Drug Free Australia series – Media suppression of alarming cannabis harms

Episode 5 – Cannabis and pain

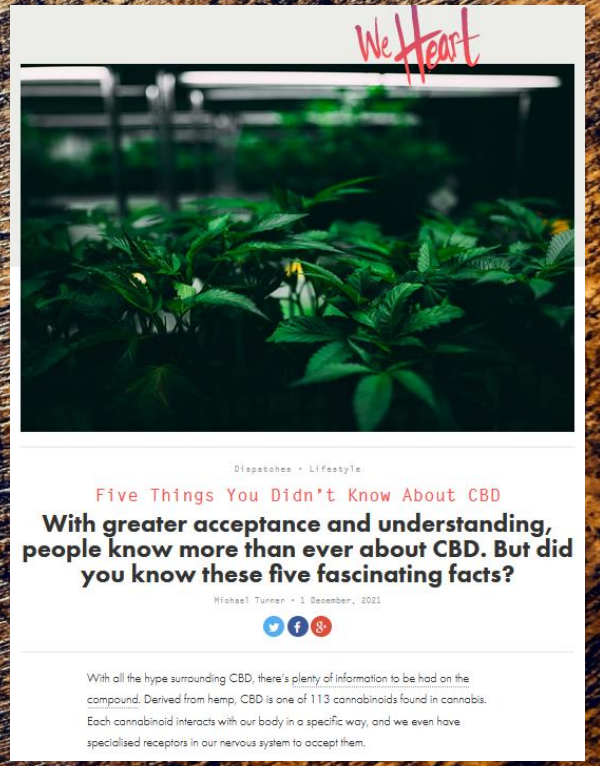
DRUG FREE AUSTRALIA

Cannabidiol (CBD)

- The wonder drug touted to cure most everything

  "1. It's One Of The Fastest-Growing Industries In History: You can buy pharmaceutical grade CBD oil in stores and at several online providers all over the country. This massive spread of CBD products is due to the incredible demand for CBD and CBD-based products; causing the industry to become one of the fastest-growing in history."

- Chief application is for chronic pain
  - non-psychoactive constituent of cannabis
  - promoted as benign, not causing psychosis like THC



https://www.we-heart.com/2020/04/13/five-things-you-didnt-know-about-cbd/

Fact

- 62% of Australians in 2020 using cannabis for ‘chronic pain’
  - another 12% for other pain conditions – migraines etc
  - so 3 in every 4 patients using cannabis for pain

