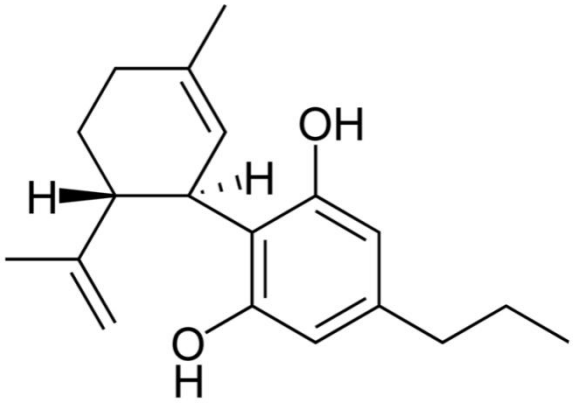
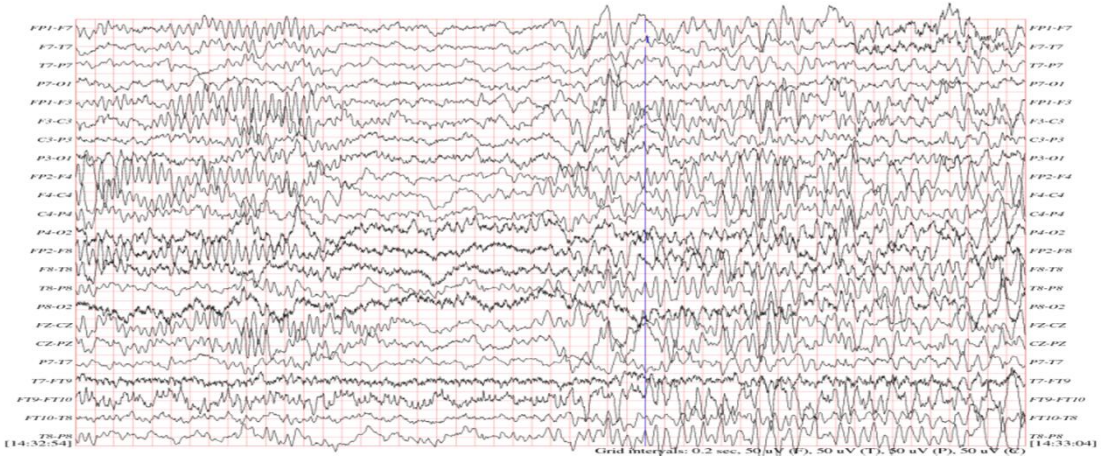
School of Chemistry, Food Biosciences & Pharmacy

University of Reading





Cannabis and epilepsy

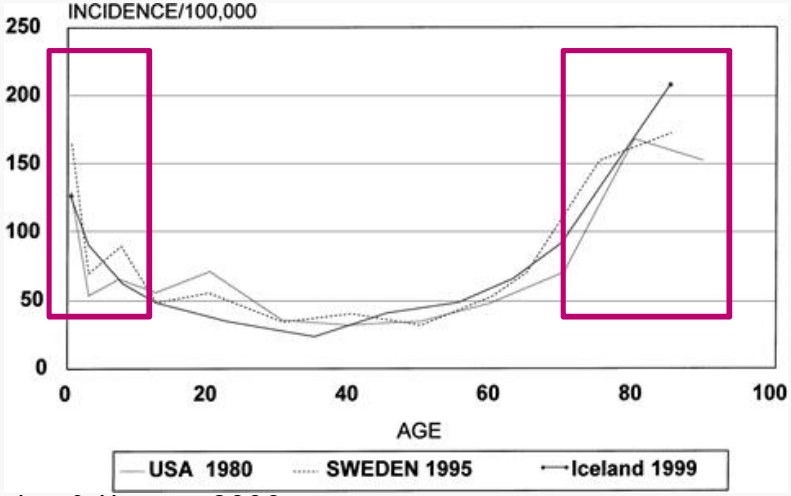
from recreational abuse to therapeutic use

B. Whalley

Epilepsy and public health

University of Reading

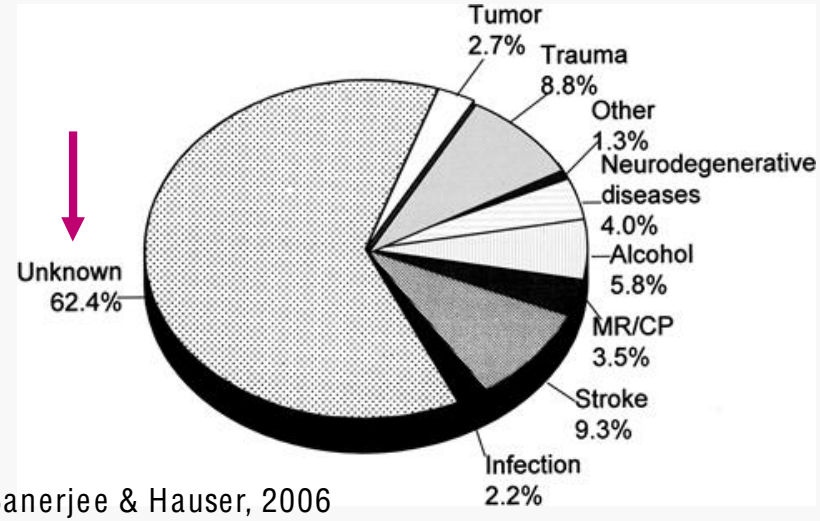
- Chronic, progressive neurological disorder characterised by spontaneous, recurrent seizures.
- ~10% of people will have a seizure in their lifetime of which ~30% will subsequently develop epilepsy.
- Lifetime prevalence ~1%.
- Third most prevalent neurological disorder after migraine and Parkinson's Disease (both ~0.7-1.2%).
- Affects 50 million people worldwide and accounts for 1% of the global burden of disease.



