



— Press Release —

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**American Herbal Pharmacopoeia<sup>®</sup>**  
***Therapeutic Compendium***

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***AHP Releases Cannabis in the Management and Treatment of Seizures and Epilepsy: A Scientific Review***

Pre-publication release for public domain dissemination

The American Herbal Pharmacopoeia (AHP) today announced the release of a section of the soon-to-be-completed *Cannabis Therapeutic Compendium Cannabis in the Management and Treatment of Seizures and Epilepsy*. This scientific review is one of numerous scientific reviews that will encompass the broad range of science regarding the therapeutic effects and safety of cannabis. In recent months there has been considerable attention given to the potential benefit of cannabis for treating intractable seizure disorders including rare forms of epilepsy. For this reason, the author of the section, Dr. Ben Whalley, and AHP felt it important to release this section, in its near-finalized form, into the public domain for free dissemination. The full release of AHP's *Therapeutic Compendium* is scheduled for early 2014.

Dr. Whalley is a Senior Lecturer in Pharmacology and Pharmacy Director of Research at the School of Pharmacy of the University of Reading in the United Kingdom. He is also a member of the UK Epilepsy Research Network. Dr. Whalley's research interests lie in investigating neuronal processes that underlie complex physiological functions such as neuronal hyperexcitability states and their consequential disorders such as epilepsy, ataxia and dystonias, as well as learning and memory. Since 2003, Dr. Whalley has authored and co-authored numerous scientific peer-reviewed papers on the potential effects of cannabis in relieving seizure disorders and investigating the underlying pathophysiological mechanisms of these disorders.

The release of this comprehensive review is timely given the growing claims being made for cannabis to relieve even the most severe forms of seizures. According to Dr. Whalley: "Recent announcements of regulated human clinical trials of pure components of cannabis for the treatment of epilepsy have raised hopes among patients with drug-resistant epilepsy, their caregivers, and clinicians. Also, claims in the media of the successful use of cannabis extracts for the treatment of epilepsies, particularly in children, have further highlighted the urgent need for new and effective treatments." However, Dr. Whalley added, "We must bear in mind that the use of any new treatment, particularly in the critically ill, carries inherent risks. Releasing this section of the monograph into the public domain at this time provides clinicians, patients, and their caregivers with a single document that comprehensively summarizes the scientific knowledge to date regarding cannabis and epilepsy and so fully support informed, evidence-based decision making." This release also follows recommendations of the Epilepsy Foundation, which has called for increasing medical research of cannabis and epilepsy and made the following

statement: “The Epilepsy Foundation supports the rights of patients and families living with seizures and epilepsy to access physician-directed care, including medical marijuana.” AHP’s *Therapeutic Compendium Use of Cannabis in Epilepsy* represents the first step in increasing awareness of the currently existing research.

AHP’s *Cannabis Therapeutic Compendium* is a companion to AHP’s *Cannabis Quality Control Monograph*, which was released in December 2013. The *Quality Control Monograph* and *Therapeutic Compendium* were developed in collaboration with Americans for Safe Access (ASA), a medical marijuana advocacy group in Washington, DC.

Please visit: [\*AHP Therapeutic Compendium: Cannabis in the Management and Treatment of Seizures and Epilepsy: A Scientific Review.\*](#)

AHP is a nonprofit research organization of herbal medicine in Scotts Valley, CA. AHP and the author encourage the free distribution of this section on epilepsy to help increase awareness of the evidence base regarding the use of cannabis for this indication and to encourage further research in this area.

Questions regarding the monograph should be directed to: Roy Upton ([ahp@herbal-ahp.org](mailto:ahp@herbal-ahp.org)); questions pertaining to research regarding cannabis and seizure disorders should be directed to: Benjamin Whalley: [b.j.whalley@reading.ac.uk](mailto:b.j.whalley@reading.ac.uk).



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## **CANNABIS IN THE MANAGEMENT AND TREATMENT OF SEIZURES AND EPILEPSY: A SCIENTIFIC REVIEW**

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## **PUBLIC DOMAIN DOCUMENT**

The following analysis is intended to provide a review of the literature regarding the scientific investigation of the use of cannabis and cannabinoids in the management and treatment of seizures and epilepsy. This section is part of a larger *Therapeutic Compendium* under development by the American Herbal Pharmacopoeia® (AHP) due for release in 2014 and is a companion to AHP's *Standards of Identity, Analysis, and Quality Control Cannabis* monograph. This specific draft, *CANNABIS IN THE MANAGEMENT AND TREATMENT OF SEIZURES AND EPILEPSY*, is a public domain document and can be freely disseminated.

## **LEGAL NOTIFICATION**

In the United States, cannabis is a Schedule I controlled substance under federal law; therefore, any use or possession of cannabis and its preparations is illegal except pursuant to the compassionate use Investigational New Drug exemption. This review is not intended to support, encourage, or promote the illegal cultivation, use, trade, or commerce of cannabis. Individuals, entities, and institutions intending to possess or utilize cannabis and its preparations should consult with legal and/or medical counsel prior to engaging in any such activity.

## **MEDICAL DISCLAIMER**

The information contained in this monograph represents a synthesis of the authoritative scientific data. All efforts have been made to ensure the accuracy of the information and findings presented. Those seeking to utilize cannabis as part of a health care program should do so under the guidance of a qualified health care professional.

## **STATEMENT OF NON-ENDORSEMENT**

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## THERAPEUTIC COMPENDIUM

### CANNABIS IN THE MANAGEMENT AND TREATMENT OF SEIZURES AND EPILEPSY

#### INTRODUCTION—HISTORICAL USE OF CANNABIS IN SEIZURES AND EPILEPSY

Seizures are the characteristic and principal symptom of epilepsy, a chronic progressive disorder that affects approximately 1% of the world's population and is, in the majority of cases, idiopathic or cryptogenic in nature. Approximately 30% of individuals with epilepsy do not obtain adequate seizure control from existing anticonvulsant medications, some of which can themselves cause debilitating and life-threatening side effects. Up to 50% of people with epilepsy ultimately develop seizures that are resistant to currently available medication. These factors drive both patient and commercial searches for more effective and better-tolerated therapies, which may include cannabis.

The use of cannabis for seizure control was described as long ago as 1100 AD by Arabic writer al-Mayusi (Lozano 2001), Ibn al-Badri in the 15<sup>th</sup> century (Mechoulam 1986), and by medical practitioners in the 1800s (e.g., McMeens 1856; 1860; O'Shaughnessy 1840; Reynolds 1890; see History of complete *AHP Cannabis Therapeutic Compendium* in press). Medical practitioners have attributed various degrees of efficacy to cannabis. More recent reports describing the effects of cannabis upon seizure states fall into two principal groups: those describing the effects of whole cannabis (or its preparations) upon seizures, and those using isolated phytocannabinoids. This distinction is notable since the former is closely linked to the historical, yet continued, use of cannabis as an herbal medicine that must, however, be tempered by the well-known psychoactive effects of  $\Delta^9$ -THC; conversely, the latter is largely driven by conventional development of new anticonvulsant drugs based upon individual, isolated and/or purified cannabis constituents — i.e. discrete phytocannabinoids such as CBD. (Karler and Turkanis 1976; 1981).

