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Medicinal Cannabis
Evidence for Efficacy
Clinical Guidance Development

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Chief Medical ADVISER
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History

- Use of cannabis as medicine is thousands of years old
- Described in Chinese pharmacopeia *Shennong Bencaojing* (c 100 CE)
- Used as an anaesthetic by Chinese surgeon Hua Tuo (c 140-208 CE)
- Chinese term for anaesthesia (麻醉) means “cannabis intoxication”
- Cannabis is one of the 50 fundamental herbs in traditional Chinese medicine

However…

- Cannabis contains >60 pharmacologically active cannabinoids
- Usual pharmacokinetic, pharmacodynamic, bioavailability and toxicology studies lacking
- GMP variable
- Non-standardisation of extracts and dosage
- Potential for harm, addiction and abuse

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Australian Advisory Council on the Medicinal Use of Cannabis and clinical review of evidence

- Established in 2016
- Chaired by Professor Jim Angus
- To assist the Council, States and Territories and clinicians, DoH has commissioned academics from the Universities of NSW, Sydney and Queensland to review the evidence for the use of cannabinoids in palliative care, epilepsy, multiple sclerosis, chemotherapy-induced nausea and vomiting and chronic pain

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Review activity and timelines

1. October 2016-February 2017:
    - Analysis of critical reviews of evidence (5 conditions)
    - Review of existing clinical guidance documents and guideline development approaches
2. February 2017:
    - Agreement on remaining systematic reviews to conduct
3. Remainder 2017:
    - Conduct & publication of remaining systematic reviews
    - Drafts of clinical guidance for consultation

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Review team

- Professor Louisa Degenhardt
- Professor Michael Farrell
- Professor Wayne Hall
- Dr Megan Weier
- Dr Suzanne Nielsen
- Professor Jan Copeland
- Professor Nicholas Buckley
- Clinical experts:
  - *Epilepsy* – A/Professor Geoffrey Herkes
  - *Palliative care* - Professor Meera Agar; A/Professor Melanie Lovell (and later Professor Martin Meucke)
  - *Pain* – Dr Bridin Murnion
  - *Nausea and vomiting* – Professor Meera Agar
  - *Multiple sclerosis* – Dr John Pollard

Literature search (1)

- Multiple databases searched using specific search terms
  - Search strategy guided by specialist Librarian
- Review protocols all registered to Prospero during initial search or early data extraction phase
- Systematic reviews:
  - Priority to randomised controlled trials conducted since 1980
  - Also included observational studies, e.g. case reports, retrospective chart reviews, self-report surveys

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Literature search (2)

- Two reviewers independently examined titles and abstracts for relevance, using Covidence Software
- Relevant articles were obtained in full, and independently assessed by two reviewers for suitability for inclusion
- Reasons for exclusion were documented in Covidence
- Disagreements addressed and consensus reached

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Data assessment and extraction (1)

- Two independent reviewers for all extraction
- Cochrane Risk of Bias (RoB) tool
  - Original tool used for randomised trials – classified as low, medium or high risk of bias
  - Revised tool used for non-randomised studies – classified as low, moderate, serious or critical risk, or no information
- GRADE methodological quality
  - Quality of empirical studies
- Details of authors' disclosed funding and conflicts of interest reviewed

Data assessment and extraction (2)

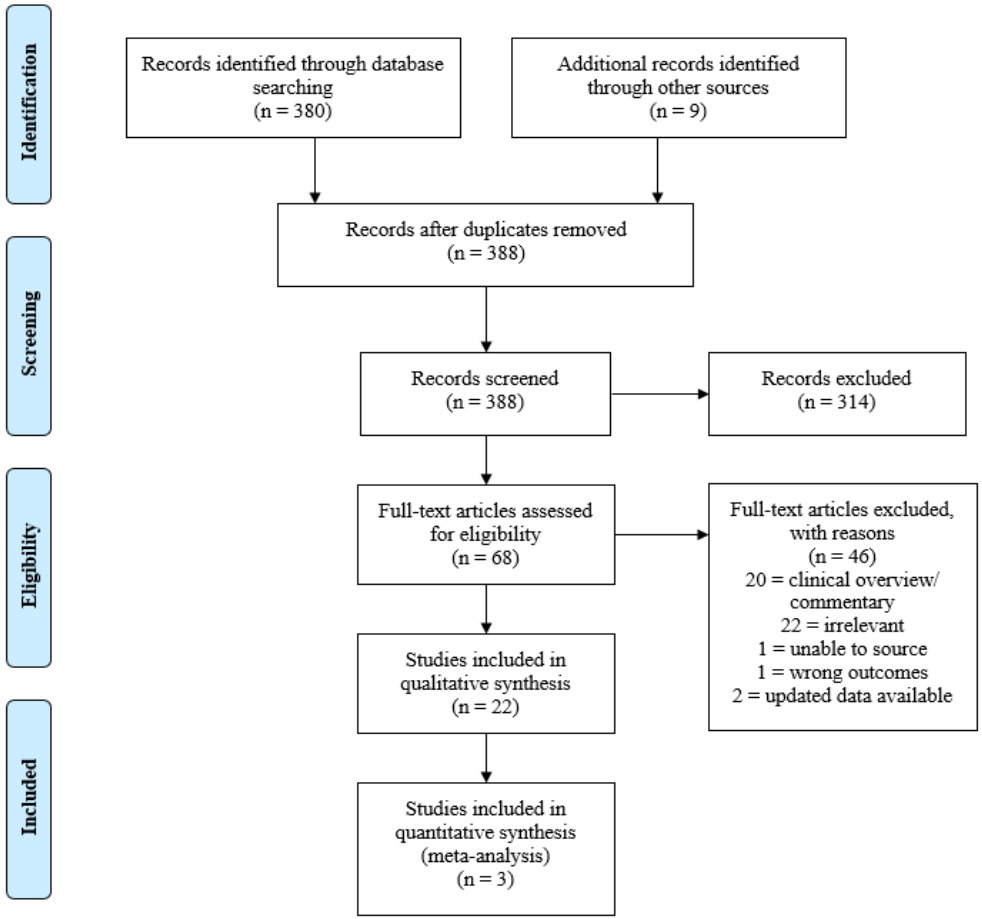
- Study summary
  - Author, aims, publication type, study design, years of study, conditions examined, types of cannabinoids, risk of bias rating (randomised or non-randomised),GRADE rating, cannabinoid place on therapeutic hierarchy, funding and COIs
- Intervention details
  - Conditions examined, age and gender range of participants, treatment duration, comparators used, cannabinoid used and dosage, pharmaceutical grading
- Outcome
  - Outcomes measured as identified in review protocol (dichotomous or continuous outcome variables), comparator outcomes (if available), withdrawals, adverse events