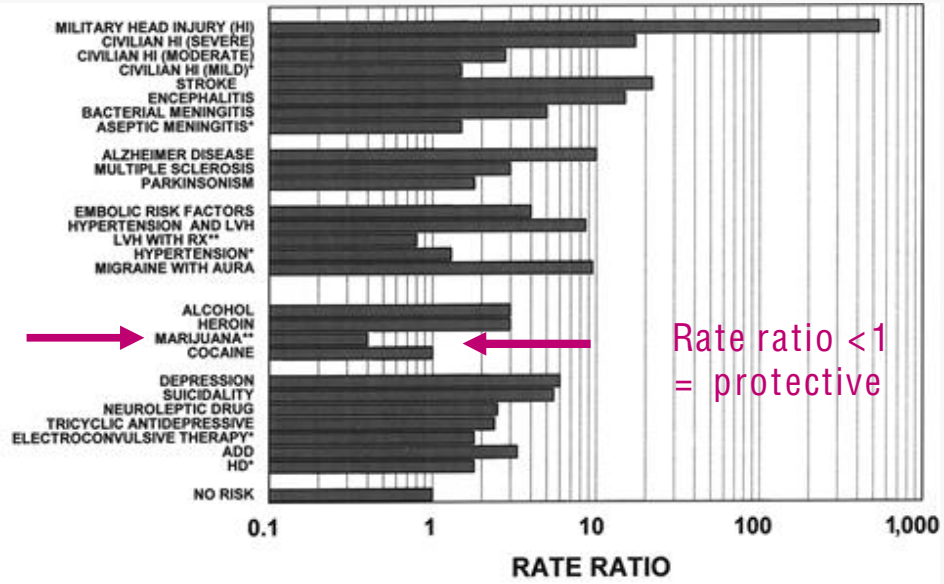
Banerjee & Hauser, 2006

Aetiology of epilepsy

- ~60% of cases are idiopathic (WHO, 2012)
- Remainder are cryptogenic or secondary to insults such as hypoxia (or other trauma) at birth, head trauma, drug use, stroke and CNS infection or tumour.
- Age is an independent risk factor and febrile seizure specific to childhood
- A small minority are due to specifically identifiable molecular/genetic causes.



Banerjee & Hauser, 2006



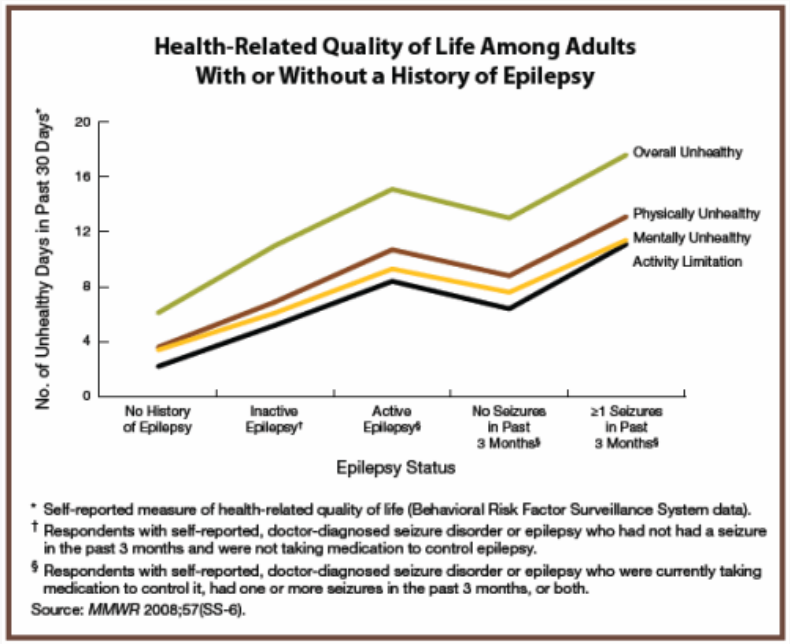
*Not significant **Protective.

Disease burden and co-morbidities

University of Reading

- Example disease burden: $ 15.5 billion per year in US (CDC, 2008)

- Premature mortality is 2-3 times higher in epilepsy patients (maximum reported: 8.8).
  - Significant causes: SUDEP, *status epilepticus*, accidents as a consequence of seizure, aspiration pneumonia after seizure, drug toxicity and idiosyncratic ADRs and suicides (Lhatoo et al, 2006)



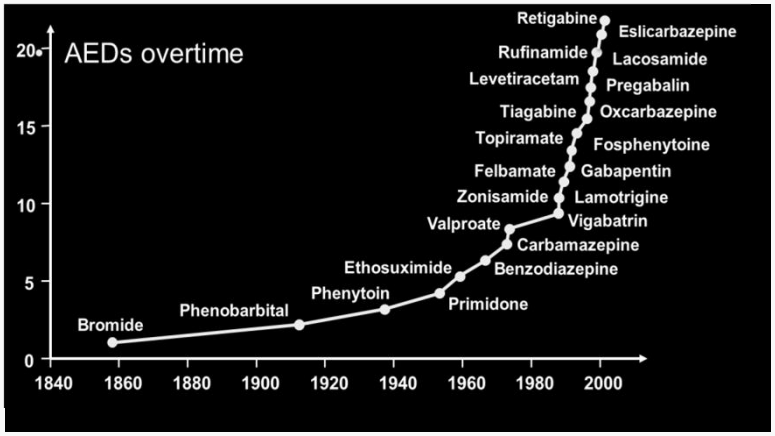
- Co-morbidities include:
  - Cognitive decline (drug and disease-related)
  - Anxiety
  - Depression
  - Agitation, anger and emotional outbursts
  - Suicide (5-15x more likely)
  - ADHD
  - Reproductive problems (make and female)
  - Insomnia
  - Migraine

