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Simplified cannabinoid guidelines

PEER PATIENTS EXPERIENCE EVIDENCE RESEARCH

Medical Cannabinoid Guideline: Sorting out Doobie-ous Claims with 'High' level Evidence

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Faculty/Presenter Disclosure

- **Faculty/Presenter: Mike Allan,**
- **Where we get Personal $:** CFPC, University of Alberta, rural locum billings
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PROGRAMS AND PRACTICE SUPPORT

Background

- **Manufactured:** Nabilone, Nabiximols (Sativex®)

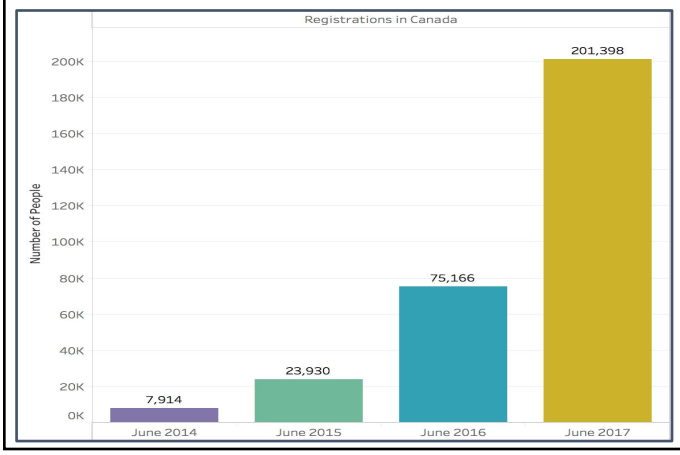
What is presently happening…

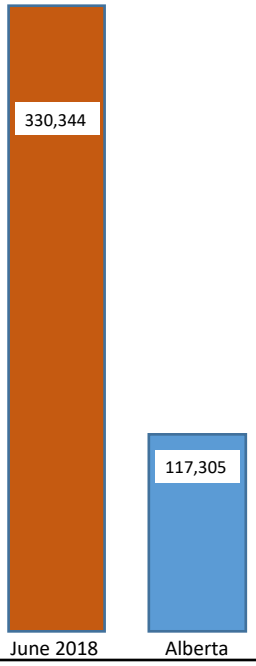
- Marijuana use ~7% in last 30 days, ~35% lifetime (USA)
  - 11% say it's medical and 36% says its medical/recreational
- Most common reason for MM is chronic pain: 58-84%.
  - Others include mental disorders: anxiety, sleep disorders.
- ≥70% MM users believe they get moderate+ Sx control.
- 15-20% of patients chronic pain or MS use Cannabis.

Am J Prev Med 2016;50(1):1–8Drug Alcohol Depend. 2017;177:1-13.
Health Canada. Market Data. Government of Canada. 2017

Canada

Health Canada. Market Data. Government of Canada. 2018





Some of the promoted medical uses for Cannabinoids

1. Tourette Syndrome
2. Amyotrophic Lateral Sclerosis
3. Huntington's Disease
4. Parkinson's Disease
5. Dystonia
6. Glaucoma
7. Traumatic Brain Injury/Intracranial Hemorrhage
8. Addiction
9. Anxiety
10. Depression
11. Sleep Disorders
12. Posttraumatic Stress Disorder
13. Schizophrenia/Other Psychosis
14. Osteoarthritis
15. Fibromyalgia
16. Neuropathic Pain
17. HIV Pain
18. Dementia
19. Cancer
20. Chemotherapy-Induced Nausea & Vomiting
21. Anorexia and Weight Loss
22. Irritable Bowel Syndrome
23. Epilepsy
24. Spasticity Associated with Multiple Sclerosis or Spinal Cord Injury

Our First Challenge: Limited Research

- Gluacoma: 1 RCTs with 6 people (no effect)
- Anxiety: 1 RCT of 24 patients tested for simulated public speaking found more improvement on mood visual analogue scale.
- IBS: 1 RCT of 36 pts given dronabinol for 2.5, 5mg or placebo BID x2 days: Focused on transit times.
- Depression: No RCTs (case reports only)

JAMA. 2015;313(24):2456-2473. National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press. doi: 10.17226/24625.