Findings

- Epilepsy
- Palliative Care

Epilepsy

- Study-level search - 383 articles
  - Clinical trials and observational studies
  - 314 articles excluded
  - 62 articles full text screening
  - 22 studies extracted
    - 5 randomised controlled trials (3 studies for meta-analysis)
    - 4 non-randomised clinical trials
    - 13 observational or self-report studies



Outcomes - Epilepsy

- Complete seizure freedom
- 50% or greater reduction in seizure frequency (responder rate)
- Quality of life outcomes
- Withdrawals – adverse events or any reason
- Adverse events
- Serious adverse events

Study type	N	Cannabinoid examined (N)	Pharmaceutical grade product (N)	Comparator (N)	GRADE range
RCT	5	CBD (3)	Yes (2) No (1) Not stated (2)	Placebo (5)	2-4
Open label clinical trial	4	CBD (4)	Yes (4)	None (4)	3
Observational	9	CBD (4); cannabis sativa (2); THC (2); CBD:THC (3)	Yes (2); No (3); Not stated (2)	None (100)	1-2
Self-report	4	CBD:THC (1); CBD only (2); Not reported (1)	No (100)	None (100)	1

GRADE scores:

4	= high
3	= moderate
2	= low
1/0	= very low

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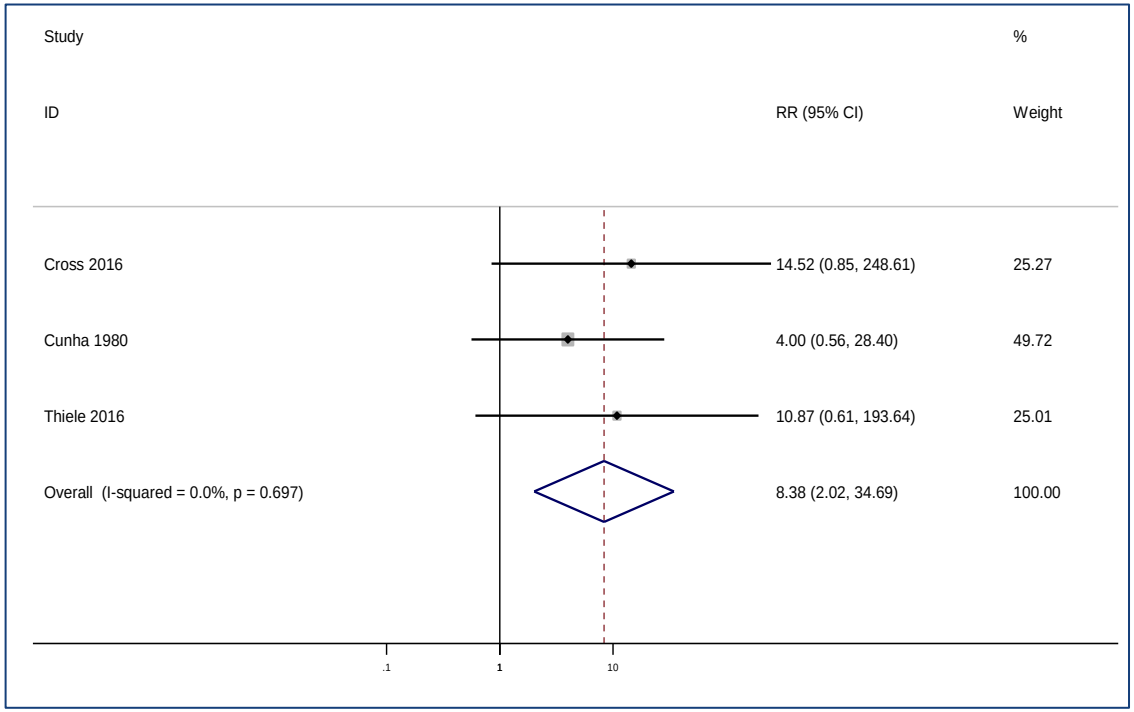
Products and doses

Cannabinoid	Commercial or pharma product names	Dose range	Delivery form and method
CBD	Epidiolex; Rheem Oil	RCT: 20mg/kg/day Observational: 2-50mg/kg/day	Oral – capsule or oil
CBD:THC	Charlotte's Web	1-28mg CBD/kg/day: 0.1-0.7 mg THC/kg/day	Oral – oil
THC		0.07-0.14mg/kg/day	Oral – oil or tincture
Cannabis sativa		0.5-8.0g/day	Smoked, vaporised or drunk

Complete seizure freedom

Studies	Participants	Pooled relative risk [95% CI]	I^2	Non-randomised studies	Non-randomised participants	Non-randomised studies pooled estimate [95%CI]	I^2
3	307	**8.38 [2.02; 34.69]; p = 0.003**	0.0	8	523	**10% [5;16]; p =0.00**	71.8



