Cannabis and Cannabidiol in Pediatric Epilepsy

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Cannabis for Seizures

- Epilepsy affects 0.5% of population, or some 1.5 million children in the USA.
- Of these, 10% or 150,000 are intractable, fail to respond adequately to existing pharmacotherapy, and would be candidates for alternative therapies.
- Epilepsy carries a mortality rate 2-3 times normal.

Sumeria, 2200 BCE

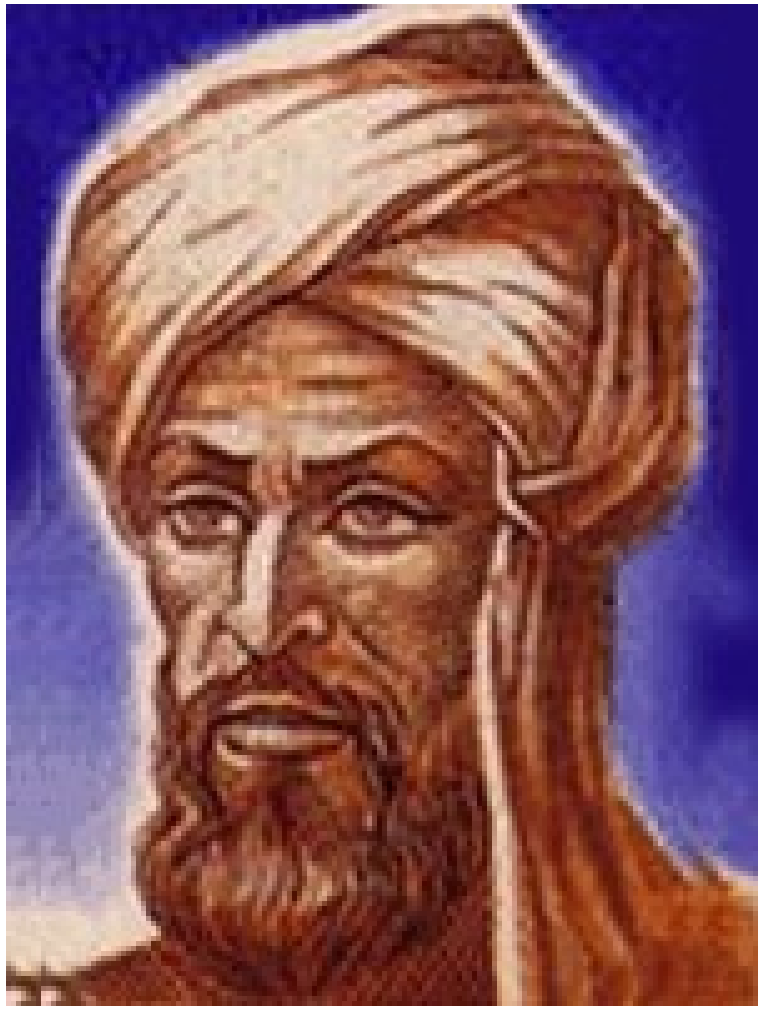
"A.ZAL.LA U.HI.A sindi sa qat etemmi" and translated (p. 21), "Root of caper which is on a grave, root of acacia, right horn of an ox, left(?) horn of a kid that has been covered, seed of tamarisk, seed of laurel, ***Cannabis; these seven drugs are a cataplasm for the hand of a ghost, with which to bind his temples****."* Thompson, R.C. (1930b): Assyrian prescriptions for treating bruises or swellings. *American Journal of Semitic Languages and Literatures* 47(1): 1-25.

"Hand of ghost" was identified as nocturnal epilepsy.

Wilson, J. V. & Reynolds, E. H. (1990). Texts and documents. Translation and analysis of a cuneiform text forming part of a Babylonian treatise on epilepsy. *Med Hist,* 34, 185-98.

Russo EB (2007). History of cannabis and its preparations in saga, science and sobriquet. *Chemistry & Biodiversity* 4(8): 2624-2648.

al-Mayusi, circa 1100 CE



Described the intranasal administration of cannabis leaf juice to treat epilepsy.

Lozano, I. (2001). The therapeutic use of *Cannabis sativa* L. in Arabic medicine. *Journal of Cannabis Therapeutics,* 1, 63-70.

al-Badri, 15th Century

Described a “cure” of epilepsy, but requiring regular administration of cannabis.

Mechoulam, R. (1986). The pharmacohistory of *Cannabis sativa. In:* Mechoulam, R. (ed.) *Cannabinoids as therapeutic agents.* Boca Raton, FL: CRC Press.

John Parkinson, 1640.

Chided Matthiolus for his use of a decoction of European hemp seed in the “falling sickness” of children, wherein he apparently saw no success.

Theatrum botanicum: The theater of plants; or, An herball of a large extent. London: Tho. Cotes.

William O'Shaughnessy, 1839.

ON THE PREPARATIONS

OF THE

INDIAN HEMP, OR GUNJAH

(CANNABIS INDICA);

THEIR EFFECTS ON THE ANIMAL SYSTEM IN HEALTH, AND THEIR UTILITY IN THE TREATMENT OF TETANUS AND OTHER CONVULSIVE DISEASES

By W. B. O'SHAUGHNESSY, M.D.,

Assistant-Surgeon, and Professor of Chemistry, &c.

In the Medical College of Calcutta.

Presented October, 1839.

The narcotic effects of Hemp are popularly known in the south of Africa, South America, Turkey, Egypt, Asia Minor, India, and the adjacent territories of the Malays, Burmese, and Siamese. In all these countries Hemp is used in various forms, by the dissipated and depraved, as the ready agent of a pleasing intoxication, In the popular medicine of these nations, we find it extensively employed for a multitude of affections. But in Western Europe, its use either as a stimulant or as a remedy, is equally unknown. With the exception of the trial, as a frolic, of the Egyptian 'Hasheesh,' by a few youths in Marseilles, and of the clinical use of the wine of Hemp by Mahneman, as shewn in a subsequent extract, I have been unable to trace any notice of the employment of this drug in Europe.

