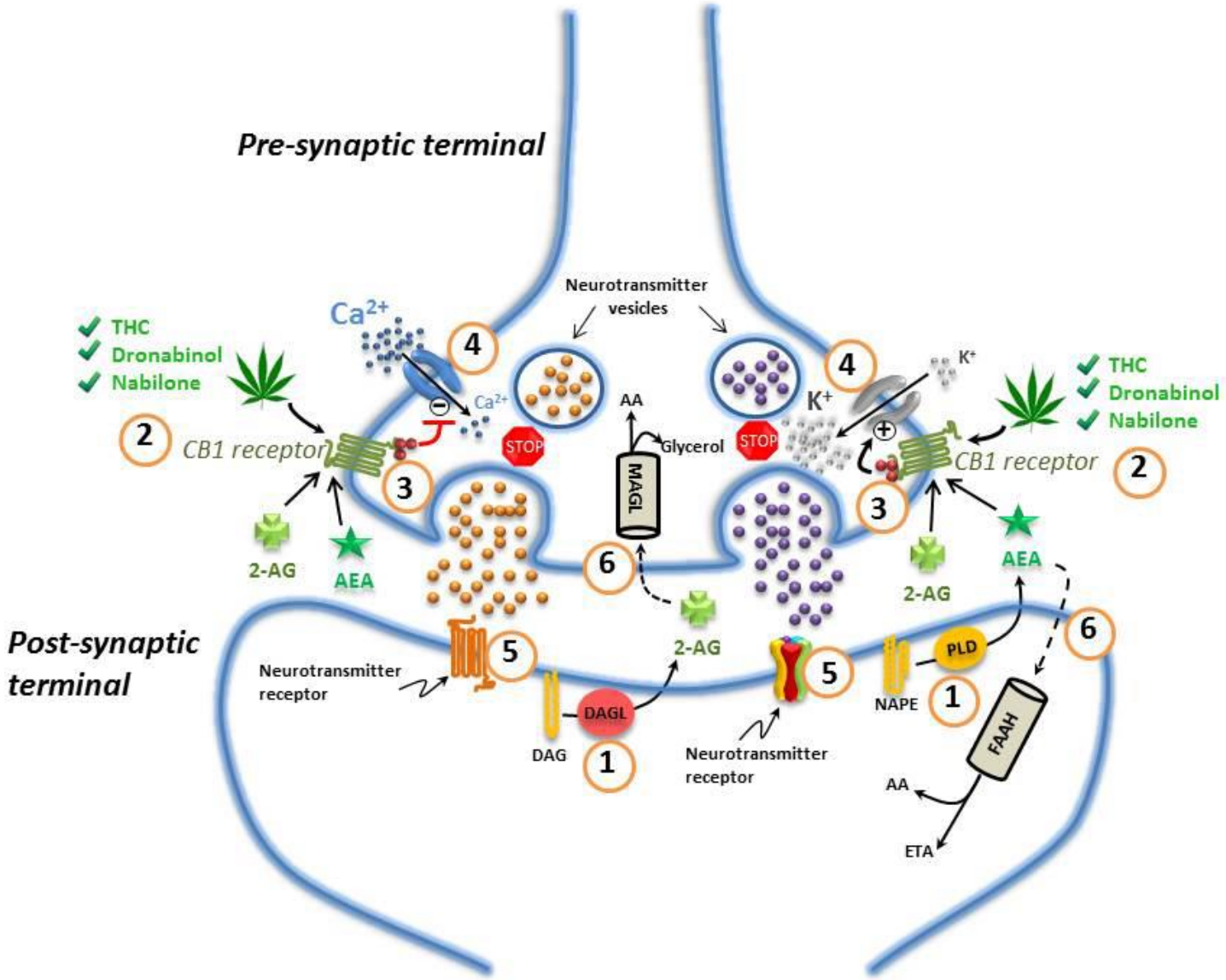
Dr. Vishwanath Kishan Mahabir, MD. FRCPC
Nephrologist, Internist, Medical Cannabis Expert
Toronto, Ontario

DISCLOSURES

- I am receiving an honorarium for this presentation
- Medical Director of CB2 insights/Sail Cannabis
  - Canadian-based medical cannabis technology company
  - Standardizing practice to drive real-world evidence
  - 40+ clinics across 10+ states in the US
  - Pilot project UK "Twenty21"; 20000 patients
- Medical Director of The Clinic Network
  - 14 clinics in Ontario
  - Consultation, education, prescription, ongoing follow-up

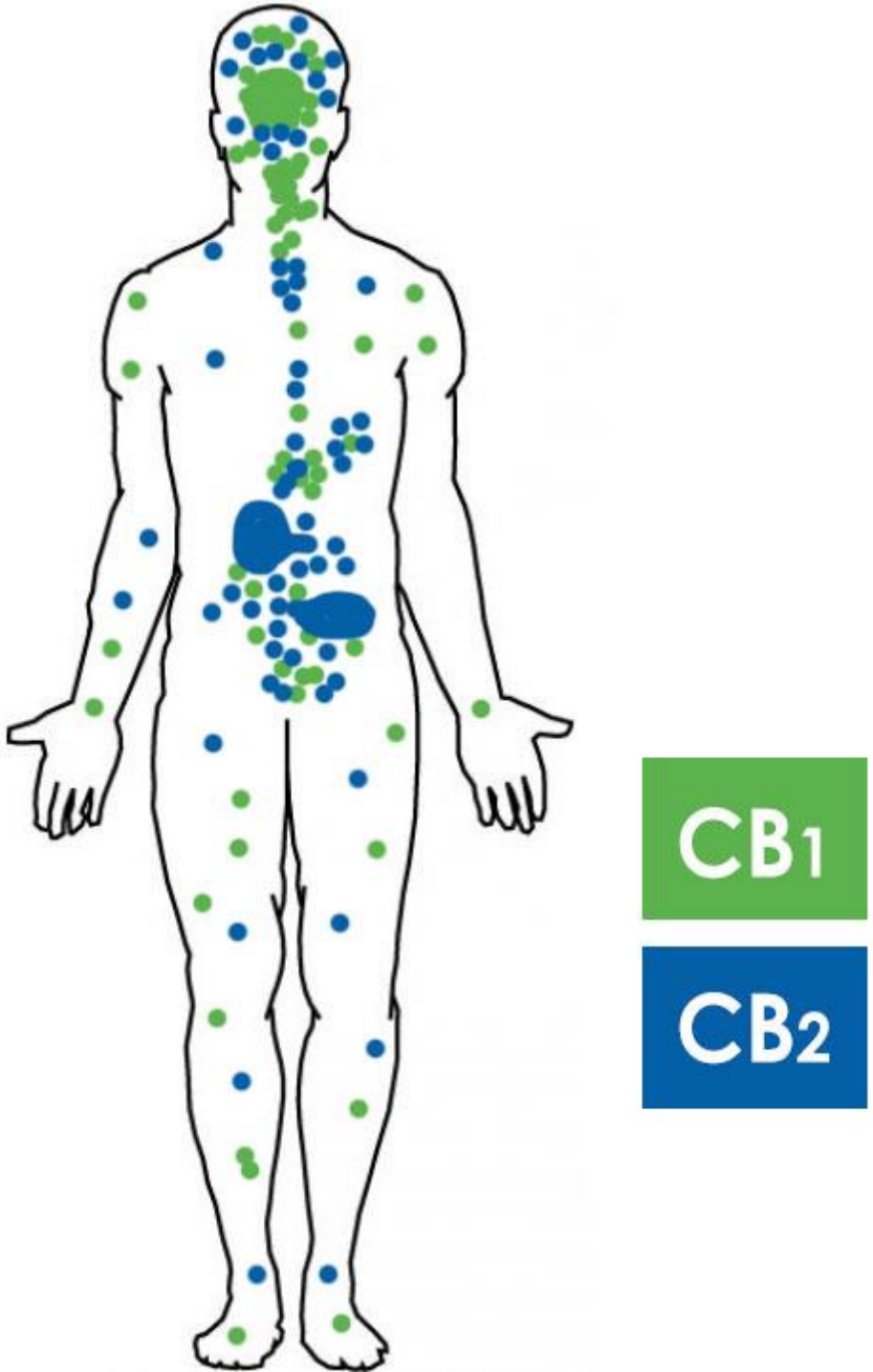
ENDOCANNABINOID SYSTEM

ENDOCANNABINOID SYSTEM



CB1/CB2 RECEPTOR DISTRIBUTION

- CB1: mainly in CNS and PNS
- CB2: Mainly in immune cells
- Organs: varied distribution of both



EXOGENOUS CANNABINOIDS: SYNTHETIC VS. PLANT BASED

- Whole plant vs. single molecule cannabinoids (Cesemet;nabilone) = ENDLESS COMBINATIONS
- 500 distinct compounds within the cannabis plant
  - 100+ phytocannabinoids ; THC and CBD being the predominant
  - Turpenes, flavonoids and other products
- Poly-Phytocannabinoid + Poly-terpenoid **"entourage effect"**
- A, B, C
- A, A+B, A+C, A+B+C, B, B+A, B+C…….

PHARMACOLOGIC EFFECTS OF CANNABINOIDS

Analgesic

Antispasmodic

Anti-anorectic

Antiemetic

Anti-cancer

Anti-proliferative
Anti-metastatic
Anti-angiogenesis

Antioxidant

Antibacterial

Antifungal

Antiparasitic

Anti-inflammatory

Immunosuppressive

Anti-host vs. graft

Neuroprotectant

Dermatologic

Anti-psoriatic

Anti-eczema

Anti-keratotic

Anti-pruritic

UV light reducing

Intestinal anti-prokinetic

Bronchodilatory
Anti-glaucoma
Anti-diabetic
Bone-stimulant
Anxiolytic
Antipsychotic
Antidepressant
Vasorelaxant
Anti-ischemic
Anticonvulsant

Anxiety

Changes in visual perceptions

Decreased sperm count

Slowed pupillary response to light

Reduced tear flow

Dry mouth

(and possibly associated caries and periodontitis)