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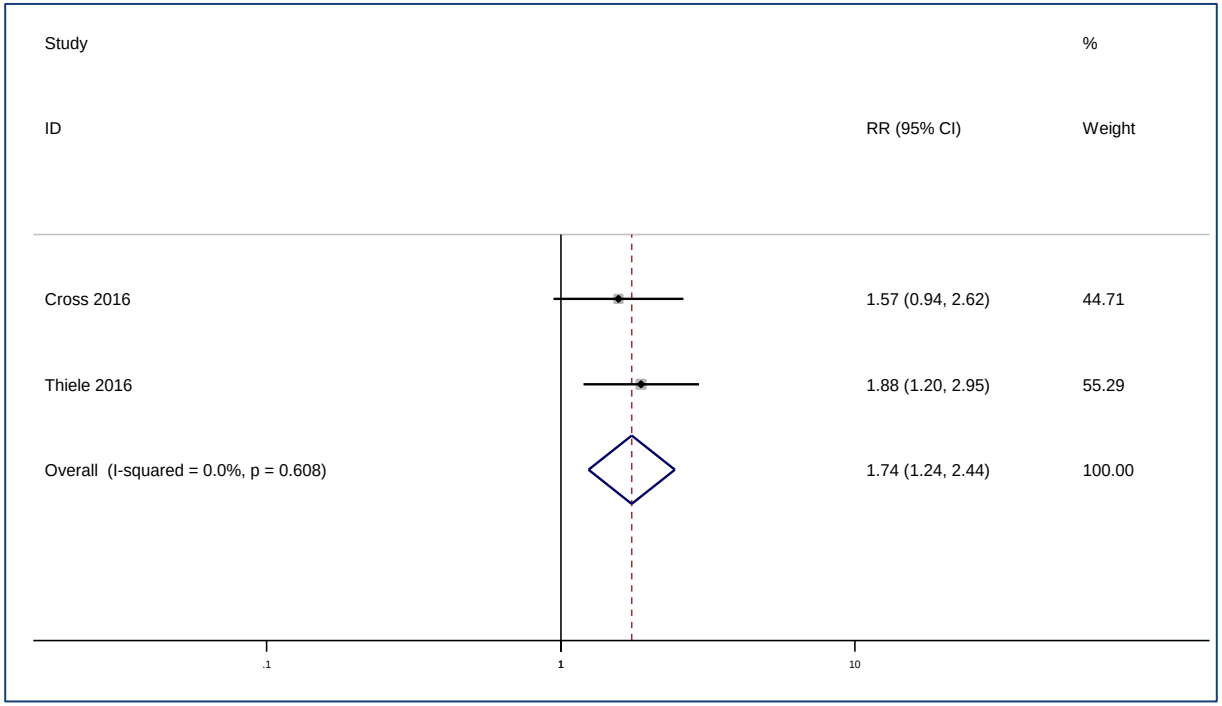
50% or greater reduction in seizure frequency

Studies	Participants	Pooled relative risk [95% CI]	I^2	Non-randomised studies	Non-randomised participants	Non-randomised studies pooled estimate [95%CI]	I^2
2	290	**1.74 [1.24; 2.44]; p = 0.001**	0.0	14	780	**56% [40;72]; p = 0.00**	94.9



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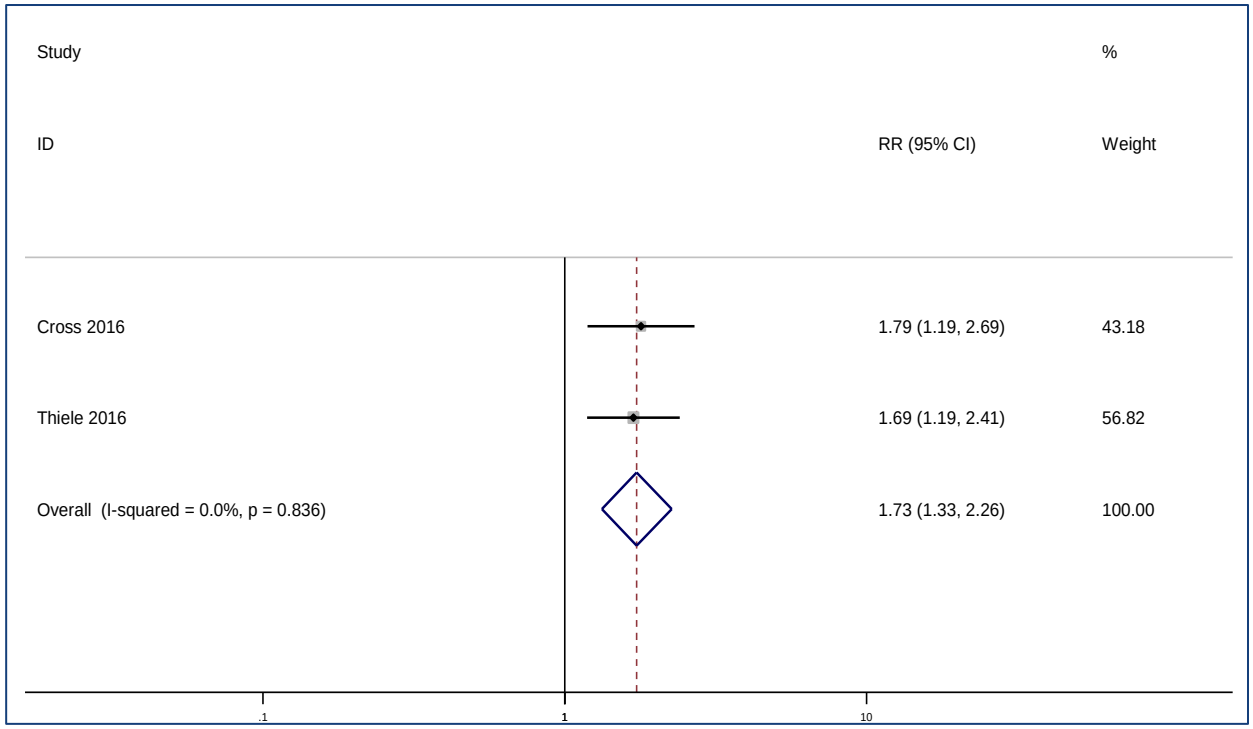
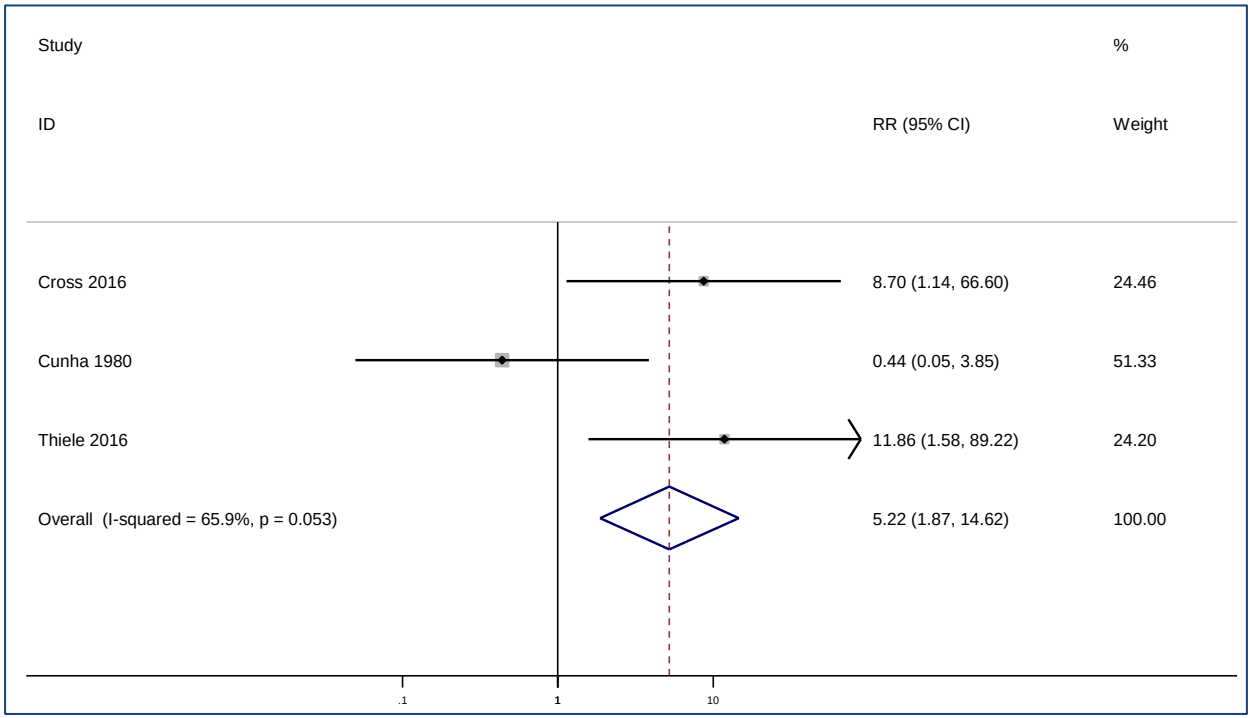
Quality of Life

