Cannabinoids and Health
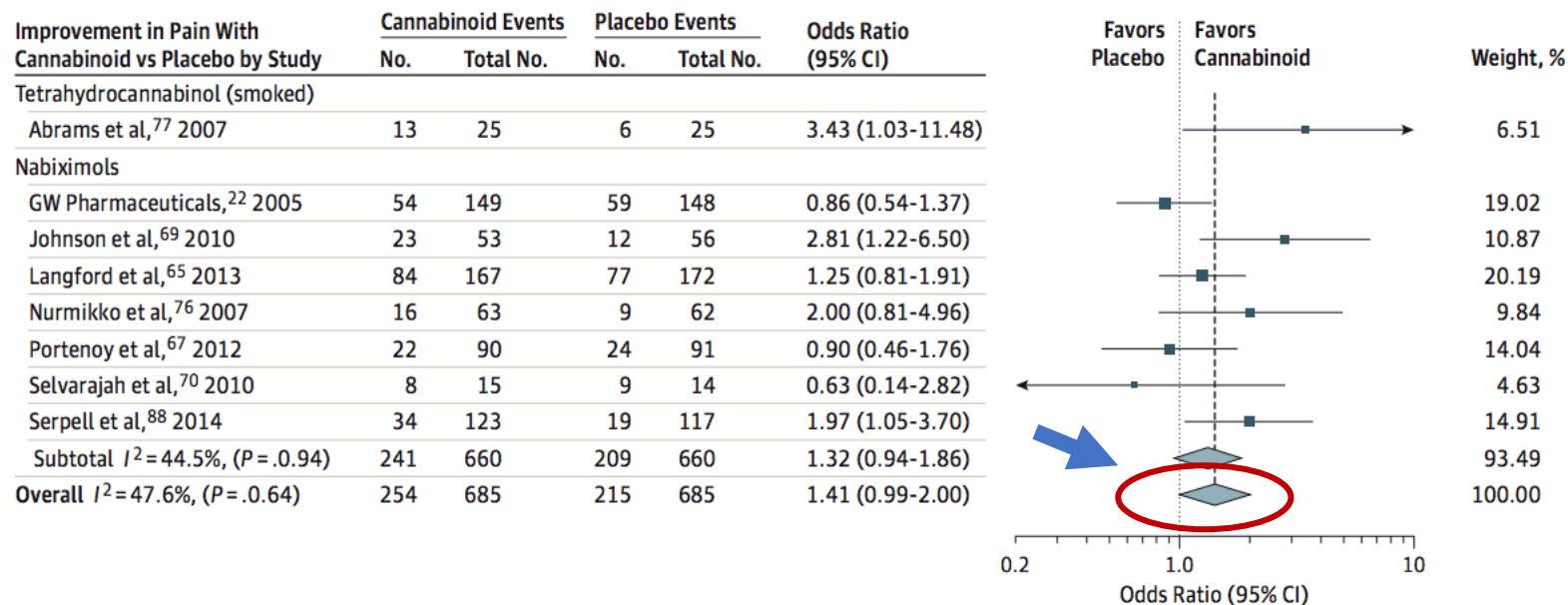
Module 5

Lecture 5: Cannabis and Chronic Pain

Chronic Pain and Cannabis

- Studies suggest that the majority of individuals using cannabis for medical reasons are using it for pain (~62% medical users; Boenke et al., 2019 for latest analysis)

- Analyses of medicare prescription data in MMJ states suggest reduction in prescription meds (Bradford & Bradford, 2016)

- The NAS report found 5 systematic reviews

- Whiting et al. (2015) most comprehensive, recent, relevant of the reviews
  - Included 28 randomized controlled trials with total of 2454 patients
  - 22 of them involved plant-derived products
  - Significant odds (OR = 1.41) of improvement noted for cannabinoids
  - Did not vary significantly across pain conditions