Much difference of opinion exists on the question, whether the Hemp so abundant in Europe, even in

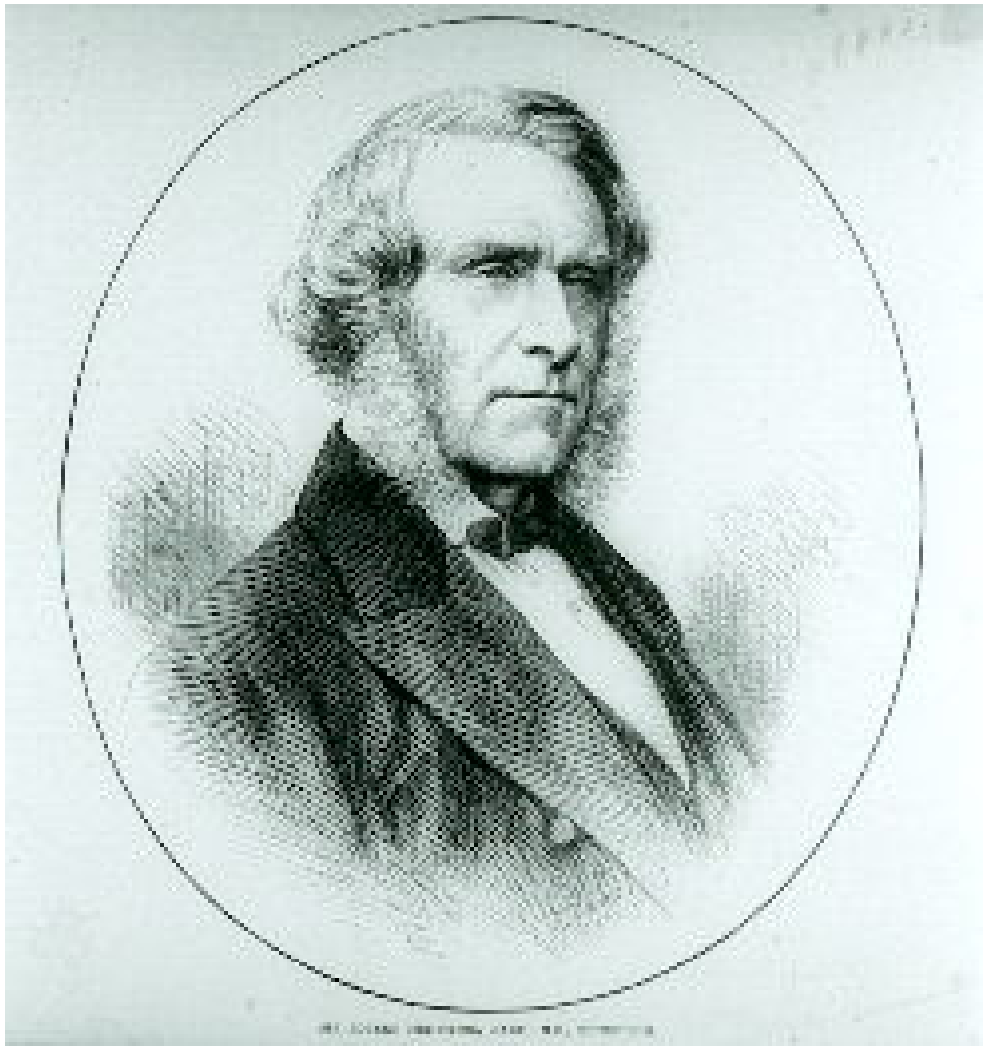
William O'Shaughnessy, 1839.

- A case of infantile convulsions
- 40 day old
- Heroic doses of tincture of Indian hemp utilized without narcosis to control spells.
- After 20 days, "The child is now (23rd November) in the enjoyment of robust health, and has regained her natural plump and happy appearance."

LEY, W. 1842. On the efficacy of Indian hemp in some convulsive disorders. Provincial Medical and Surgical Journal, 4, 407-409.

Based on O'Shaughnessy's reports from abroad, he successfully abrogated seizures with Indian hemp in a 9-month old infant.

Robert Christison, 1848.



"**Indian hemp** has been used as antispasmodic in hydrophobia, tetanus, malignant cholera, and **infantile convulsions**, with marked relief in repeated instances."

Christison, R. A dispensatory or commentary on the pharmacopoeias of Great Britain and the United States. Philadelphia: Lea and Blanchard; 1848. (p 974)

R.R. McMeens, 1856

Employed tincture of *Cannabis indica* successfully in 4 children, notably in a 7-week old female infant who had many seizures a day for 15 days:

"It was given in small and repeated doses until its inebriant influence was perceptible, which was manifested by dilation of pupil, general relaxation, and the degree of lassitude and composure, when its repetition was gradually extended, until entirely abandoned; and, **from the time of its adoption, the patient never experienced another symptom of convulsion**; to the joy of its parents, the satisfaction of the doctor, our 'extreme gratification,' and the discomfiture of the homeopathists." (p. 329)

McMeens, R. R. (1856). Cannabis indica in convulsions. *Western Lancet*, 327-331.

Isaac P. Willis, 1859

“ I was led to the use of hemp in puerperal convulsions, having also seen its beneficial effects in convulsions in general, after all the common remedies had been tried without relief.” (p. 176)

Willis, I. P. (1859). *Cannabis indica*. *Boston Medical and Surgical Journal,* 61, 173-178.

McMeens, R.R. 1860. Report of the Ohio State Medical Committee on *Cannabis indica*. White Sulphur Springs, OH: Ohio State Medical Society.

Beyond success in treating pediatric seizures, noted success in 3 of 4 cases of chronic epilepsy in adults

Sir John Russell Reynolds, 1868.

Saw varying degrees of **benefit on epilepsy in** two adults and **one child.**

Therapeutical uses *and toxic effects of Cannabis Indica*, *Lancet* 1:637-638.