The identification and isolation of phytocannabinoids (see Mechoulam and Gaoni 1967) aided investigations of their individual effects upon a number of disease states, including

seizures. The multiple constituents of cannabis interact with one another and with ongoing disease states in a pharmacologically and pathophysiologically complex manner. The complexity of this interaction was summarized in an early review of Feeney (1978), who noted that low pre-drug baseline seizure frequency or intensity may be activated by  $\Delta^9$ -THC; whereas against a high pre-drug baseline, seizures may be attenuated. In order to properly understand this interaction and establish whether non-THC, and hence likely non-psychoactive, cannabis constituents have specific pro- and/or anticonvulsant effects, many preclinical investigations and small-scale clinical trials have examined the effects of individual phytocannabinoids.

The evidence describing cannabis effects upon seizures exists as either small trials, individual case studies, or from surveys of cannabis users. No specific clinical trials have been undertaken using cannabis itself, as the still-limited studies of this nature have thus far only been conducted using individual phytocannabinoids (see *Preclinical Research* below).

## HUMAN STUDIES

### *Case Studies—Cannabis*

Both anticonvulsant and proconvulsant effects have been reported with cannabis use. In 1967, a single case report of an epileptic patient who had been historically seizure-free from the use of conventional anticonvulsant medication (phenytoin and phenobarbital) was presented after the return of his seizure symptoms following a period of cannabis use (seven times within three weeks). The subject experienced three tonic-clonic seizures during this time, but the seizures were neither correlated with intoxication nor did they occur in the period of immediate withdrawal (Keeler and Riefler 1967).

In contrast to this report, a case of a 24-year-old was reported who, in addition to taking regular doses of phenobarbital (30 mg qds) and phenytoin (100 mg qds), which did not fully control his tonic-clonic seizures (breakthrough seizure every 1–2 months), required the smoking of 2–5 cannabis cigarettes daily to obtain full seizure control (Consroe et al. 1975). The investigators estimated that the overall  $\Delta^9$ -THC dose used was  $\sim 6 \mu\text{g}/\text{kg}$ . Thereafter, a 29-year-old male, diagnosed with bipolar disorder in addition to alcoholism and chronic daily cannabis use, reported new onset complex partial seizures following abrupt cessation of his cannabis use (Ellison et al. 1990). As seizures are independently associated with both bipolar disorder (Mula et al. 2008) and alcoholism (Mattoo et al. 2009), it is difficult to draw conclusions from this latter report.

Cannabis was also reported to produce a “marked improvement” in seizure control in a 45-year-old cerebral palsy patient, epileptic since age 18 years, who experienced premature birth, as well as a concussion at age 8 (Mortati et al. 2007). Scanning MRI revealed an infarct of the left superior medial frontoparietal lobe; no EEG was undertaken. Here, the patient presented with multiple seizure types (night-time ‘screaming’ seizures [2–3 times per night]), waking seizures with associated motor dysfunction (weekly) and generalized tonic-clonic seizures (every three months), which were not controlled by conventional medication (valproate 2.5 g, zonisamide 400 mg, and clonazepam 1.5 mg). Six months after initial presentation, his screaming seizures ceased but with no change to conventional medication provided he smoked cannabis each evening at bedtime (no details of cannabis type or quantity smoked were reported); screaming seizures reliably returned on evenings when cannabis was not smoked. The occurrence of daytime partial seizures (weekly instances reduced 2–3 seizures in 12 months of cannabis use) and tonic-clonic convulsions (instances every three months to one instance in 12 months) were also markedly reduced.

Another pair of case studies was reported by Hegde et al. (2012), who described patients whose seizures associated with focal epilepsy were exacerbated following cessation of cannabis consumption. In the first case, an otherwise healthy 43-year-old man who had exhibited violent ‘flailing limb’ seizures during sleep from the age of 24 months experienced ~20 seizures per night (each ~60 seconds in duration) prior to hospital admission; levetiracetam and phenytoin were ineffective although carbamazepine halved seizure frequency and, with maximum tolerated doses, eventually reduced frequency to 5–6 seizures per night. At this point, the patient began smoking cannabis (~40 mg *Cannabis sativa* each night) and the seizure frequency fell to 1–2 seizures per night. Cessation of cannabis consumption on admission to hospital saw him experience 10 seizures on the first night, which was reduced to one seizure when he consumed (po) cannabis brought to him by his spouse. Ultimately, the patient underwent surgical intervention that rendered him seizure-free six months after surgery and so permitted discontinuation of cannabis use. The in-patient nature of the observed effects prior to surgery makes this a valuable, modern case study. In the second case reported by the same authors, a 60-year-old man presented with amnesic episodes suspected to be seizure-related although there was no history of epilepsy, he took no anticonvulsants and did not experience auras or other symptoms associated with partial seizures. The patient reported a 40-year history of cannabis smoking, ostensibly for chronic abdominal pain, although use stopped on admission to hospital whilst other conventional medications were continued (two anti-hypertensive agents, a proton pump inhibitor, and a statin). After 24 hours of cannabis cessation, the patient entered *status epilepticus* and experienced five seizures in a 12-hour period with persistently abnormal interictal

EEG activity. The seizures were stopped by treatment with lorazepam and valproate, and his subjective account of the seizures experienced in the hospital environment was consistent with those associated with his previously reported amnesic states. The patient ultimately discharged himself, experienced intermittent seizures — which were refractory to valproate but only in part to phenytoin — and continued his earlier cannabis use. Interestingly, Hegde et al. (2012) make the argument that the widespread but often intermittent use of cannabis suggests that the appearance of seizures in these individuals reflects an anticonvulsant effect of cannabis and not part of a withdrawal phenomenon.

This small collection of case studies that describe possible cannabis-related interactions with seizure events is very limited by the number of cases and the diverse concomitant drug use and disease states amongst the cases. These reports did, however, highlight the apparent interaction between cannabis and seizures and encouraged the more controlled surveys and trials that were subsequently undertaken.

## *SURVEYS*

Given the widespread nature of recreational cannabis use and/or abuse, a number of surveys have, either as their stated intent or as a serendipitous outcome, reported pertinent results to seizures and/or epilepsy. However, given the illicit nature of cannabis consumption in most Western countries and the fact that many of the surveys were conducted by patient advocacy groups, surveys in which cannabis consumption, composition, or effects are not directly and objectively assessed may over-report positive and under-report negative effects.