Sedation

Altered sense of time

Reduced coordination

Decreased eye blink rate

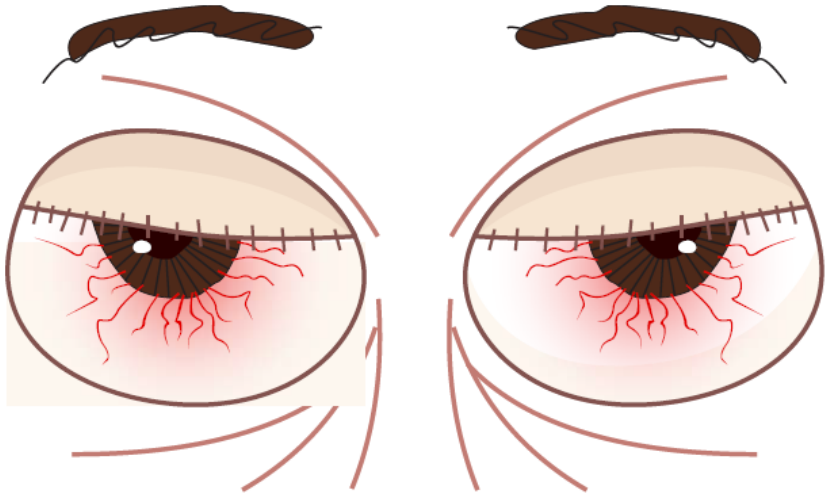
Ataxia

Bronchitis

Cough

Dizziness

Dysphoria



Reddened eyes

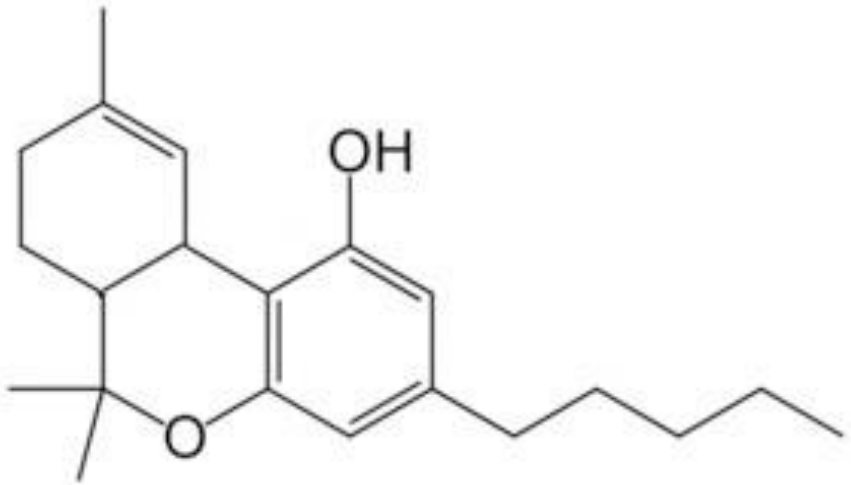
(Ashton 1999, Hall and Solowij 1998, Handbook on Cannabis 2015)

TETRAHYDROCANNABINOL (THC)

- Principal psychoactive compound
- Medicinal Effects
  - Analgesic
  - Anti-inflammatory
  - Antiemetic
  - Antispasmodic
  - Sedation

MECHANISM

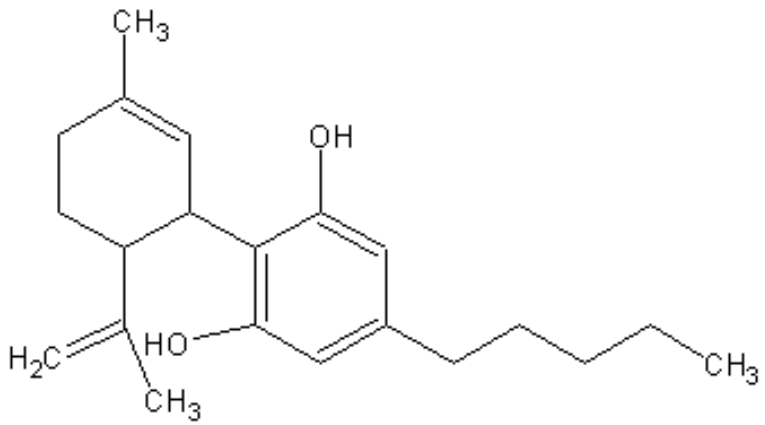
- Binds CB1 and CB2 receptors



CANNABIDIOL (CBD)

- Considered to have more medicinal application than THC - FALSE
- Minimal psychoactive effect
- Antidepressant, anxiolysis
  - Analgesia, anti-inflammatory
- Anti-psychotic, antiepileptic

- MECHANISM:
- CBD is a weak antagonist of CB1 receptors (which may be associated with its analgesic properties)
- CBD is a strong negative allosteric modulator of the CB1 receptor (substantially attenuates psychoactive psychotic activity of THC – of course in the situation which they are administered together, but generally this property might be linked antipsychotic and sedative effects of cannabidiol
- CBD is a weak inverse agonist of the CB2 receptor (which is associated with its anti-inflammatory properties),
- CBD is an inhibitor of fatty acid amides hydrolase (slowing down the decomposition of anandamide)
- CBD is an anandamide reuptake inhibitor (keeps its concentration in the synapses at a high level)



Cannabidiol

TOLERANCE

- Secondary to CB1 downregulation from THC
- Could appear after few doses; however, rapidly dissipates after withdrawal
- Dose dependent

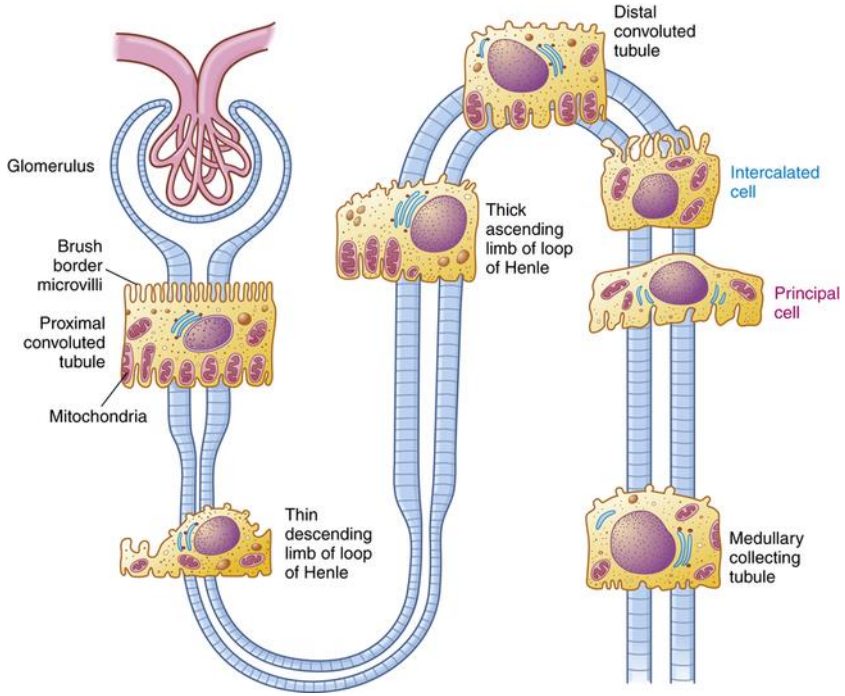
DEPENDENCE

- Dependence
  - 9% lifetime prevalence of cannabis dependence among those who ever used cannabis
  - 17% in those who started as teenagers
  - 25-50% in chronic daily users
- Physical Dependence (physical withdrawal)
  - appear at day 1-2, peak effects between days 2 and 6, resolve within 1-2 weeks
- No Good treatment; Some promise with Sativex (nabiximol oral mucosal spray 1:1 CBD:THC)

ENDOCANNABINOIDS AND THE KIDNEY

DISTIBUTION OF CB1/CB2 RECEPTORS

Renal Location	CB1/CB2
Glomeruli	CB1/CB2
Proximal Convoluted Tubules	CB1/CB2
Distal Convoluted Tubules	CB1
Intercalated cells	CB1
Thick Ascending loop of Henle	CB1
Podocytes	CB1/CB2
Mesangial Cells	CB1/CB2

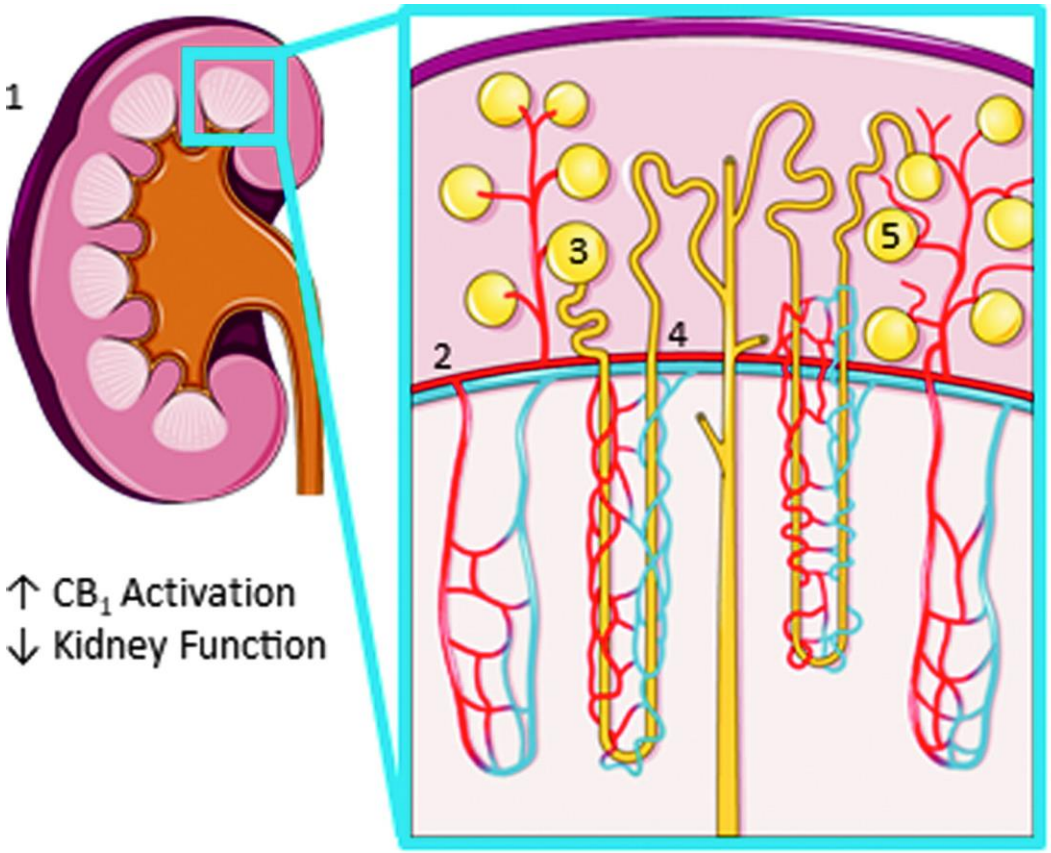


Chua et al. (2019, March). **Endocannabinoid System and the Kidneys: From Renal Physiology to Injury and Disease** .https://www.liebertpub.com/doi/full/10.1089/can.2018.0060

ENDOCANNABINOID AND THE KIDNEY

CB1 receptor activation can lead to progression

CB2 receptor activation has protective properties



# - Structure	Receptor	Ligand	Physiological Effect	Source
1 – Kidney	CB_1	AEA	↑ Oxidative & Nitrosative Stress Markers ↑ Apoptosis ↑ Inflammation	35
2 – Juxta-medullary afferent and efferent arterioles	CB_1	AEA	↑ Vasodilation	17, 31
3 – Glomerular blood vessels	?	AEA	↑ Blood Flow ↓ Filtration Rate	17
4 – Thick ascending Loop of Henle	CB_1	AEA	↑ NO_2 Production ↓ Na^+ Transport	18
5 – Podocytes and mesangial cells	CB_1	WIN 55 212-2	↑ Urinary Protein Excretion ↑ VEGF Expression ↓ Nephrin Expression & Levels	40