Sir John Russell Reynolds, 1890.

- **Childhood convulsions**
- Use in “temper disease” of Marshall Hall
- In teething, even in infants
- Migraine
- Spasmodic dysmenorrhoea

Therapeutical uses and toxic effects of *Cannabis indica*. *Lancet* 1:637-638.

Perez-Reyes, M. & Wingfield, M. (1974). Letter: Cannabidiol and electroencephalographic epileptic activity. *JAMA,* 230, 1635.

In a 1974 letter, it was reported that CBD IV infusion in an epileptic patient aggravated pre-existing spike-wave activity. However, no actual seizures resulted.

[As a general observation, attempted correlations of EEG severity to clinical efficacy of medication are quite risky.]

Carlini, E. A. & Cunha, J. M. (1981). Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol,* 21, 417S-427S.

Fifteen patients with frequent attacks of unresponsive “secondarily generalized epilepsy” (seizures of partial onset with secondary generalization), aged 14-49, were treated with CBD vs. placebo in double-blind fashion.

Three of eight treated patients had complete seizure control with 200 mg of CBD per day, and a fourth with 300 mg per day.

One was improving, but moved away and was unavailable for follow-up. One other was markedly improved, two somewhat, and one not at all.

Neither laboratory changes, nor major adverse effects were noted; merely some somnolence in four subjects.

Ames, F. R. & Cridland, S. (1986). Anticonvulsant effect of cannabidiol. *S Afr Med J,* 69, 14.

A double-blind placebo-controlled study of CBD in South Africa with doses of about 200 mg/d in 12 subjects, published only in abstract form, failed to demonstrate any benefit on their seizures.

Trembly, B. & Sheman, M. Double-blind clinical study of cannabidiol as a secondary anticonvulsant. Marijuana '90 International Conference on Cannabis and Cannabinoids, July 1990 Kolympari, Crete, Greece.

An unpublished series of studies revealed no effect of CBD on seizure frequency at doses of 300 mg/d in 10 subjects over six months. One additional subject showed no response with CBD doses of 900-1200 mg/d.

Pelliccia A, Grassi G, Romano A, Crocchiolo P, . Treatment with CBD in oily solution of drug-resistant paediatric epilepsies. International Association of Cannabinoid Medicines; 2005 Sept. 9-10, 2005; Leiden, Netherlands.

Treated a series of 18 drug-resistant epileptic children with low-dose CBD in corn oil (? 25-27.5 mg). They noted improvements in seizure frequency and severity as well as cognition in most, including two with LGS, but only half continued treatment due to high costs (300 Euros/month).

What Went Wrong in Some Early CBD Trials?

- Some experiments were likely done with pure (crystalline) CBD.
- Bioavailability was probably extremely poor as:
  - Cannabidiol requires a lipid-carrier and/or dispersant agent to be most effective.
- These negative results are probably quite misleading in terms of CBD's anticonvulsant efficacy and dosage levels required.

Wallace, M. J. et al. 2003. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther* 307 (1):129-37.

