CANNABIS FOR THE RHEUMATOLOGIST

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Disclosures

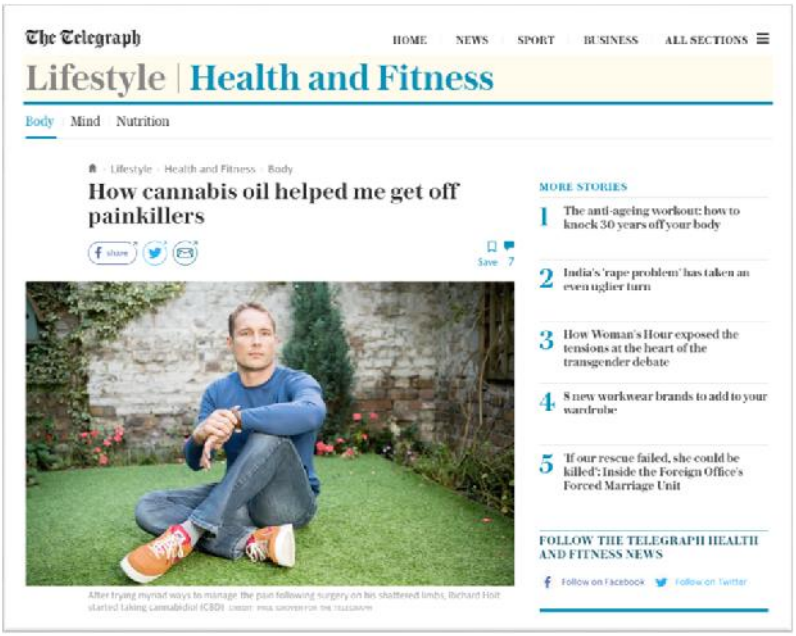
- None

Overview

- The history of cannabis use
- Anecdotal use of cannabis in chronic pain
- The biology of cannabinoids
- Types of medical cannabis / cannabinoid medication
- Evidence for the use of cannabinoids in diseases
- Evidence for the use of cannabinoids in chronic pain

The history of cannabis use

- First use 5000 years ago by early Chinese as a treatment for malaria, constipation, rheumatic pains and an analgesic during childbirth
- W.B. O'Shaughnessy, a doctor with the Bengal army and professor of chemistry in 1843 demonstrated it's use in various indications
- Sir John Russell Reynolds, physician to Queen Victoria and president of RCP London wrote in Lancet in 1890 about it's medicinal uses
- Adopted into US and UK pharmacies until 1940s
- Although currently illegal in the US, certain states have legalised it's use for medical reasons such as for severe pain



The Telegraph

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How cannabis oil helped me get off painkillers

Save 7

After trying myriad ways to manage the pain following surgery on his shattered limbs, Richard Holt started taking cannabidiol (CBD)

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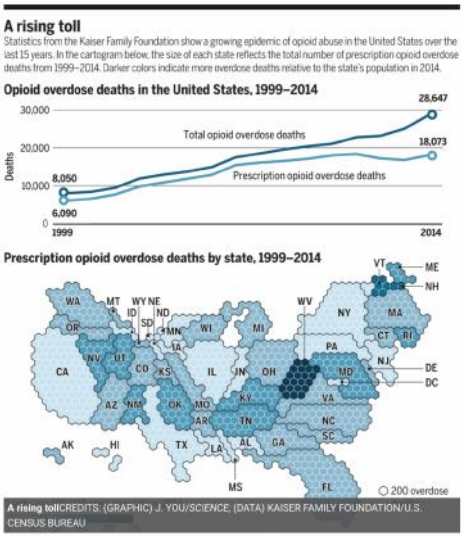
Opioid related deaths in the US rose from 1999-2014



Opioid prescriptions are decreased in states with legalised cannabis

- 23.08 million daily doses of opioid dispensed each year per state on average
- 3.742 million fewer daily doses in states with dispensaries
- 1.792 million fewer daily doses in states with legal home cultivation

JAMA Intern Med. 2018;178(5):667-672

CANNABIS 101

Types of cannabis available from US dispensaries

- Marijuana – dried plant product – smoked or vaporised
- Hashish – resin cake that can be ingested or smoked
- Tincture – liquid that is taken sublingually
- Hashish oil – oil obtained from plant by solvent extraction
- Infusion – plant material mixed with butter or cooking oil to be ingested

