Dr Ian Rosemergy

Consultant Neurologist

Capital and Coast DHB

Saturday, August 10, 2019

(Plenary)

12:00 - 12:10 The Evidence in Epilepsy

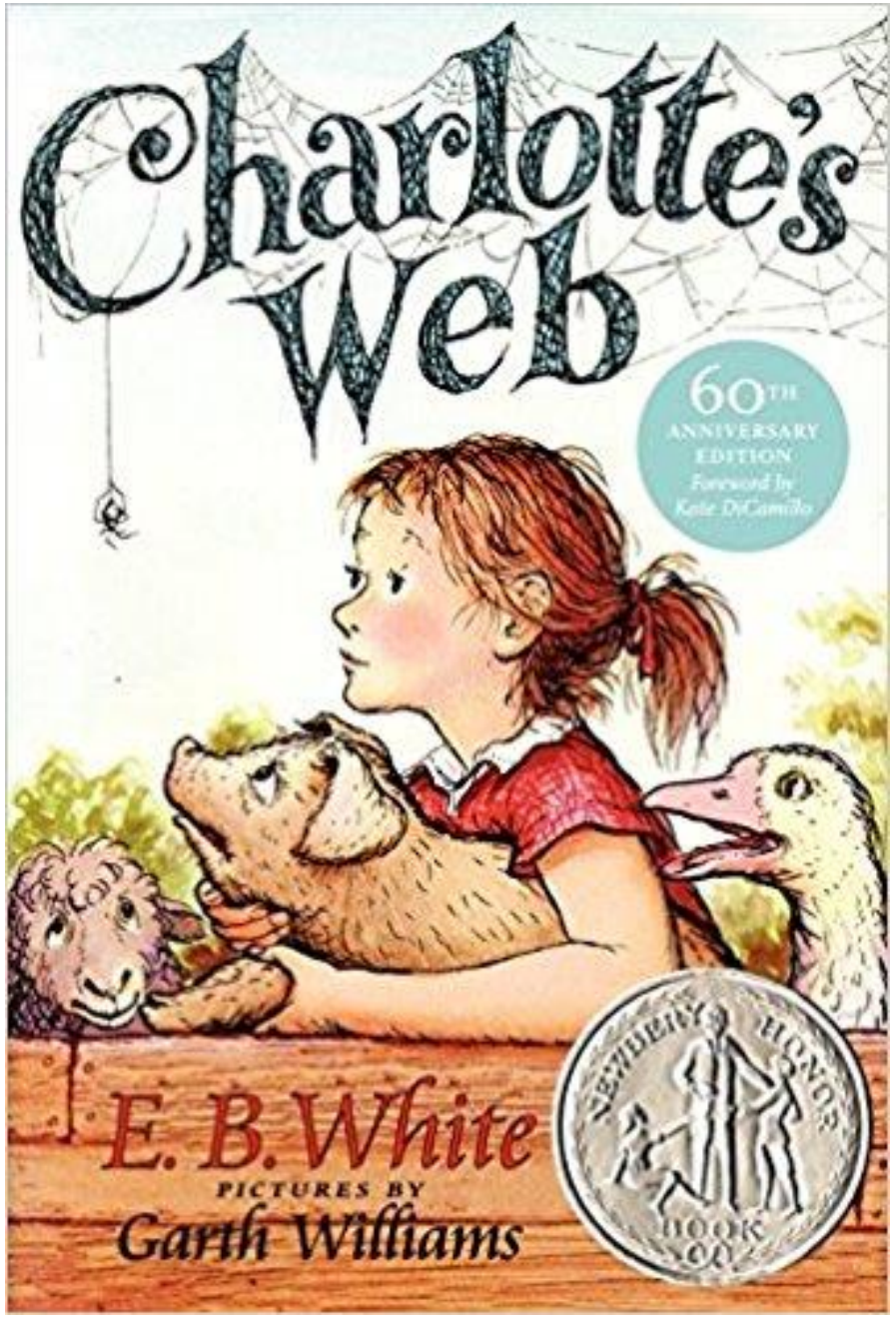
The evidence for the use of cannabis products in the treatment of epilepsy