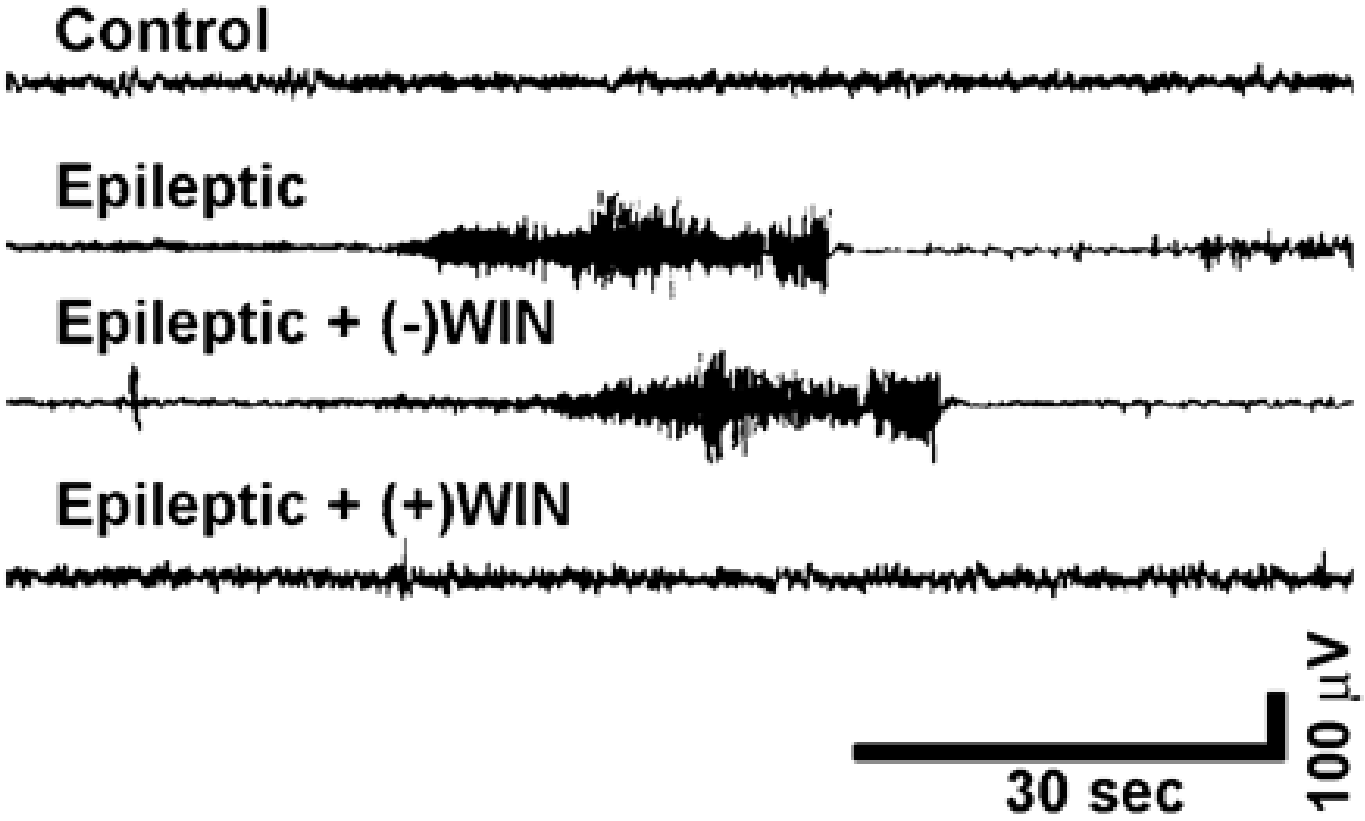


Fig. 1. The effects of CB1 receptor modulation on epileptiform activity in control and epileptic animals. Representative EEG recordings of control, epileptic, *S*(–)WIN55,212-, [(–)WIN]-treated (5 mg/kg i.p.) epileptic animals and *R*[(+)WIN]55,212-, [(+)WIN]-treated (5 mg/kg i.p.) epileptic animals. Treatment with *R*(+)WIN55,212 (5 mg/kg i.p.) completely abolished seizure activity.

Wallace, M. J. et al. 2003. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther* 307 (1):129-37.

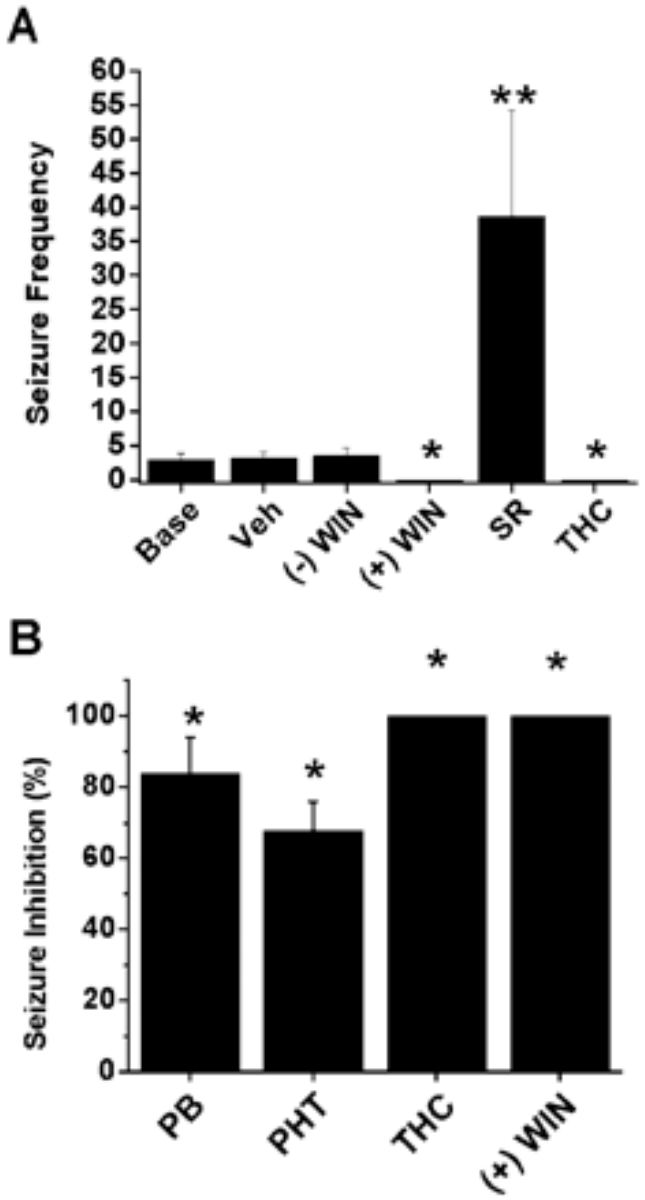


Fig. 2. The effects of CB1 receptor activation and blockade on the seizure frequency of epileptic rats demonstrated in single-injection experiments. A, seizure frequency per 10 h for baseline (base) and treatment with vehicle (Veh), *S*(–)WIN55,212, [(–)WIN] (5 mg/kg i.p.), *R*(+)WIN55,212, [(+)WIN] (5 mg/kg i.p.), SR141716A (SR) (10 mg/kg i.p.), and THC (30 mg/kg i.p.). Data represent mean ± S.E. (*n* = 6 per drug treatment; , *p* 0.05; , *p* 0.001). B, inhibition of seizure activity at high therapeutic concentrations (Morris et al., 2001) by the anticonvulsants phenobarbital (PB; 40 mg/kg i.p.) and phenytoin (PHT; 100 mg/kg i.p.) and the cannabinoids THC (30 mg/kg i.p.) and *R*(+)WIN55,212, (+)WIN (5 mg/kg i.p.) (*n* = 6 per drug treatment; , *p* 0.01 in comparison with epileptic animals). Only THC and (+)WIN completely abolished seizure activity. These single-injection experiments directly evaluated the effects of each agent on seizure frequency in multiple animals.

Wallace, M. J. et al. 2003. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther* 307 (1):129-37.