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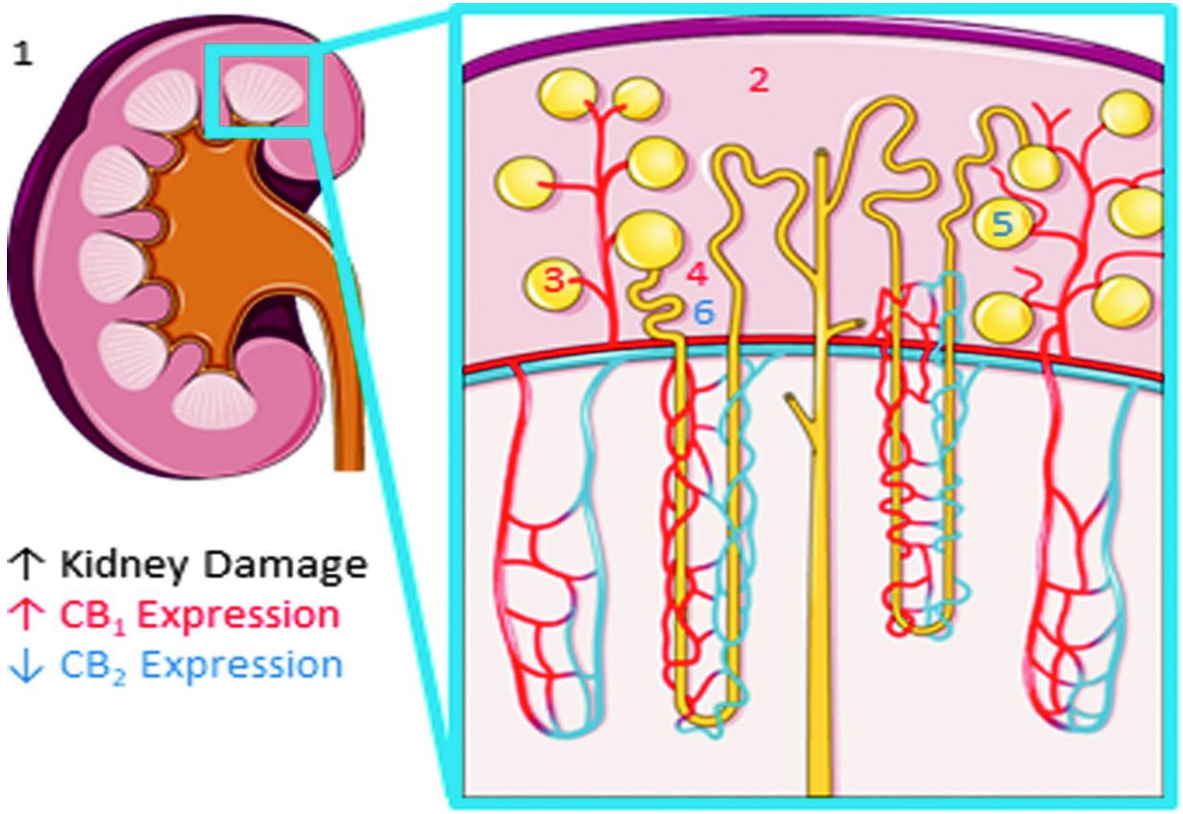


# - Structure	Insult	Pathological Effect ↑	Source
1 – Kidney	Primary/ Secondary Hypertension	↑ AEA ↑ 2AG	72
1 – Kidney	Bilateral ischemia reperfusion model of AKI	↑ 2AG	73
1 – Kidney	Cisplatin – induced AKI	↑ AEA	35
2 – Renal cortex	UUO Model of Renal Fibrosis	↑ CB_1 Expression ↑ 2AG	20
3 – Podocytes and mesangial cells	Diabetic Nephropathy	↑ CB_1 Expression	19, 30
3 – Mesangial cells	Increased Glucose	↑ CB_1 Expression	30
4 – Proximal tubule cells	Increased Albumin	↑ CB_1 Expression	15
5 – Podocytes	STZ-induced Diabetic Nephropathy	↓ CB_2 Expression	48
6 – Proximal tubule cells	Increased Glucose or Albumin	↓ CB_2 Expression	34

Chua et al. (2019, March). **Endocannabinoid System and the Kidneys: From Renal Physiology to Injury and Disease**
.https://www.liebertpub.com/doi/full/10.1089/can.2018.0060

RISK OF CKD PROGRESSION

- ASSESS-AKI post-hoc analysis
  - Mean annual rate of decline in eGFR was 3.22 mL/min/1.73 m^2 in patients whose eGFR <60 compared to -1.4 mL/min/1.73 m^2 per year
    - Cannabis consumers were more likely to be younger (mean age, 54 vs. 65 years), white (78%), men (78%) and heavy tobacco users, which was defined as smoking 20 or more cigarettes per day (26% vs. 8%).
    - No incident CKD or albuminuria
- Cardia Cohort Trial (Baseline eGFR 111)
  - Compared with no use, daily current use and ≥5 marijuana-years of cumulative use were associated with lower $eGFR_{cys}$ at year 10: −4.5% (95% confidence interval, −8.1 to −0.7%; *P*=0.02) and −3.0% (95% confidence interval, −5.6 to −0.4%; *P*=0.03), respectively.
  - Marijuana use was not significantly associated with $eGFR_{cys}$ change, rapid $eGFR_{cys}$ decline, or prevalent albuminuria.

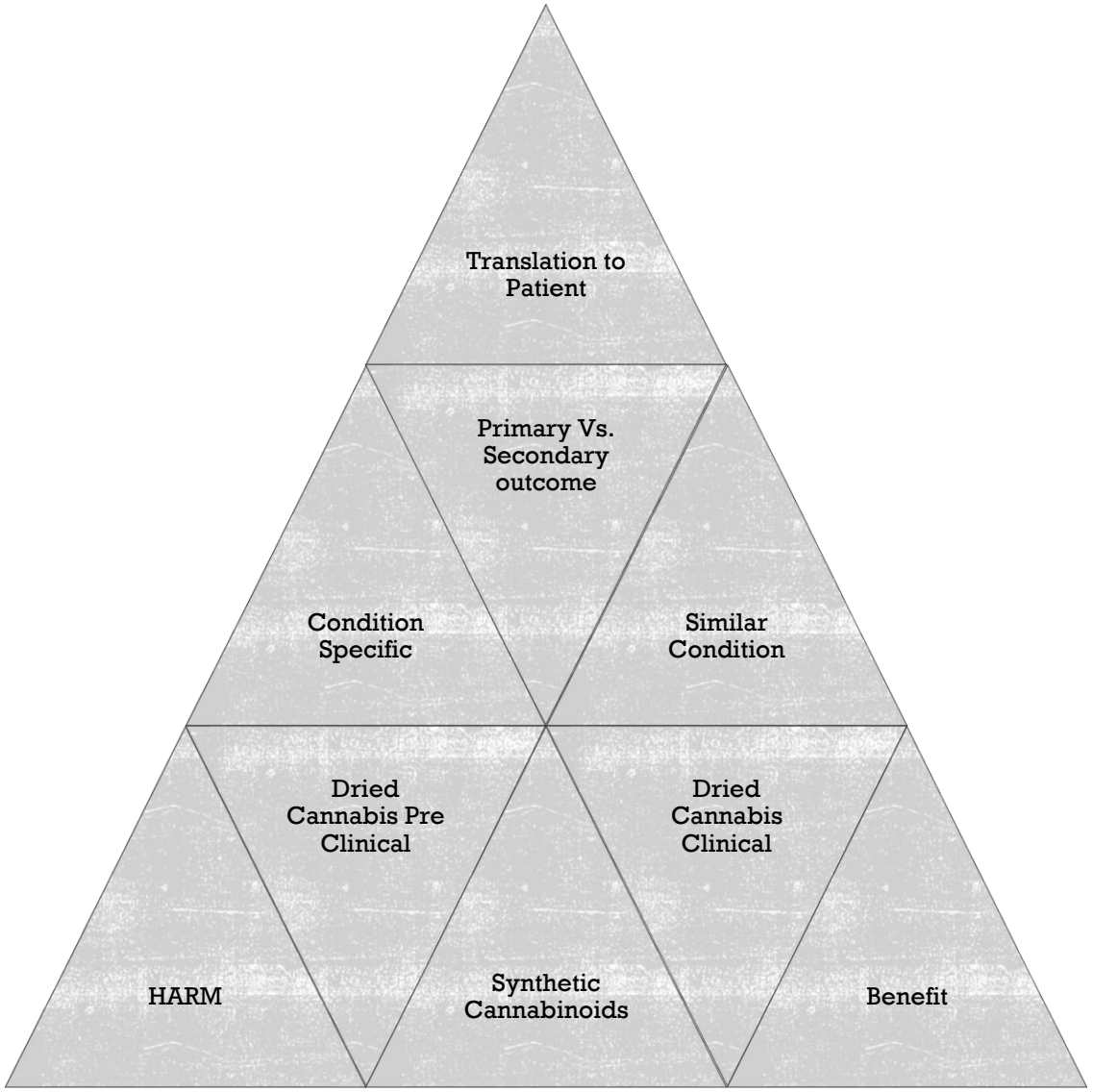
UNDERSTANDING THE EVIDENCE

PUBMED search Sept 26th, 2019

Medical Cannabis: 7500

Cannabis: 20,600

UNDERSTANDING THE EVIDENCE



Every Patient is a Trial of 1 (N=1)

1. Evidence for conventional therapy is weak
2. Evidence for medical cannabis/potential benefit>Harm of medical cannabis
3. Risk of medical cannabis < risk of conventional therapy

CONDITIONS SPECIFIC TO CKD

- Chronic pain
- Insomnia
- Nausea and vomiting
- Anorexia
- Anxiety/Depression
- Pruitis

UNDERSTANDING THE EVIDENCE: PAIN

	Sativex	Drobanilol	Nabilone	Dried Cannabis (smoked/vaporized/oral)
Neuropathic	Good pain and sleep response in Peripheral neuropathy	Good pain response; MS associated central pain	Good pain response; Diabetic neuropathy and HIV associated neuropathy	Good pain response; DM, MS, HIV, CRPS, spinal cord injury, post surgical, post-herpetic neuralgia
General Non-Cancer pain	Good pain relief	Not-Completed	Not-Completed	Good pain response; Fibromyalgia, MSK, arthritis, sickle cell
Fibromyalgia	Not-Completed	Decreased pain perception, decreased depression and decreased use of other analgesics; NSAIDs, opiates, anti-convulsants and depressants	Decreased pain, anxiety, Improved sleep	Pain improvement not statistically sig, improved sleep, improved overall QOL, but slight worsening in MH status
Osteoarthritis	Not-Completed	Not-Completed	Not-Completed	MMAR still allows approval
Rheumatoid Arthritis	Improved pain, sleep and QOL	Not-Completed	Not-Completed	Not-Completed