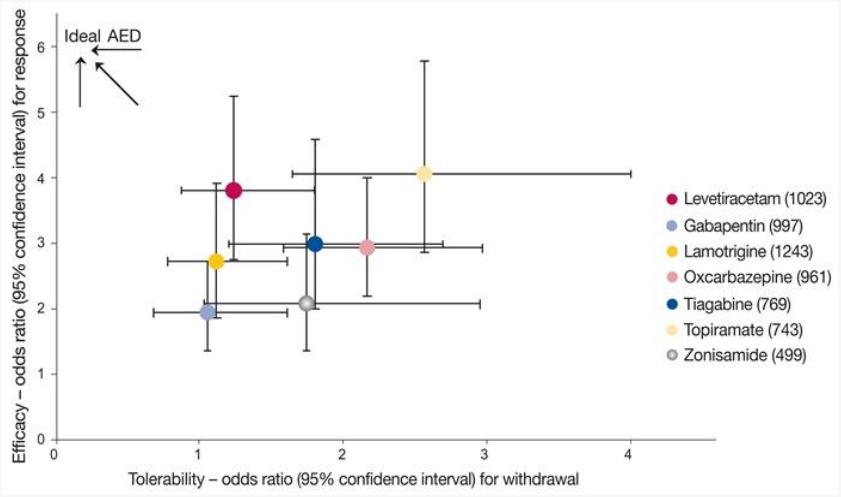
- Co-morbidities more frequent and severe in refractory patients

University of Reading

Clinical need for new AEDs

- The introduction of new AEDs since 1990 onwards has had no effect upon the number of pharmacologically intractable/refractory epilepsy patients.
  - Of 525 people with newly diagnosed epilepsy with 2–16 years of follow up, 37% still exhibited seizures at the final clinic visit whilst the remainder were seizure free for ≥1 year.
  - Seizure-free rate did not differ significantly between those treated with a single established drug (67%) and those treated with a single new drug (69%). Thus, new AEDs have not reduced pharmacoresistance (Kwan & Brodie, 2000).
- New AEDs achieve some benefit via improved side-effect profiles.
- New, better tolerated and more effective AEDs are clearly required to benefit the 15-20M people experiencing pharmacologically refractory seizures.





http://www.ncbi.nlm.nih.gov

University of Reading

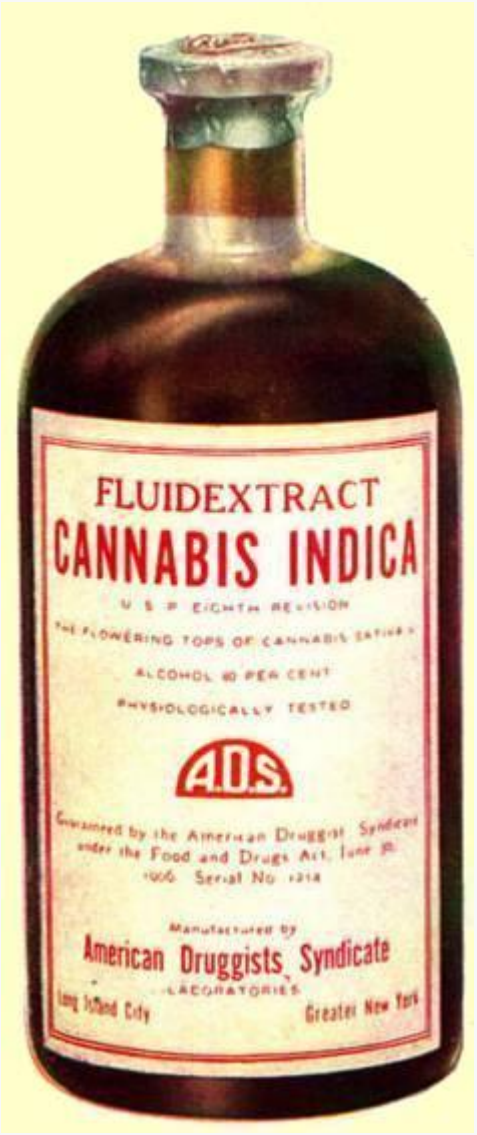
Rational drug design

- How have successful drugs been discovered?
  - Serendipity e.g. valproate, levetiracetam
  - Secondary use of existing drugs e.g. phenobarbital
  - Screening related compounds e.g. phenytoin, ethosuximide
    - 'me too' drugs
  - Modification of existing drugs e.g. oxcarbazepine, pregabalin
  - "Rational"/target oriented design e.g. vigabatrin, tiagabine
- The least successful have come from rational/target-based development.
- Related and modified compounds are typically only effective in epilepsies that already respond to existing treatments.

Historical use of cannabis in epilepsy

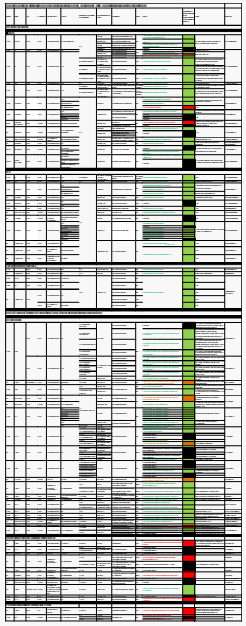
University of Reading

- 1100AD: al-Mayusi makes first written record of its use for this purpose
- C15th: Ibn al-Badri notes "*the epileptic son of the caliph's chamberlain*" was treated with *Cannabis* and "*it cured him completely, but he became an addict who could not for a moment be without the drug*"
- C19th: O'Shaughnessy, McMeens, Moreau and Reynolds independently tested the efficacy of a crude extract against seizures.
- J.R. Reynolds, Queen Victoria's personal physician said *Cannabis* is "*the most useful agent with which I am acquainted*" in the treatment of "*attacks or violent convulsions*," which "*may recur two or three times in the hour*," claiming that such attacks "*may be stopped with a full dose of hemp*"



Evidence from preclinical models

University of Reading



- Only whole animal models shown since seizures and epilepsy can only be poorly modelled *in vitro*

Compound	Species	Number of discrete conditions/models/designs	Dose	Anticonvulsant	No effect	Proconvulsant
THC	6	31	0.25-200 mg/kg	61%	29%	10%
CBD	2	21	1-400 mg/kg	81%	19%	0%
Other plant cannabinoids	2	7	N/A	100%	0%	0%
CB1 receptor agonists	2	55	N/A	73%	18%	2% (7% mixed effect)

- Results strongly support an overall anticonvulsant effect of plant cannabinoids and synthetic CB1R agonists.