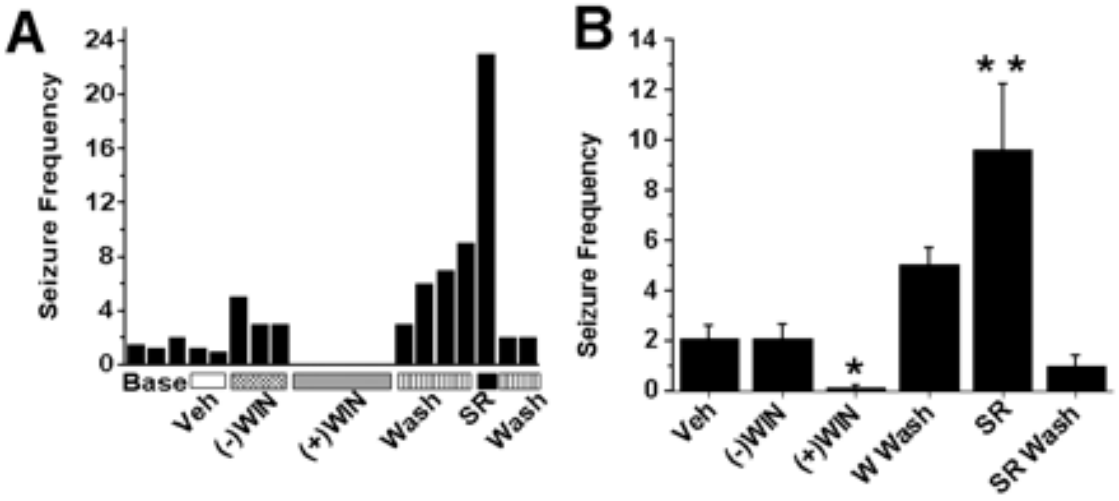


Fig. 3. The effects of CB1 receptor activation and blockade on the seizure frequency in eight epileptic rats sequentially treated with a multiple drug regimen that includes a CB1 receptor agonist and antagonist. These experiments evaluate the effects of each drug in comparison with the other drugs in the same animal. A, seizure frequency per 12 h in a representative epileptic animal after consecutive administration of vehicle, *S*(–)WIN55,212, (–)WIN (5 mg/kg i.p.), *R*(+)WIN55,212, (+)WIN (5 mg/kg i.p.), *R*(+)WIN55,212 (5 mg/kg i.p.) washout (W wash), SR141716A, SR (10 mg/kg i.p.), and SR141716A washout (SR wash). Bars represent the number of seizures observed in a representative epileptic animal for each 12-h monitoring period. B, mean seizure frequency (per 12 h) of eight epileptic animals treated with the same drug regimen shown in Fig. 3A. This figure presents the mean data for the multiple drug experiments for each experimental condition and analyzes the data statistically. Data represent the mean ± S.E. (seizures per 12 h) (*n* = 8; RM ANOVA; , *p* 0.05; , *p* 0.01).

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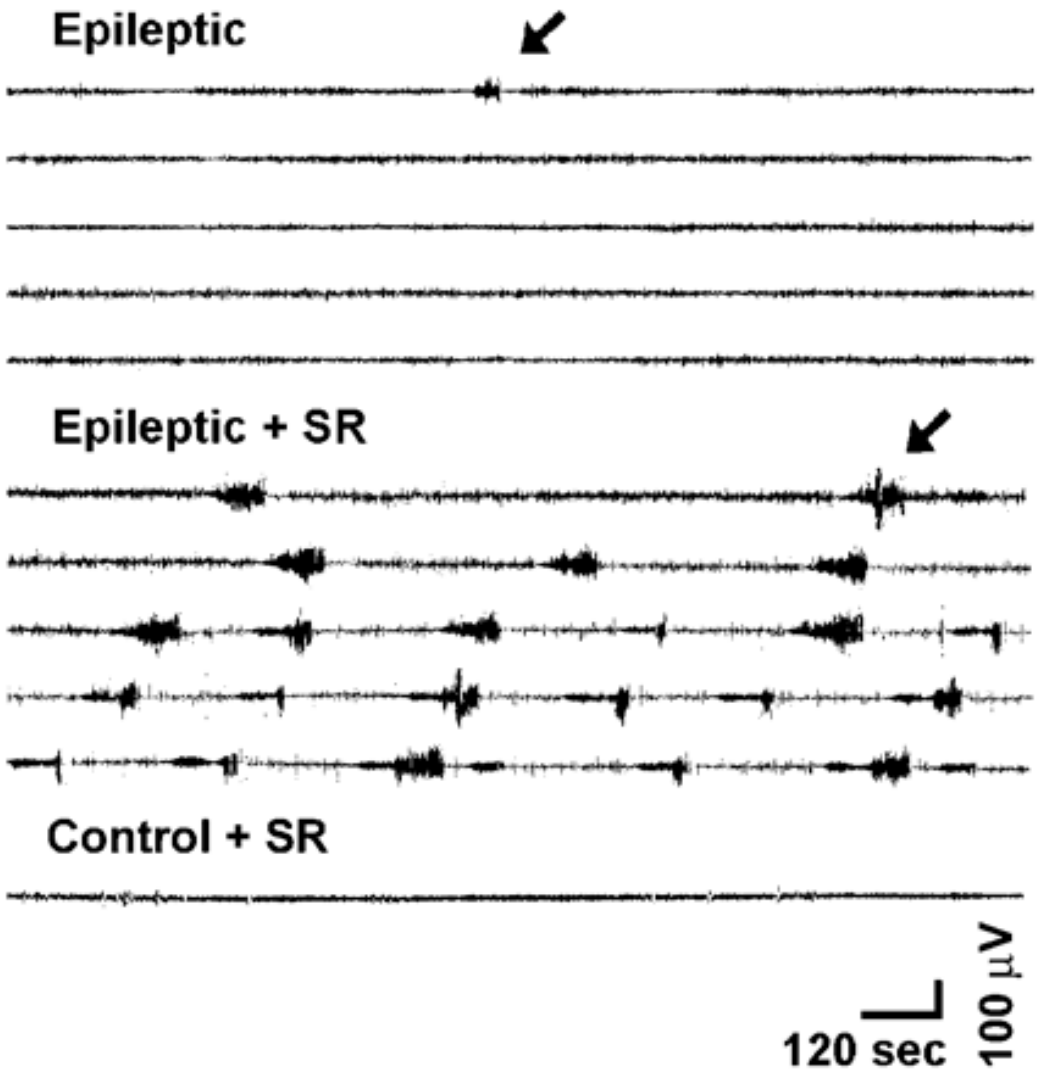

Fig. 4. Antagonism of the CB1 receptor by SR141716A (10 mg/kg i.p.) caused increased seizure frequency and produced status epilepticus in some animals. The data represent EEG and behavioral seizures observed over the 1-h recording period for epileptic and epileptic + SR conditions. These recordings represent continuous EEG recordings from an epileptic rat 60 min before and 60 min after treatment with SR141716A. Arrows represent individual seizures. The representative EEG recording from an epileptic animal manifested one spontaneous recurrent seizure in the 1 h of recording. SR treatment in epileptic animals caused a marked increase in seizure frequency. During the numerous seizures shown for SR141716A treatment in the 1-h recording, the animal was not responsive in between seizures for more than 30 min. Thus, SR141716A produced status epilepticus in this animal, employing the standard definition of SE that includes intermittent seizure activity lasting for more than 30 min without regaining consciousness between seizures. The Control + SR representative EEG recording demonstrates that treatment of control (nonepileptic) animals with SR141716A did not produce seizure activity.