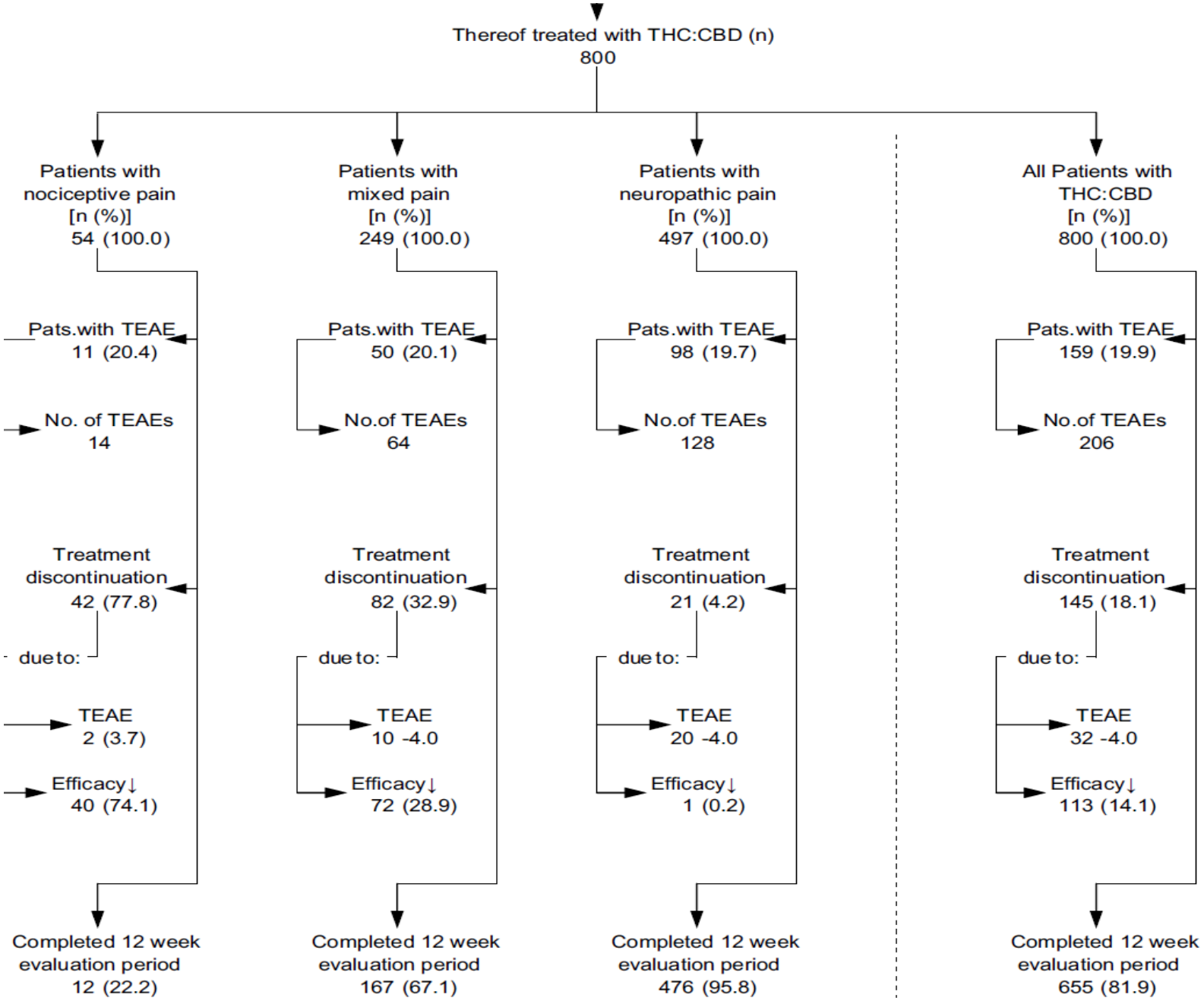
Key Points:

1) Initial studies in synthetic cannabinoids
2) Plant derived cannabinoids studies mainly in THC
3) Most improvement in neuropathic pain

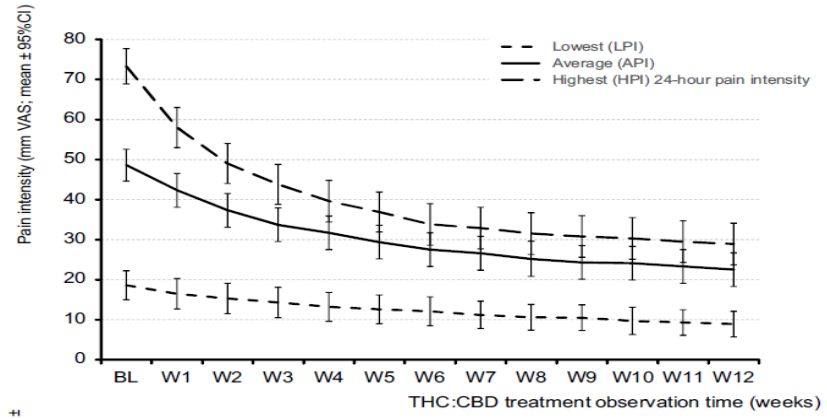
Effectiveness and tolerability of THC:CBD oromucosal spray as add-on measure in patients with severe chronic pain: analysis of 12-week open-label real-world data provided by the German Pain e-Registry

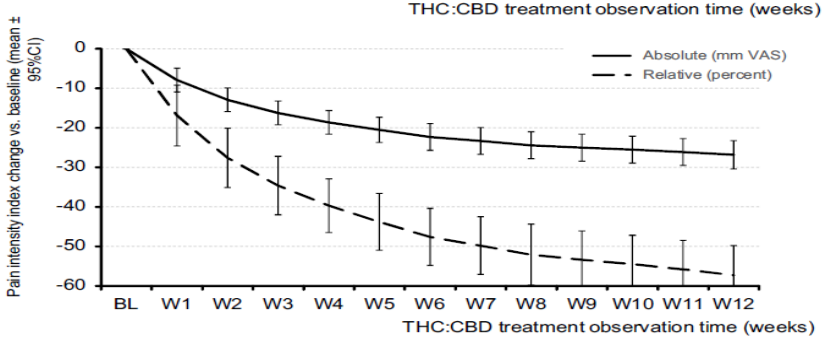
Michael A Ueberall[1]
Ute Essner[2]
Gerhard HH Mueller-Schwefe[3]

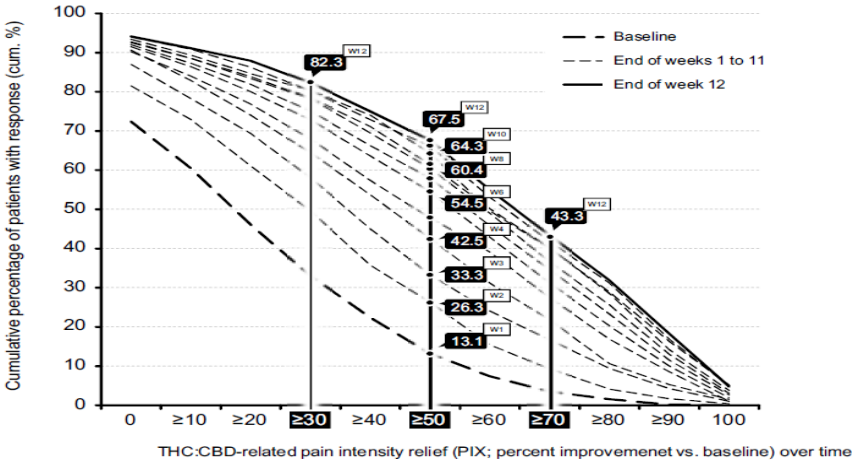
Journal of Pain Research. 2019

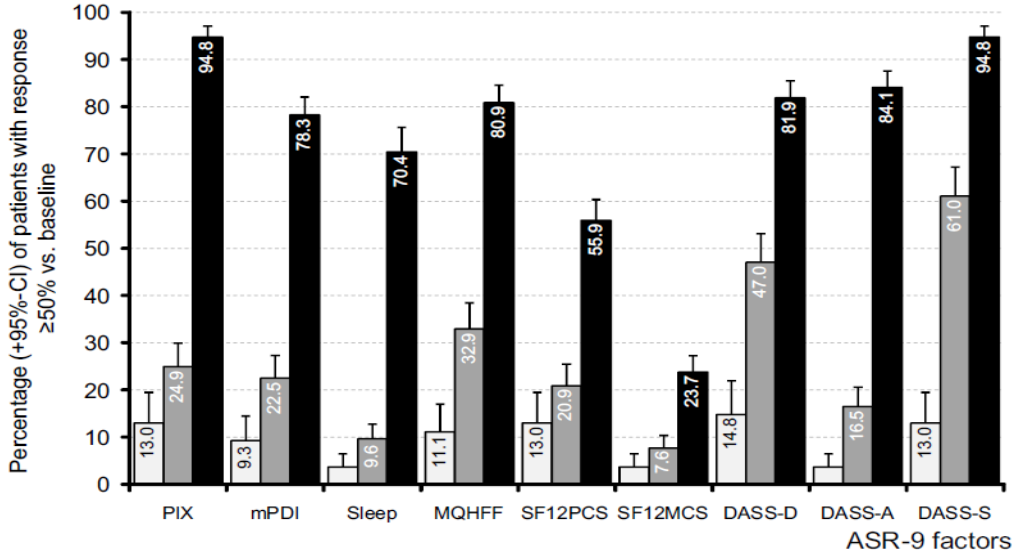


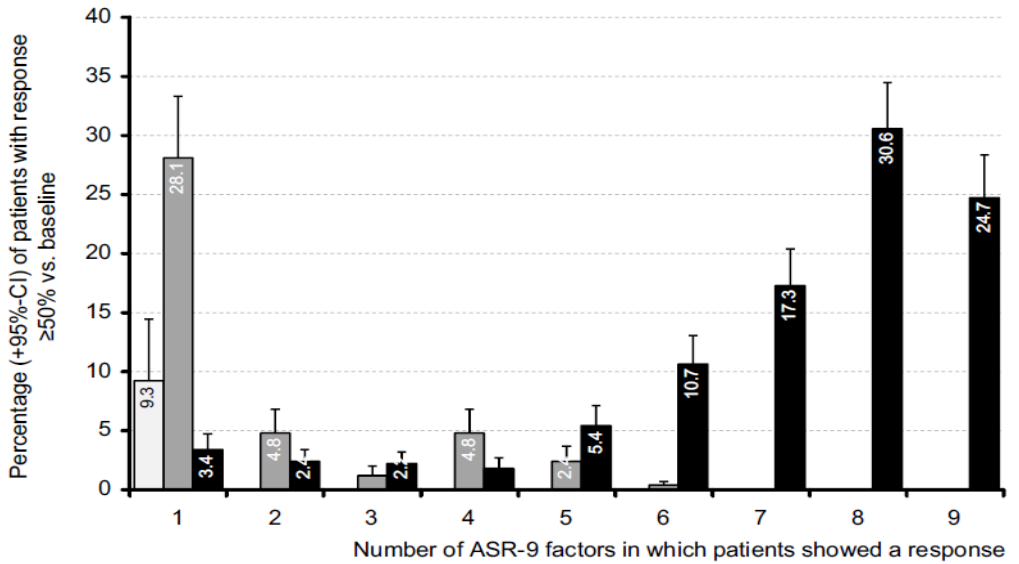
Journal of Pain Research. 2019











□Nociceptive pain (n=54) ▩Mixed pain (n=249) ■Neuropathic pain (n=497)