Ian Rosemergy

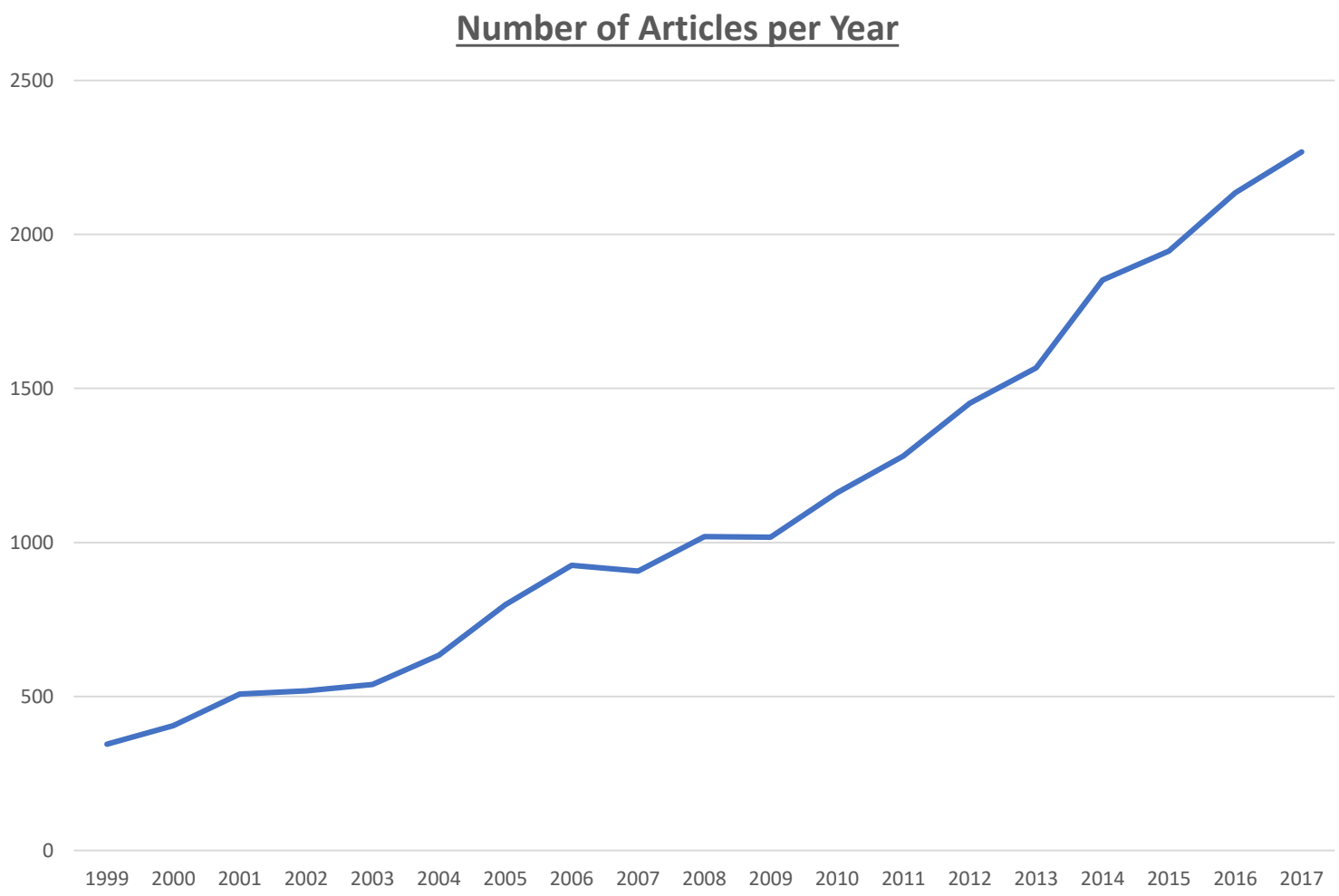
Neurologist

Disclosures

- Member of Neurology PTAC subcommittee for Pharmac
- I am <u>not</u> a paediatric neurologist
- No financial disclosures