Application Date	Status	Decision Date	Indication	Consulting Locations. State or Territory	SUSMP Schedule	Patient Gender	Previous SAS Number
24/8/2020	Approved	25/8/2020	Achalasia	NSW	Schedule 4	Male	No
10/5/2020	Approved	11/5/2020	Achalasia	VIC	Schedule 4	Male	No
17/4/2020	Approved	17/4/2020	Achalasia	QLD	Schedule 4	Male	No
16/1/2020	Approved	16/1/2020	Achalasia	QLD	Schedule 4	Female	No
6/1/2020	Approved	6/1/2020	Achalasia	SA	Schedule 4	Female	No
20/12/2019	Approved	23/12/2019	Achalasia	VIC	Schedule 4	Male	Yes
5/12/2019	Approved	5/12/2019	Achalasia	VIC	Schedule 4	Male	No
20/9/2019	Approved	20/9/2019	Achalasia	NSW	Schedule 4	Male	No
22/3/2020	Approved	23/3/2020	AD - Alzheimer's disease	VIC	Schedule 4	Male	No
7/3/2020	Approved	10/3/2020	AD - Alzheimer's disease	VIC	Schedule 4	Female	No
2/12/2019	Approved	3/12/2019	AD - Alzheimer's disease	VIC	Schedule 4	Female	Yes
10/11/2019	Approved	12/11/2019	AD - Alzheimer's disease	VIC	Schedule 4	Female	Yes
8/11/2019	Approved	8/11/2019	AD - Alzheimer's disease	VIC	Schedule 4	Female	No
25/10/2019	Approved	25/10/2019	AD - Alzheimer's disease	VIC	Schedule 4	Female	No
11/10/2019	Approved	11/10/2019	AD - Alzheimer's disease	VIC	Schedule 4	Female	Yes
29/9/2020	Approved	30/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 8	Male	No
29/9/2020	Approved	30/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 8	Male	Yes
28/9/2020	Approved	29/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 8	Male	No
24/9/2020	Approved	28/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 8	Male	No
23/9/2020	Approved	24/9/2020	ADHD - Attention deficit disorder with hyperactivity	VIC	Schedule 8	Male	No
22/9/2020	Approved	24/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 8	Male	No
22/9/2020	Approved	24/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 8	Male	No
22/9/2020	Approved	24/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 8	Male	Yes
22/9/2020	Approved	24/9/2020	ADHD - Attention deficit disorder with hyperactivity	VIC	Schedule 8	Male	No
21/9/2020	Approved	22/9/2020	ADHD - Attention deficit disorder with hyperactivity	NSW	Schedule 8	Male	No
18/9/2020	Approved	22/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 8	Male	No
15/9/2020	Approved	16/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 8	Male	No
14/9/2020	Approved	15/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 4	Male	No
14/9/2020	Approved	15/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 4	Male	No
14/9/2020	Approved	16/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 8	Male	No
10/9/2020	Approved	11/9/2020	ADHD - Attention deficit disorder with hyperactivity	QLD	Schedule 4	Male	No
9/9/2020	Approved	10/9/2020	ADHD - Attention deficit disorder with hyperactivity	VIC	Schedule 8	Female	No

Australian prescriptions

The science

- CBD no better than placebo in 15 of 16 random control trials
  - varying amounts of CBD by product
  - contain other, sometimes harmful, chemicals
  - linked to adverse events and liver damage

The JOURNAL of PAIN USASP

FOCUS ARTICLE | ARTICLES IN PRESS

Cannabidiol (CBD) products for pain: ineffective, expensive, and with potential harms

Andrew Moore Jr. BS • Sebastian Straube • Emma Fisher • Christopher Eccleston

Published: October 18, 2023 • DOI: https://doi.org/10.1016/j.jpain.2023.10.009

Highlights

- CBD products may have varying amounts of CBD, varying from none to much more than advertised.
- CBD products may contain other chemicals than CBD, some of which may be harmful.
- 16 RCTs for pain used pharmaceutical CBD in oral, buccal/sublingual, and topical forms.
- 15 of the 16 RCTs were negative: no greater pain-relieving effect for CBD than for placebo.
- Meta-analyses link CBD to increased rates serious adverse events and hepatotoxicity.

Abstract

Cannabidiol (CBD) attracts considerable attention for promoting good health and treating various conditions, predominantly pain, often in breach of advertising rules. Examination of available CBD products in N America and Europe demonstrate that CBD content can vary from none to much more than advertised, and that potentially harmful other chemicals are often included. Serious harm is associated with chemicals found in CBD products, and reported in children, adults, and the elderly. A 2021 International Association for the Study of Pain task force examined the evidence for cannabinoids and pain but found no trials of CBD. Sixteen CBD randomised trials using pharmaceutical supplied CBD or making preparations from such a source and with pain as an outcome have been published subsequently. The trials were conducted in 12 different pain states, using three oral, topical, and buccal/sublingual administration, with CBD doses between 6 and 1600 mg, and durations of treatment between a single dose and 12 weeks. Fifteen of the 16 showed no benefit of CBD over placebo. Small clinical trials using verified CBD suggest the drug to be largely benign; while large scale evidence of safety is lacking there is growing evidence linking CBD to increased rates of serious adverse events and hepatotoxicity. In January 2023, the FDA announced that a new regulatory pathway for CBD was needed. Consumers and health care providers should rely on evidence-based sources of information on CBD, not just advertisements. Current evidence is that CBD for pain is expensive, ineffective, and possibly harmful.