University of Reading

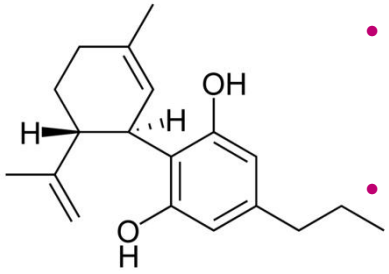
Evidence from anecdotal use

- No modern, valid human clinical trials have been conducted
- Six modern case studies report clinically assessed anticonvulsant effects of cannabis
- Five large surveys concluded that some individuals using 'medical marijuana' do so to control symptoms of epilepsy
- Personal correspondence with ~50 UK PWE using cannabis for control of seizures.
- One small scale clinical trial (1981) demonstrated that CBD was anticonvulsant in 7/8 patients treated (no change in placebo group).

University of Reading

Cannabidivarin (CBDV) pharmacology

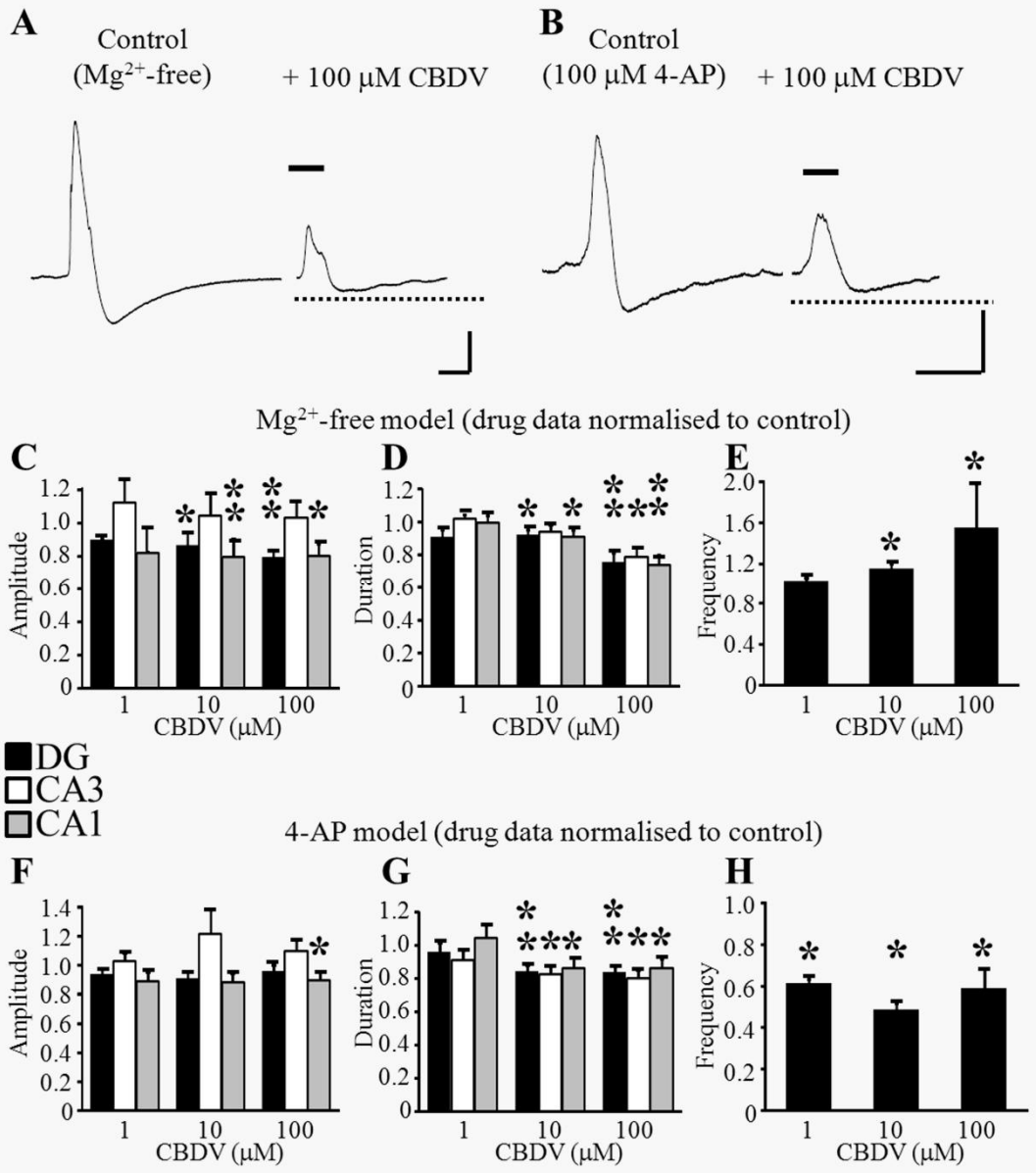
- Cannabidivarin (CBDV; also 'cannabidivarol') is a propyl analogue of cannabidiol (CBD).
- First isolated from hashish in 1969 (Vollner et al., 1969) although there is little extant evidence about pharmacological properties or therapeutic uses.
- Existing evidence of pharmacological effects:
  - Stimulates recruitment of bone marrow mesenchymal stromal cells via a CB2 receptor-dependent mechanism (direct effect on CB2 not shown; Scutt & Williamson, 2007)
  - Differential effects at transient receptor potential (TRP) channels *in vitro:*
    - Acts as an hTRPA1, hTRPV1 and hTRPV2 agonist (EC_{50}: 0.42, 3.6 and 7.3μM respectively) in transfected HEK-293 cells (De Petrocellis et al, 2011a, De Petrocellis et al, 2011b)
    - Acts a TRPM8 antagonist (IC_{50}: 0.90 μM) in transfected HEK-293 cells (De Petrocellis et al, 2011a).
    - Relevance of TRP target in epilepsy unknown



- Inhibits diacylglycerol lipase a (DAGLa; IC_{50}: 16.6μM) *in vitro*, the primary synthetic enzyme of the endocannabinoid, 2-arachidonoylglycerol (De Petrocellis et al, 2011a) but relevance to epilepsy unknown.
- Relevance of affinity for these targets for epilepsy remains unclear.