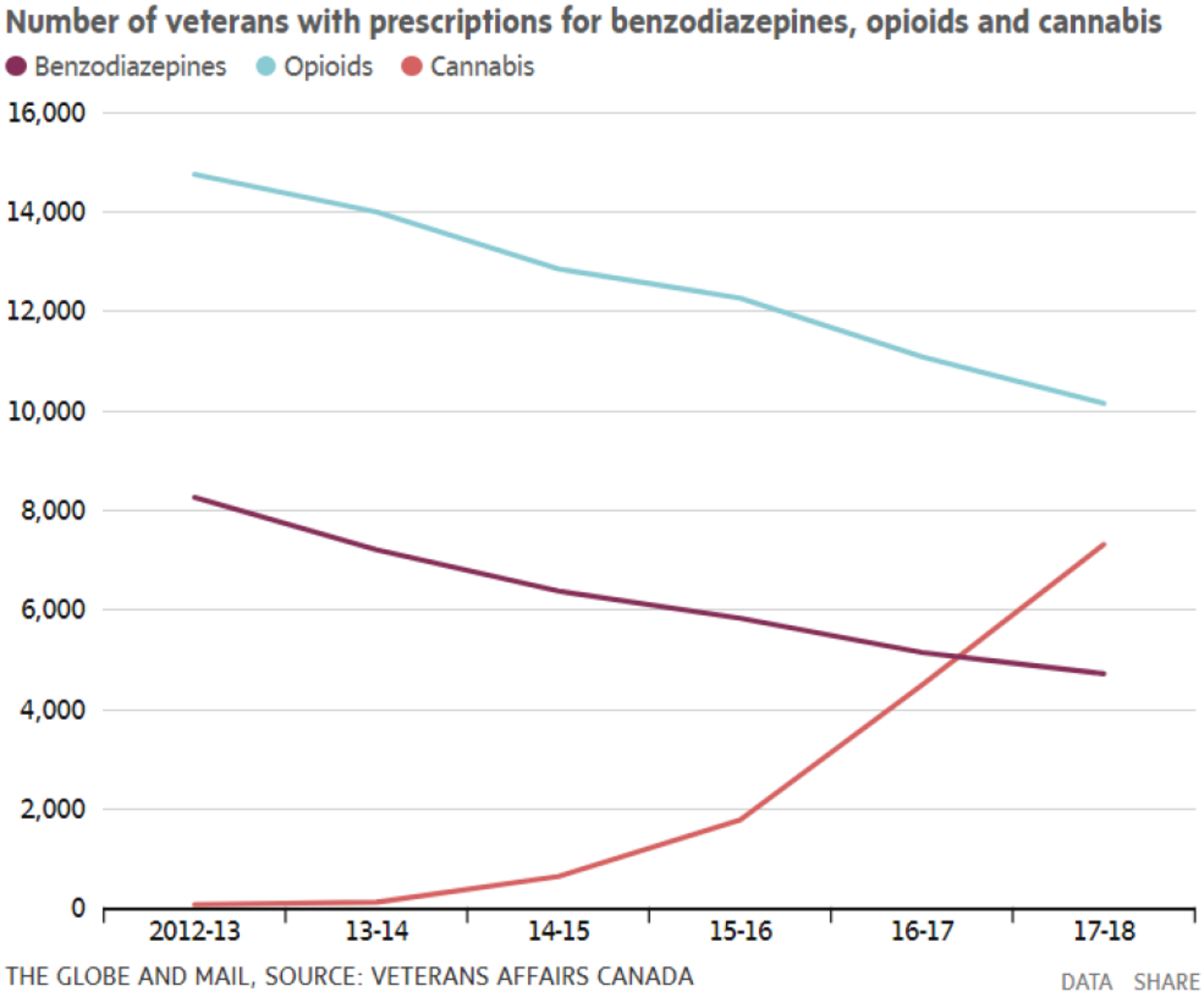
Table 3 Summary of analgesic medications taken at baseline (ie, before) and at the end of the 12-week observation period with THC:CBD

	Nociceptive pain (n=54)			Mixed pain (n=249)			Neuropathic pain (n=497)			All patients (n=800)			
Maintenance analgesic treatment with	**Baseline**	**Week 12**	**Δ (W12→BL)**	**Baseline**	**Week 12**	**Δ (W12→BL)**	**Baseline**	**Week 12**	**Δ (W12→BL)**	**Baseline**	**Week 12**	**Δ (W12→BL)**	**Significance**
…non-opioid analgesics [n (%)]	32(59.3)	32(59.3)	0(0.0)	101(40.6)	95(38.2)	-6(-5.9)	105(21.1)	73(14.7)	-32(-30.5)	238(29.8)	200 (25.0)	-38(-16)	p=0.033
… nsaids [n (%)]	34(63.0)	34(63.0)	0(0.0)	157(63.1)	144 (57.8)	-13(-8.3)	110(22.1)	97(19.5)	-13(-11.8)	301(37.6)	275 (34.4)	-26(-8.6)	p=0.176
…mild opioids [n (%)]	16(29.6)	17(31.5)	1(2.6)	71(28.5)	63(25.3)	-8(-11.3)	42(8.5)	35(7.0)	-7(-16.7)	129(16.1)	115 (14.4)	-14(-10.9)	p=0.330
…strong opioid analgesics [n (%)]	27(50.0)	32(59.3)	5(18.5)	178(71.5)	159 (63.9)	-19(-10.7)	487(98.0)	381 (76.7)	-106(-21.8)	692(86.5)	572 (71.5)	-120(-17.3)	p<0.001
…antidepressants [n (%)]	21(38.9)	24(44.4)	3(9.1)	91(36.5)	88(35.3)	-3(-3.3)	291(58.6)	252 (50.7)	-39(-13.4)	403(50.4)	364 (45.5)	-39(-9.7)	p=0.051
…anticonvulsants [n (%)]	5(9.3)	5(9.3)	0(0.0)	100(40.2)	97(39.0)	-3(-3.0)	312(62.8)	285 (57.3)	-27(-8.7)	417(52.1)	387 (48.4)	-30(-7.2)	p=0.008
…others [n (%)]	9(16.7)	9(16.7)	0(0.0)	51(20.5)	50(20.1)	-1(-2.0)	308(62.0)	261 (52.5)	-47(-15.3)	368(46.0)	320 (40.0)	-48(-13)	p=0.015
…none [n (%)]	0(0.0)	0(0.0)	0(0.0)	0(0.0)	7(2.8)	7(2.8)	0(0.0)	7(1.4)	7(1.4)	0(0.0)	14(1.8)	14(1.8)	p<0.001

Table 3 (Continued).

	Nociceptive pain (n=54)			Mixed pain (n=249)			Neuropathic pain (n=497)			All patients (n=800)			
Maintenance analgesic treatment with	**Baseline**	**Week 12**	**Δ (W12→BL)**	**Baseline**	**Week 12**	**Δ (W12→BL)**	**Baseline**	**Week 12**	**Δ (W12→BL)**	**Baseline**	**Week 12**	**Δ (W12→BL)**	**Significance**
…decrease [n (%)]	5(9.3)			48(19.3)			232(46.7)			285(35.6)			
Significance	p=0.353			p=0.043			p<0.001			p<0.001			
Analgesic rescue medication with	**Baseline**	**Week 12**	**Δ (W12→BL)**	**Baseline**	**Week 12**	**Δ (W12→BL)**	**Baseline**	**Week 12**	**Δ (W12→BL)**	**Baseline**	**Week 12**	**Δ (W12→BL)**	**Significance**
…non-opioid analgesics [n (%)]	10(18.5)	10(18.5)	0(0.0)	54(21.7)	43(17.3)	-11(-20.4)	123(24.7)	57(11.5)	-66(-53.7)	187(23.4)	110 (13.8)	-77(-41.2)	p<0.001
… nsaids [n (%)]	24(44.4)	24(44.4)	0(0.0)	134(53.8)	112(45)	-22(-16.4)	309(62.2)	138 (27.8)	-171(-55.3)	467(58.4)	274 (34.3)	-193(-41.3)	p<0.001
…mild opioids [n (%)]	13(24.1)	15(27.8)	2(4.9)	74(29.7)	46(18.5)	-28(-37.8)	174(35)	101 (20.3)	-73(-42)	261(32.6)	162 (20.3)	-99(-37.9)	p<0.001
…strong opioid analgesics [n (%)]	5(9.3)	14(25.9)	9(18.4)	36(14.5)	31(12.4)	-5(-13.9)	111(22.3)	64(12.9)	-47(-42.3)	152(19)	109 (13.6)	-43(-28.3)	p=0.004
…others [n (%)]	3(5.6)	7(13)	4(7.8)	18(7.2)	17(6.8)	-1(-5.6)	44(8.9)	39(7.8)	-5(-11.4)	65(8.1)	63(7.9)	-2(-3.1)	p=0.854
…none [n (%)]	14(25.9)	13(24.1)	-1(-7.1)	58(23.3)	102 (41.0)	44(23)	77(15.5)	212 (42.7)	135(32.1)	149(18.6)	327 (40.9)	178(27.3)	p<0.001
Number of rescue analgesic [mean±SD (median)]	1.0 ± 0.8 (1)	1.3 ± 1.0 (1)		1.3 ± 0.9 (1)	1.0 ± 1.0 (1)		1.5 ± 0.9 (2)	0.8 ± 0.8 (1)		1.4 ± 0.9 (2)	0.9 ± 0.9 (1)	-0.5 ± 0.7 (0)	
Difference W12→BL [mean±SD (median)]	0.3 ± 0.6 (0)			-0.3 ± 0.5 (0)			-0.7 ± 0.7 (-1)			-0.5 ± 0.7 (0)			
Demand of rescue analgesics: 0 [n (%)]	14(25.9)	13(24.1)		58(23.3)	102 (41.0)		77(15.5)	212 (42.7)		149(18.6)	327 (40.9)		
1 [n (%)]	26(48.1)	19(35.2)		86(34.5)	70(28.1)		126(25.4)	181 (36.4)		238(29.8)	270 (33.8)		
2 [n (%)]	13(24.1)	15(27.8)		85(34.1)	52(20.9)		247(49.7)	94(18.9)		345(43.1)	161 (20.1)		
3 [n (%)]	1(1.9)	7(13.0)		20(8.0)	25(10.0)		47(9.5)	10(2.0)		68(8.5)	42(5.3)		
Patients with …increase [n (%)]	18(33.3)			9(3.6)			0(0.0)			27(3.4)			
…no change [n (%)]	33(61.1)			164(65.9)			193(38.8)			390(48.8)			
…decrease [n (%)]	3(5.6)			76(30.5)			304(61.2)			383(47.9)			
Significance	p=0.104			p=0.002			p<0.001			p<0.001			

Abbreviations: Δ, difference (delta); W12, week 12; BL, baseline.