Perspective

There is no good reason for thinking that CBD relieves pain, but there are good reasons for doubting the contents of CBD products in terms of CBD content and purity.

https://www.jpain.org/article/S1526-5900(23)00582-5/fulltext

The science

- Placebo response very high in cannabis studies

"The unusually high attention and engagement linked to cannabinoid pain trials was independent of the clinical results and may uphold high expectations and placebo responses in future trials. In particular, we found that news articles and blogs had a strong positive bias toward the efficacy of cannabinoids in pain therapy. The positive media attention on cannabinoids for pain relief could partly explain the placebo responses seen in this systematic review."

JAMA Network Open

Original Investigation | Pharmacy and Clinical Pharmacology

Placebo Response and Media Attention in Randomized Clinical Trials Assessing Cannabis-Based Therapies for Pain

A Systematic Review and Meta-analysis

Filip Gedin, PhD; Sebastian Blomé, MSc; Mina Pontén, PhD; Maria Lalouni, PhD; Jens Fust, PhD; André Raquette, DC; Viktor Vadenmark Lundquist, MSc; William H. Thompson, PhD; Karin Jensen, PhD

Abstract

IMPORTANCE Persistent pain is a common and disabling health problem that is often difficult to treat. There is an increasing interest in medicinal cannabis for treatment of persistent pain; however, the limited superiority of cannabinoids over placebo in clinical trials suggests that positive expectations may contribute to the improvements.

OBJECTIVE To evaluate the size of placebo responses in randomized clinical trials in which cannabinoids were compared with placebo in the treatment of pain and to correlate these responses to objective estimates of media attention.

DATA SOURCES A systematic literature search was conducted within the MEDLINE and Embase databases. Studies published until September 2021 were considered.

STUDY SELECTION Cannabinoid studies with a double-blind, placebo-controlled design with participants 18 years or older with clinical pain of any duration were included. Studies were excluded if they treated individuals with HIV/AIDS or severe skin disorders.

DATA EXTRACTION AND SYNTHESIS The study followed the Preferred Reporting Items for Systematic Review and Meta-analyses reporting guideline. Data were extracted by independent reviewers. Quality assessment was performed using the Risk of Bias 2 tool. Attention and dissemination metrics for each trial were extracted from Altmetric and Crossref. Data were pooled and analyzed using a random-effects statistical model.

MAIN OUTCOMES AND MEASURES Change in pain intensity from before to after treatment, measured as bias-corrected standardized mean difference (Hedges *g*).

RESULTS Twenty studies, including 1459 individuals (mean [SD] age, 51 [7] years; age range, 33-62 years; 815 female [56%]), were included. Pain intensity was associated with a significant reduction in response to placebo, with a moderate to large effect size (mean [SE] Hedges *g*, 0.64 [0.13], $P < .001$). Trials with low risk of bias had greater placebo responses ($Q_1 = 5.47$; $I^2 = 82.08$; $P = .02$). The amount of media attention and dissemination linked to each trial was proportionally high, with a strong positive bias, but was not associated with the clinical outcomes.

CONCLUSIONS AND RELEVANCE Placebo contributes significantly to pain reduction seen in cannabinoid clinical trials. The positive media attention and wide dissemination may uphold high expectations and shape placebo responses in future trials, which has the potential to affect the

(continued)

Key Points

Question What is the size of the placebo response in cannabinoid trials for clinical pain, and is the magnitude of placebo response associated with media attention on the trials?

Findings This meta-analysis of 20 studies of 1459 individuals found a significant pain reduction in response to placebo in cannabinoid randomized clinical trials. Media attention was proportionally high, with a strong positive bias, yet not associated with the clinical outcomes.

Meaning These findings suggest that placebo has a significant association with pain reduction as seen in cannabinoid clinical trials, and the positive media attention may shape placebo responses in future trials.

+ Supplemental content

Author affiliations and article information are listed at the end of this article.