Biology of cannabinoids

- Marijuana contains over 60 active cannabinoids
- Activate 2 GPCRs
  - CB1 – mainly in the basal ganglia, cerebellum, hippocampus, association cortices, spinal cord and peripheral nerves
  - CB2 – mainly on immune cells
- Can directly inhibit release of
  - Acetylcholine
  - Dobamine
  - Glutamate
- Indirectly affects
  - GABA
  - NMDA
  - Opioid receptors
  - Serotonin receptors

Primary cannabinoids in marijuana

- Δ^9 – tetrahydrocannabinol – THC
  - Euphoric and psychotic effects
- Cannabidiol – CBD
  - Not psychoactive and may have anti anxiety and anti psychotic effects
- Ratios of THC to CBD can be different in various strains of marijuana

Physiological effects of cannabinoid receptor activation

- Euphoria
- Psychosis
- Impaired memory and cognition
- Reduced locomotor function
- Increased appetite
- Other effects such as antiemetic, pain relieving, anti-spasticity, sleep-promoting effects

Types of cannabinoid medication

- Herbal cannabis – phytocannabinoids
  - Nabiximols, Cannador
  - THC
  - CBD
- Endocannabinoids – endogenous compounds made by mammals
  - Anandamide
  - 2-arachidonylglycerol (2-AG)
- Synthetic analogues
  - Dronabinol
  - Levonantradol
  - Nabilone

EVIDENCE FOR USE OF CANNABINOID MEDICATIONS IN CHRONIC PAIN

Evidence for the use of cannabis-derived medication in chronic pain

- Systematic review of 79 trials involving 6462 participants

Chronic Pain

- Assessed in 28 studies – 2454 participants
  - 13 studies nabiximols
  - 4 smoke THC
  - 5 nabilone
  - 3 THC oromucosal spray
  - 2 dronabinol
  - 1 vaporised cannabis
  - 1 ajuvenic acid
  - 1 oral THC

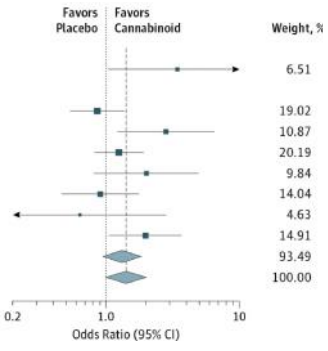
  - One trial compared nabilone with amitryptyline
  - One trial nabilone was an adjunct to gabapentin

- Conditions
  - 12 neuropathic pain
  - 3 cancer pain
  - 3 diabetic peripheral neuropathy
  - 2 fibromyalgia
  - 2 HIV associated sensory neuropathy
  - 1 for RA and others

Whiting et al. JAMA. 2015;313(24):2456-2473

Greater reduction in pain of at least 30% is greater with cannabinoids than placebo

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)
Tetrahydrocannabinol (smoked)					
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)
Nabiximols					
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)
Subtotal I^2=44.5%, (P=.0.94)	241	660	209	660	1.32 (0.94-1.86)
Overall I^2=47.6%, (P=.0.64)	254	685	215	685	1.41 (0.99-2.00)



Whiting et al. JAMA. 2015;313(24):2456-2473

Increased risk of adverse events with cannabinoids

- Any adverse event – **OR 3.03** (2.42-3.80)
- Serious adverse event – **OR 1.41** (1.04-1.92)
- Withdrawal due to adverse event – **OR 2.94** (2.18-3.96)
- Dizziness **OR 5.09** (4.10-6.32)
- Dry mouth, nausea, fatigue, somnolence

An overview of systematic reviews of cannabinoids for chronic pain suggests there are inconsistencies

- 10 SRs were included
- 4 high quality, the rest moderate

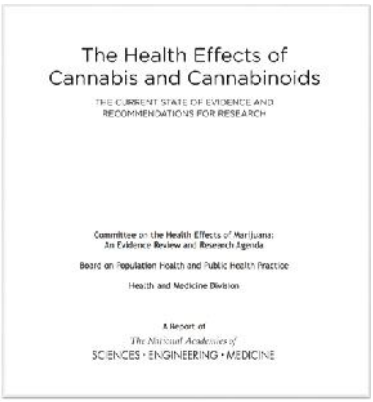
Conclusion

Inconsistent findings of the efficacy, tolerability and safety of cannabis-based medicines for the management of cancer and non-cancer pain