Figure 2. Improvement in Pain

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events		Placebo Events		Odds Ratio (95% CI)	Favors Placebo / Favors Cannabinoid	Weight, %
	No.	Total No.	No.	Total No.			
Tetrahydrocannabinol (smoked)							
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)		6.51
Nabiximols							
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)		19.02
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)		10.87
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)		20.19
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)		9.84
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)		14.04
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)		4.63
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)		14.91
Subtotal $I^2 = 44.5\%$, ($P = .94$)	241	660	209	660	1.32 (0.94-1.86)		93.49
Overall $I^2 = 47.6\%$, ($P = .64$)	254	685	215	685	1.41 (0.99-2.00)		100.00

Odds indicate 30% or greater improvement in pain with cannabinoid compared with placebo, stratified according to cannabinoid. The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weigh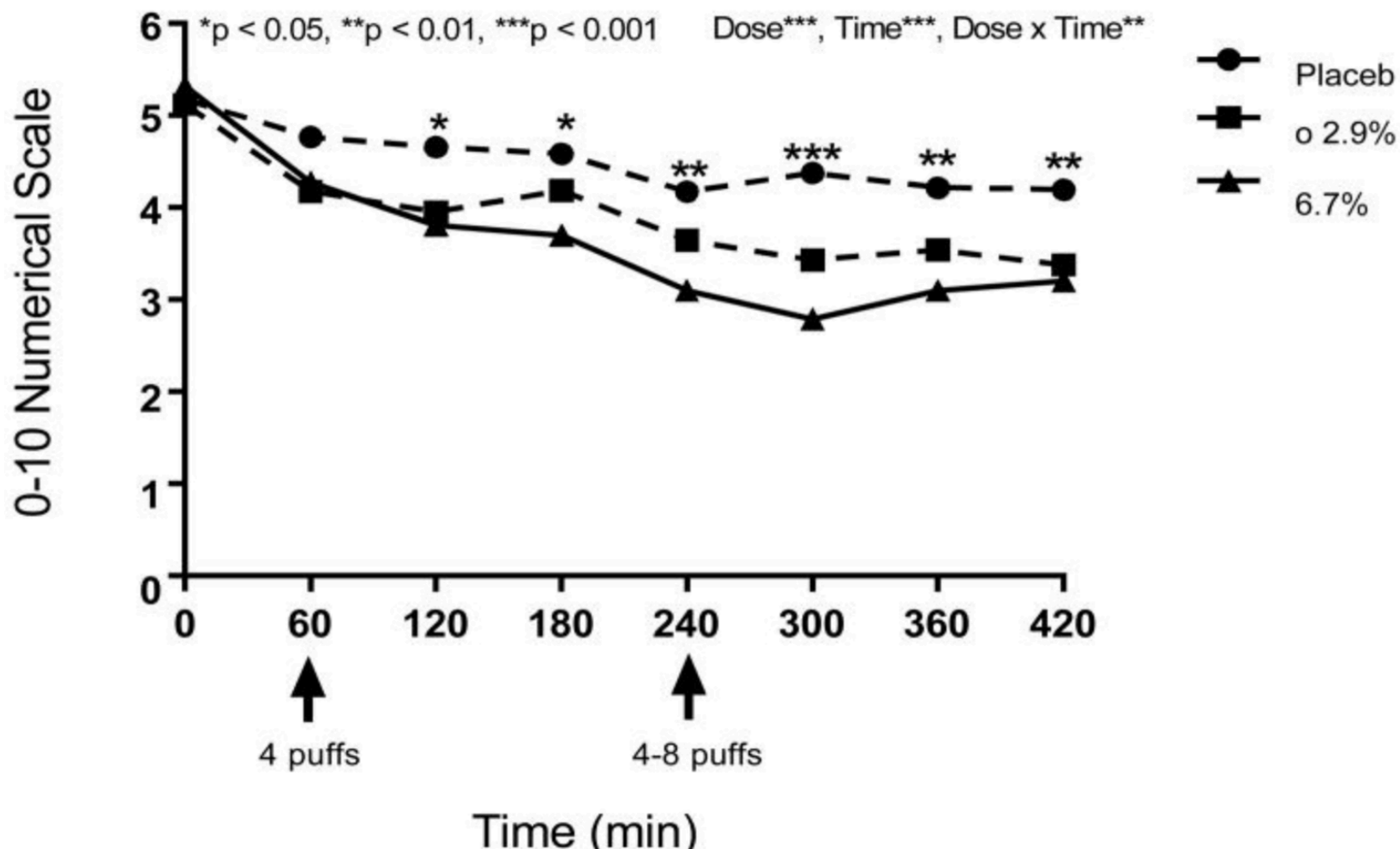t of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall OR and 95% CI. The vertical dashed line shows the summary effect estimate, the dotted shows the line of no effect (OR = 1).