Charlotte's Web
60TH ANNIVERSARY EDITION
Foreword by Kate DiCamillo
E. B. White
PICTURES BY
Garth Williams
NEWBERY HONOR BOOK

- Dravet syndrome
- Up to 300 GTCS’s per week
- Cognitive decline
- Stanley brothers (x6)
  - Low THC, high CBD product
  - Couldn’t sell it
- Seizures decreased to 3/month
- Language + motor development


Number of Articles per Year
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Randomised Controlled Trials

Author	Year	Placebo arm	Treatment arm	
Mechoulam et al	1978	5	4	Partial benefit
Cunha et al	1980	7	8	Partial benefit
Ames et al	1986	6	6	No difference
Trembley et al	1990	10 (cross over)		No change
Devinsky et al	2016			Decreased motor seizures
Devinsky et al	2017	59	61	43% decrease frequency 5% were seizure free
STAR1	2018			

Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome

- 120 children and young adults with the Dravet syndrome and drug-resistant seizures
- CBD oral solution (20 mg per kg/day) or placebo, in addition to standard antiepileptic treatment.
- Decrease median frequency of convulsive seizures/month
  - **Cannabidiol** group **12.4 to 5.9**
  - **Placebo** group 14.9 to 14.1
- 50% reduction in convulsive- seizure frequency
  - **Cannabidiol** 43%
  - **Placebo** 27% (OR 2.0)
- Seizure freedom 5% with cannabidiol and 0% with placebo (P = 0.08)

NEJM 376;21 nejm.org May 25, 2017

Evidence for cannabis and cannabinoids for epilepsy: a **systematic review** of controlled and observational evidence

- Plant based and pharmaceutical cannabinoids to prevent or treat epilepsy and epileptic seizures in participants of any age, with any type of epilepsy or seizure.
  - Variety of epilepsy syndromes but mostly Lennox Gastaut and Dravet's
- Variety of study types
  - Few RCT's
- CBD range of 2.5–20 mg/kg/day across a mean treatment length of 14 weeks.

Stockings E, et al. J Neurol Neurosurg Psychiatry 2018;0:1–13.

Table 4 An overview of the research evidence on cannabis and cannabinoids in the treatment of epilepsy

	50% reduction in seizures n=19 studies (2 RCTs)	Complete seizure freedom n=17 studies (3 RCTs)	Quality of life n=14 studies (2 RCTs)	Withdrawals n=12 studies (4 RCTs)	Adverse events n=16 studies (4 RCTs)
Cannabis sativa/extract	Two studies (no RCT)	No studies	Two studies (no RCT)|	No studies	Two studies (no RCT)
Findings	Positive effect		Positive effect		AEs reported by 13%
Evidence GRADE	⊕◯◯◯ VERY LOW		⊕◯◯◯ VERY LOW		⊕◯◯◯ VERY LOW
Risk of bias	Serious to critical risk		Critical risk		Critical risk
Conclusion	Insufficient evidence		Insufficient evidence		Insufficient evidence
CBD	11 studies (2 RCT)	13 studies (3 RCT)	9 studies (2 RCT)	8 studies (3 RCT)	11 studies (4 RCT)
Findings	Small effect	Positive effect	Positive effect	Patients more likely to withdraw from CBD	AEs reported by 11%–100%
Evidence GRADE	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW
Risk of bias	Low to serious risk	Low to critical risk	Low to critical risk	Low to critical risk	Low to critical risk
Conclusion	Some evidence of effect	Some evidence of effect	Some evidence of effect	Greater likelihood of withdrawal	Mild-to-moderate AEs likely
Oral THC	No studies	No studies	No studies	No studies	One study (no RCT)
Findings					AEs reported by 12.5%
Evidence GRADE					⊕◯◯◯ VERY LOW
Risk of bias					No information
Conclusion					Insufficient evidence
CBD:THC	Five studies (no RCTs)	Three studies (no RCTs)	Two studies (no RCT)	Two studies (no RCT)	Two studies (no RCT)
Findings	Positive effect	Small effect	Positive effect	Withdrawal rate 14%	AEs reported by 42%
Evidence GRADE	⊕⊕◯◯ LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW
Risk of bias	Serious to critical risk	Serious to critical risk	Serious risk	Serious risk	Serious to critical risk
Conclusion	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence
Oral cannabis extracts	One study (no RCT)	One study (no RCT)	One study (no RCT)	One study (no RCT)	No studies
Findings	Positive effect	Small effect	Positive effect	Withdrawal rate 15%	
Evidence GRADE	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	⊕◯◯◯ VERY LOW	
Risk of bias	Critical risk	Serious risk	Serious risk	Serious risk	
Conclusion	Insufficient evidence	Insufficient evidence	Insufficient evidence	Insufficient evidence	