In vitro efficacy

University of Reading



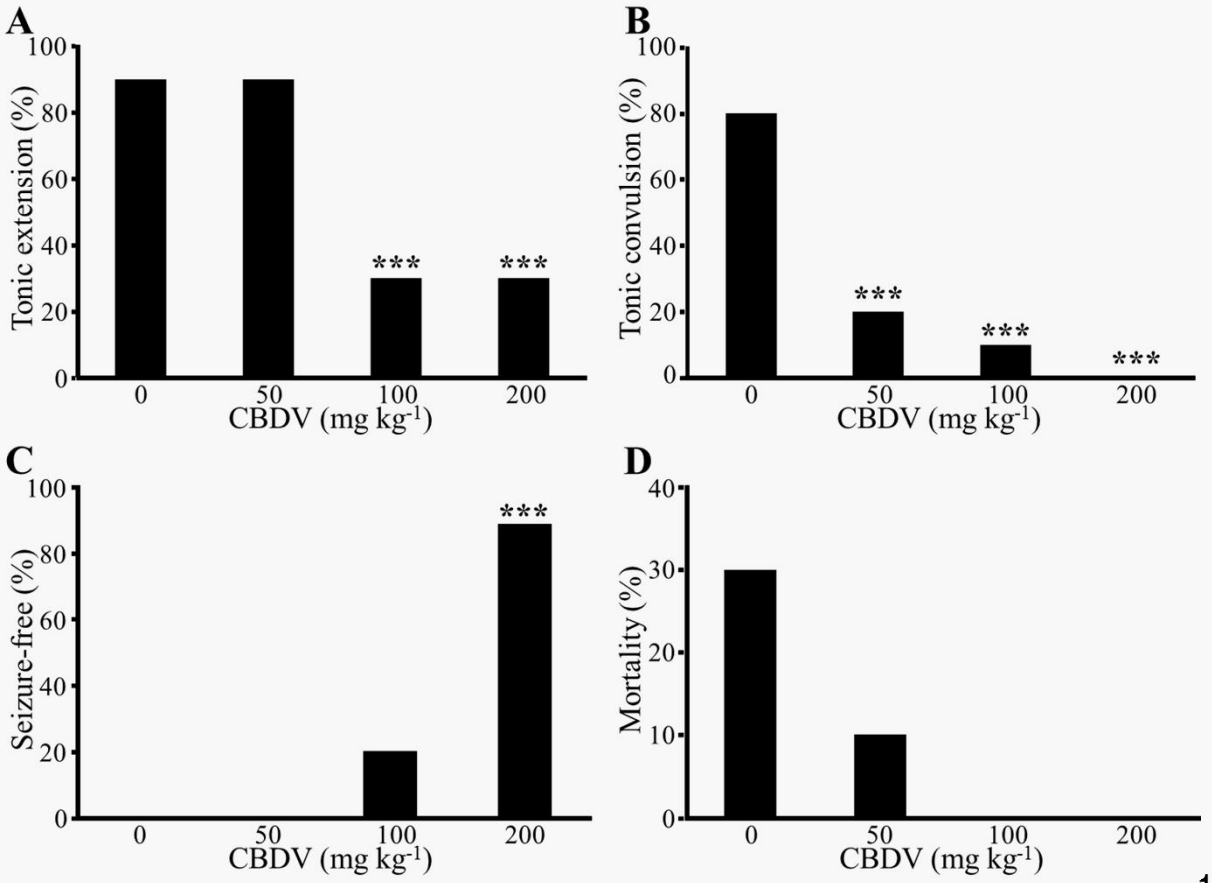
Efficacy *vs* maximal electroshock seizures and audiogenic seizures

University of Reading

- First line *in vivo*, mouse models for AED screening
- Both reveal whether or not broad anticonvulsant effects are present.