Additional Data on Effectiveness

- Only one study of flower was included in Whiting and it provided the largest effect size
- Positive but modest effect size consistent with other reviews
- NAS also reviewed studies too recent to be included in Whiting et al. (2015)
- Several other studies with flower also suggested larger effect size
- NAS concluded that there was substantial evidence suggesting effect of cannabinoids on pain
  - Note substantial evidence of effect is not the same as substantial effect (seems to be a modest effect)
- Begs two questions? 1) does it actually work; under what conditions, doses, routes of administration; 2) is it analgesic, psychological or other; 3) THC or CBD or terpenes or other?

Pain Intensity

*p < 0.05, **p < 0.01, ***p < 0.001   Dose***, Time***, Dose x Time**

Legend:
- ● Placeb
- ■ o 2.9%
- ▲ 6.7%

X-axis: Time (min); arrows at 60 min "4 puffs" and at 240 min "4-8 puffs"
Y-axis: 0-10 Numerical Scale

An Exploratory Human Laboratory Experiment Evaluating Vaporized Cannabis in the Treatment of Neuropathic Pain From Spinal Cord Injury and Disease.

Wilsey B[1], Marcotte TD[2], Deutsch R[2], Zhao H[3], Prasad H[3], Phan A[3].
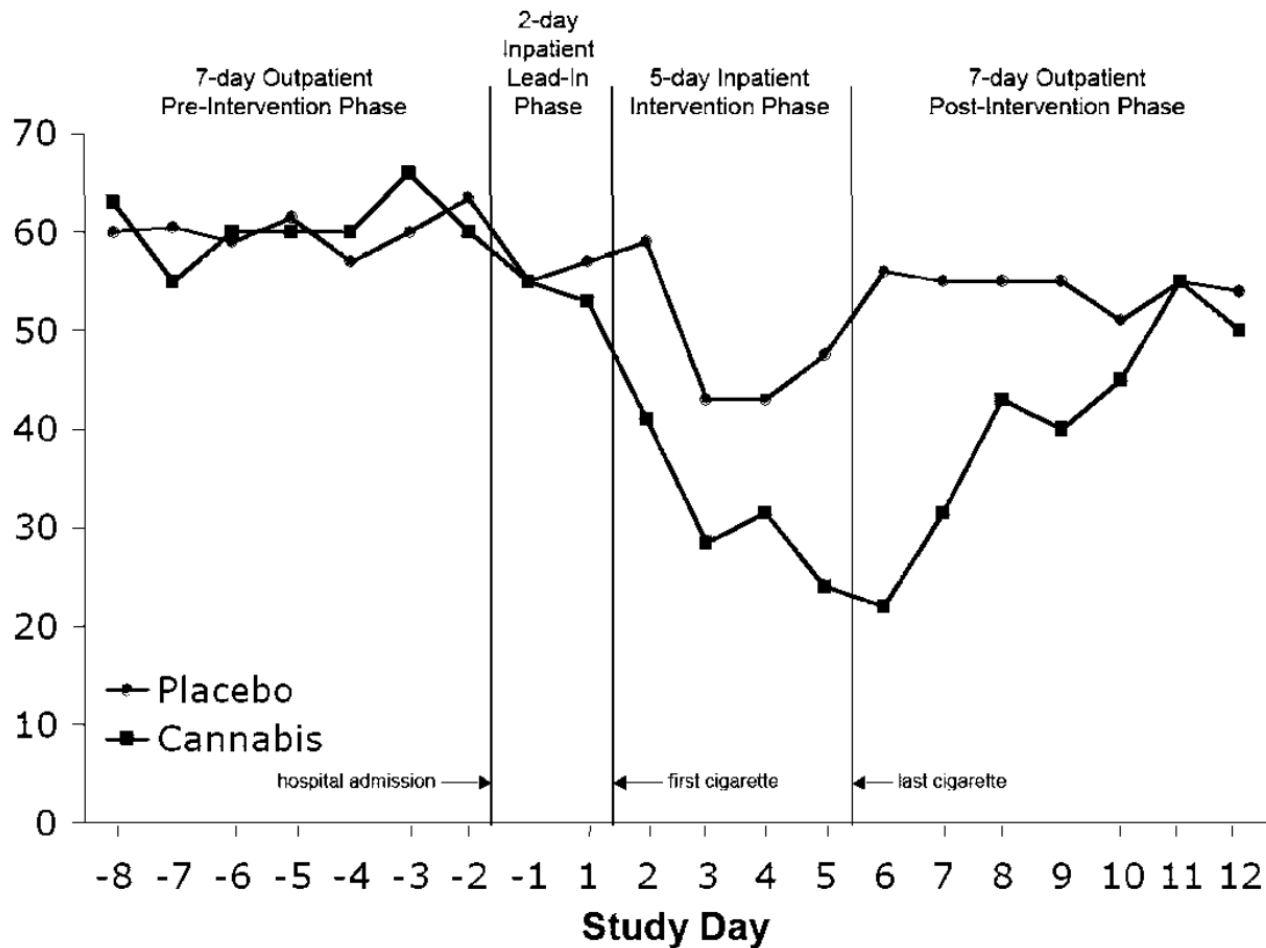
Cannabis in painful HIV-associated sensory neuropathy

A randomized placebo-controlled trial

D.I. Abrams, MD; C.A. Jay, MD; S.B. Shade, MPH; H. Vizoso, RN; H. Reda, BA; S. Press, BS;
M.E. Kelly, MPH; M.C. Rowbotham, MD; and K.L. Petersen, MD

Important to note

- Not all studies find an analgesic effect (i.e., reduction in pain)

- What are the reasons for some differences?

- Study methods

- Formulation (e.g., Sativex is unpleasant to administer, synthetic produces unpleasant effects)

- Administration

- Dose

- Or there might be other mechanisms that mediate the effects

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Figure 1. Forest Plot of Meta-analysis for 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

Favors Hyperalgesia / Favors Analgesia
Hedges g (95% CI)

Association of Cannabinoid Administration With Experimental Pain in Healthy Adults
A Systematic Review and Meta-analysis

Martin J. De Vita, MS; Dezarie Moskal, MS; Stephen A. Maisto, PhD; Emily B. Ansell, PhD