JAMA Network Open. 2022;5(11):e2243848. doi:10.1001/jamanetworkopen.2022.43848 November 28, 2022 1/12

https://jamanetwork.com/journals/jamanetworkopen/fullarticle/2799017

US population

- Results for cancer types
  - cigarettes 14
  - alcohol use disorder 9
- Cannabis constituents (cannabinoids)
  - THC 9
  - Cannabidiol (CBD) 12
  - Cannabichromene 6
  - Cannabinol 9
  - Cannabigerol 7
- Cannabis causal in 27 cancers in all in the US data

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Research | Open access | Published: 30 March 2022

Geotemporospatial and causal inferential epidemiological overview and survey of USA cannabis, cannabidiol and cannabinoid genotoxicity expressed in cancer incidence 2003–2017: part 1 – continuous bivariate analysis

Albert Stuart Reece & Gary Kenneth Hulse

Archives of Public Health **80**, Article number: 99 (2022) | Cite this article

2923 Accesses | **17** Citations | **29** Altmetric | Metrics

A Research to this article was published on 30 March 2022

A Research to this article was published on 30 March 2022

Abstract

Background

The genotoxic and cancerogenic impacts of population-wide cannabinoid exposure remains an open but highly salient question. The present report examines these issues from a continuous bivariate perspective with subsequent reports continuing categorical and detailed analyses.

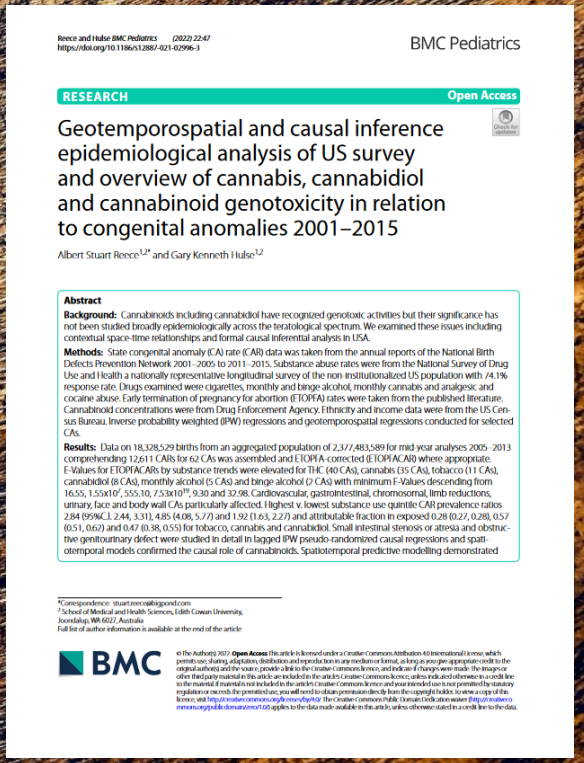
Methods

Age-standardized state census incidence of 28 cancer types (including "All (non-skin) Cancer") was sourced using SEER*Stat software from Centres for Disease Control and National Cancer Institute across US states 2001–2017. It was joined with drug exposure data from the nationally representative National Survey of Drug Use and Health conducted annually by the Substance Abuse and Mental Health Services Administration 2003–2017, response rate 74.1%. Cannabinoid data was from Federal seizure data. Income and ethnicity data sourced from the US Census Bureau. Data was processed in R.

https://archpublichealth.biomedcentral.com/articles/10.1186/s13690-022-00811-8

US population

- Results for birth defects
  - tobacco 11
  - alcohol 5
- Cannabis constituents (cannabinoids)
  - THC 40
  - Cannabidiol (CBD) 8
- Cannabis causal in 45 of 62 birth defects in all in the US data



Reece and Hulse *BMC Pediatrics* (2022) 22:47
https://doi.org/10.1186/s12887-021-02996-3

BMC Pediatrics

RESEARCH Open Access

Geotemporospatial and causal inference epidemiological analysis of US survey and overview of cannabis, cannabidiol and cannabinoid genotoxicity in relation to congenital anomalies 2001–2015

Albert Stuart Reece[1,2*] and Gary Kenneth Hulse[1,2]

Abstract

Background: Cannabinoids including cannabidiol have recognized genotoxic activities but their significance has not been studied broadly epidemiologically across the teratological spectrum. We examined these issues including contextual space-time relationships and formal causal inferential analysis in USA.