The first modern (1976) critical review of the extant literature at the time found that results from historical studies of cannabis effects upon seizures were inconclusive despite the majority proposing an overall effect of reduced seizure activity (Feeney et al. 1976). This finding led to a small survey of approximately 300 respondents, which revealed that approximately 30% of youthful, epileptic patients smoked cannabis with no reported effect upon their seizure patterns, although one respondent claimed that cannabis decreased his symptoms, whilst another reported that it “*caused [his] seizures*” (Feeney et al. 1976). In a final report, these researchers concluded that  $\Delta^9$ -THC exhibited both pro- and anti-convulsant effects (see also below for  $\Delta^9$ -THC-specific effects) in a manner that may be seizure type- and/or species-dependent. For example,  $\Delta^9$ -THC triggered tonic-clonic seizures in epileptic beagles, yet abolished generalized, maximal electroshock (MES)-induced seizures in rats (Feeney et al. 1976). Whilst this series of surveys and reviews did not reach unequivocal conclusions, they formalized the scientific

community's view that evidence regarding cannabis effects on seizures was thus far complex and inconclusive.

A 1989 retrospective survey of patients, presenting with “recreational drug-induced [generalized tonic-clonic] seizures” on admission to a San Francisco Emergency Department between 1975 and 1987, 21% of whom had previously experienced seizures “*temporally associated with drug abuse,*” examined data from 47 patients (28 male, 19 female), which included prescription drug use, seizure features, and physical and laboratory examination results (Alldredge et al. 1989). Cannabis use occurred in approximately 10% of the cases examined, although, in all of these cases, other drugs had also been consumed (cocaine, amphetamine, or LSD) at or around the same time. It is notable that no cases of seizure within this population followed use of cannabis alone, whilst, conversely, the numbers of cases noted following either cocaine (approximately 45%) or amphetamine (approximately 15%) use alone were notably larger. An important caveat associated with these findings is that all subjects had used ‘street’ drugs, the true content of which cannot be reliably ascertained.

Thereafter, in a large epidemiological survey of heroin, cannabis, and cocaine use by individuals prior to their presentation with a first seizure (308 patients with seizures and 294 controls) in New York City between 1981 and 1984, cannabis use was found to be protective against both provoked and unprovoked first seizures in men (Brust et al. 1992; Ng et al. 1990). In 1997, a critical review of the above evidence also included qualitative reports that described the successful treatment of two further epilepsy patients with cannabis (Grinspoon and Bakalar 1997). Here, the first patient reported that cannabis smoking abolished petit mal seizures unresponsive to conventional anti-epileptic drugs. The second patient reported that cannabis fully abolished his grand mal seizures and reduced the incidence of petit mal seizures by ~50%, leading to a successful reduction in the conventional anticonvulsant medication employed. Moreover, and in the same year, a further 11 epileptic patients were identified as applicants to the US Compassionate Use Investigational New Drug program that provides legal medical exemption from prosecution for cannabis possession and use (Petro 1997). In three more surveys, 3.6% of German medical cannabis users employed cannabis for seizure control (Schnelle et al. 1999), whilst cannabis was used for that purpose by 4% of patients (population size: 77) supported by a medical cannabis program in the US (Corral 2001) and by 1% of patients (population size: ~2500) using medical cannabis in California, US (Gieringer 2001).”

In 2001, the outcomes of informal interviews conducted with more than 215 cannabis-using patients with active epilepsy (defined by the investigators as those having “*a history of seizure in the last 5 years and/or current use of anticonvulsant medicines plus intermittent or regular cannabis use*”)

were published. Here, 90.2% of patients did not identify a relationship between cannabis use and their seizure frequency or severity. Of these respondents, 7.4% thought their seizures were less frequent, whilst 2.3% felt they were more frequent around the time of cannabis use. Notably, these findings were presented cautiously as the collected information was based on retrospective recollections in a population with frequent short-term memory impairments due to cannabis use (Puighermanal et al. 2009) and seizures (Meador 2007). Additionally, some subjects may have consumed alcohol, missed doses of their anti-epileptic drugs, and/or been subject to sleep deprivation near the time of cannabis use, thereby limiting the depth of interpretation.

A telephone survey of patients treated at a tertiary-care epilepsy center in Canada in 2004 revealed that 21% of respondents had used cannabis in the 12 months prior to the survey “*with the majority of active users reporting beneficial effects on seizures*” and that 24% thought “*cannabis was an effective therapy for epilepsy.*” Moreover, 68% reported beneficial effects of cannabis upon seizure severity, whilst 54% reported that cannabis reduced seizure frequency (Gross et al. 2004).

More recently Porter and Jacobson (2013) published the results of a survey of parents of a pediatric, drug-resistant epilepsy population who were given cannabidiol-rich cannabis preparations. All subjects ( $n = 19$ ) but one (intractable for 16 months prior to cannabis treatment) were unresponsive to conventional treatments for more than three years prior to commencing cannabis treatment. The children were reported to exhibit Dravet syndrome (13), Doose syndrome (4), Lennox–Gastaut syndrome (1), and idiopathic epilepsy (1), which, together, include focal, tonic–clonic, myoclonic, atonic, absence, and infantile seizures. The subjects had previously been treated with an average of 12 antiepileptic drugs (AEDs). Treatment with CBD-rich extracts (based on analyses of the preparations reported by participants) ranged from  $<0.5$  mg/kg/day to 28.6 mg/kg/day CBD and 0–0.8 mg/kg/day  $\Delta^9$ -THC (differences in pharmacological potency and molecular mechanisms between CBD and  $\Delta^9$ -THC follow). The frequency of seizures ranged from 2/week to 250/day. Overall, 84% of parents (16) reported a reduction of seizure frequency, among which two reported a complete cessation of seizures for up to four months after commencing cannabis treatment. Eight subjects reported a reduction of seizures by approximately 80%, three reported a reduction of  $>50\%$ , and three reported a reduction of  $>25\%$ ; no change in the remaining three subjects that met the inclusion criteria of the survey was reported. In addition to claims of reducing seizure frequency, parents reported additional beneficial effects including increased alertness (74%), better mood (79%), improved sleep (68%), and decreased self-stimulation (32%) whilst adverse effects included drowsiness (37%) and fatigue (16%). Twelve parents reportedly weaned their child from conventional antiepileptic drugs after commencing cannabis treatment. Notable limitations of

this survey are numerous in that there is no objective way to confirm the results reported; the preparations and doses used were highly varied; the survey population was self-selectively positively biased as participants belonged to an epilepsy-cannabis social media support group; and there was no medical oversight regarding any of the reporting. It should also be noted that the reported ‘additional benefits’ may be indirect since they are entirely consistent with improvements control of seizures and/or withdrawal or reduction of conventional anti-epileptic drugs (and their associated side effects). To address the accuracy of reporting, the researchers provided comparable questions to a different parent support group for children with Dravet syndrome. The questionnaire was identical except that cannabis was substituted with the orphan drug, stiripentol, which is used in the treatment of epilepsy and, specifically, Dravet syndrome. Comparison between the patient groups revealed sufficient consistency for the investigators to conclude that the reported high efficacy in this population with highly refractory epilepsy warranted further, formal investigation of CBD in drug-resistant pediatric epilepsies. A properly regulated trial has now begun although pure CBD — not highly variable, crude extracts — is employed (GW Pharma 2013).