Studies	Participants	Pooled relative risk [95% CI]	I^2	Non-randomised studies	Non-randomised participants	Non-randomised studies pooled estimate [95%CI]	I^2
2	274	**1.73 [1.33; 2.26]; p = 0.000**	0.0	8	214	**38% [28;48]; p = 0.00**	92.8



Withdrawals

Studies	Participants	Pooled relative risk [95% CI]	I^2	Non-randomised studies	Non-randomised participants	Non-randomised studies pooled estimate [95%CI]	I^2
3	307	**5.23 [1.87; 14.62]; p = .002**	65.9	3	311	**8% [2;12]; p = 0.00**	0.0



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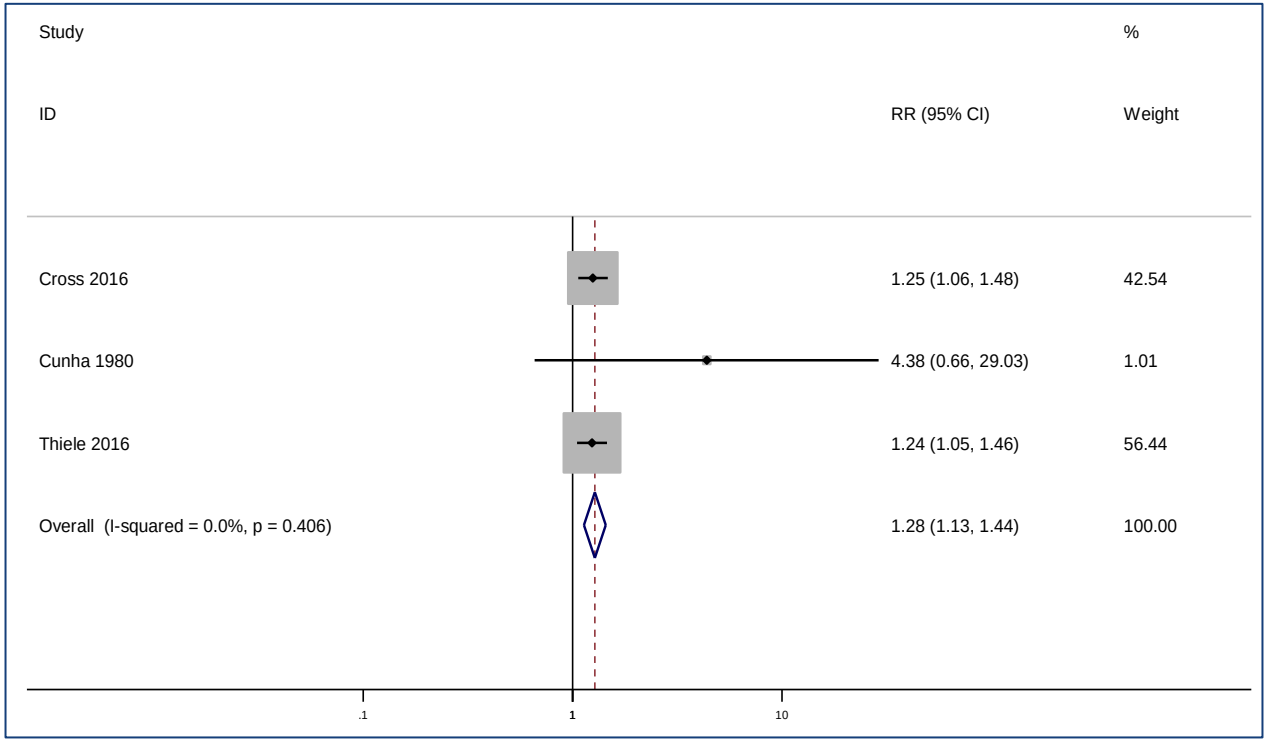
Adverse Events

Studies	Participants	Pooled relative risk [95% CI]	I^2	Non-randomised studies	Non-randomised participants	Non-randomised studies pooled estimate [95%CI]	I^2
3	307	**1.28 [1.13; 1.44]; p = .001**	0.0	10	504	**46% [28;65]; p = 0.00**	95.1