Wallace, M. J. et al. 2003. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther* 307 (1):129-37.

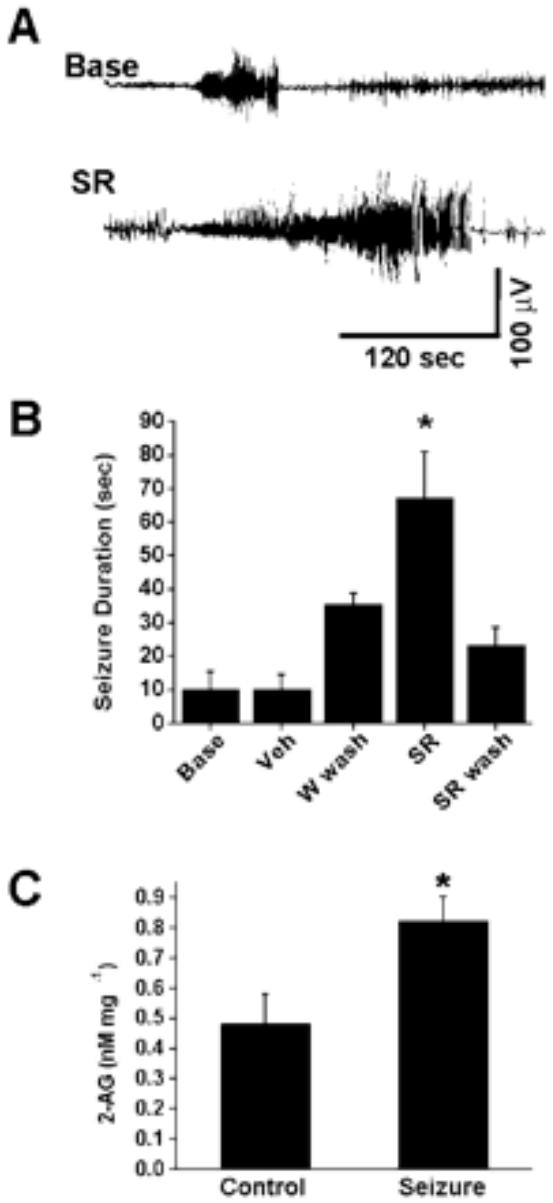

Fig. 5. CB1 receptor-dependent regulation of seizure duration in epileptic rats. A, a representative EEG recording of a seizure in an epileptic (Base) and an epileptic animal treated with SR141716A (SR) (10 mg/kg i.p.) demonstrating increased seizure duration produced by SR. B, mean seizure duration for the treatments shown in Fig. 3 B. Data represent the mean ± S.E. (*n* = 8 animals; RM ANOVA; , *p* 0.01). C, hippocampal endogenous 2-AG levels in control and seizure animals (15 min after seizure onset). The data represent the mean ± S.E. (*n* = 7; , *p* 0.01; Student's *t* test)

Wallace, M. J. et al. 2003. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther* 307 (1):129-37.