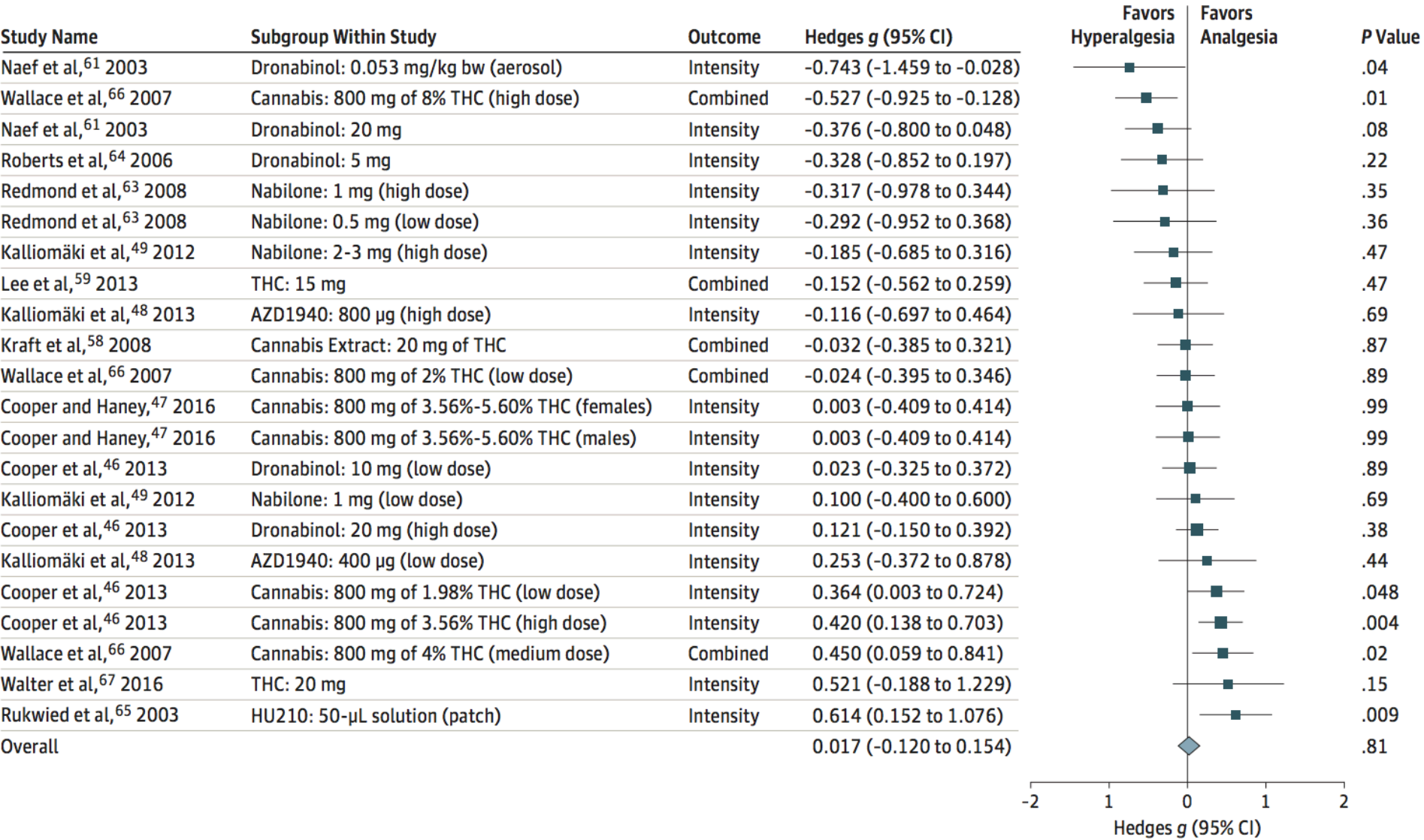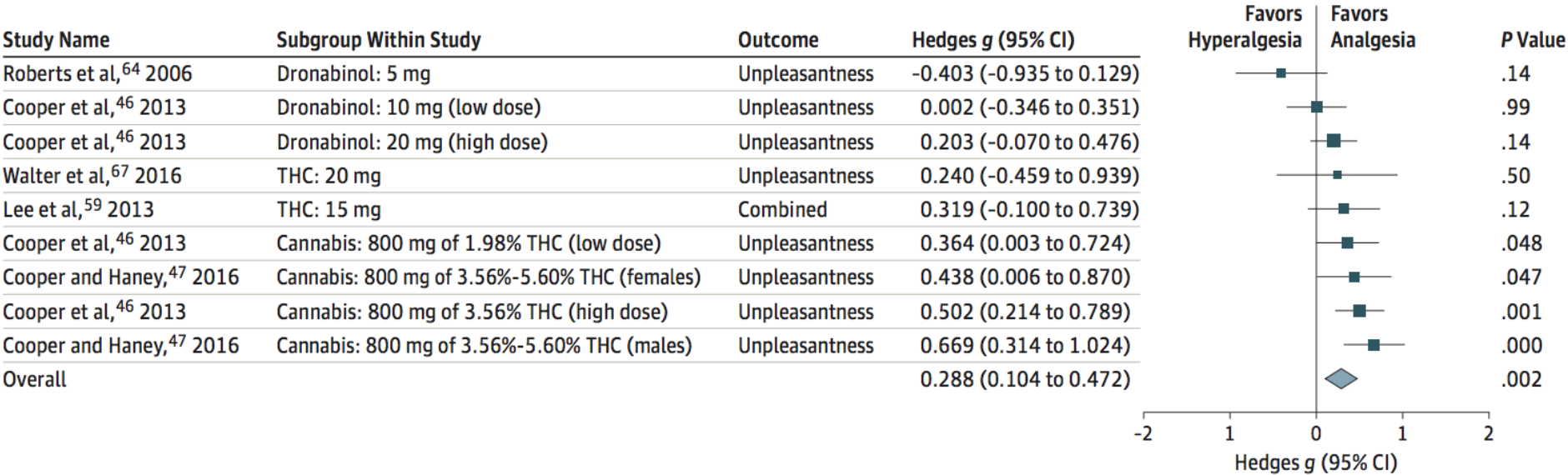**Figure 2. Forest Plot of Meta-analysis for Ongoing Pain Intensity**