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Conclusions - Epilepsy

- Limited RCTs indicate there may be therapeutic benefit of CBD in treating epilepsy and seizures – both seizure freedom and significant reduction in seizures
- CBD relatively well tolerated; evidence for THC and CBD:THC products are all observational
- Observational trials are positive, but many limited by lack of control and data on dosing
- Safety issues: dosing, product concentrations, interactions with other medications, non-medically supervised delivery

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Original Article

Trial of Cannabidiol for drug-resistant seizures in the Dravet Syndrome

Orrin Devinsky, M.D., J. Helen Cross, Ph.D., F.R.C.P.C.H., Linda Laux, M.D., Eric Marsh, M.D., Ian Miller, M.D., Rima Nabbout, M.D., Ingrid E. Scheffer, M.B., B.S., Ph.D., Elizabeth A. Thiele, M.D., Ph.D., Stephen Wright, M.D., for the Cannabidiol in Dravet Syndrome Study Group

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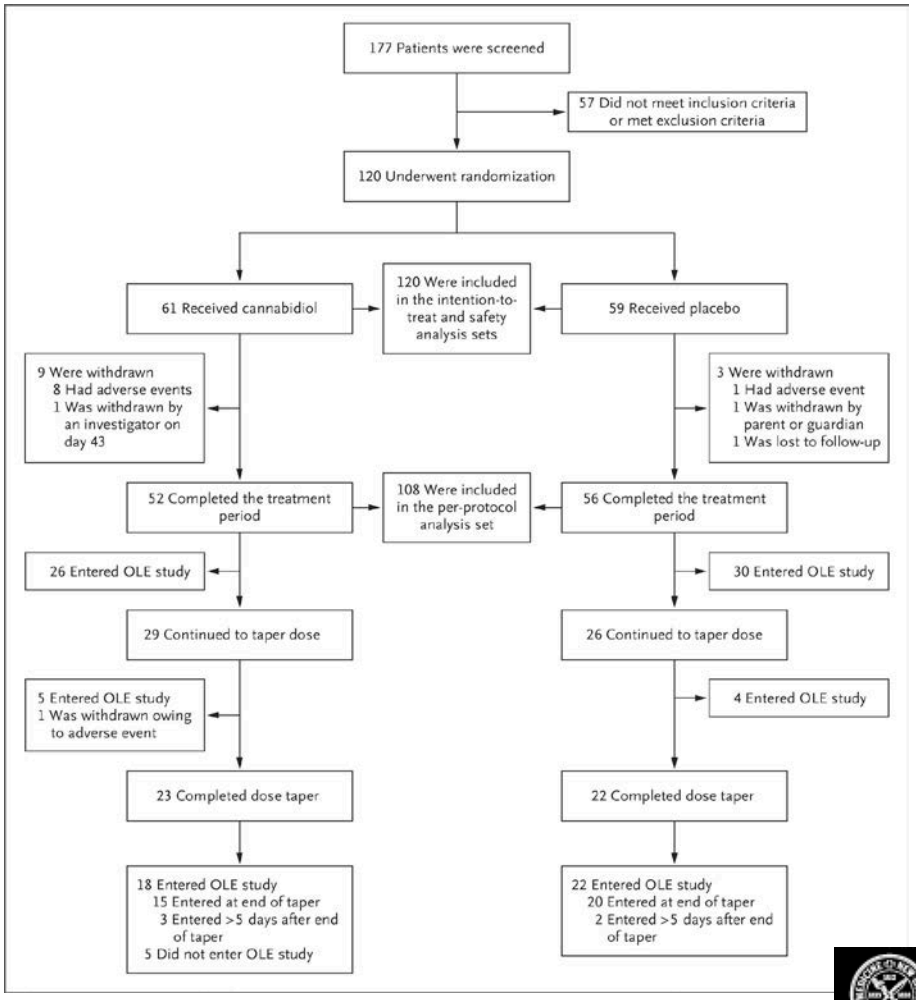
Screening, randomization, treatment period, and taper period



Key baseline characteristics of the trial groups

Table 1. Key Baseline Characteristics of the Trial Groups.*

Characteristic	Cannabidiol (N=61)	Placebo (N=59)	Total (N=120)
Age — yr			
Mean	9.7±4.7	9.8±4.8	9.8±4.8
Median (range)	9.1 (2.5–18.0)	9.2 (2.3–18.4)	9.2 (2.3–18.4)
Sex — no. (%)			
Female	26 (43)	32 (54)	58 (48)
Male	35 (57)	27 (46)	62 (52)
Geographic region — no. (%)			
United States	35 (57)	37 (63)	72 (60)
Rest of world	26 (43)	22 (37)	48 (40)
Body-mass index at baseline†	18.3±4.5	19.1±4.7	18.7±4.6
No. of previous antiepileptic drugs‡	4.6±4.3	4.6±3.3	4.6±3.8
No. of concomitant antiepileptic drugs	3.0±1.0	2.9±1.0	2.9±1.0
Antiepileptic drugs — no. (%)			
Clobazam	40 (66)	38 (64)	78 (65)
Valproate, all forms	37 (61)	34 (58)	71 (59)
Stiripentol	30 (49)	21 (36)	51 (42)
Levetiracetam	16 (26)	17 (29)	33 (28)
Topiramate	16 (26)	15 (25)	31 (26)
Other interventions — no. (%)			
Ketogenic diet	6 (10)	4 (7)	10 (8)
Vagus-nerve stimulation	6 (10)	9 (15)	15 (12)

* Plus–minus values are means ±SD.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ These drugs were no longer being taken.

Primary efficacy end point of percentage change in convulsive-seizure frequency in each trial group

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.