Risk of bias=low to high in randomised trials; low to critical risk in non-randomised studies, no information where information not available.

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Evidence GRADE	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW	⊕⊕◯◯ LOW
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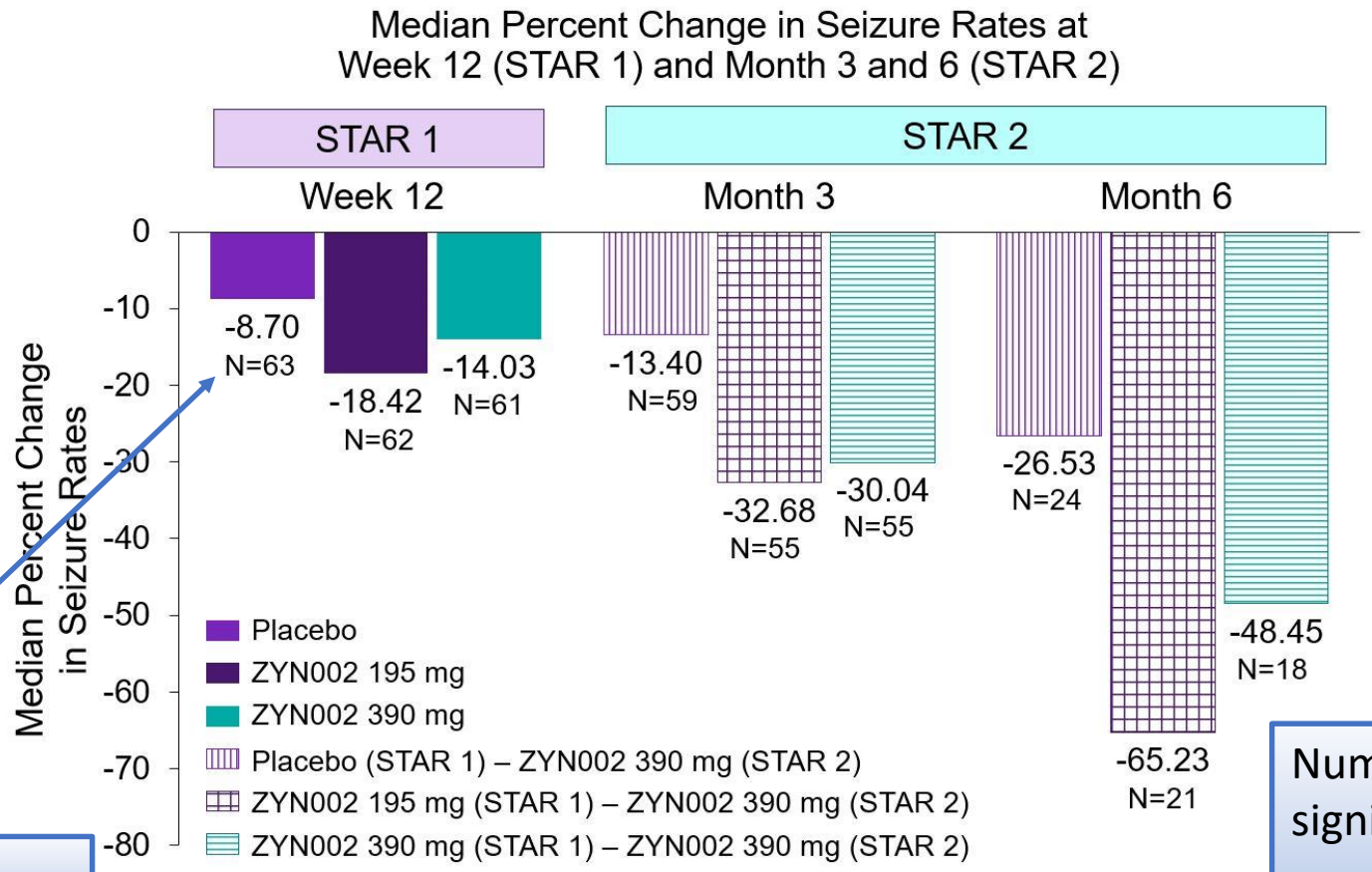
Conclusion	Some evidence of effect	Some evidence of effect	Some evidence of effect	Greater likelihood of withdrawal	Mild-to-moderate AEs likely