Seizures

- RCT cannabinoids treatment-resistant Dravet syndrome (aged 2-18 years, 120 kids, x14 weeks)
  - From ~12-15 seizures/month to 6 vs 14 / month (p=0.01)
  - ≥50% reduction frequency: 43% v 27% OR 2.0 (0.93-4.30)
  - Usual harms (diarrhea, somnolence, vomiting)
- RCT (Lennox-Gastaut Syndrome); median reduction (14 weeks): 43.9% cannabidiol versus 21.8% placebo
- RCT (Lennox-Gastaut): 225 patients, reduced 38% v18%
- **Bottom-Line**: positive data within seizure disorders but not ready for primary care yet!

Cochrane Database Syst Rev 2014;(3)CD009270. N Engl J Med. 2017;376(21):2011-20. Lancet 2018;391(10125):1085-96

Evidence: Two Primary Problems

- **Blinding: Attempted but rarely tested**
  - In 2 Inhaled cannabis cross-over RCTs
    - 1st: 57% identified all 6 phases
    - 2nd: 90% identified active vs cannabis cigs without THC/CBD
  - Dronabinol, 95% of patients identified active (as did 85% of nurses. (nabilone study similar)
- **Inclusion: Previous users often focused on.**
  - Of 6 inhaled RCTs: 3 required past use, 2 no limitation and 1 did not report.
  - In Nausea/vomiting, previous use led to great response
  - Naive users (more likely to report psychosis).
- Together, these introduce profound bias

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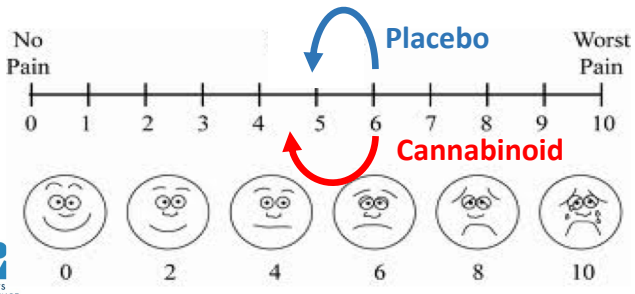
Pain Outcomes: Change in Scale

- On a 0-10 point scale: Baseline ~6/10.
  - Placebo reduces things ~1
  - Cannabinoids: ~1.5



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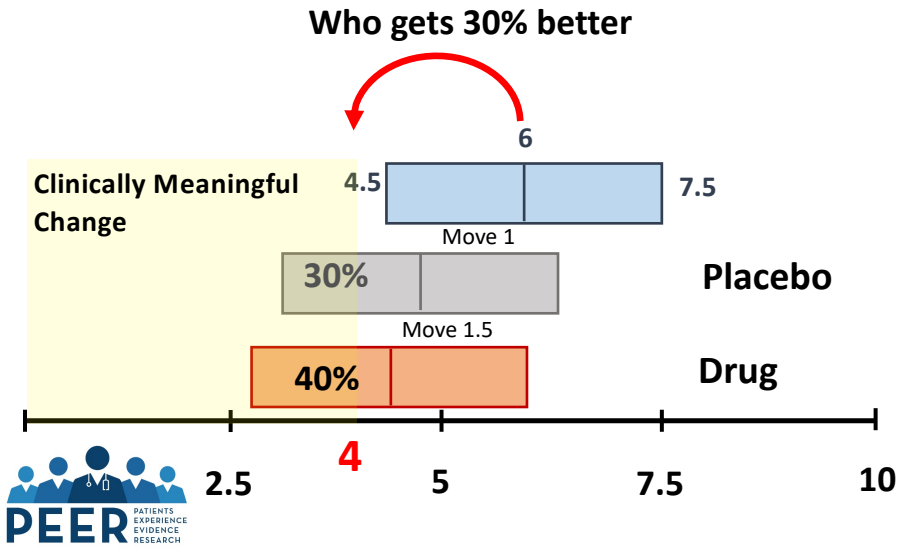
How do these numbers work?