Vetrans Affairs Canada

- 43% decrease in benzodiazepine
- 31% decrease in opiate use

Hager. 2018

INSMONIA

- The endogenous cannabinoid neurotransmitter system in our brain is not directly involved in the onset or maintenance of normal sleep cycles.
- Human trials*
  - Low dose THC decreases sleep latency, increases slow wave sleep (NREM), decreases REM sleep
  - High dose THC disturbs both NREM and REM
  - Consequences; risk for obesity, significant memory problems and mood disorders.
- Benefits:
  - The effect on sleep was measured as a secondary outcome in most studies of plant based cannabis/synthetic cannabis

*Shierenbeck et al. (2008, Oct) **Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. Sleep Medicine Review**

UREMIC PRUITIS

- Physiology
  - Immunohypothesis (T-cell mediated) + Opioid receptor imbalance (Higher Mu activation and lower Kappa activation)
  - Cannabis modulates Mu receptors as well as immunogenic response
- Studies
  - CB1/CB2 receptor agonist HU-210 (similar to nabilone); experimentally induced histamine related pruitis[1]
  - Pyoderma Gangrenosum: 3 patient case-series in CBD:THC 7mg/mL:7mg/mL[2]
  - N-acetylethanolamine and N-palmitoylethanolamine in the form of a topical cream (Physiogel AI cream®) applied twice daily for 3 weeks effectively reduced both pruritus and xerosis.84 Pruritus and xerosis were completely eliminated in 38.1% and 81% of patients, respectively[3]

1. Dvorak M et al. (2003). Histamine induced responses are attenuated by a cannabinoid receptor agonist in human skin. Inflamm Res.
2. Maida V et al. (2017, Nov)Topical medical cannabis: A new treatment for wound pain-three cases of pyoderma gangrenosum. J Pain Symptom Managemenet.
3. Szepietowski JC et al. (2005). Efficacy and tolerance of cream containing structured physiological lipids with endocannabinoids in the treatment of uremic pruritus: a preliminary study. Acta Dermatovenerol Croat.

NAUSEA/VOMITTING

- Evidence derived from chemotherapy induced nausea/vomiting in moderate emetogenic chemotherapy regimens
  - Nabilone/Drobanilol found non-inferior to prochlorperazine, ondansetron [1]
  - Sativex (plant derived 1:1 CBD:THC) showed benefit in refractory cases [2]
  - 2 small studies in smoked THC based cannabis showed non-inferiority [3]

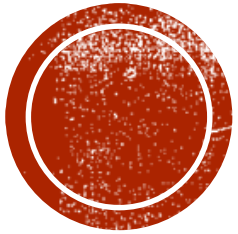
  - Interesting; anticipatory nausea improved with synthetic and plant derived cannabis more so than conventional therapy

1. Smith LA et al. (2015) Cannabinoids for nausea and vomiting in adults with cancer receiving chemotherapy. Cochrane Databaes Syst Rev
2. Duran M et al. (2010) Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. Br J Clin Pharmacol.
3. Chang AEet al. (1979)Delta-9- tetrahydrocannabinol as an antiemetic in cancer patients receiving high-dose methotrexate; a prospective, randomized evaluation. Ann Intern Med.

APPETITE STIMULATION

- THC induces appetite by activating CB1 receptors
  - centrally for homeostatic regulation of feeding
  - peripherally to signal the nutritional state of the gut
- Evidence derived from HIV associated wasting syndrome [1]
  - 40 patients, 3.9%THC inhaled; dose dependent increase in weight/caloric intake
- Cancer related anorexia-cachexia [2]
  - 234 patient trial, 2.5 mg oral THC showed no improvement in QOL or appetite
- Uremic related anorexia-cachexia
  - Not studies

1. Haney M et al. (2005) Dronabinol and marijuana in HIV+ marijuana smokers: acute effects on caloric intake and mood. Psychopharmacology
2. Strasser F et al. (2006) Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, doubleblind, placebo-controlled clinical trial from the cannabis-incachexia-study group. J Clin Oncol



DRUG INTERACTIONS

DRUG INTERACTIONS

- THC and CBD are metabolized by CYP3A4 and CYP2C9 (Yamaori et al 2012, Watanabe et al 2007).
  - CYP3A4 inhibitors slightly increase THC levels.
  - CYP3A4 inducers slightly decrease THC and CBD levels.
  - CBD, but not THC, is metabolized by CYP2C19 (Stout and Cimino 2014).

DRUG INTERACTIONS

- THC is a CYP1A2 inducer
  - ***Theoretically***, THC can decrease serum concentrations of *clozapine, duloxetine, naproxen, cyclobenzaprine, olanzapine, haloperidol, and chlorpromazine (*Flockhart 2007, Watanabe et al 2007).
- CBD is an inhibitor of the CYP1A2
  - Overall effect is minimal and not clinically relevant at the doses prescribed (Yamaori et al. 2010)
- CBD inhibitor of CYP2A19
  - ***Theoretically***, CBD can increase serum concentrations of *lansoprazole, omeprazole, pantoprazole, diazepam, phenytoin, phenobarbitone, amitriptyline, carisoprodol, citalopram, clomipramine, clopidogrel, cyclophosphamide, imipramine, labetalol, proguanil, voriconazole*

CYP3A4 PATHWAY

- CBD is a potent inhibitor of CYP3A4 and CYP2D6.
  - As CYP3A4 metabolizes about a quarter of all drugs, CBD ***may*** increase serum concentrations of *macrolides, calcium channel blockers, benzodiazepines, cyclosporine, sildenafil (and other PDE5 inhibitors), antihistamines, haloperidol, antiretrovirals, and some statins (atorvastatin and simvastatin, but not pravastatin or rosuvastatin).*
  - CYP2D6 metabolizes many antidepressants, so CBD ***may*** increase serum concentrations of *SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids (including codeine and oxycodone).*
    - In a small study, cannabis did not have additive CNS effects when combined with opioids (Abrams et al 2011).

CYP3A4 PATHWAY AND THC/CBD: CLINICAL STUDIES

- In-vitro studies shows minimal interaction with THC/CBD

- Indinavir/Nelfinavir: Oral THC (2.5 mg 3 times daily) or inhaled cannabis (up to 1 joint 3 times daily, with each joint containing ~35 mg of THC)
  - Minor decreases (<15% reduction) were seen

- Irinotecan/docetaxel: 2 weeks of daily high-THC cannabis did not significantly change levels of the CYP3A substrates irinotecan or docetaxel. (Engels et al. 2007)

- Tacrolomis/Cyclosporine: CBD (50-100 mg/day oral)
  - No clear effect on Tacrolimus. No significant effect on cyclosporine (Cunetti et al. 2018)

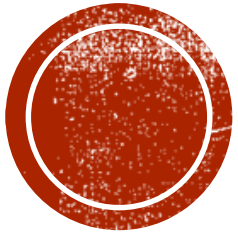
SPECIFIC MEDICATIONS

- Warfarin
  - THC and CBD increase warfarin levels (Yamaori et al 2012). Frequent cannabis use has been associated with increased INR.
- Clobazam
  - CBD (20-25 mg/kg/day oral) increased N-CLB levels 5-fold (Geffery et al. 2015)
  - CBD (5-50mg/kg/day oral) increased N-CLB (Gaston et al. 2017)
  - CBD (5+ mg/kg/day oral) increased N-CLB levels about 2-fold (Devinsky et al. 2018)
- DOAC
  - Apixiban 50% hepatic metabolism CYP3A4
  - Rivaroxaban 33-50% metabolized CYP3A4

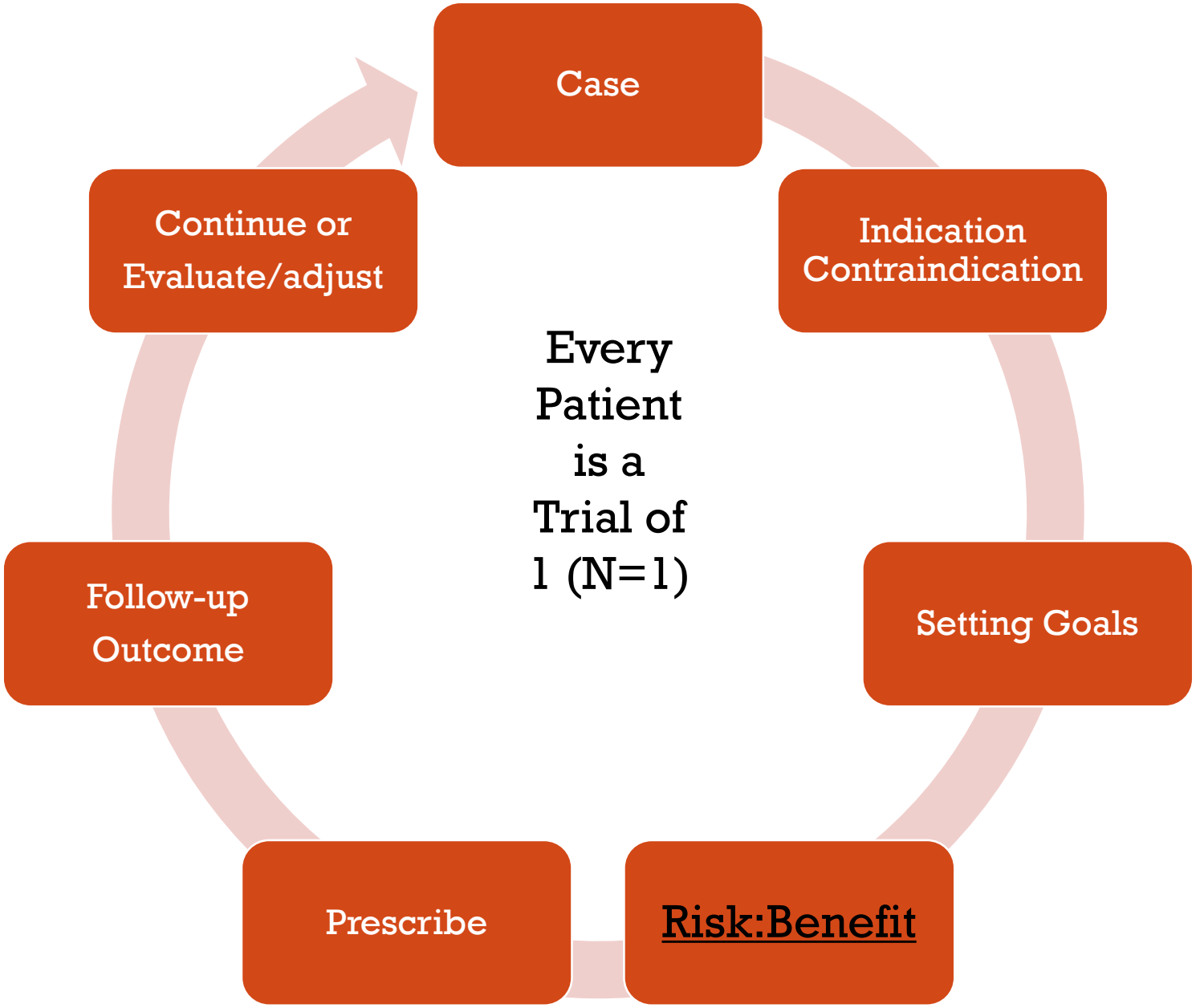
DRUG INTERACTION SUMMARY

CBD more *potential/theoretical* drug interactions

THC less drug interaction, but more cannabis specific side-effects



MY PRACTICAL APPROACH

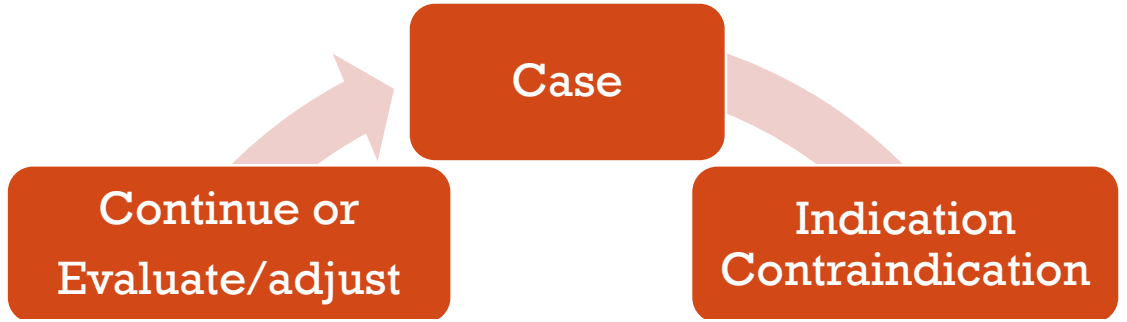


Risk:Benefits

1. Evidence for conventional therapy is weak
2. Evidence for medical cannabis/potential benefit>Harm of medical cannabis
3. Risk of medical cannabis < risk of conventional therapy