STAR1 – topical CDB gel

Product	N=	Median reduction in sz
195 mg daily	63	18.4%
390 mg daily	62	14%
Placebo	63	8.7%

Results not statistically significant

Results



STAR 2 results based on data collected through mid-August 2017 and in patients who reported seizure frequency data during the respective time period.

High rate of seizure reduction in placebo group

Numerical but not statistically significant reduction in seizures

STAR2 “clinically meaningful” reduction in seizures

Paediatric study underway

- Prof Mike Barnes (UK based neurologist)
  - Radio NZ interview (16 July 2019)
- Interviewer:
  - “is there a precedent for not waiting for the clinical trials ……. for learning as we go?”
- Prof Barnes :
  - ” … in epilepsy … we have to accept a slightly different view of the evidence at the moment and accept case studies and a whole range of observational trials and not be too obsessed with the standard medical randomized placebo controlled studies.”

Nine to Noon, Radio NZ, 16 July 2019

Conclusion

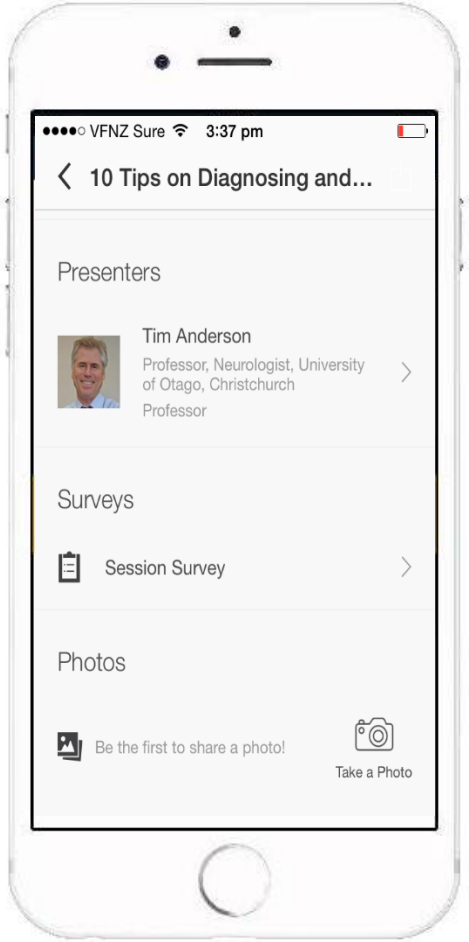
- I disagree
- Epilepsy is a significant disorder
- Cannabis products are held to a different standard
- Need to be honest about where cannabis products are placed in treatment regimen
- No RCT data to support CBD, marijuana, cannabis for the treatment of adult epilepsies
- Some RCT evidence in specific paediatric epilepsy syndromes