However it is becoming more widespread and consideration should be made about driving ability especially with THC containing products and also the possible ingestion by children

Häuser, Petzke and Fitzcharles. Eur J Pain. 22 (2018) 455-470

Challenges in this area


The Health Effects of Cannabis and Cannabinoids

THE CURRENT STATE OF EVIDENCE AND RECOMMENDATIONS FOR RESEARCH

Committee on the Health Effects of Marijuana: An Evidence Review and Research Agenda

Board on Population Health and Public Health Practice

Health and Medicine Division

A Report of

The National Academies of

SCIENCES • ENGINEERING • MEDICINE

ple, in 2015 between 498,170 and 721,599 units of medical and recreational cannabis edibles were sold per month in Colorado (Colorado DOR, 2016, p. 12). Pain patients also use topical forms (e.g., transdermal patches and creams). Thus, while the use of cannabis for the treatment of pain is supported by well-controlled clinical trials as reviewed above, very little is known about the efficacy, dose, routes of administration, or side effects of commonly used and commercially available cannabis products in the United States. Given the ubiquitous availability of cannabis products in much of the nation, more research is needed on the various forms, routes of administration, and combination of cannabinoids.

CONCLUSION 4-1 There is substantial evidence that cannabis is an effective treatment for chronic pain in adults.

CANNABINOID MEDICATIONS IN EXPERIMENTAL PAIN

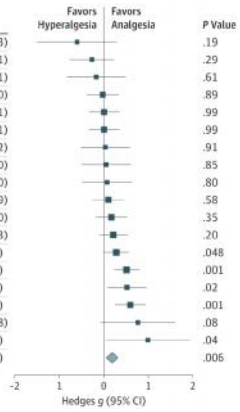
Association of cannabinoid administration with experimental pain in healthy adults

- Systematic review and meta-analysis
- 18 placebo controlled studies with 442 participants
- Although meta-analyses have shown evidence for the use of cannabinoids in chronic pain, there are often no objective experimental measures of pain

De Vita et al. JAMA Psychiatry. 2018;75(11):1118-1127

Cannabinoids cause a small increase in the pain threshold

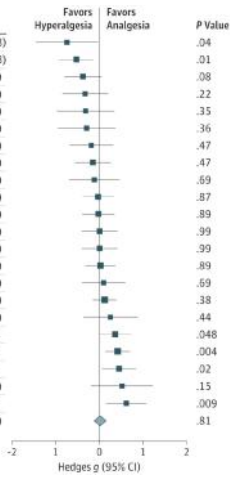
Study Name	Subgroup Within Study	Outcome	Hedges g (95% CI)	P Value
Hill et al,[22] 1974	Cannabis: 1 g of 1.4% THC	Threshold	-0.605 (-1.504 to 0.293)	.19
Libman and Stern,[56] 1985	THC: 10 mg (low dose)	Threshold	-0.271 (-0.773 to 0.231)	.29
Kraft et al,[58] 2008	Cannabis extract: 20 mg of THC	Combined	-0.172 (-0.835 to 0.491)	.61
Rukwied et al,[65] 2003	HU210: 50-µl solution (patch)	Combined	-0.027 (-0.393 to 0.340)	.89
Cooper et al,[46] 2013	Cannabis: 800 mg of 1.98% THC (low dose)	Threshold	0.002 (-0.346 to 0.351)	.99
Cooper et al,[46] 2013	Dronabinol: 10 mg (low dose)	Threshold	0.002 (-0.346 to 0.351)	.99
Wallace et al,[66] 2007	Cannabis: 800 mg of 8% THC (high dose)	Combined	0.034 (-0.525 to 0.592)	.91
Wallace et al,[66] 2007	Cannabis: 800 mg of 4% THC (medium dose)	Combined	0.052 (-0.506 to 0.610)	.85
Wallace et al,[66] 2007	Cannabis: 800 mg of 2% THC (low dose)	Combined	0.072 (-0.486 to 0.630)	.80
Kalliomäki et al,[49] 2012	Nabilone: 1 mg (low dose)	Threshold	0.100 (-0.250 to 0.449)	.58
Kalliomäki et al,[49] 2012	Nabilone: 2-3 mg (high dose)	Threshold	0.169 (-0.182 to 0.520)	.35
Cooper and Haney,[47] 2016	Cannabis: 800 mg of 3.56%-5.60% THC (females)	Threshold	0.211 (-0.112 to 0.533)	.20
Cooper et al,[46] 2013	Dronabinol: 20 mg (high dose)	Threshold	0.278 (0.002 to 0.553)	.048
Cooper et al,[46] 2013	Cannabis: 800 mg of 3.56% THC (high dose)	Threshold	0.509 (0.221 to 0.797)	.001
Naef et al,[61] 2003	Dronabinol: 20 mg	Combined	0.519 (0.079 to 0.959)	.02
Cooper and Haney,[47] 2016	Cannabis: 800 mg of 3.56%-5.60% THC (males)	Threshold	0.592 (0.244 to 0.939)	.001
Greenwald and Stitzer,[57] 2000	Cannabis: 750-990 mg of 3.55% THC	Threshold	0.763 (-0.083 to 1.608)	.08
Libman and Stern,[56] 1985	THC: 20 mg (high dose)	Threshold	0.989 (0.052 to 1.926)	.04
Overall			0.186 (0.054 to 0.318)	.006