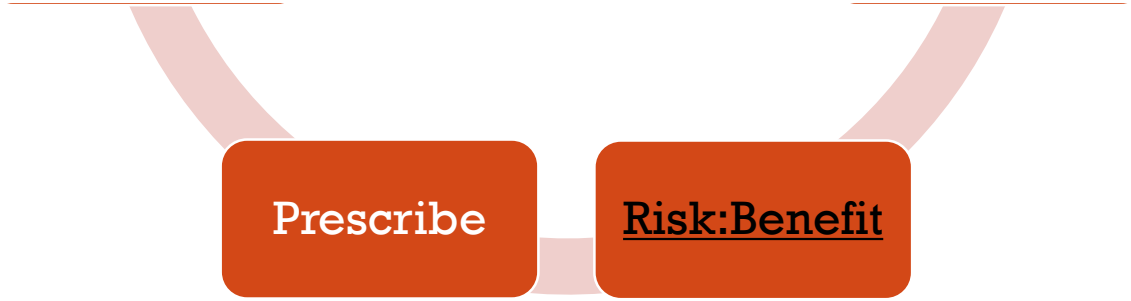
CASE

- 47 Y.O. Male post MVA with chronic traumatic pain in his cervical spine with no neuropathic component
- Other issues: Anxiety, insomnia
- PMHX: Diabetes, MI with PCI, HTN, Dyslipidemia, CKD stage III (eGFR47)
- Current meds: tramacet, lorazepam, bisoprolol, ramipril, atorvastatin, Aspirin
- Occupation: Disability
- Pain: Past therapy; acetaminophen(paracetamol), Naproxen, codeine, physio, chiro, Massage
- Insomnia: Past therapy; melatonin, trazodone, zoplicone
- Anxiety: counselling

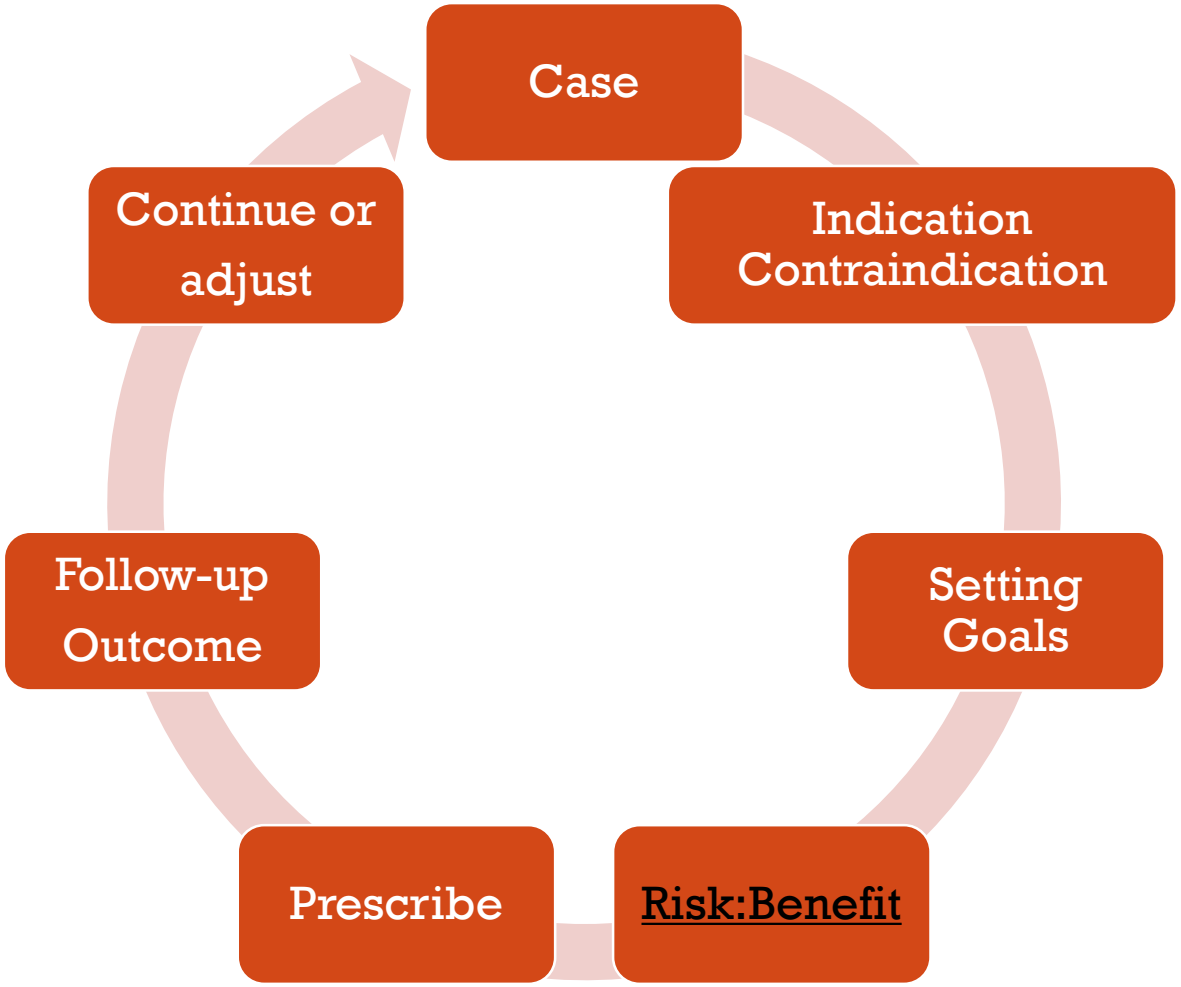


Contraindications:

Pregnant, breastfeeding, cannabis use disorder, active cardiac disease, concurrent medications, active psychosis, Occupation



CASE



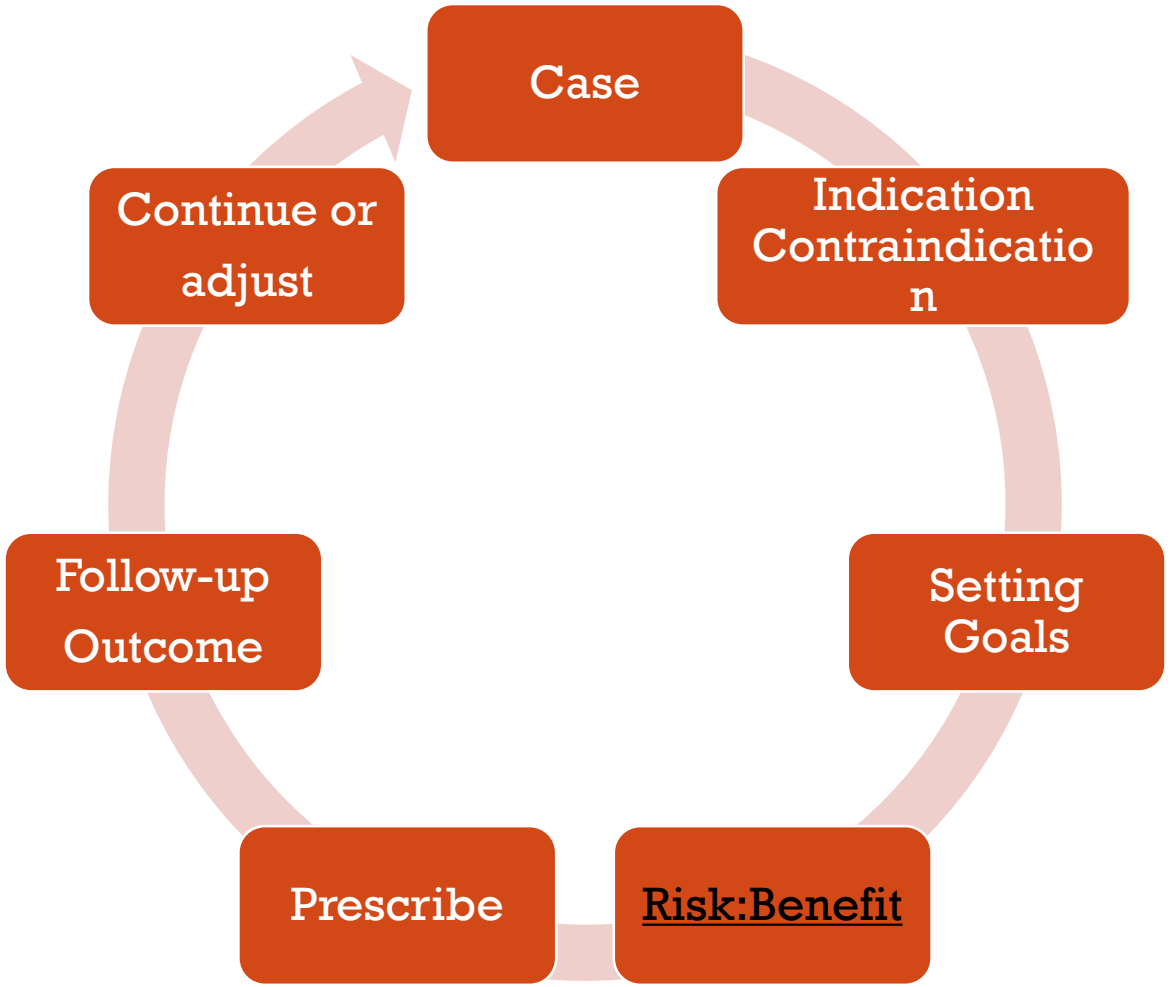
Primary condition: Pain
Secondary Condition: Insomnia
Age >25
No contraindications
Failed Conventional therapy for pain and insomnia.