MES

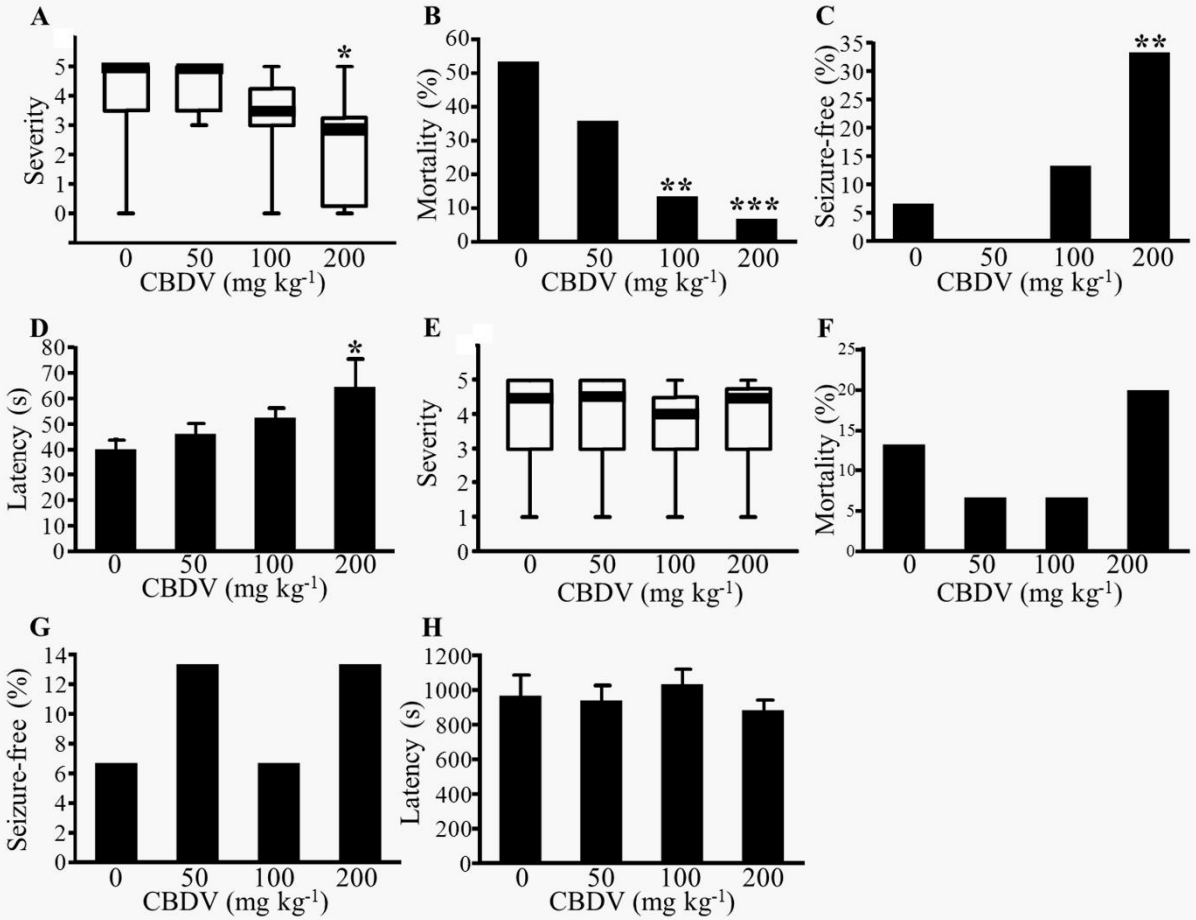
Audiogenic in DBA/2



Efficacy against acute PTZ and pilocarpine induced seizures

University of Reading

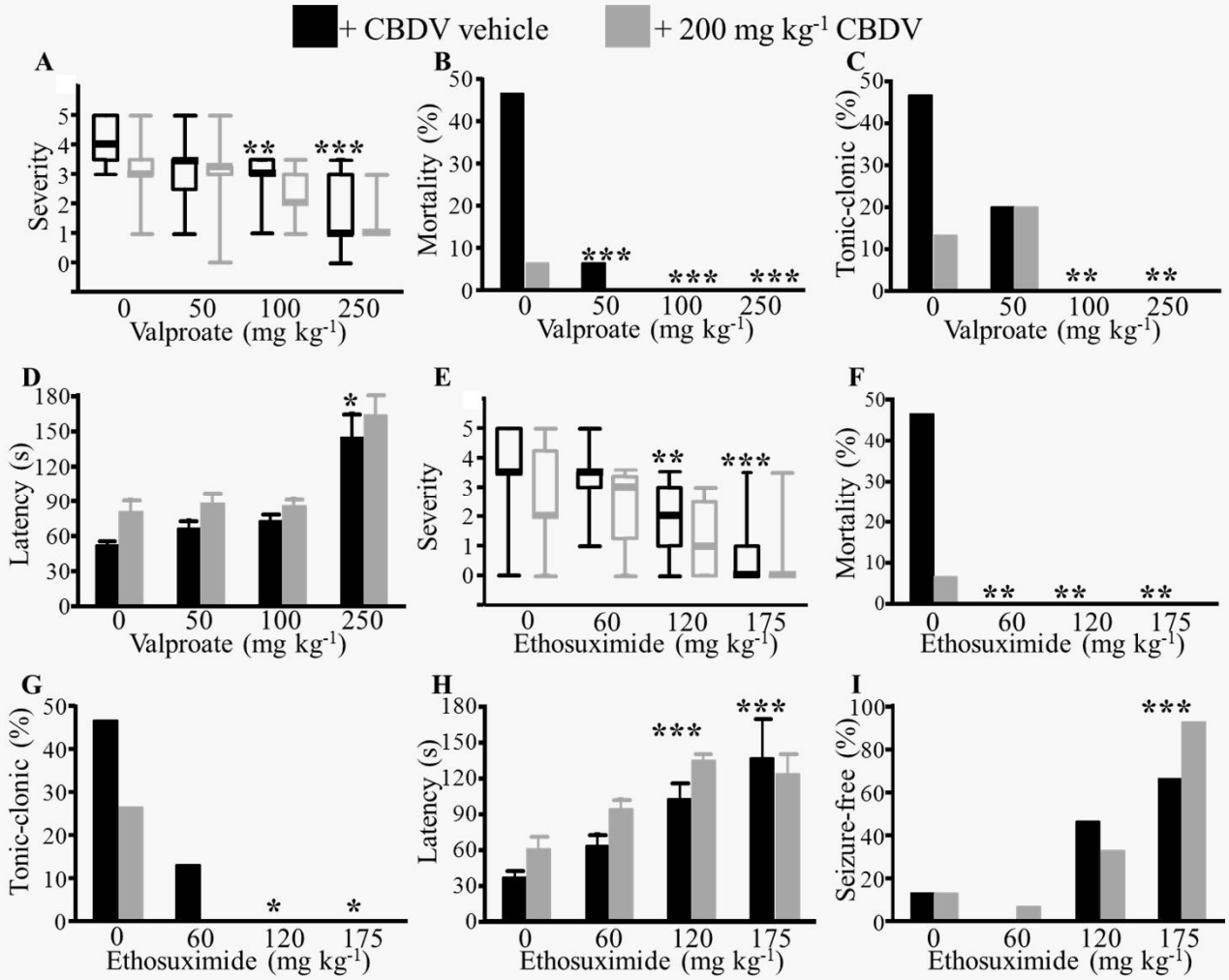
- PTZ (panels A-D): model of generalised seizure also indicative of efficacy against absence seizures
- Acute pilocarpine (panels E-H): model of temporal lobe seizures and *status epilepticus*



- Significant anticonvulsant effects against acute PTZ-induced generalised seizures
- No significant effect against acute, pilocarpine-induced TLS/*status epilepticus* (in this study).