Study Name	Subgroup Within Study	Outcome	Hedges g (95% CI)	Favors Hyperalgesia / Favors Analgesia	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

Hedges g (95% CI)

Figure 3. Forest Plot of Meta-analysis for 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

Favors Hyperalgesia | Favors Analgesia

Hedges g (95% CI)

THC indicates Δ^9-tetrahydrocannabinol.

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Key Points

Question What is the association between acute cannabinoid administration and experimental pain reactivity in healthy adults?

Findings This systematic review and meta-analysis of 18 studies including 442 adults found that cannabinoid drugs were associated with modest increases in experimental pain threshold and tolerance, no reduction in the intensity of ongoing experimental pain, reduced perceived unpleasantness of painful stimuli, and no reduction of mechanical hyperalgesia.

Meaning Cannabinoid analgesia may be largely driven by an affective rather than a sensory component. These findings have implications for understanding the analgesic properties of cannabinoids.

Mechanisms?

- Directly impacts pain?
- Impacts perception/interpretation of pain?
- Anxiety?
- Sleep
- Does CBD work by itself?
  - No studies have tested CBD
  - Seems unlikely
  - Data come from mostly studies of 1:1
- Side effect profile changes – remember that one of the main things is cognitive change – but this depends on baseline state of the person.
- How effective/efficient is the cognitive processing of someone who is constantly in pain and maybe on other drugs like opioids?

Additional Points and Questions

- Some reviews suggest that cannabinoids should be a third tier option?

- Why make it a third tier option and not a first tier option?

- Why has GW not pursued Sativex in U.S.? Or Epidiolex for pain?

- Why is it controversial?

Conclusions

- Chronic pain is a HUGE problem
- Majority of people who use medicinally are using for pain
- Strong evidence that there are beneficial effects in pain patients
- Mechanisms are not clear
  - May be analgesic
  - May be psychological or affective
- Optimal formulation, route of administration, dose, cannabinoid profile not clear
- Effects will be clarified with new research