## *TETRAHYDROCANNABINOL (THC) AND SEIZURES*

### *Case Studies*

In the late 1940s, the effects of two isomeric forms of what were later identified as a  $\Delta^9$ -THC homologue (1,2-dimethyl heptyl) were investigated in a small trial on five institutionalized epileptic children whose seizures had previously been unresponsive to phenobarbital or phenytoin. The study found that “*severe anticonvulsant resistant grand mal epilepsy [was] controlled*” in two children with no change noted in the remaining three children (Davis and Ramsey 1949). The researchers concluded that the equivocal findings justified a larger study in a non-institutionalized population. Since then, the only other relevant case studies are contained within a report of Lorenz (2004) describing  $\Delta^9$ -THC effects in a variety of chronic and, in many cases, terminal disorders presenting in pediatric patients. Here, a 12-year-old girl with seizures and spasticity arising from hypoxia (from fetomaternal transfusion) experienced improved spasticity symptoms and a ‘noticeable reduction in the number of seizures’ when given 0.07 mg/kg po  $\Delta^9$ -THC each day. A second case, within the same report, of a 13-year-old boy exhibiting spasticity and myoclonic, focal, and generalized epileptic seizures of uncertain aetiology, saw a reduction in severity of myoclonus but not other seizure types when treated with 0.14 mg/kg po  $\Delta^9$ -THC daily. The report also described the case of another 12-year-old girl with mitochondriopathy who

was treated with 0.09 mg/kg po  $\Delta^9$ -THC each day, which, interestingly, resulted in an initial and temporary increase in seizure severity followed by a considerable improvement of her tonic seizures. Finally, the third relevant case in this report described a 14-year-old boy who exhibited severe idiopathic early infantile grand mal epilepsy with tonic-clonic seizures and began treatment with 0.12 mg/kg po  $\Delta^9$ -THC daily. However, no data was presented for THC effects upon his seizures since concurrent changes to conventional antiepileptic medication made assessment of  $\Delta^9$ -THC effects impossible. Subsequent data are largely limited to a concentrated series of preclinical animal studies undertaken during the 1970s and 1980s.

## *CANNABIDIOL (CBD) AND SEIZURES*

### *Human Trials and Case Studies*

To date, cannabidiol (CBD) is the only phytocannabinoid other than  $\Delta^9$ -THC investigated for anticonvulsant effects in human subjects. The first report of an effect of CBD upon seizure appeared as a single case study of a 24-year-old male whose centrencephalic epilepsy was characterized by symmetrical spike-and-wave EEG activity during light sleep (Perez-Reyes and Wingfield 1974). The subject was sedated using 2 g chloral hydrate, followed by administration of CBD (40 mg iv, 2.4 mg/min). The investigators reported that CBD “*did not decrease the abnormal epileptic electroencephalographic activity ... and perhaps increased it,*” which would be consistent with a pro-convulsant effect. It is also worth noting that the patient’s “*tonic-clonic seizures were under control with medication,*” and no note was made of its withdrawal prior to the study. Consequently, one cannot rule out potential interactions between CBD, the sedative used in the study, and the patient’s unspecified concomitant anticonvulsant medication.

In 1978, Mechoulam and Carlini randomized nine patients to either 200 mg/day of pure cannabidiol or a placebo (Mechoulam and Carlini 1978). During the three-month trial, two of four patients treated with cannabidiol became seizure-free, whereas seizure frequency was unchanged in the five patients who received placebo.

A small ( $n = 15$ ) population of adult patients who exhibited partial seizures with secondary generalization that were uncontrolled by conventional treatment were enrolled in a double-blind, placebo-controlled, add-on study to examine the effect of CBD ( $\leq 300$  mg/day) for 4.5 months (Carlini and Cunha 1981; Cunha et al. 1980). Of the patients who received CBD ( $n = 8$ ), four exhibited no sign of seizure, one “*improved markedly,*” one “*improved somewhat,*” one showed no improvement, and one withdrew from the study. Of the placebo-treated patients ( $n =$

7), one showed “*a little improvement,*” whilst six showed no change. Four of the CBD-treated patients reported that CBD caused some sedation. The investigators concluded that CBD could be of benefit to patients with secondary generalized epilepsy for whom existing medicines were ineffective. Furthermore, in a later open-label clinical trial employing CBD (900–1200 mg/day for 10 months), “*seizure frequency was markedly reduced in the patient*” consistent with the findings presented above (Tremblay and Sherman 1990). However, in a separate study, 12 epileptic patients were given CBD (200–300 mg/day) as an adjunct to existing treatments, but no change in seizure incidence was found. The results of these two latter studies were published in an abstract form, preventing full examination of the study details and a detailed insight into the relevance of the findings (Ames and Cridland 1986).

In 2005, Pelliccia et al. (2005) reviewed population data of epileptic children resistant to conventional anti-epileptic medications and subsequently instituted treatment for some of these subjects using an oil-based formulation of CBD (2.5% corn oil solution; further characterization unknown). Doses were titrated gradually according to individual responses up to a dose of 20 drops daily (specific drop volume unknown). The seizures in one 11-year-old girl with highly drug-resistant Lennox-Gastaut syndrome were lessened in both intensity and frequency. Awareness, postural tone and speaking ability also improved to a degree that allowed for the reduction of barbiturate dosage, and she was able to discontinue hospital care soon after CBD administration commenced. In contrast to these marked improvements, a 17-year-old boy administered 30 drops of the same solution experienced only “*slight improvement*” regarding seizures but marked behavioral improvement that led to the reduction in barbiturate treatment. Subsequent to these reports, 16 more symptomatic drug-resistant children were started on CBD. In most of the treated children, an improvement of the crises was obtained equal to, or higher than, 25% (specific measures were not provided) and a clear improvement of consciousness and spasticity was observed. Specific incidence of side effects was not reported; however, no side effects warranting discontinuation of the CBD solution occurred.