Efficacy and tolerability retained with other AEDs (acute PTZ)

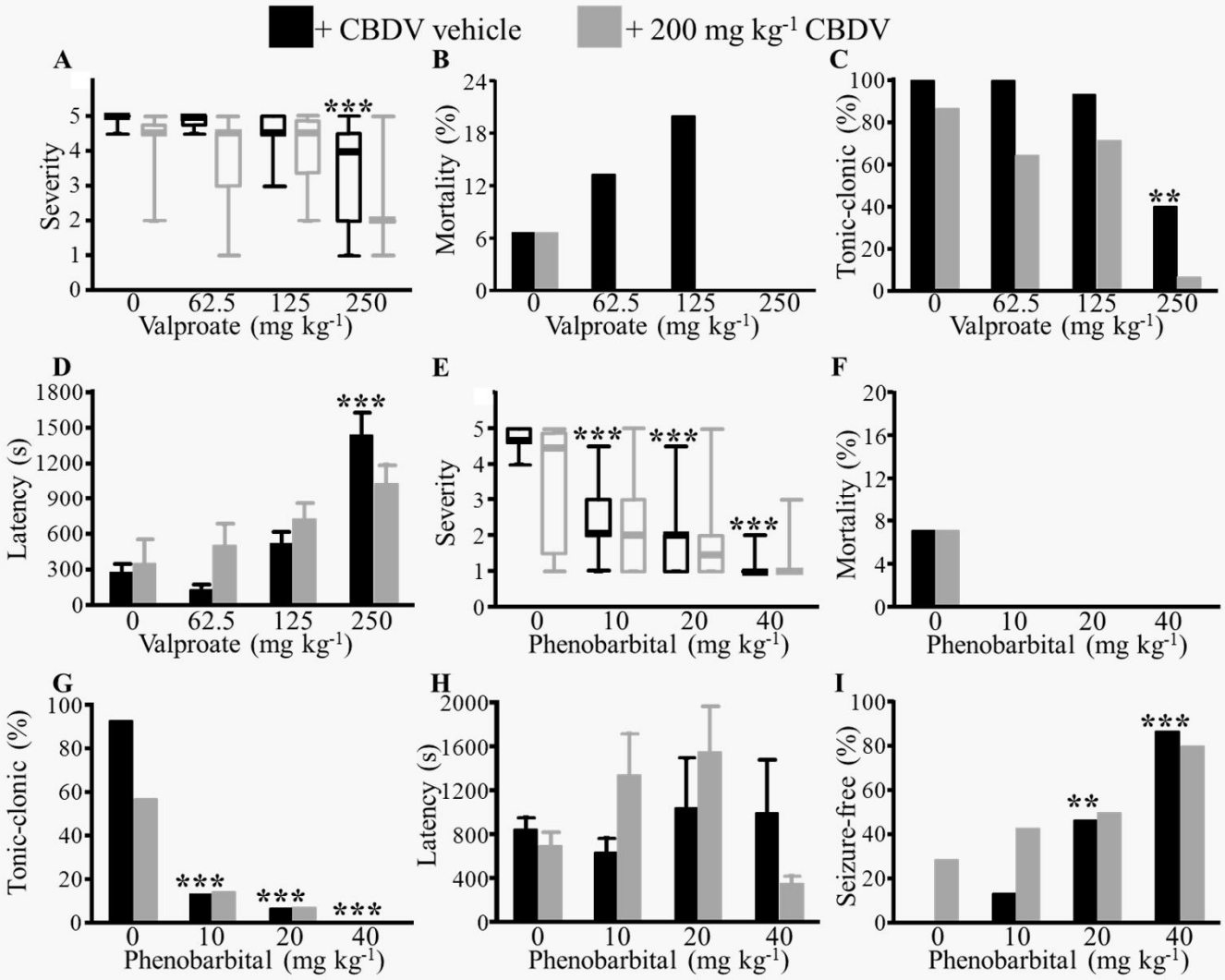
University of Reading



- Safe when co-administered?
- Study drug effect retained?
- Synergism of effects?

Efficacy and tolerability retained with other AEDs (acute pilocarpine)