De Vita et al. JAMA Psychiatry. 2018;75(11):1118-1127

Cannabinoids do not reduce intensity of ongoing experimental pain

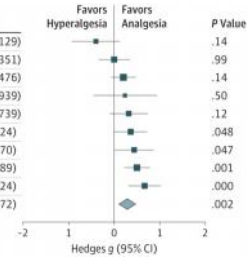
Study Name	Subgroup Within Study	Outcome	Hedges g (95% CI)	P Value
Naef et al,[61] 2003	Dronabinol: 0.053 mg/kg bw (aerosol)	Intensity	-0.743 (-1.459 to -0.028)	.04
Wallace et al,[66] 2007	Cannabis: 800 mg of 8% THC (high dose)	Combined	-0.527 (-0.925 to -0.128)	.01
Naef et al,[61] 2003	Dronabinol: 20 mg	Intensity	-0.376 (-0.800 to 0.048)	.08
Roberts et al,[64] 2006	Dronabinol: 5 mg	Intensity	-0.328 (-0.852 to 0.197)	.22
Redmond et al,[63] 2008	Nabilone: 1 mg (high dose)	Intensity	-0.317 (-0.978 to 0.344)	.35
Redmond et al,[63] 2008	Nabilone: 0.5 mg (low dose)	Intensity	-0.292 (-0.952 to 0.368)	.36
Kalliomäki et al,[49] 2012	Nabilone: 2-3 mg (high dose)	Intensity	-0.185 (-0.685 to 0.316)	.47
Lee et al,[59] 2013	THC: 15 mg	Combined	-0.152 (-0.562 to 0.259)	.47
Kalliomäki et al,[48] 2013	AZD1940: 800 µg (high dose)	Intensity	-0.116 (-0.697 to 0.464)	.69
Kraft et al,[58] 2008	Cannabis Extract: 20 mg of THC	Combined	-0.032 (-0.385 to 0.321)	.87
Wallace et al,[66] 2007	Cannabis: 800 mg of 2% THC (low dose)	Combined	-0.024 (-0.395 to 0.346)	.89
Cooper and Haney,[47] 2016	Cannabis: 800 mg of 3.56%-5.60% THC (females)	Intensity	0.003 (-0.409 to 0.414)	.99
Cooper and Haney,[47] 2016	Cannabis: 800 mg of 3.56%-5.60% THC (males)	Intensity	0.003 (-0.409 to 0.414)	.99
Cooper et al,[46] 2013	Dronabinol: 10 mg (low dose)	Intensity	0.023 (-0.325 to 0.372)	.89
Kalliomäki et al,[49] 2012	Nabilone: 1 mg (low dose)	Intensity	0.100 (-0.400 to 0.600)	.69
Cooper et al,[46] 2013	Dronabinol: 20 mg (high dose)	Intensity	0.121 (-0.150 to 0.392)	.38
Kalliomäki et al,[48] 2013	AZD1940: 400 µg (low dose)	Intensity	0.253 (-0.372 to 0.878)	.44
Cooper et al,[46] 2013	Cannabis: 800 mg of 1.98% THC (low dose)	Intensity	0.364 (0.003 to 0.724)	.048
Cooper et al,[46] 2013	Cannabis: 800 mg of 3.56% THC (high dose)	Intensity	0.420 (0.138 to 0.703)	.004
Wallace et al,[66] 2007	Cannabis: 800 mg of 4% THC (medium dose)	Combined	0.450 (0.059 to 0.841)	.02
Walter et al,[67] 2016	THC: 20 mg	Intensity	0.521 (-0.188 to 1.229)	.15
Rukwied et al,[65] 2003	HU210: 50-µL solution (patch)	Intensity	0.614 (0.152 to 1.076)	.009
Overall			0.017 (-0.120 to 0.154)	.81