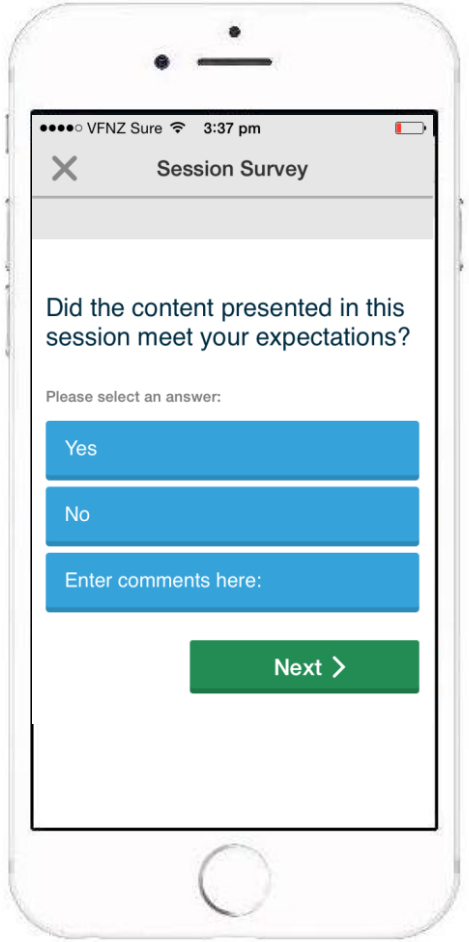
Watchdog declines to back NHS cannabis treatment for epilepsy (The Guardian. Thu 8 Aug 2019)

- Medical cannabis cannot be approved for use in children with severe epilepsy on the NHS because there is not enough evidence to prove it helps, a watchdog (Nice) has ruled
- ..... doctors have been reluctant to prescribe cannabis-based medicines in the UK despite the rescheduling of the drug in November because of the lack of clinical trial evidence of its benefits and safety. Nice is calling for more traditional “gold standard” randomised controlled trials.....

- Prof Mike Barnes, the chair of the Medical Cannabis Clinicians Society, said Nice was wrong to want to assess medical cannabis on the basis of the same sort of trials used to approve conventional medicines.
- Barnes, who is medical director of a chain of private clinics using medicinal cannabis currently advertising to recruit more doctors, said it had “failed to take into account alternative, valid sources of evidence” and he claimed the Nice committee was made up of people with negative views about cannabis. “Those with positive views were excluded from the process,” he said.

Don't forget to take the session survey!





Thank You

Denying elderly stroke patients medical cannabis a form of elder abuse, Grey Power branch says

11 Apr, 2018 12:33pm

3 minutes to read

Background

- 2 principal G-protein coupled receptors
  - CB1 (pre synaptic) – hippocampus, amygdala, cerebral cortex, basal ganglia, brainstem
  - CB2 - Peripheral tissues (including immune cells) and brain (new finding)
- 2 principal cannabinoids
  - THC – actions mediated principally via CB_1R receptors (psychoactive effects)
  - CBD – minimal direct CB_1R agonist (no psychotropic effects)
- CBD anti-seizure properties <u>not</u> related to the direct action on CBR's,
  - different mechanisms that include the agonist and antagonist effects on multiple receptor targets

Comments

- Pervasive topic that has generated comment – both informed and ill informed
- Few high profile cases (particularly in neurology) have driven public debate
- High level of public **interest**
- High level of public **belief** in treatment benefits
- **Blurring of lines** between medical science and other social causes
  - Social justice, decriminalization, criminal justice