## **PRECLINICAL RESEARCH**

### ***Whole Cannabis***

Preclinical studies of cannabis’ effects upon seizures are limited in number. Such studies have an intrinsic value in their use of tightly controlled variables, as compared, for example, with the surveys and individual clinical case reports cited above. In a 1978 study (Ghosh and Bhattacharya 1978), the effects of cannabis resin (17%  $\Delta^9$ -THC) upon MES-induced seizures in rats were

investigated following administration of the resin alone or in combination with a wide range of brain monoamine or catecholamine modulators (Richelson 2001), none of which affected the seizure measure used when co-administered alone at the same doses. The use of such agents was rationalized by the fact that pharmacological modulation of monoamine and catecholamine levels affect MES seizures (Bhattacharya et al. 1976; Kleinrok et al. 1991), in addition to known interactions between cannabis constituents and serotonin, norepinephrine, and dopamine (summarized in Ghosh and Bhattacharya 1978). Consequently, modulators of these systems were used to elucidate mechanisms of anticonvulsant effects of isolated cannabinoids that had been described in earlier studies (Karler et al. 1973; Loewe and Goodman 1947). The study reported monoamine involvement in the anticonvulsant effect of cannabis due to the loss of the effect when cannabis was co-administered with reserpine, which inhibits central presynaptic vesicular norepinephrine, serotonin, and dopamine via a blockade of the vesicular monoamine transporter (Weihe and Eiden 2000). This involvement was further dissected following 5-6-dihydroxytryptamine (DHT) or 6-hydroxydopamine (6-HD) co-administration, which selectively ablate central serotonergic and adrenergic neurons, respectively. Here, DHT, but not 6-HD, abolished the anticonvulsant effect of cannabis, implicating serotonergic, but not adrenergic, involvement, which was further supported by the abolition of cannabis effects on seizure by inhibitors of serotonin biosynthesis and serotonin receptor antagonists, but not by adrenoreceptor or dopamine receptor antagonists. The investigators then presented additional phenomenological evidence (see Ghosh and Bhattacharya 1978 for details) that fully supported the findings above before concluding that the anticonvulsant effects of cannabis in MES seizures are likely to be mediated by a serotonergic mechanism of action. Unfortunately, the cannabinoid composition of the cannabis extract used – beyond the  $\Delta^9$ -THC content assayed – was not presented, such that it remains unclear which cannabinoid, non-cannabinoid, or combination thereof was responsible for the serotonergically mediated anticonvulsant effect seen.

Labrecque et al. (1978) investigated the effects of sub-convulsant penicillin following acute and chronic cannabis administration in dogs (15–25 kg). Each cannabis cigarette contained 6 mg  $\Delta^9$ -THC and was ‘smoked’ via a tracheotomy, such that acutely and chronically treated animals consumed eight cigarettes and four cigarettes per day, respectively, for 10 weeks before testing. During testing, animals received morphine (4 mg/kg im) and penicillin G (750,000 IU iv) before observation and electrocorticographic (ECoG) recording. Here, the control cohort showed no behavioral response to penicillin, except for a single animal that exhibited occasional jerks. In ECoG recordings from this group, no abnormal activity was observed. However, four out of five dogs acutely treated with cannabis exhibited muscular jerks and one showed clonic movements. In ECoG recordings from this group, characteristic arousal activity following

application of an external stimulus was replaced by epileptiform activity in the occipital cortex that lasted 3–6 seconds. In chronically treated animals, administration of penicillin caused spontaneous appearance of similar epileptiform activity in the occipital and frontal cortices that was followed by generalization of the epileptiform activity and the appearance of grand mal seizures 90 minutes after penicillin administration. The researchers thus proposed that these effects might have been due to cannabis-induced reduction of the seizure threshold and/or increase in blood-brain barrier (BBB) permeability to penicillin. However, in addition to noting that the co-administration of morphine for analgesic purposes could confound these results via the significant interactions between endogenous cannabinoid and opioid systems that have now been better identified (Fattore et al. 2004), the hypothesis of  $\Delta^9$ -THC-induced changes to BBB permeability was not borne out in a study conducted around the same time (Segal et al. 1978).

Finally, although unrelated to preclinical investigations of seizure *per se*, it should be noted that high doses of cannabis can induce vertical jumping in rats (Rosenkrantz and Braude 1974), which bears some phenomenological comparison to the myoclonic jerks associated with seizures, particularly seizure onset (discussed in detail in Feeney et al. 1976).

### ***Tetrahydrocannabinol***

A number of animal studies have explored the action of  $\Delta^9$ -THC in various seizure models. In one of the earliest studies,  $\Delta^9$ -THC (2.5–10 mg/kg  $\Delta^9$ -THC 15 min prior to seizure trigger and 10 mg/kg  $\Delta^9$ -THC 15–45 min prior to seizure trigger) was found to effectively inhibit audiogenic seizures in C57BL/6 mice, significantly reducing the number of animals exhibiting seizure signs (Boggan et al. 1973). Here, 2.5–10 mg/kg  $\Delta^9$ -THC administered 15 min prior to the seizure trigger and 10 mg/kg  $\Delta^9$ -THC administered 15–45 min prior to seizure trigger significantly reduced the number of animals exhibiting seizure signs.  $\Delta^9$ -THC administration after priming had no effect upon seizures. Around the same time, the effects of  $\Delta^8$ -THC and  $\Delta^9$ -THC upon maximal electroshock (MES)- and pentylenetetrazole-induced seizures in rats were examined (McCaughran et al. 1974). Here and after initial experiments to determine the time at which cannabinoid effects were maximal, 15–200 mg/kg i.p. of either cannabinoid was administered 60 minutes prior to convulsant challenge. In the MES model, the investigators reported an ED<sub>50</sub> of 58 mg/kg and 72 mg/kg for  $\Delta^8$ -THC and  $\Delta^9$ -THC respectively, with  $\Delta^8$ -THC showing a marginally lower TD<sub>50</sub> value (3.4 mg/kg vs. 4.3 mg/kg) assessed by the appearance of abnormal behaviors.

Thereafter,  $\Delta^9$ -THC (1–80 mg/kg po 30 min prior to seizure induction) produced no significant effect upon generalized seizures induced by administration of pentylenetetrazole (1.9 mg/min iv) in QS strain mice (Chesher and Jackson 1974). Conversely, significant effects of  $\Delta^9$ -THC (25–200 mg/kg) upon hind limb extension in the MES model of seizure in the same study and mouse strain were observed. Here,  $\Delta^9$ -THC (>160 mg/kg) protected against hind limb extension. Interestingly, although this study showed that oral  $\Delta^9$ -THC at 20 and 75 mg/kg significantly lengthened hind limb extension time, suggestive of a pro-convulsant effect within this lower dose range, 20 mg/kg iv  $\Delta^9$ -THC significantly decreased hind limb extension time, indicating route-specific variation of the effect. Furthermore, in the same study, co-administration of 50 mg/kg  $\Delta^9$ -THC (p.o.) with CBD plus cannabidiol (CBN; both 50 mg/kg po; doses separately shown to have no effect upon MES seizures, see below) led to a highly significant ( $P < 0.02$ ) anticonvulsant effect. Notably, this could underlie the variability in responsiveness seen in human epileptics using cannabis, since cannabis strain, storage conditions, and mode of consumption will likely affect phytocannabinoid proportions present. Finally, the study also demonstrated a significant reduction in ED<sub>50</sub> of phenytoin by co-administration of  $\Delta^9$ -THC (50 mg/kg po), with even higher reduction achieved by co-administration of  $\Delta^9$ -THC plus CBD (each 50 mg/kg po), consistent with Loewe and Goodman's (1947) observation that phenytoin and cannabis may interact synergistically. Similarly,  $\Delta^9$ -THC and CBD (each at 50 mg/kg p.o. 2 hours prior to MES) each significantly potentiated the effect of phenobarbitone (9.3–40 mg/kg i.p. one hour prior to MES) on the presence and duration of hind limb extension in the MES model of generalized seizure in QS mice (Chesher et al. 1975). The larger magnitude of the  $\Delta^9$ -THC effect led the researchers to describe it as “*more active.*” Co-administration of  $\Delta^9$ -THC plus CBD (each at 25 mg/kg) with phenobarbitone produced a potentiation of phenobarbitone's effects that did not differ significantly from the potentiation seen following 50 mg/kg  $\Delta^9$ -THC co-administration with phenobarbitone (Chesher and Jackson 1974).