Methods: State congenital anomaly (CA) rate (CAR) data was taken from the annual reports of the National Birth Defects Prevention Network 2001–2005 to 2011–2015. Substance abuse rates were from the National Survey of Drug Use and Health a nationally representative longitudinal survey of the non-institutionalized US population with ⁄4.1% response rate. Drugs examined were cigarettes, monthly and binge alcohol, monthly cannabis and analgesic and cocaine abuse. Early termination of pregnancy for abortion (ETOPFA) rates were taken from the published literature. Cannabinoid concentrations were from Drug Enforcement Agency. Ethnicity and income data were from the US Census Bureau. Inverse probability weighted (IPW) regressions and geotemporospatial regressions conducted for selected CAs.

Results: Data on 18,328,529 births from an aggregated population of 2,377,483,589 for mid year analyses 2005–2013 comprehending 12,611 CARs for 62 CAs was assembled and ETOPFA-corrected (ETOPFACAR) where appropriate. E-Values for ETOPFACARs by substance trends were elevated for THC (40 CAs), cannabis (35 CAs), tobacco (11 CAs), cannabidiol (8 CAs), monthly alcohol (5 CAs) and binge alcohol (2 CAs) with minimum E-Values descending from 16.55, 1.55×10^{7}, 555.10, 7.53×10^{19}, 9.30 and 32.98. Cardiovascular, gastrointestinal, chromosomal, limb reductions, urinary, face and body wall CAs particularly affected. Highest v. lowest substance use quantile CAR prevalence ratios 2.84 (95%CI. 2.44, 3.31), 4.85 (4.08, 5.77) and 1.92 (1.63, 2.27) and attributable fraction in exposed 0.28 (0.27, 0.28), 0.57 (0.51, 0.62) and 0.47 (0.38, 0.55) for tobacco, cannabis and cannabidiol. Small intestinal stenosis or atresia and obstructive genitourinary defect were studied in detail in lagged IPW pseudo-randomized causal regressions and spatiotemporal models confirmed the causal role of cannabinoids. Spatiotemporal predictive modelling demonstrated

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BMC

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8767720/pdf/12887_2021_Article_2996.pdf

Metabolises to THC

- Cannabidiol, when metabolised, transforms to THC
  - FDA-listed Adverse Reactions for CBD include THC-like symptoms such as suicidal ideation, depression and anxiety. This is the ‘tell’.
  - Even admitted by Hemp Connoisseur magazine

    “Could anomalies in results have resulted from the way gastric juices break down CBD within the human body? In a 2016 study published in Cannabis and Cannabinoid Research, by John Merrick and associates, it was noted that, “In recent epilepsy research, pediatric subjects receiving orally administered CBD showed a relatively high incidence of adverse events (≤44%), with somnolence (≤21%) and fatigue (≤17%) among the most common.”4 This led the researchers to more closely investigate the accepted premise that CBD is non-psychoactive. They came to the conclusion that, “Gastric fluid without enzymes converts CBD into the psychoactive components Δ9-THC and Δ8-THC, which suggests that the oral route of administration may increase the potential for psychomimetic adverse effects from CBD.”

https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=8bf27097-4870-43fb-94f0-f3d0871d1eec&type=display

https://hcmagazine.com/does-cbd-convert-to-thc-when-ingested-the-findings-from-one-study-conclude-it-is-possible/

Mainline media?

crickets

Next episode

- More detail in future episodes:
  - Cannabis and cancer
  - Cannabis and birth defects
  - Cannabidiol (CBD), cancer and birth defects
  - Cannabis and pain
  - Cannabis and driving
  - Hemp and psychoactive metabolites
  - Cannabis and psychosis
  - Cannabis and violence/homicide
  - Cannabis and suicide
  - Cannabis – its other harms