Goals:

1. Reduce background pain during day and night
2. Reduce episodes of acute pain with certain activities
3. Getting to sleep and staying asleep
4. Decreasing/stopping tramacet/lorazepam

Every Patient is a Trial of 1
(N=1)

CASE



- Patient specific considerations

1. Comorbidities
   1. Anxiety
   2. Coronary artery disease
   3. CKD
2. Medication interactions
   1. CBD could potentially interact with lorazepam, BB, atorvastatin - MINIMAL
3. Cardiac Disease
   1. THC can contribute to enhanced sympathetic effects: Tachy-arrhythmias, rare instance MI
4. Anxiety:
   1. Reduce risk of psychoactive potential with CBD based therapy

Every Patient is a Trial of 1
(N=1)

RECOMMENDATION: CHOOSING STRAIN

Choose the right strain profile

Choose the right modality

Choose the right dose

RECOMMENDATION: CHOOSING THE RIGHT STRAIN

- 500 distinct compounds within the cannabis plant
  - 100+ phytocannabinoids
  - Turpenes, flavonoids and other products
- Principal phytocannabinoids
  - Delta-9-tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)
  - Cannabinol (CBN) – THC oxidation, effects not well studied
  - Cannabichromene (CBC)
  - Cannabigerol (CBG) – in vivo studies showing some COX inhibition
  - Tetrahydrocannabivarin (THCV) -pre-clinical studies suggest it may have anti-epileptiform/anti-convulsant, anti-nociceptive and potential anti-psychotic properties

RECOMMENDATION: CHOOSING THE RIGHT STRAIN

SATIVA VS. INDICA

- Subjective and patient-reported
- Scientifically invalid
- Classical characterization not very helpful when you're trying to understand what the active agents in the product are going to be.

CBD VS. THC

RECOMMENDATION: CHOOSING THE RIGHT STRAIN

TURPENES

- Chemical compounds that make one cannabis strain smell like lemons (‘limonene‘), or another like pine needles (‘pinene‘).
- When combined with THC/CBD it could produce some mild altering effects
  - Mood elevating (limonene)
  - Mood depressing (myrocene)
- Next tool in classification of cannabis

CBD VS. THC

RECOMMENDATION: CHOOSING THE RIGHT STRAIN

STRAIN PROFILE

CBD Predominant	2:1 Mix	1:1 Mix	THC Predominant
20-25 mg/mL	10:5 mg/mL	10:10 20:20 Mg/mL	20-25 mg/mL

RECOMMENDATION: CHOOSING THE RIGHT STRAIN

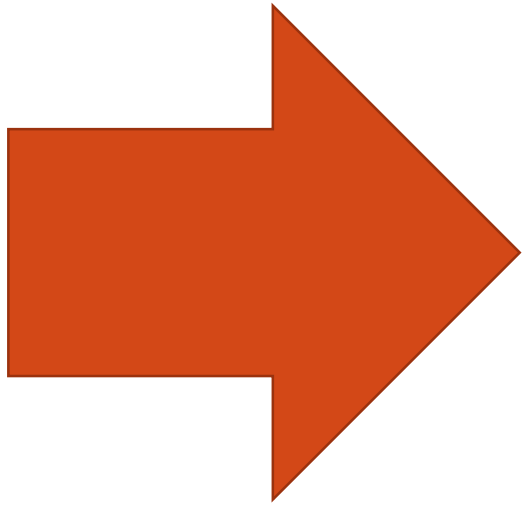
Think Simple

1st – Primary and Secondary condition

2nd – Goals

3rd – Drug interactions/Comorbidities

4th – Patient Preference



RISKS:BENEFITS

CBD Predominant

THC Predominant

Mood Disorders
- Anxiety
- Depression
- PTSD
- OCD

Seizures
- Dravet's

As the ratio of CBD:THC Increases, CBD tends to mitigate some of the effects of THC (2:1-8:1 ratios)

As the ratio of CBD:THC decreases, CBD tends to potentiate the effect of THC (<1:1 ratios)

Appetite Stimulation
- HIV associated cachexia/wasting
- Anorexia

Glaucoma

Insomnia

Tremor

PAIN

Alzheimer, Parkinson

Active State

Relaxed State

RECOMMENDATION: CHOOSING THE RIGHT STRAIN

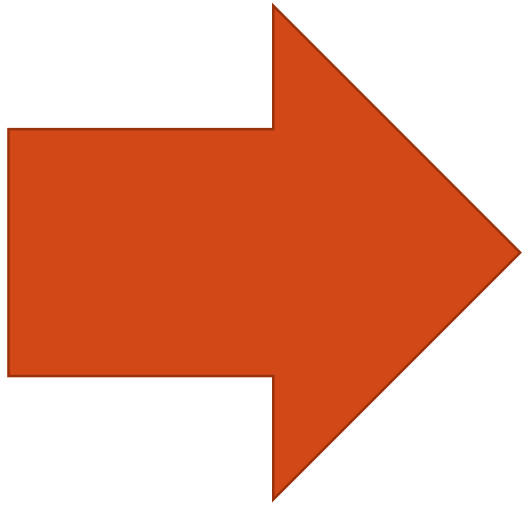
Think Simple

1st – Primary and Secondary condition

2nd – Goals

3rd – Drug interactions/Comorbidities

4th – Patient Preference

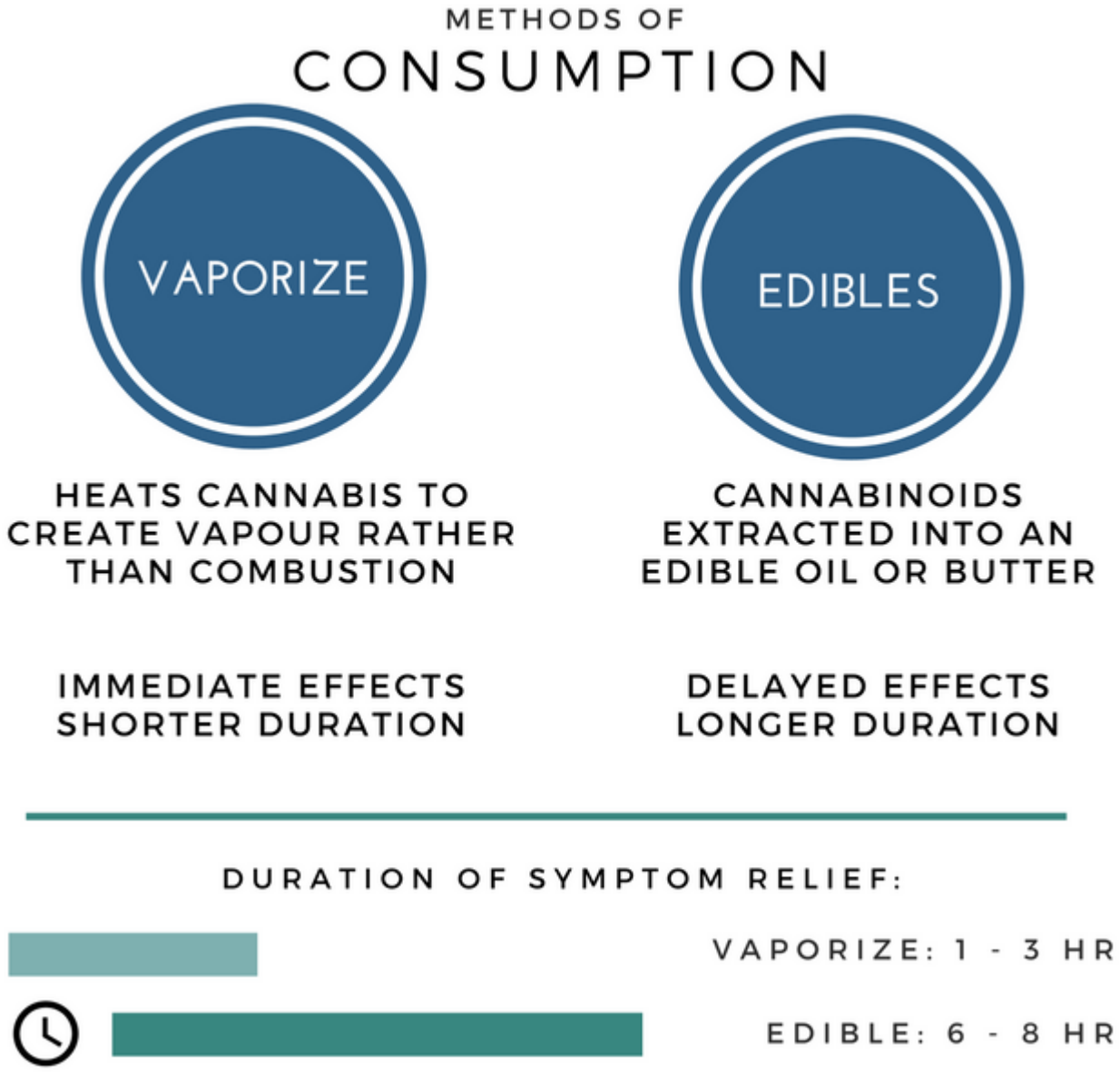


RISKS:BENEFITS

Chose the right
CBD/THC profile

RECOMMENDATION:

- Inhaled
- Oral
- Topical



RECOMMENDATION: CHOOSING THE RIGHT AMOUNT

- Amount:
  - 3g/day mean Self-Medicated use (Hazekamp A. et al. 2013)
  - Cannabis for Medical Purposes Regulations (ACMPRs) showed an average of 2.1-2.5 g/day of dried cannabis
  - 1.2 g/day is the average prescription in Canada/USA for naïve users (Sail Data. 2019)

Conversion g to ml
1g/day = 30 g/month = 3 bottles of the 10g/bottle or 6 bottles of the 5g/bottle

1 Bottle = 40-60 ml = 5 to 10g of cannabis

MAXIMUM DOSE

- CBD-predominant strains
  - Studies used 300(anxiety/psychosis)-2500mg (seizures) (leweke et al. 2012, Devinsky et al. 2017, Blessing et al. 2015)
  - For most indications 5–20 mg per day divided BID-TID
  - Attenuate expense by micro dosing
  - My rule: Individual dose equal to 60 mg CBD is my threshold for consideration of review

MAXIMUM DOSE

- THC-predominant strains
  - Inhaled/oral dose of 10 - 20 mg THC, up to max 40 mg can produce significant psychotropic effects or induce tolerance without improving efficacy
- Daily oral dose as low as 2.5 mg Δ^9-THC is associated with a therapeutic effect (e.g. treatment of AIDS-related anorexia/cachexia)

CASE: THERAPEUTIC OPTIONS

Chronic Pain	Acute episodes of pain	Sleep	Reduce Medications
• CBD predominant therapy (25mg/mL) • Oil ingestion • Starting at 0.25 mL and titrate using protocol • Can use 3-4x/day	• CBD based therapy (as per chronic pain) • Consider dry cannabis via vaporization	• CBD based therapy to treat pain and see if sleep follows • CBD:THC combination at night via oil	• medication need may decrease if GOALS achieved

FOLLOW-UP:

+ Benefit - Harm	- Benefit +Harm	-Benefit -Harm	+Benefit +Harm
• Continue current therapy	• Review the right strain, amount, medication interactions • Decrease or discontinue current therapy • Consider alternate CBD/THC profile	• Urine test • Consider up-titration of current therapy • Consider alternate CBD/THC profile	• Continue current CBD/THC profile and discuss Risk:Benefit • Consider decrease dose • Consider alternate CBD/THC profile

FOR REFERRALS

https://theclinicnetwork.ca/
Please note Dr. Mahabir's name on referral form