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Pain Outcomes: 30% pain reduction & others

Type of Pain	Risk Ratio	Cannabis	Placebo	NNT
Chronic Pain	1.23 (0.98-1.56)	37%	31%	~19
Smoked, Neuropathic	1.62 (1.24-2.12)	47%	29%	6
Neuropathic	1.34 (1.04-1.74)	38%	30%	14
Cancer	1.35 (0.63-2.09)	NR	NR	NR
Palliative	1.34 (0.96-1.86)	30%	23%	~15
Chronic Pain	**1.37 (1.14- 1.64)**	**39%**	**30%**	**11**

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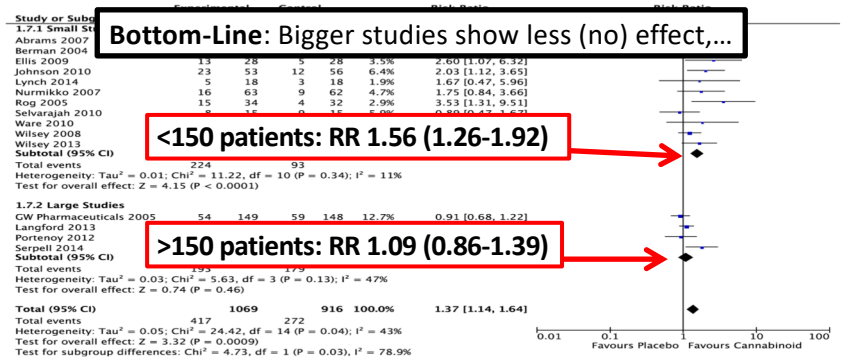
Can Fam Physician 2018 (submitted). JAMA. 2015;313:2456-73. J Pain 2015;16:1221-32. Schmerz 2016; 30: 62-88. Medwave 2016;16 Suppl 3:e6539. Curr Med Res Opin 2007;23:17-24. Der Schmerz 2016;30:25-36.

Example of Does Size Matter?



Can Fam Physician. 2018 Feb;64(2):e78-e94

What factors influence Cannabinoid pain effect?

Comparison	Subgroup	Risk Ratios	Difference
Type of Cannabinoid	Inhaled	1.52 (1.17-1.99)	P=0.34
	Buccal	1.28 (1.02-1.61)	
Size of RCT	<150	1.56 (1.26-1.92)	P=0.03
	>150	1.09 (0.86-1.39)	
Duration of RCT	<1 week	1.58 (1.13-2.20)	P=0.01
	2-5 wks	1.79 (1.32-2.43)	
	9-15 wks	1.07 (0.87-1.32)	

Bottom-Line: When you examine higher quality studies (larger & longer), cannabinoids do not appear to have an effect on pain.

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Additional Variables in Pain

- Nabilone (oral): 2 best trials
  - RCT Fibromyalgia 40 patients, 1mg PO BID x4 wks
    - 14.6 more than placebo on 100mm VAS.
  - RCT: 73 x3 wks, 500 µg v 60 mg dihydrocodeine QID.
    - 10 on 100mm VAS: 19% dihydrocodeine vs 5% nabilone.
- Rheumatologic Pain: Insufficient evidence
- Acute Pain: decrease (1), worse (1) & no effect (5)
- Function not reported and QoL unchanged.