The researchers entertained the prospect that cannabinoid-mediated modulation of phenobarbitone metabolism was responsible for the potentiation seen, on the basis that CBN, CBD, and  $\Delta^9$ -THC have previously been shown to potentially interfere with barbiturate metabolism (Siemens et al. 1974). However, this hypothesis was discounted since the metabolic effects of CBD and  $\Delta^9$ -THC are comparable, yet, when co-administered with phenobarbitone, their individual effects upon seizure differed significantly. In another investigation,  $\Delta^9$ -THC (up to 80 mg/kg ip) caused a marked increase in latency to hind limb extension in MES-induced seizure model, but provided no protection against strychnine-, pentylenetetrazole-, or nicotine-

induced seizures (Sofia et al. 1974). Lastly,  $\Delta^9$ -THC (100 mg/kg) and CBD (120 mg/kg ip) either as single doses or daily for 3–4 days, were examined in the 6 Hz and MES seizure models, with CBD ineffective and  $\Delta^9$ -THC lowering threshold to seizure in the 6 Hz test (Karler and Turkanis 1980), confirming the differences in effects of  $\Delta^9$ -THC and CBD that the investigators had previously described (Karler et al. 1974; Turkanis et al. 1974). In the repeated dosing arms of the study, whilst tolerance to phenobarbitone appeared in the 6 Hz model, the effects (or lack thereof) of phenytoin,  $\Delta^9$ -THC, and CBD were unchanged.  $\Delta^9$ -THC and CBD withdrawal after 3–4 days treatment caused decreased and increased thresholds, respectively.

In a study that shed further light on the issue of tolerance, a spontaneously epileptic adult gerbil strain that was proposed as a model of idiopathic human epilepsy (Loskota et al. 1974; Loskota and Lomax 1975), acute (single dose) and chronic (daily for six days) treatment with  $\Delta^9$ -THC, no significant effects upon any seizure measures were seen following acute or chronic 20 mg/kg ip  $\Delta^9$ -THC treatment, whereas significant decreases in latency to seizure, duration of seizure, and seizure score were seen in animals acutely, but not chronically, treated with 50 mg/kg  $\Delta^9$ -THC, which may suggest a tolerance effect.

Interestingly, whilst many of the above studies reported anticonvulsant effects of  $\Delta^9$ -THC, a study employing electrocorticographic methods (surface electrodes over frontal cortex and depth electrodes in hippocampus, thalamus, amygdala, and cerebellum) found that ‘polyspikes’ — spike discharges induced by the electrode implantation in cortex, amygdala, and cerebellum but not hippocampus or thalamus — which spontaneously appeared ~2–9 weeks after surgery were augmented by either acute or chronic (daily up to 140 days) 10 mg/kg po  $\Delta^9$ -THC treatment (Stadnicki et al. 1974). However, spontaneous seizure activity (jerking movement of head and paws) was seen in only 1 of 6 animals treated with  $\Delta^9$ -THC, which, together with the uncertain aetiology of the ‘polyspike’ discharges, hinders generalizable conclusions. Further to this apparently proconvulsant effect of  $\Delta^9$ -THC in rats, in 1976 a report described  $\Delta^9$ -THC-induced convulsions in a susceptible population of rabbits (Martin and Consroe 1976). Here, a specific subpopulation of laboratory rabbits was found to exhibit limb clonus, head tuck, body torsion, mydriasis and nystagmus in response to  $\Delta^9$ -THC doses as low as 0.5 mg/kg iv, which the investigators suggested reduced in frequency and severity with repeated  $\Delta^9$ -THC treatment.

The investigators also examined the effect of a number of other plant cannabinoids (CBN: 10 mg/kg, CBD: 10–20 mg/kg, and CBC: 8 mg/kg) in addition to 11-OH- $\Delta^9$ -THC (0.5 mg/kg) and  $\Delta^8$ -THC (0.5 mg/kg), finding that whilst the THC forms and CBN produced similar

convulsions, neither CBD nor CBC exerted any detectable effect. Subsequently, the same group (Consroe et al. 1977) investigated the effects of a number of conventional anticonvulsants upon convulsions caused by  $\Delta^9$ -THC (0.5 mg/kg; iv) in the same rabbit strain. Here, carbamazepine (ED<sub>50</sub>: 2 mg/kg), diazepam (ED<sub>50</sub>: 4.7 mg/kg), and phenytoin (ED<sub>50</sub>: 10.9 mg/kg) were each found to inhibit  $\Delta^9$ -THC-induced seizures in these animals. Phenobarbital (ED<sub>50</sub>: 56.9 mg/kg) and ethosuximide (ED<sub>50</sub>: 306 mg/kg) were also found to inhibit seizures but only at doses that also produced toxic effects. Interestingly, CBD (ED<sub>50</sub>: 19.7 mg/kg) also inhibited these seizures but only when given prior to (cf concurrently)  $\Delta^9$ -THC administration. Whilst very interesting reports, from a modern perspective and like the surgically induced polyspike discharges described above (Stadnicki et al. 1974), the lack of a mechanistic basis for the rabbits' genetic susceptibility to these seizures prevents the drawing of more widely generalizable conclusions from these results.

Whilst not a study of  $\Delta^9$ -THC in models of seizure or epilepsy, per se, it is notable that prolonged (>6 months) treatment ( $\Delta^9$ -THC 12.5–50 mg/kg po) in rats and mice (particularly females) caused seizures via as-yet-unknown mechanisms (Chan et al. 1996). Interestingly, these seizures appear to diminish in frequency several weeks after first manifestation, confounding conventional perceptions of kindling, and have not been reported in other common laboratory species.

In a final study comparing the effects of  $\Delta^9$ -THC (up to 80 mg/kg) with those of phenytoin, chlordiazepoxide, and phenobarbitone upon MES-, pentylenetetrazol-, nicotine-, and strychnine-induced seizures in mice (Sofia et al. 1974), using a dose-response approach, the following results were reported: 1) In MES seizures,  $\Delta^9$ -THC caused a marked increase in latency to hind limb extension that was mirrored by the three standard comparators used; 2) In both strychnine- and pentylenetetrazol-induced seizures, phenobarbitone and chlordiazepoxide had predictably protective effects, whilst neither phenytoin nor  $\Delta^9$ -THC protected against these seizures; 3) None of the tested compounds exerted any effect in the nicotine-induced seizure model used. The investigators interpreted these effects as indicative of a specific anticonvulsant effect of phenytoin and  $\Delta^9$ -THC, which is in contrast to the generalized sedative-hypnotic, GABA-mediated action underlying chlordiazepoxide and phenobarbitone effects upon all bar-one models used.