Devinsky O et al. N Engl J Med 2017;376:2011-2020

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Summary of Secondary End-Point Results during the Treatment Period (Intention-to-Treat Analysis Set)

Table 3. Summary of Secondary End-Point Results during the Treatment Period (Intention-to-Treat Analysis Set).*

End Point	Cannabidiol vs. Placebo		P Value†
	Difference (95% CI)	Odds Ratio (95% CI)‡	
Change from baseline in CGIC score	−1.0 (−1.0 to 0.0)§		0.02
Reduction in convulsive seizures from baseline¶			
≥25% reduction		2.10 (1.01 to 4.35)	0.05
≥50% reduction: key secondary end point		2.00 (0.93 to 4.30)	0.08
≥75% reduction		2.21 (0.82 to 5.95)	0.11
100% reduction	4.9 (−0.5 to 10.3)‖		0.08
Percentage change from baseline in seizure frequency**			
Total seizures	−19.20 (−39.25 to −1.17)§		0.03
Total nonconvulsive seizures	0.00 (−21.36 to 31.59)§		0.88
Reduction from baseline in duration of seizure subtypes††			
Tonic–clonic seizures		2.48 (0.94 to 6.51)	0.07
Tonic seizures		3.40 (0.52 to 22.23)	0.20
Clonic seizures		1.25 (0.15 to 10.57)	0.84
Atonic seizures		7.44 (0.27 to 204.96)	0.24
Myoclonic seizures		2.89 (0.58 to 14.47)	0.20
Countable partial seizures		6.01 (0.83 to 43.21)	0.08
Other partial seizures		1.00 (<0.01 to >999.99)	1.00
Absence seizures		0.61 (0.14 to 2.62)	0.50
Change from baseline in other variables‡‡			
Sleep-disruption score	−0.4 (−1.5 to 0.7)		0.45
Epworth Sleepiness Scale score	1.5 (−0.2 to 3.2)		0.08
Quality of Life in Childhood Epilepsy score	1.5 (−3.8 to 6.8)		0.58
Vineland-II score	−2.6 (−6.8 to 1.6)		0.21
Inpatient hospitalizations due to epilepsy	0.0 (0.0 to 0.1)		0.54

* Scores on the Caregiver Global Impression of Change (CGIC) scale range from 1 (very much improved) to 7 (very much worse). Scores on the numerical rating scale for sleep disruption range from 0 to 10, with higher scores indicating greater disruption. Scores on the Epworth Sleepiness Scale range from 0 to 24, with higher scores indicating greater daytime sleepiness. Scores on the Quality of Life in Childhood Epilepsy questionnaire range from 0 to 100, with higher scores indicating better function. Age-standardized scores on the Vineland Adaptive Behavior Scales, second edition (Vineland-II), range from 20 to 160, with higher scores indicating better behavioral adaptation.

† P values of less than 0.05 were considered to indicate statistical significance. P values for change in CGIC score and percentage change from baseline in seizure frequency were calculated with the use of a Wilcoxon rank-sum test. P values for reduction in convulsive seizures for baseline were calculated with the use of a Cochran–Mantel–Haenszel test. P values for reduction from baseline in duration of seizure subtypes were calculated with the use of ordinal logistic regression. P values for change from baseline in other variables were calculated with the use of an analysis of covariance. P values were not adjusted for multiple comparisons.

‡ Odds ratios for reduction in convulsive seizures from baseline were calculated with the use of a Cochran–Mantel–Haenszel test. Odds ratios for reduction from baseline in duration of seizure subtypes were calculated with the use of ordinal logistic regression. Values greater than 1 are in favor of cannabidiol, and values less than 1 are in favor of placebo.

§ Shown is the estimated median difference (Hodges–Lehmann estimate). Negative values are numerically in favor of cannabidiol, and positive values are numerically in favor of placebo.

¶ The number of patients in each category was as follows: reduction of 25% or more, 38 patients in the cannabidiol group and 26 patients in the placebo group; reduction of 50% or more, 26 and 16, respectively; reduction of 75% or more, 14 and 7; and 100% reduction, 3 and 0. Because there were no patients in the placebo group with a 100% reduction, an odds ratio could not be calculated.

‖ Shown is the difference in percentage points, calculated with the use of a Cochran–Mantel–Haenszel test. Positive values indicate a difference in favor of cannabidiol, and negative values indicates a difference in favor of placebo.

** The number of patients analyzed was as follows: total seizures, 61 patients in the cannabidiol group and 59 patients in the placebo group; and total nonconvulsive seizures, 37 and 41, respectively.

†† This end point was assessed by means of the Caregiver Global Impression of Change in Seizure Duration (responses included decrease, no change, or increase in average duration). The number of patients analyzed was as follows: tonic–clonic seizures, 49 patients in the cannabidiol group and 41 patients in the placebo group; tonic seizures, 12 and 15, respectively; clonic seizures, 11 and 7; atonic seizures, 3 and 7; myoclonic seizures, 14 and 18; countable partial seizures, 12 and 13; other partial seizures, 3 and 5; and absence seizures, 16 and 19.

‡‡ Shown is the adjusted mean difference, calculated with the use of an analysis of covariance. For the sleep-disruption score, Epworth Sleepiness Scale score, and Vineland-II score, negative values are numerically in favor of cannabidiol, and positive values are numerically in favor of placebo. For the Quality of Life in Childhood Epilepsy score, positive values indicate a difference in favor of cannabidiol, and negative values indicate a difference in favor of placebo.

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Adverse events occurring with a frequency of greater than 10% in either trial group, according to system organ class and preferred term

Table 4. Adverse Events Occurring with a Frequency of Greater Than 10% in Either Trial Group, According to System Organ Class and Preferred Term.*

System Organ Class and Preferred Term	Cannabidiol (N = 61)	Placebo (N = 59)
	no. of patients (%)	
Gastrointestinal		
Diarrhea	19 (31)	6 (10)
Vomiting	9 (15)	3 (5)
General		
Fatigue	12 (20)	2 (3)
Pyrexia	9 (15)	5 (8)
Infections: upper respiratory tract infection	7 (11)	5 (8)
Metabolism: decreased appetite	17 (28)	3 (5)
Nervous system		
Convulsion	7 (11)	3 (5)
Lethargy	8 (13)	3 (5)
Somnolence	22 (36)	6 (10)

* Events were classified according to the *Medical Dictionary for Regulatory Activities*, version 17.0.