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J Pain. 2008; 9(2):164-73. BMJ. 2008 Jan 26;336(7637):199-201

Pain Summary

- **Bottom-line**: **At best**, medical cannabinoids reduce pain ≥30% for one in 11 patients suffering from neuropathic pain (vs placebo).
  - This includes highly biased research, meaning the effect is likely exaggerated.
  - It is very unclear if one type medical cannabinoids is better but the best research is on nabiximol.

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Absence Nausea & Vomiting from Chemotherapy

Comparator	Outcome	Rate Ratio	Cannabis	Control	NNT
Versus Placebo	Control Sx*	3.60 (2.55 - 5.09)	47%	13%	3
	Pt Preference	4.82 (1.74-13.36)	72%	18%	2
		5.67 (3.95 - 8.15)	76%	13%	2
Versus Neuroleptics	Control Sx*	1.85 (1.18 - 2.91)	31%	16%	7
	Pt Preference	2.76 (1.88 - 4.03)	63%	19%	3
		2.39 (2.05 - 2.78)	61%	26%	3

* Done by us

JAMA 2015; 313:2456-73. Cochrane Database Syst Rev 2015; (11) CD009464. Eur J Cancer Care 2008;17:431-43 BMJ 2001;323(7303):16-21.

Additional Variables

- Most trials followed patients 1 day (after chemo)
- Older studies (1/2 ~35 years old)
- Patient preference higher than effectiveness (preference ~75% while effectiveness 47%)
  - Maybe preference based on more than effectiveness
- Medical Cannabinoids for nausea/vomiting are primarily oral agents like Nabilone (& delisted dronabinol).

JAMA 2015; 313:2456-73. Cochrane Database Syst Rev 2015; (11) CD009464. Eur J Cancer Care 2008;17:431-43 BMJ 2001;323(7303):16-21.

Nausea & Vomiting Summary

- **Bottom-Line**: Although biases, likely works, preventing nausea/vomiting in 47% vs 13% (on placebo).
- Medical cannabinoids will prevent nausea/vomiting in 31% vs 16% (Vs neuroleptics like prochlorperazine)
- Patients like it,
  - More than it works

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How well it works for spasticity

	Rate Ratio	Cannabis	Placebo	NNT
≥30% Improvement in Spasticity	1.43 (0.99-2.08)	35%	24%	~10
	1.37 (1.07-1.76)	35%	25%	10
Global Impression of Change (by us)	1.45 (1.08 – 1.95)	50%	35%	7

- Spasticity score from 0-10, Mean score: 6.2,
  - Placebo improved spasticity 0.95
  - Cannabinoid improved spasticity, over placebo, by 0.31 – 0.76

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JAMA 2015; 313(24):2456-73. BMJ 2001;323(7303):16-21.

Spasticity Summary

- **Bottom-Line**: Medical Cannabinoids reduce spasticity for 50% of patients compared to 35% of those on placebo (as assessed by patient global assessment of improvement).

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Type of AE	Cannabinoid Event Rate	Placebo Event Rate	NNH
Overall	81%	62%	6
Withdrawal	11%	~3%	14
Ataxia/Muscle Twitching	30%	11%	6
Blurred Vision/ Visual Hallucination	6%	0%	17
Central Nervous System	60%	27%	4
Disorientation/Confusion	9%	2%	15
Dissociation/ Acute Psychosis	5%	0%	20
Disturbance attention/ disconnected thought	17%	2%	7
Dizziness	32%	11%	5
Dysphoria	13%	0.3%	8
Euphoria	15%	2%	9
"Feeling High"	35%	3%	4
Hypotension	25%	11%	8
Impaired Memory	11%	2%	NS (12)**
Numbness	21%	4%	6
Psychiatric	17%	5%	9
Sedation	50%	30%	5
Speech Disorders	32%	7%	5