De Vita et al. JAMA Psychiatry. 2018;75(11):1118-1127

Cannabinoids reduce perception of ongoing pain unpleasantness

Study Name	Subgroup Within Study	Outcome	Hedges g (95% CI)	P Value
Roberts et al,[64] 2006	Dronabinol: 5 mg	Unpleasantness	-0.403 (-0.935 to 0.129)	.14
Cooper et al,[46] 2013	Dronabinol: 10 mg (low dose)	Unpleasantness	0.002 (-0.346 to 0.351)	.99
Cooper et al,[46] 2013	Dronabinol: 20 mg (high dose)	Unpleasantness	0.203 (-0.070 to 0.476)	.14
Walter et al,[67] 2016	THC: 20 mg	Unpleasantness	0.240 (-0.459 to 0.939)	.50
Lee et al,[59] 2013	THC: 15 mg	Combined	0.319 (-0.100 to 0.739)	.12
Cooper et al,[46] 2013	Cannabis: 800 mg of 1.98% THC (low dose)	Unpleasantness	0.364 (0.003 to 0.724)	.048
Cooper and Haney,[47] 2016	Cannabis: 800 mg of 3.56%-5.60% THC (females)	Unpleasantness	0.438 (0.006 to 0.870)	.047
Cooper et al,[46] 2013	Cannabis: 800 mg of 3.56% THC (high dose)	Unpleasantness	0.502 (0.214 to 0.789)	.001
Cooper and Haney,[47] 2016	Cannabis: 800 mg of 3.56%-5.60% THC (males)	Unpleasantness	0.669 (0.314 to 1.024)	.000
Overall			0.288 (0.104 to 0.472)	.002



De Vita et al. JAMA Psychiatry. 2018;75(11):1118-1127

Nabilone is effective in improving sleep in patients with fibromyalgia

- Randomised, double blind, active control crossover
- Each drug given for 2 weeks with a 2 week washout
- 31 subjects – 29 completed
- Sleep improved by both medications but nabilone superior
  - Insomnia severity index difference - 3.2 (1.2-5.3)
  - More adverse effects for nabilone - dizziness, nausea, dry mouth

Ware et al. Pain Medicine. 2010. 110(2) 604-610

Evidence for the use of Cannabidiol in Drug-Resistant seizures in Dravet syndrome

- Dravet syndrome – loss of function mutation in the *SCN1A* gene
- Randomised double-blind, placebo controlled trial

Table 2. Primary Efficacy End Point of Percentage Change in Convulsive-Seizure Frequency in Each Trial Group.*

Variable	Cannabidiol	Placebo	Adjusted Median Difference (95% CI)	P Value†
			percentage points	
No. of convulsive seizures per mo — median (range)				
Baseline	12.4 (3.9 to 1717)	14.9 (3.7 to 718)		
Treatment period	5.9 (0.0 to 2159)	14.1 (0.9 to 709)		
Percentage change in seizure frequency — median (range)	−38.9 (−100 to 337)	−13.3 (−91.5 to 230)	−22.8 (−41.1 to −5.4)	0.01

* CI denotes confidence interval.
† The P value was calculated with the use of a Wilcoxon rank-sum test with the Hodges–Lehmann approach.

Labeling accuracy of CBD extracts sold online

- 84 products from 31 companies were purchased and analysed blindly by HPLC
  - Products included oil, tincture and vaporisation liquid
  - Accurately labeled - 90-110% labeled value
  - Overlabeled - <90%
  - Underlabeled - >110%
- CBD
  - 30.95% accurately labeled
  - 26.19% overlabeled
  - 42.85% underlabeled
- Oil tended to be better than vaporisation liquid
- THC was detected in 18/84 samples

Bonn-Miller et al. JAMA. 2017. 318(17): 1708-1709

Conclusions

- Inconsistent evidence for efficacy in chronic pain
- Associated with significant adverse events including dizzyness
- Studies of whether cannabinoid medications can reduce opioid use are ongoing
- There may be significant differences in over the counter preparations