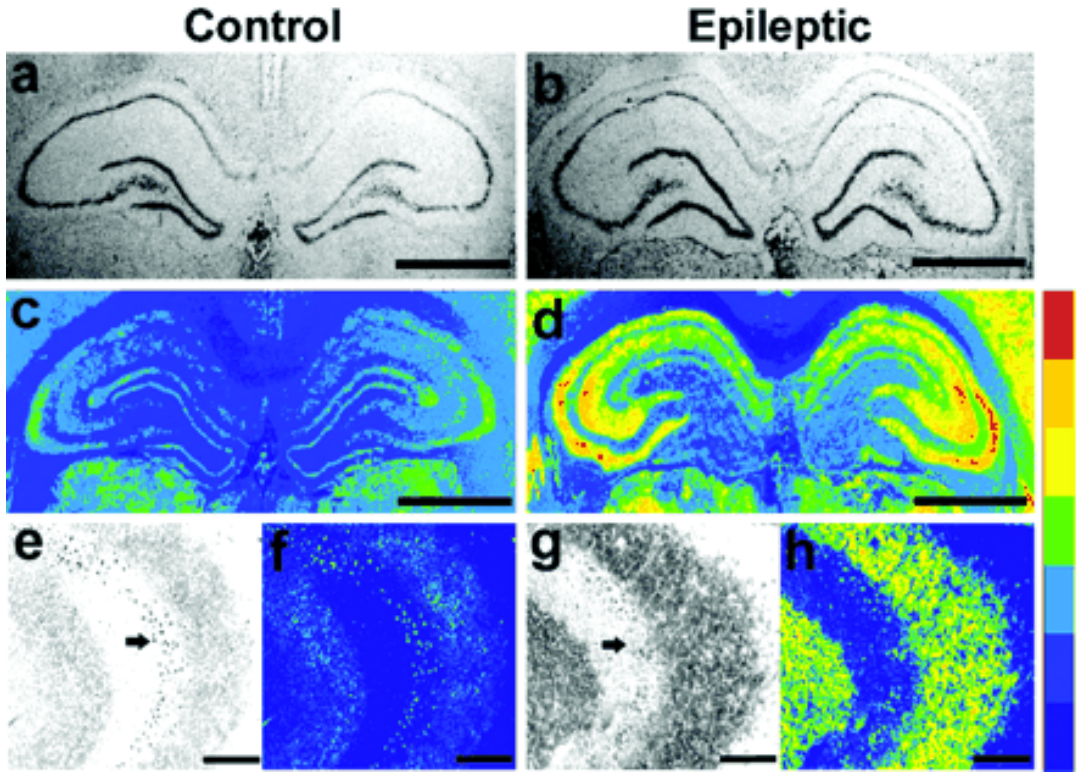

Fig. 7. Immunohistochemical detection of CB1 receptor expression in control and epileptic hippocampi. Representative Nissl staining of control (A) and epileptic (B) sections. Representative pseudocolor-enhanced immunohistochemical staining of the CB1 receptor protein in control (C) and epileptic (D) sections. The increase in CB1 receptor protein expression observed in epileptic hippocampi was representative of four epileptic versus four control animals, 15 tissue sections per animal. High magnification of CB1 receptor immunoreactivity of sham control (E) and epileptic (G) hippocampal formation demonstrated increased staining in the dendritic fields of the CA2 and CA3 regions of epileptic animals. Arrows indicate the location of the CA2 through CA3 pyramidal neurons. High magnification of pseudocolor-enhanced images of sham control (F) and epileptic (H) CA2 and CA3 regions. Bars in A through D represent 2 mm. Bars in E through H represent 200 µm. Red, highest level on color scale. The results shown are representative of several experiments.

Wallace, M. J. et al. 2003. The endogenous cannabinoid system regulates seizure frequency and duration in a model of temporal lobe epilepsy. *J Pharmacol Exp Ther* 307 (1):129-37.

- Seizure threshold is mediated by endocannabinoid mechanisms.
- In rats, THC produced a 100% reduction in seizures, whereas phenobarbital and diphenylhydantoin did not.
- Animals demonstrated both acute increases in endocannabinoid production and a long-term up-regulation of CB_1 production as apparent compensatory effects counteracting glutamate excitotoxicity.
- The anticonvulsant effect was present at sub-sedating levels.

Gottschling, S. 2001. Cannabinoide bei Kindern Gute Erahrungen bei Schmerzen, Spastik und in der Onkologie. *Angewandte Schmerztherapei und Palliativmedizin*, 55-57.

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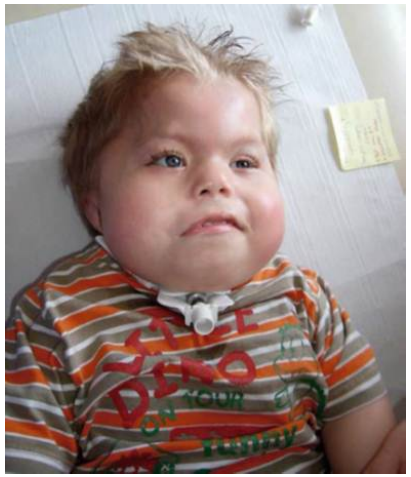
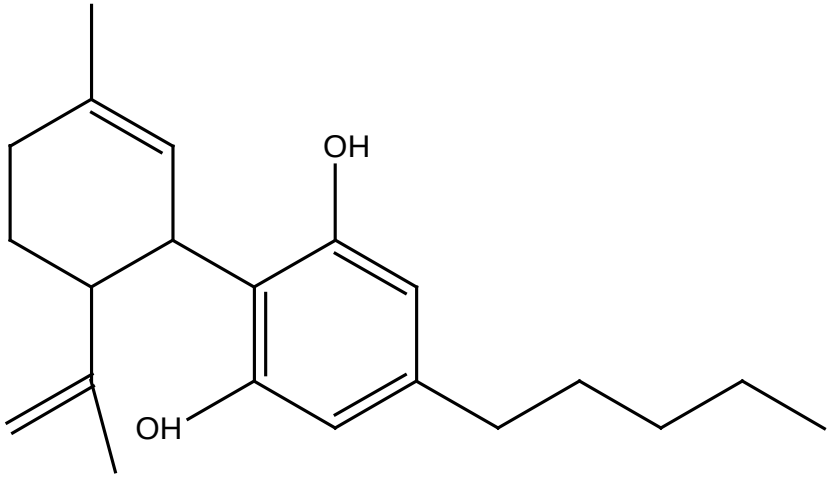


Dronabinol (average dose 0.2 mg/kg/d) was similarly administered to 13 severely neurologically impaired children, aged 7 months-17 years with uniform benefit on spasticity and pain, improved sleep in 10. The longest treatment duration was five years, and no tolerance or dose escalation was apparent. Similarly, more than 50 patients from the age of three months were treated for nausea and inanition from chemotherapy. Marked benefit was noted with no serious side effects aside from one self-limited case of 10-fold accidental overdose, and no withdrawal effects were seen even after abrupt withdrawal after months of therapy.

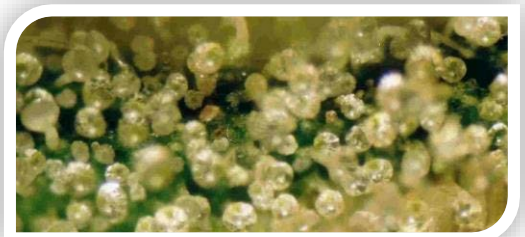
Lorenz, R. 2004. On the application of cannabis in paediatrics and epileptology. *Neuroendocrinol Lett* 25 (1-2):40-44.

- Use of Marinol® in 8 severely affected children with degenerative diseases, post-traumatic syndrome, epilepsy, hypoxic encephalopathy.
- Doses 0.04-0.12 mg/kg/d.
- Prominent positive changes noted in seizures, spasms, social interaction, with prominent palliation in fatal diseases.