~20% higher for patients taking cannabinoids

Things to consider:
Enrolled frequent users
Short duration

Adverse Events

- **Bottom-Line:**
  - Versus placebo, medical cannabinoids cause multiple different adverse events in patients, from visual disturbance or hypotension (1 in 3-10) to hallucination or paranoia (1 in 20).
  - Stopping due to adverse effects occurs in 1 in every 8-20 patients.
  - Regardless of the type of medical cannabinoid used, adverse events are common and likely underestimated.
  - Given the extensive harms, potential benefits must be impressive to warrant a trial of therapy

JAMA 2015; 313(24):2456-73. Mult Scler 2010;16(6):707-14. CMAJ 2008;178(13):1669-78. Der Schmerz 2016;30(1):25-36. Cochrane 2015; (11)CD009464. BMJ 2001;323(7303):16-21. Schmerz 2016;30(1):62-88. Pain Med 2009;10(8):1353-68.

From CMAJ 2017 (Point 2),…

1. Despite widespread availability, medical cannabinoids are still **experimental**
2. Most clinical trials use pharmaceutical cannabinoids **no**t smoked THC.
3. Although ~40% (**58%**) of strains from licensed producers contain a potency of ≥15% THC, **9.4%** is the highest percentage studied.
4. Smoked THC as a mode of delivery is not superior to oromucosal sprays based on current evidence, and may result in dose variability and unforeseen individual responses.

CMAJ 2017 July 31;189:E995. doi: 10.1503/cmaj.161395

Figure 1. Medical cannabinoid prescribing algorithm.