Several studies have been conducted that used less conventional models of seizure and/or animal species. In a continuation of early studies of acute effects of  $\Delta^9$ -THC that showed transient  $\Delta^9$ -THC-induced suppression of seizures triggered by hypothalamic or thalamic

stimulation (Corcoran et al. 1973; Wada et al. 1973), the anti-epileptic experiments and prophylactic potential of  $\Delta^8$ -THC and  $\Delta^9$ -THC (ip) upon seizures in cats, was investigated using a model employing electrical kindling of the amygdala to produce generalized seizures of focal (amygdaloid) origin (termed “stage 6”) (Wada et al. 1975). Here, in the anti-epileptic experiments, animals were treated one hour before testing for effects upon onset of kindling, at stages three (head nodding) and five (clonic jumping), and at the endpoint of kindling, which represents the establishment of a low-threshold generalized seizure trigger. At kindling onset,  $\Delta^9$ -THC (0.25 mg/kg i.p. one hour before testing upon onset of kindling) markedly inhibited epileptiform after-discharges; however, the same dose of  $\Delta^8$ -THC was ineffective. At intermediate seizure stages three (head nodding) and five (clonic jumping) and at the endpoint of kindling, neither  $\Delta^8$ -THC nor  $\Delta^9$ -THC (both 0.25–4 mg/kg i.p.) affected the seizures. Some of these findings contradict a similar investigation by the same authors using rats (Corcoran et al. 1973; Fried and McIntyre 1973) where only very high doses (15–200 mg/kg ip) of either cannabinoid were required to unreliably suppress pentylenetetrazol-induced seizures, although it needs to be noted that the evidence thus far presented supports significant species-specific differences in  $\Delta^9$ -THC responses.

In prophylaxis experiments, cats received daily injections of  $\Delta^8$ -THC and  $\Delta^9$ -THC (0.5–2.5 mg/kg ip) during the kindling process (15 days).  $\Delta^9$ -THC, but not  $\Delta^8$ -THC, suppressed undeveloped after-discharges at the start of kindling, effectively preventing the manifestation of spontaneous seizures. This study supports the assertion that  $\Delta^9$ -THC effects upon seizure are highly dependent upon the state of disease progression in epilepsy. In the same period, the effects of  $\Delta^8$ -THC and  $\Delta^9$ -THC upon a baboon species, *Papio papio*, which exhibit a photomyoclonic response in addition to being susceptible to amygdaloid kindling, were also investigated (Wada et al. 1975a). Neither  $\Delta^8$ -THC nor  $\Delta^9$ -THC (both at 0.25–1 mg/kg ip) had any effect upon the photomyoclonus; however, both isomers either completely abolished or abbreviated kindled seizures in addition to inhibiting the spread of epileptiform after-discharges. Although a full dose-response analysis was not performed in this study, the results were consistent with  $\Delta^9$ -THC exhibiting greater potency than  $\Delta^8$ -THC.

A final study used a less conventional model in chickens, some of which exhibit a genetic susceptibility to seizure following intermittent photic stimulation (IPS) at the frequency of 14 flashes per second (Crawford 1970). The animals used in this study were divided into epileptic and non-epileptic groups based on their responsiveness to IPS (Johnson et al. 1975). The effects of  $\Delta^9$ -THC (0.25–1 mg/kg iv, 0.5 or two hours before testing) upon IPS-induced seizures in

epileptic fowl and pentylenetetrazole-induced seizures in epileptic (35 mg/kg) and non-epileptic (80 mg/kg) fowl were examined.  $\Delta^9$ -THC (>0.25 mg/kg at 0.5 but not two hours) significantly reduced IPS-induced seizure number and severity in epileptic chickens (35 mg/kg iv; 0.5 but not two hours before testing), although no significant effect was seen in pentylenetetrazole-induced seizures at any dose (0.25–1 mg/kg iv, 0.5 or two hours before testing).

### *Cannabidiol and Related Compounds*

One of the earliest documented investigations of CBD effects upon seizures employed the MES model using doses of 1.5–12 mg/kg ip of CBD one hour prior to seizure induction (Izquierdo and Tannhauser 1973). In contrast to subsequent studies where much higher CBD doses were required to protect against seizures (Jones et al. 2010; 2012), this study found significant protective effects of CBD, which provided a broad anticonvulsant ED<sub>50</sub> of 3 mg/kg. In a separate investigation of cannabinoid effects upon chemically and electrically induced seizures in mice (Chesher and Jackson 1974), CBD at doses of 150 mg/kg and 50–200 mg/kg po did not affect pentylenetetrazole-induced generalized- or MES- seizures, respectively. As with  $\Delta^9$ -THC in this study, no pharmacokinetic, metabolic, or bioavailability data were presented, which makes interpretation of the negative results difficult. Consequently, the absence of the effect of CBD, when compared to several other reports describing anticonvulsant effects of CBD, could be due to the first-pass metabolic effect of p.o. administration, which renders brain CBD concentrations too low, regardless of drug administration time. Alternatively, information on the pharmacokinetics of some phytocannabinoids after i.p. administration is now available (Deiana et al. 2012; Hill et al. 2010; Jones et al. 2010) and can be used to optimize drug administration times and permit reaching maximum brain concentrations at the time seizures are induced. The absence of comparable information for the oral route means that it is not possible to assess whether the lack of CBD effect shown in this study (Chesher and Jackson 1974) is due to a paucity of CBD at the site of action or a direct lack of action.

Subsequently, a major study comparing the anticonvulsant effects of ip administration of CBD and  $\Delta^9$ -THC, in addition to a range of derivatives, against the effects of phenytoin, phenobarbitone, and ethosuximide in a variety of standard seizure models, was undertaken (Karler and Turkkanis 1978). In the MES test in mice, the following cannabinoids showed significant anticonvulsant activity (ED<sub>50</sub> values or best estimate [indicated by \*] are shown in parentheses): CBD (120 mg/kg),  $\Delta^9$ -THC (100 mg/kg), 11-OH- $\Delta^9$ -THC (14 mg/kg), 8 $\beta$ -, but not 8 $\alpha$ -OH- $\Delta^9$ -THC (100 mg/kg\*),  $\Delta^9$ -THCA (200–400 mg/kg),  $\Delta^8$ -THC (80 mg/kg), CBN (230

mg/kg), and 9-nor-9 $\alpha$ - or 9-nor-9 $\beta$ OH-hexahydro-CBN (each 100 mg/kg). Of additional interest was the data included in the same report that examined species-specific differences in relation to the response to CBD and  $\Delta^9$ -THC in the MES test, such that, compared with mice (see above),  $\Delta^9$ -THC was 20-fold and 1000-fold more potent in rats and frogs, respectively; a stark difference that was not apparent when the same comparison was made for phenobarbitone and phenytoin. Using the ED<sub>50</sub> values obtained from these experiments and median toxic dose (TD<sub>50</sub>) values derived from mice treated with the same drugs and subjected to a bar-walk test for neurotoxicity, the investigators derived protective indices (PI = TD<sub>50</sub>/ED<sub>50</sub>) for  $\Delta^9$ -THC and CBD, in addition to deriving the same values for phenytoin, in rats (Table 1).