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Cannabidiol for drug-resistant seizures in Dravet Syndrome – Conclusions

Among children and young adults with the Dravet syndrome, a developmental disorder that is associated with treatment-resistant seizures, cannabidiol:

- reduced the frequency of convulsive seizures, but
- caused sleepiness and elevated liver enzymes in some patients

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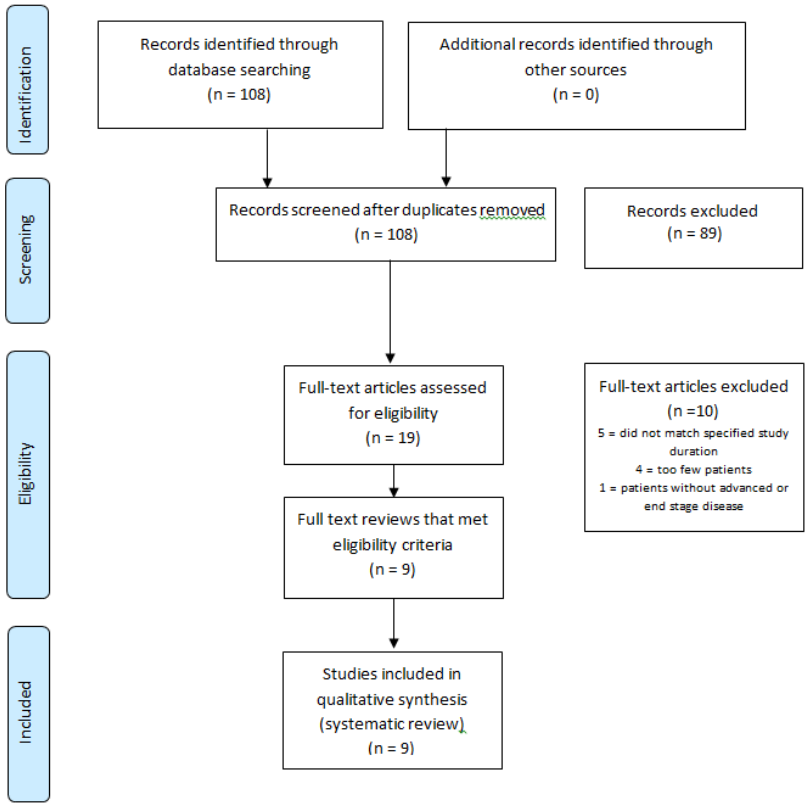
Palliative Care

- Insufficient quality systematic reviews or meta-analyses to conduct review of reviews
- One recent systematic review and meta-analysis by Meucke et al. (2016)
  - Contacted author, agreement to update study-level review
  - No new studies identified since earlier review search
  - 9 studies, examining advanced tumour illness (N=5), HIV (N=3), and Alzheimer's disease (N=1)



Outcomes: Palliative Care

- Change in pain intensity
- Percentage of patients reporting a 30% reduction in pain
- Other analgesic use
- Functional status; physical functioning
- Functional status; emotional functioning
- Quality of life: Participant ratings of global improvements and satisfaction (including weight loss or gain)
- Improvements in quality of sleep
- Digestive discomfort measures (nausea, vomiting, appetite)
- Adverse events

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Study type	N	Cannabinoid examined (N)	Pharmaceutical grade product (N)	Comparator (N)	GRADE range
RCT	6	THC (4); Dronabinol (2); THC:CBD (1); Nabiximols (1); OCE* (1)	Yes (2); No (4)	Placebo (6)	2-3
Double-blind randomized trial	1	Dronabinol (1)	No (1)	Active comparator (1); Placebo (1)	3
Cross-over study	1	Dronabinol (1)	Yes (1)	Placebo (1)	2
Randomized open-label study	1	Dronabinol (1)	Yes (1)	Active comparator (1)	1

GRADE scores:
4 = high
3 = moderate
2 = low
1/0 = very low

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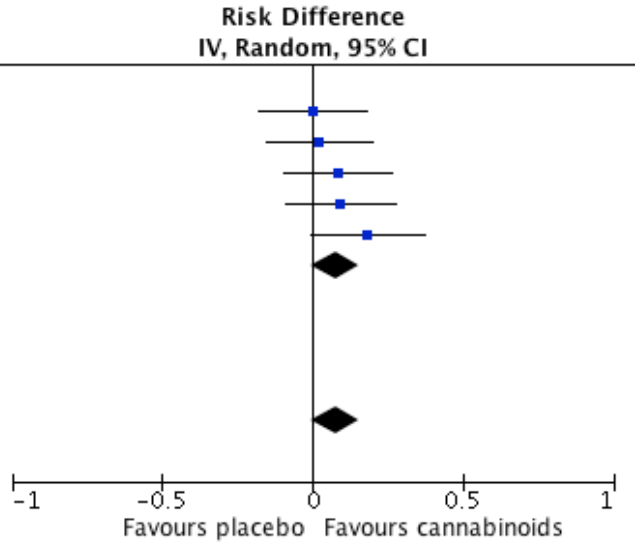
>30% Pain reduction

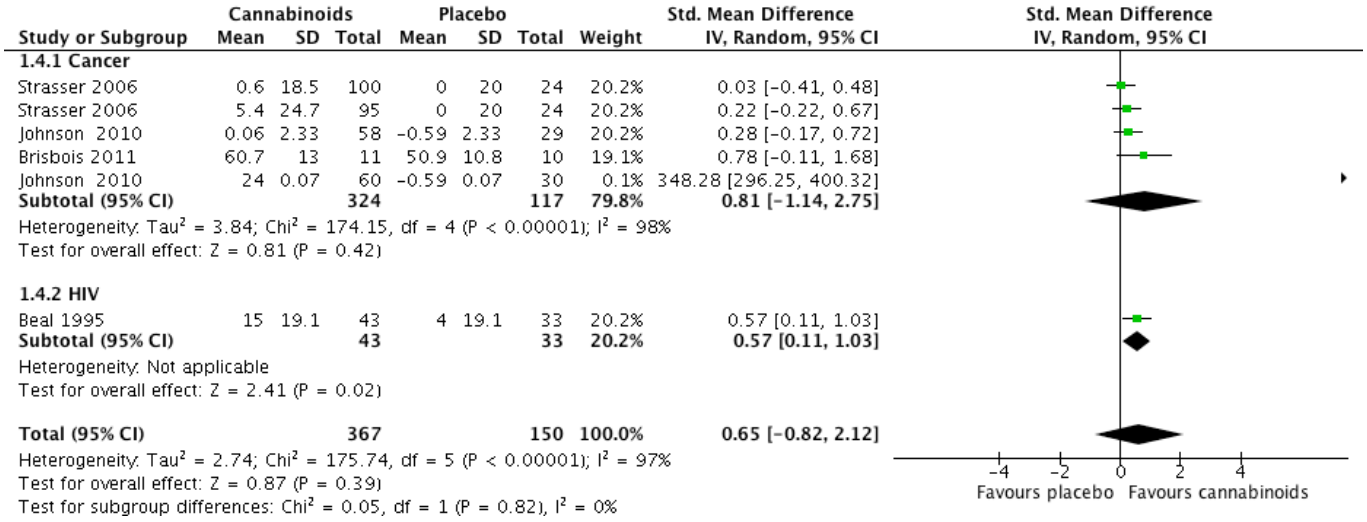
Condition	N Studies	Effect estimate	Author conclusion on effect
Cancer	2	0.07 [-0.0; 0.16]; p = 0.07	Trend towards favouring cannabinoids

