Pot luck or proven cure?

Marijuana in paediatric epilepsy

Dr Michelle Lorentzos  Epilepsy Masterclass, SCHN
18th November 2015
The story so far

- August 2013 – CNN aired story of child gaining excellent control from medical cannabis

- November 2013 - Orphan Designation from the FDA for Epidiolex (GW Pharmaceuticals) for Dravet syndrome

- November 2014 - I spoke about medical marijuana at the Annual Neurology Update

- December 2014 – Premier Mike Baird announced trials for epileptic children, terminally ill adults and cancer patients

- June 2015 – Lambert family donate $33 million to University of Sydney for cannabis in epilepsy research

- October 2015 – Premier Mike Baird announced MOU signed for trial of cannabis and refractory epilepsy
Two years ago- the rare patient

A 2yo boy multiple seizure types and encephalopathy
  hundreds of seizures daily
  family sceptical of conservative medication
  refractory to medications

“Doctor, I want to try marijuana for my child.”
Now – many patients

A 9 month old baby with infantile spasms and delay
   now well controlled on clobazam
family from a regional town in NSW and have been speaking with friends

“Doctor, everyone has been telling us to try marijuana.”
What is all the fuss about?
CNN Documentary Part 1
Zero Tolerance of Pain & Suffering

Scientific matters can only be clarified by prolonged, faithful bona fide observations in friendly exchange of opinion, never by imprisonment. A person's right to know, to learn, to inquire, to make bona fide errors, to investigate must, by all means, be safe, if the word FREEDOM should ever be more than an empty political slogan.

2013 NSW Government Inquiry into the use of cannabis for medical purposes.
Use of cannabis for medical purposes (Inquiry)

The Inquiry will examine the efficacy and safety of using cannabis for medical purposes; and how cannabis should be supplied for medical use; the legal implications and issues concerning the use of cannabis for medical purposes and any other related matters. The Inquiry will examine a range of modes by which the chemical properties of cannabis may be accessed for therapeutic purposes, from smoking of the plant to the manufacturing of pharmaceutical products consumed in nasal sprays, tablet or other forms.

- Submissions to the Inquiry
- Submission from Mullaways
- Submission from Dr Ian Webster AO
- Cannabis and chronic pain: the poor man's analgesic
- Public Hearing 1 Transcript 11 March 2013
  Mullaways on Pages 31 to 39 of Transcript
- Public Hearing 2 Transcript 18 March 2013
- Executive Summary & Recommendations
What do we know about cannabis and the brain?
What is cannabis?

- Smoke from dried leaves of cannabis contains several phytocannabinoids including 9-tetrahydrocannabinoids 9-THC (the psycho-active form)
- Medical marijuana can contain less THC (or no THC) than recreational forms
- The human brain produces several endogenous cannabinoids which are lipid molecules important in synaptic signaling
  - preliminary research suggests defect in endocannabinoid system in people with epilepsy*
- Inhibits cytochrome P450 enzyme (may increase valproate and clobazam)

Cannabis in Epilepsy

- Cannabinoid receptors are found in brainstem, neocortical and limbic areas
- They influence levels of catecholaminergic neurotransmitters
- Cannabinoids bind to specific receptors, designated CB1 and CB2
- Binding to presynaptic CB1 receptors inhibits release of neurotransmitters
- Animal studies show anti-convulsant properties of CB1 receptor activation
Is there any evidence?
The Current Epidiolex Trial

• FDA approved study, led by Dr Orrin Devinsky
• Trial of cannabidiol without THC
• Assess dose tolerability in an open-label design
• Children with severe epilepsy
  – Preliminary findings (n=137)
    • at least 12 weeks of treatment
    • the median reduction in the number of seizures was 54%

2 studies suggested seizure reduction

Cunha 1980
• 15 patients
• CBD n=7 versus placebo n=8
• Follow up for 4 ½ months
• 4/7 CBD and 1/8 placebo patients were seizure free

Mechoulam 1978
• 9 patients
• CBD n=4 versus placebo n=5
• Follow up for 3 months
• 2/4 CBD and no placebo patients were seizure free
2 studies with no clear difference

Ames 1985
• 12 patients with intellectual disability and seizures
• Randomised to sunflower oil or placebo
• Follow up for 4 weeks
• No statistically significant reduction in seizures

Trembly 1990
• 12 patients with epilepsy in cross over trial
• Follow up 18 months
• No statistically significant difference
• Nineteen responses were received
• Thirteen children had Dravet syndrome, four had Doose syndrome, and one each had Lennox-Gastaut syndrome and idiopathic epilepsy.
• The average number of antiepileptic drugs (AEDs) tried before using cannabidiol-enriched cannabis was 12.
Results of the survey

16 (84%) of the 19 parents reported a reduction in their child's seizure frequency while taking cannabidiol-enriched cannabis.

2 (11%) reported complete seizure freedom
8 (42%) reported a greater than 80% reduction in seizure frequency
6 (32%) reported a 25-60% seizure reduction.

Other beneficial effects included increased alertness, better mood, and improved sleep. Side effects included drowsiness and fatigue.
Can anyone reference this quote?

“It is a valuable addition to the physician's armamentarium in the battle against epilepsy. Its use should be restricted, for the present, to that group of patients who do not respond to the less toxic forms of therapy previously in common use.”
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Merritt, H. H.; Putnam, T. J., Sodium Diphenyl Hydantoinate in the Treatment of Convulsive Disorders, JAMA 1938; 111:1068-1073
Some complicating factors regarding the research

• Accounting for placebo factors
  – Study of families who moved to Colorado for epilepsy treatment versus families already residing in Colorado
  – Benefits reported in 47% vs 22% *

• Navigating the changing political/legal landscape in order to plan studies and educate families

• As clinicians, how do we achieve the right balance between responding from the publics “call to arms” and waiting for clinical evidence

• Issues of supply and demand – who makes it?, who gets it?, who much?

The future in NSW
SCHN Medicinal Cannabis Program

Epidiolex

Special Access Scheme

Epidiolex US approval

Possible patient rollover

Epidiolex TGA Registration

Phase IV: Health Economics & Safety

Phase II: Tuberous Sclerosis Complex

CBDV*

Phase I/II Epilepsy w/post trial supply

Phase III Epilepsy

PBS Listing

2016

2017

2018

2019

n = 40

n ~ 50 - 100

* Specific compound TBD

With thanks to Michael Revius, Clinical Trial Project Manager, SCHN
Families independently sourcing cannabis

• Does this child have severe epilepsy that is proving refractory to other medications?

• Are the parents acting in the best interest of their child and are they informed about the uncertainty surrounding this therapy?

• Are you able to see the child for regular reviews and are you satisfied there has been no deterioration since cannabis was commenced?


Dr Andrew Katelaris. Picture: Ryan Osland, Newcastle Herald
References


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• Porter J.E, Jacobson, C., Report of parent survey of cannabidiol-enriched cannabis in paediatric treatment-resistant epilepsy. Epilepsy Behaviour, 20103; Dec 29 (3), 574-7

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