Cannabidiol (CBD) and Epilepsy I



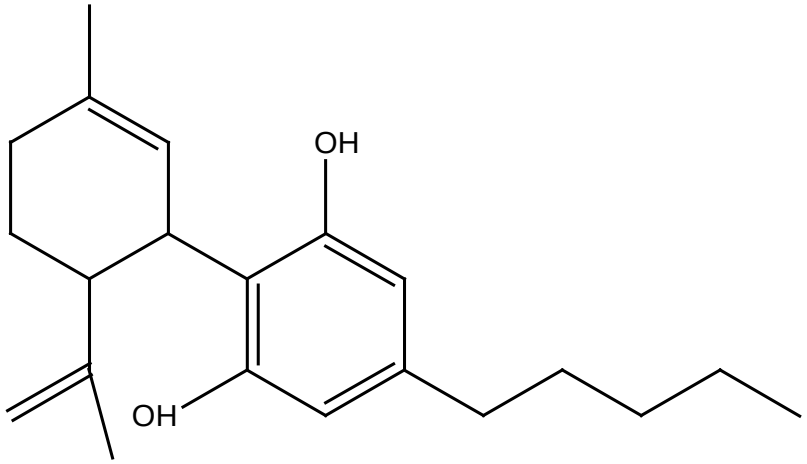
cannabidiol



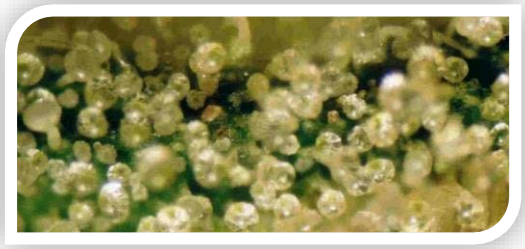
G5 CBD trichomes
Photo DJP

- Isolated 1940 (Adams), but identified positively in 1963 (Mechoulam & Shvo)
- CBD hardly binds to cannabinoid receptors (Thomas 2007)
- **Neuroprotective AO, strongly inhibits glutamate excitotoxicity, also anti-oxidant > Vitamins C and E (Hampson et al. 1998)**
- **Now known to be a $TRPV_1$ agonist with EC_{50} 3.2-3.5 µM (Bisogno et al. 2001), possibly an anticonvulsant mechanism (Shu 2013; Iannotti 2014)**
- **Inhibits uptake of the anandamide (AEA, the endocannabinoid) and weakly inhibits its hydrolysis (Bisogno et al. 2001)**
- Alerting vs. THC in clinic (Nicholson 2004)

Cannabidiol (CBD) and Epilepsy II



cannabidiol



G5 CBD trichomes
Photo DJP

- **Antagonizes tumor necrosis factor alpha (TNF-α) in rodent rheumatoid arthritis (Malfait 2000), an anti-inflammatory effect.**
- Not COX-1 or COX-2 inhibitor (Stott 2005)
- **Displays agonistic activity at 5-HT1A receptor (Russo-Parker 2005), possible basis for** observed anxiolysis (Resstel 2009; Soares 2010), CVA reduction (Mishima 2005), nausea (Limebeer 2009), improvement of cognition in hepatic encephalopathy (Magen 2009), **and anticonvulsant activity (Henry 2013)**
- **Voltage-gate Na+ channel blockade is not the anticonvulsant mechanism (Hill 2014)**
- **Enhances adenosine receptor A2A signaling via inhibition of an adenosine transporter (Carrier 2006), suggesting an important therapeutic role in various inflammatory and chronic pain states**

Porter, B. E. & Jacobson, C. (2013). Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav,* 29, 574-7.

- Solicited data from an online Facebook survey of 150 families whose children were using cannabidiol-enriched cannabis to treat drug resistant seizures
- 19 responses (12.7%): 13 Dravet syndrome, 4 Doose syndrome, 1 Lennox-Gastaut syndrome, 1 idiopathic epilepsy
- These children had used an average of 12 ACDs previously!

Porter, B. E. & Jacobson, C. (2013). Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav,* 29, 574-7.

Overall, 84% noted decreased seizure frequency on CBD:

- 2 (11%) had complete remission
- 8 (42%) had >80% reduction in seizure frequency
- 6 (32%) had 25-60% reduction

Porter, B. E. & Jacobson, C. (2013). Report of a parent survey of cannabidiol-enriched cannabis use in pediatric treatment-resistant epilepsy. *Epilepsy Behav,* 29, 574-7.

Cannabidiol was associated with adverse events:

Drowsiness: 37%

Fatigue: 16%

With some side benefits:

Better mood: 79%

Increased alertness: 74%

Better sleep: 68%

Study Limitations:

A preliminary survey of limited duration

A self-selected population with low response rate

No control group

“Because of the therapeutic failures and because of the toxicity associated with the currently used antiepileptics, the search for relatively non-toxic drugs with different mechanisms of action is an obvious goal in epilepsy research. Both the lack of toxicity and the anticonvulsant properties of CBD combine to enhance its therapeutic potential as an antiepileptic.”

What year would you guess this observation was made?

Karler, R., and S. A. Turkanis. 1979. "Cannabis and epilepsy." In *Marihuana biological effects: Analysis, metabolism, cellular responses, reproduction and brain.*, edited by G. G. Nahas and W. D. M. Paton, 619-641. Oxford, UK: Pergamon Press.

“Because of the therapeutic failures and because of the toxicity associated with the currently used antiepileptics, the search for relatively non-toxic drugs with different mechanisms of action is an obvious goal in epilepsy research. Both the lack of toxicity and the anticonvulsant properties of CBD combine to enhance its therapeutic potential as an antiepileptic.”

p. 639

My Thought

Clinical Cannabis will never be fully accepted in mainstream America until it can be proven safe and effective in serious disorders in children.

Russo, E.B. 2003. Future of cannabis and cannabinoids in therapeutics. *Journal of Cannabis Therapeutics* 3 (4):163-174.

> “If and when cannabis establishes its efficacy in pediatric diseases, it shall have achieved a fair measure of redemption from the derision it has elicited during the past century.”