Study or Subgroup	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Difference IV, Random, 95% CI
1.1.1 Cancer						
Johnson 2010	12	58	6	29	20.2%	0.00 [-0.18, 0.18]
Portenoy 2012	23	90	7	30	21.2%	0.02 [-0.15, 0.20]
Portenoy 2012	28	88	7	30	20.3%	0.08 [-0.10, 0.26]
Portenoy 2012	32	91	8	31	19.7%	0.09 [-0.09, 0.28]
Johnson 2010	23	60	6	30	18.5%	0.18 [-0.01, 0.37]
Subtotal (95% CI)		**387**		**150**	**100.0%**	**0.07 [-0.01, 0.16]**
Total events	118		34			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.32$, df = 4 (P = 0.68); $I^2 = 0\%$						
Test for overall effect: Z = 1.80 (P = 0.07)						
Total (95% CI)		**387**		**150**	**100.0%**	**0.07 [-0.01, 0.16]**
Total events	118		34			
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.32$, df = 4 (P = 0.68); $I^2 = 0\%$						
Test for overall effect: Z = 1.80 (P = 0.07)						
Test for subgroup differences: Not applicable						



Appetite

Condition	N Studies	Effect estimate	Author conclusion on effect
HIV/AIDS	1	**0.57 [0.11; 1.03] p = 0.02**	Cannabinoids significantly better than cannabinoids
Cancer	3	0.81 [-1.14; 2.75] p = 0.42	Not significantly different to placebo
Total	4	0.65 [-0.82; 2.12] p = 0.39	Not significantly different to placebo



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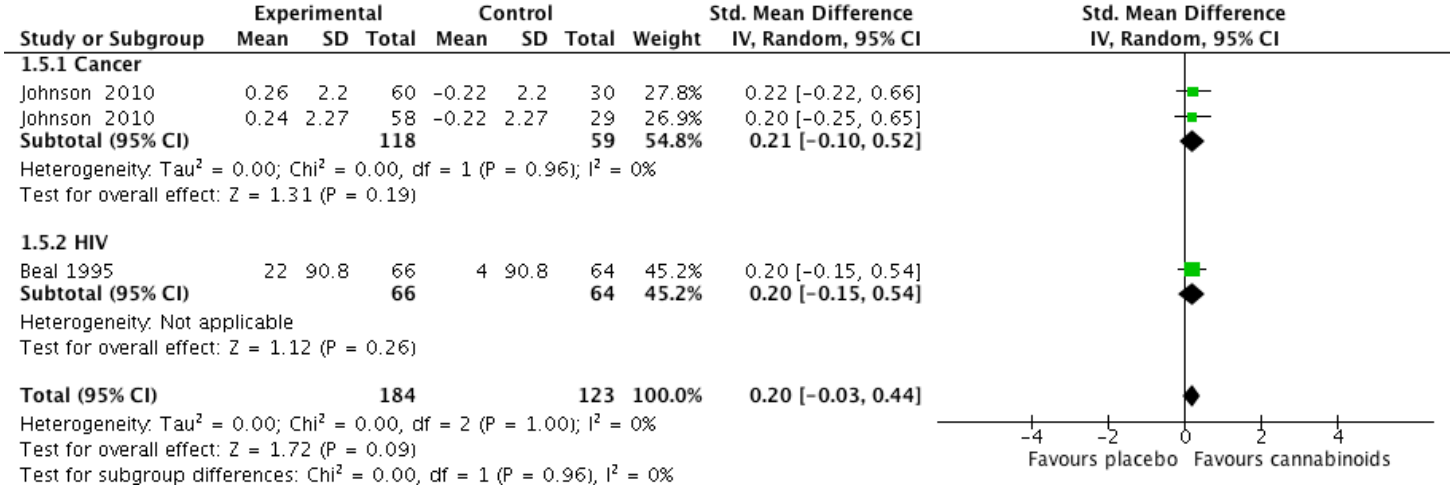
Nausea and Vomiting

Condition	N Studies	Effect estimate	Author conclusion on effect
Cancer	1	0.21 [-0.10; 0.52] p = 0.19	Not significantly different to placebo
HIV/AIDS	1	0.20 [-0.15; 0.54] p = 0.26	Not significantly different to placebo
Total	2	0.20 [-0.03; 0.44] p = 0.09	Mixed, favours cannabinoids



Conclusions: Palliative care

- Low level of evidence for use of cannabinoids in cancer
  - Trend towards benefit in reducing pain and depressed mood
  - Megestrol acetate > Dronabinol in
    - increasing appetite, weight gain, and health-related quality of life
    - significantly better tolerability
- Low level of evidence supporting use of cannabis in HIV palliative care
  - Greater weight gain and increase in appetite
  - Trend toward more symptoms of mental illness
- Low level of evidence for use of cannabis in Alzheimer's disease
  - More weight gain & less negative affect for Dronabinol
  - Cross-over trials

Aims of guidance documents

- Overview of current evidence for use (based on review)
- Working group consultation
- Grade strength and quality of evidence
- International approaches to condition
- Products used and suggested dosing
- Expected side effects, tolerance, and safety
- Auditing outcomes