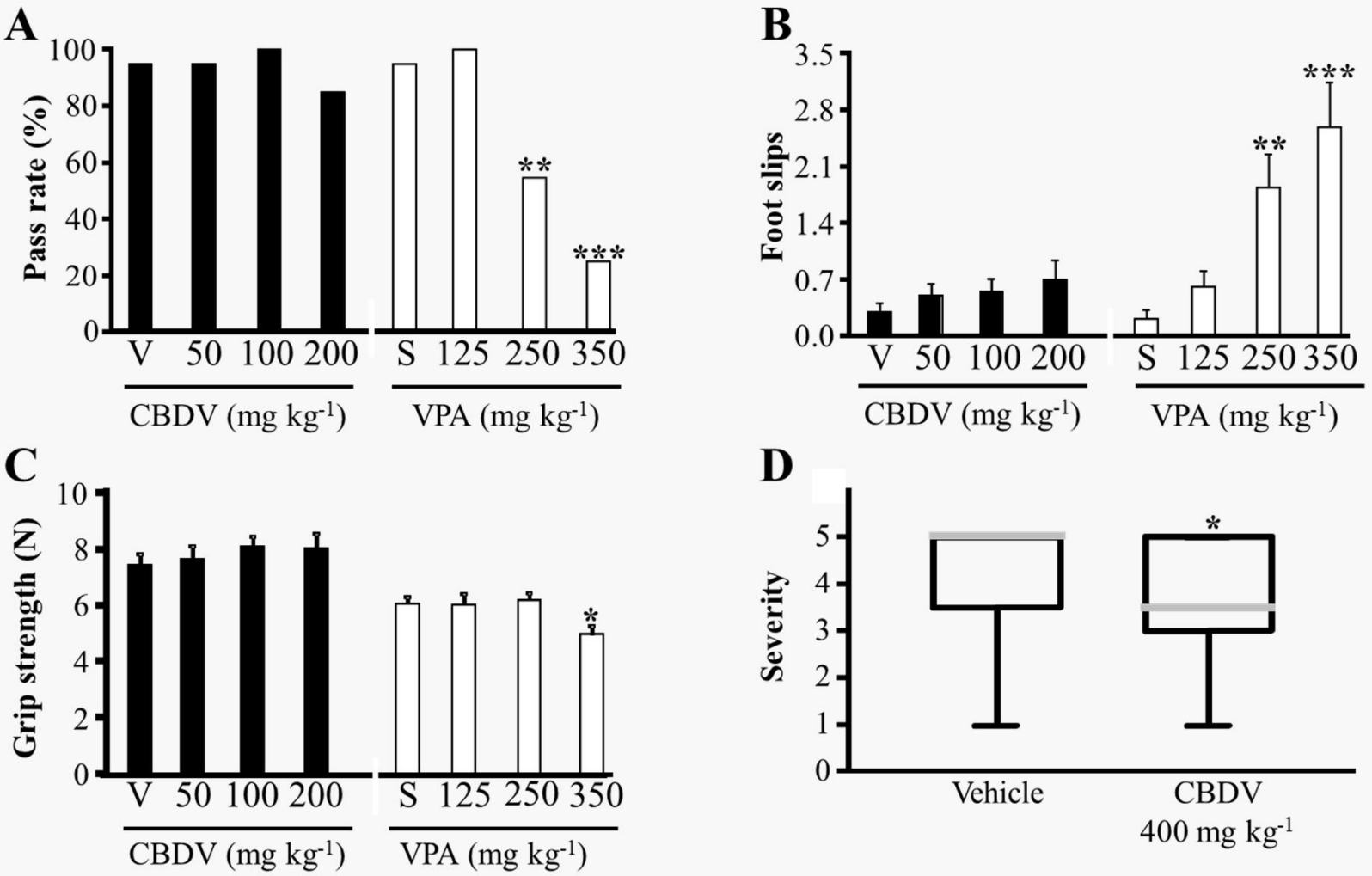
University of Reading



- Safe when co-administered?
- Study drug effect present?
- <u>Synergism of effects?</u>
- Notably, in this more highly powered study (more animals received study drug), CBDV was anticonvulsant against acute, pilocarpine-induced TLS/*status epilepticus*

Tolerability and oral efficacy vs PTZ

University of Reading



Acknowledgements

- Collaborators: Dr C. Williams, Dr G. Stephens, Dr G. Woodhall (Aston, UK), Prof. L. Sander (NEC & UCL, UK), Prof. E. Williamson & Prof. R. Hampson (Wake, USA).
- Researchers (past and present): Dr A. Hill, Mr N. Jones, Dr S. Weston, Dr J. Farrimond, Dr I. Smith, Dr X. Wang, Dr Y. Yamasaki, Mr T. Hill, Mrs C. Hill, Mr N. Amada, Miss I. Peres, Mrs R. Hadid, Mrs A. Al-Husaini, Mr S. Akiyama, Dr A. Futamura, Miss M. Mercier, Mr S. Marshall.

Sponsors: GW Pharmaceuticals and Otsuka Pharmaceuticals for continued financial and material support.

University of Reading

References

- Banerjee & Hauser (2006) in Epilepsy: a comprehensive textbook Lippincott & Williams (Eds: Engel & Pedley) Chapter 5, pp15
- Center for Disease Control (2008) Morbidity and Mortality Weekly Report 57; SS-6
- De Petrocellis, Ligresti, Moriello, Allara, Bisogno, Petrosino, Stott & Di Marzo (2011) Effects of cannabinoids and cannabinoid-enriched cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *Br J Pharmacol* 163:1479-1494.
- De Petrocellis, Orlando, Moriello, Aviello, Stott, Izzo & Di Marzo (2011) Cannabinoid actions at TRPV channels: effects on TRPV3 and TRPV4 and their potential relevance to gastrointestinal inflammation. *Acta Physiol (Oxf)*.
- EMEA (2000) Guidance on Clinical Investigation of Medicinal Products in the Treatment of Epileptic Disorders http://www.emea.eu.int/pdfs/human/ewp/056698en.pdf
- Engel (2006) Report of the ILAE Classification Core Group. *Epilepsia*. 2006;47:1558-1568
- Farrimond, Mercier, Whalley and Williams (2011) Cannabis sativa and the endogenous cannabinoid system Phytotherapy Research 25(2):170-88.
- Gastaut (1970) Clinical and electroencephalographical classification of epileptic seizures Epilepsia 11; 102
- Hill, Jones, Williams, Stephens & Whalley (2010) Development of multi-electrode array screening for anticonvulsants in acute rat brain slices. *J Neurosci Methods* 185:246-256.
- Hill, Williams, Whalley and Stephens (2012) Phytocannabinoids as novel therapeutic agents in CNS disorders. Pharmacology & Therapeutics 133(1):79-97.
- Hill, Mercier, Hill, Glyn, Jones, Yamasaki, Futamura, Duncan, Stott, Stephens, Williams and Whalley* (2012; ePub ahead of print) Cannabidivarin is anticonvulsant in mouse and rat in vitro and in seizure models British Journal of Pharmacology
- Kwan & Brodie (2000) Early identification of refractory epilepsy. N Engl J Med 342(5):314–9.
- Lhatoo, Sander & Tomson (2006) in Epilepsy: a comprehensive textbook Lippincott & Williams (Eds: Engel & Pedley) Chapter 10, pp1
- Vollner, Bieniek, & Korte F (1969) Hashish. XX. Cannabidivarin, a new hashish constituent. *Tetrahedron Lett* 145-147.
- WHO (2012) http://www.who.int/mediacentre/factsheets/fs999/en/index.html (last accessed 06/01/2012)
- Scutt & Williamson (2007) Cannabinoids stimulate fibroblastic colony formation by bone marrow cells indirectly via CB2 receptors. *Calcif Tissue Int* 80:50-59.