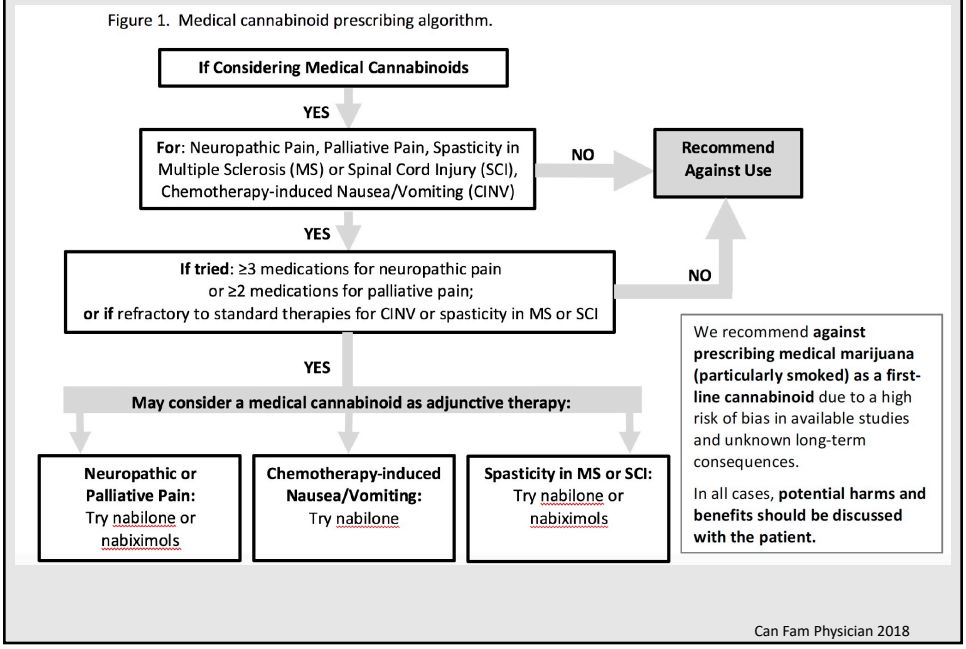

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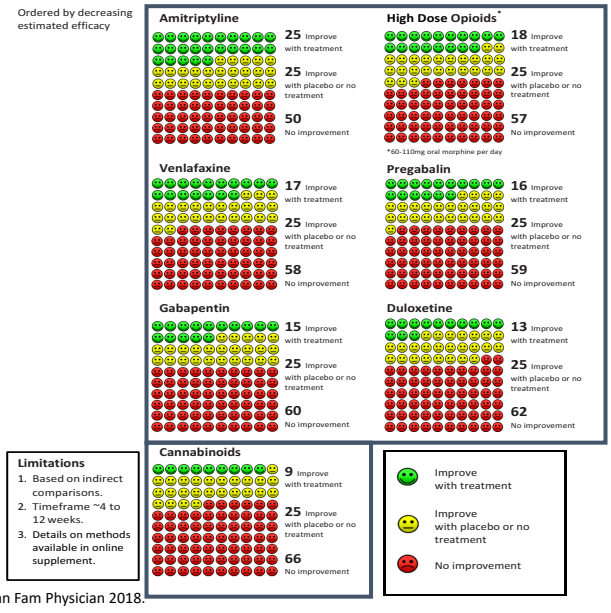
Figure 2: Neuropathic Pain: Pharmacotherapy Treatment

Outcome: Meaningful (~30% Pain Improvement

Neuropathic Pain

Benefit Comparison



Limitations
1. Based on indirect comparisons.
2. Timeframe ~4 to 12 weeks.
3. Details on methods available in online supplement.

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Last Thoughts… Smoked

- Prescribing guides recommend max 9% THC
  - 1 inhalation ("drag") = 100mg once a day
  - Titrate up to QID = ~half a "joint"/day (400mg/day)
- What is ACTUALLY being used:
  - In Canada: 27% THC is maximum but many ~15%,
  - Can smoke 5 grams/day (~6 "joints")
- Presently patients can easily attain **20x** the recommended dose.

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Can Fam Physician. 2014 Dec;60(12):1083-90.

Costs

Drug	Daily Dose[2]	Approximate cost/month
Nabilone*[1]	2 to 6 mg	$94 to $305
Nabiximols*	4 to 12 sprays	$226 to $903
Medical Marijuana Dried	1 to 3 g *typical* use	$250 to $750 Based on $8.37/g

Manufacturer list price, does not reflect pharmacy dispensing fees.
[1]Only generic nabilone covered by most provincial drug plans.
[2]Studied doses: Nabilone 0.5mg to 8mg/day, nabiximols 4 to 48 sprays/day, smoked marijuana had THC concentrations ranging 1 to 8% up to three times a day as tolerated. Daily doses from drug monographs and Health Canada.

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THC/CBD

Blazing through the components of cannabinoids

Cannabis

- **>400 chemical compounds**
- First discovered was cannabinol in 1899
- It wasn't until 1963 that the second compound, cannabidiol (CBD) was discovered.
- A year later, THC was discovered.

The Evidence

4 RCTs (THC, CBD or combined versus each other or placebo)

- RCT (n=243, terminal cancer and weight loss) [1]
  - **Results:** No difference in appetite or adverse events
- RCT (n=177, refractory cancer pain on ~270mg morphine) [2]
  - **Results:** ≥30% pain reduction: 38% THC/CBD vs 21% THC, (NNT 6)
    - AEs not significantly different between THC/CBD and THC.
- RCT (n=48, brachial nerve injury with baseline pain ~7.5/10) [3]
  - **Results:** Both THC/CBD & THC pain ~1.3 better vs 0.6 placebo
    - AEs not significantly different between THC/CBD and THC.
- RCT (N of 1) n=24, chronic pain who benefits from THC/CBD[4]
  - **Results:** Patients with ≥ pain control vs THC/CBD (given before trial)
    - **38% THC/CBD** vs **33% THC** vs **17% CBD.**

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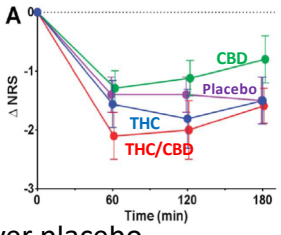
Strasser 2006, Johnson 2010, Berman 2004, Notcutt 2004

Newest THC/CBD RCT

- 20 fibromyalgia – single doses 2 wks apart, x 4 products (cross-over)
  1. 22% THC and <1%CBD: Received 100 mg with 22.4-mg THC + ≤1-mg CBD.
  2. 6.3% THC and 8% CBD: Received 200 mg with 13.4-mg THC + 17.8-mg CBD.
  3. 9% CBD and <1% THC. Received 200 mg with <1-mg THC + 18.4-mg CBD
  4. Placebo
- Results: at 3hours!
  - Who got a ≥30% response,…
  - 90% THC/CBD, 65% THC, 55% placebo, 40% CBD
  - Drug High correlated with pain response
  - THC had more "psychedelic" effects,
  - Paranoid/anxiety & some AE (nausea) less with CBD



- **Bottom-Line**: The effects are often not much over placebo, associated with being high & may depend on THC. CBD does have some less negative effects.

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Pain. 2019 Apr;160(4):860-869.

THC/CBD Bottom Line

- **Non-clinical research:** Limited evidence supports a difference in adverse effects with CBD vs THC/CBD vs THC:
  - Most studies: healthy people, many with drug use history.
  - Even less evidence on % concentrations
- **Clinical Research:** 5 RCTs of THC, CBD or both for treatment:
  - Possible that THC/CBD better than either component alone
- **Bottom-Line**: Possible that THC/CBD is better than either alone. Pain relief may be tied to high. CBD may dampen some of the psychological effects of THC.

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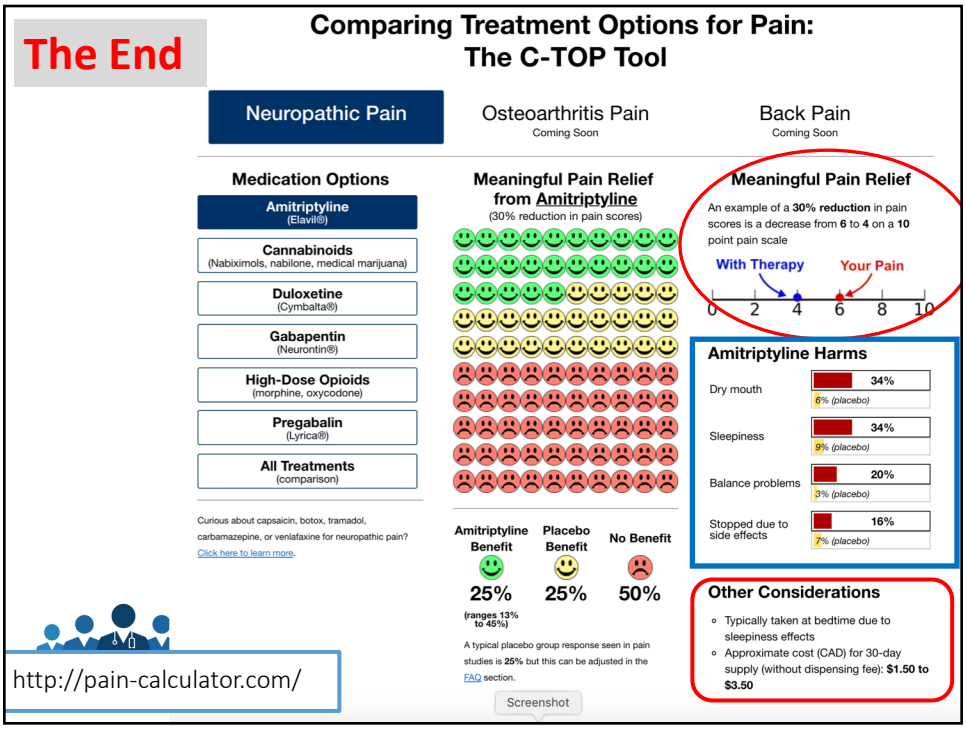
The End



http://pain-calculator.com/