**Table 1 Comparison of median effective dose (ED<sub>50</sub>) and protective index (PI) values (where available) for species examined for anticonvulsant effects of cannabinoids**

Drug	Mouse		Rat	
	ED <sub>50</sub>	PI	ED <sub>50</sub>	PI
Phenytoin	9	6	5	5
Phenobarbitone	12	1.5	12	
CBD	120	1.5	50	60
$\Delta^9$ -THC	100	0.8	5	2

**Source:** Summarized from Karler and Turkanis (1978).

The same group (Turkanis et al. 1979) later reported that in electrically kindled limbic seizures in rats, CBD (0.3–3 mg/kg ip) raised epileptic after-discharge threshold (electrophysiologically recorded) in a manner consistent with the known effects of phenytoin in this model, but, in common with the effects of ethosuximide in this model, CBD also decreased after-discharge amplitude, duration, and propagation. Notably, the investigators concluded that, compared with phenytoin and ethosuximide, CBD was “*the most efficacious of the drugs tested against limbic [after-discharges] and convulsions.*” Furthermore, a subsequent study (Turkanis and Karler 1981) specifically examining the electrophysiological effects of CBD upon evoked corticolimbic responsiveness in non-epileptic states in rats revealed a selectively depressant effect, consistent with the earlier studies (e.g., Karler and Turkanis 1978). Conversely,  $\Delta^9$ -THC was found only to increase seizure threshold, an anticonvulsant effect shared by phenytoin (Karler and Turkanis 1978). These data, coupled with the findings of Karler and Turkanis (1980 cited above), led the investigators to conclude that, despite the potency differences between the two drugs, CBD most closely resembles phenytoin in its overall anticonvulsant profile, suggesting usefulness in

the treatment of grand mal, cortical focal, and complex partial seizures (with or without secondary generalization) (Karler and Turkanis 1981). Moreover, the consistently anti- and not pro-convulsant effects of CBD (compared with  $\Delta^9$ -THC), combined with the indication that its effects arise via mechanisms that are discrete from conventional anticonvulsants, support potential clinical utility of CBD (Izzo et al. 2009).

Effects of CBD (60 mg/kg ip bid.) were examined in rats rendered chronically epileptic by cortical implantation of cobalt, which produces partial seizures with a secondary generalization 7–10 days after implantation. Although  $\Delta^9$ -THC was also examined in the same study and was found to exert a short-term (approximately one day) anticonvulsant effect, CBD had no discernible effect in this model (Colasanti et al. 1982). It is, however, noteworthy that cobalt-induced seizures share many common features with human absence seizures (Loscher 1997) and have little in common with the seizure models in which CBD exerts a significant anticonvulsant effect or the epilepsies in which it has been proposed to have potential utility (Karler and Turkanis 1978). Such model-specific effects were also exemplified by a separate study that employed a battery of acute models which included MES-, 3-mercaptopropionic acid, picrotoxin-, isonicotinic acid hydrazine-, bicuculline-, pentylenetetrazole-, and strychnine-induced seizures (Consroe et al. 1982). Here and as assessed by comparison of ED<sub>50</sub> values, the anticonvulsant effect of CBD (50–400 mg/kg ip) was comparable in the MES and all GABA-inhibition-based models but was entirely ineffective against strychnine-induced convulsions, thereby partially recapitulating, in addition to extending, the findings previously reported (Sofia et al. 1974).

Following the intense investigation of cannabinoid effects upon seizure during the 1970s and early 1980s, very little research was undertaken despite the potential suggested by many of the earlier studies. However, more recently, CBD effects upon chemically induced epileptiform activity in acute hippocampal sections have been examined (Jones et al. 2010). Here, spontaneous epileptiform local field potentials (LFP) were induced by omission of Mg<sup>2+</sup> ions ('Mg<sup>2+</sup>-free') from or by addition of a K<sup>+</sup> channel blocker, 4-aminopyridine (4-AP), to the bathing solution. In the Mg<sup>2+</sup>-free model, CBD (100  $\mu$ M) decreased epileptiform LFP burst amplitude and duration despite an increase in burst frequency. In the 4-AP model, CBD (100  $\mu$ M) decreased LFP burst amplitude in one hippocampal region (dentate gyrus) only but decreased burst duration in CA3 and dentate gyrus and burst frequency in all regions. CBD had no effect upon the propagation of epileptiform activity across the slice preparation used. The same report also recapitulated the previous investigation of CBD effects upon pentylenetetrazol-induced, acute, generalized seizures in Wistar-Kyoto rats (Consroe et al. 1982) and found that

CBD (100 mg/kg ip) significantly decreased mortality and the incidence of tonic-clonic seizures. The same researchers (Jones et al. 2010) used radioligand-binding studies to determine CBD affinity for cortical CB<sub>1</sub> receptors in Wistar rat and found that CBD exhibited low affinity for CB<sub>1</sub> receptors with no agonist activity, which supports a CB<sub>1</sub>-receptor-independent mechanism for CBD's anticonvulsant action.

Whilst, strictly speaking, a non-CBD cannabinoid in its own right, consideration of the evidence describing significant anti-epileptiform and anticonvulsant effects of cannabidivarin (CBDV), the propyl variant of CBD, alongside its parent compound is expedient. CBDV, previously known as 'cannabidivarol,' was first isolated from hashish in 1969 (Vollner et al. 1969), although understanding of its pharmacology remains very limited. Whilst there remains only a single report of CBDV's effects in models relevant to epilepsy (Hill et al. 2012), the results reported therein span two in vitro models and four in vivo models of seizure and tolerability testing that represents a sizeable, although isolated, body of evidence. Here, using the same in vitro models of epileptiform activity described above (Jones et al. 2010), the application of CBDV attenuated *status epilepticus*-like epileptiform LFPs at concentrations  $\geq 10 \mu\text{M}$  in both the Mg<sup>2+</sup>-free and 4-AP models. CBDV, administered i.p. 60 minutes prior to convulsant stimulus, significantly reduced tonic hindlimb extension caused by MES in ICR mice (100–200 mg/kg) in addition to significantly reducing tonic convulsions (50–200 mg/kg), increasing the number of animals remaining free from any sign of seizure (200 mg/kg), and ablating all seizure-related deaths (100–200 mg/kg). Furthermore, in the PTZ (85 mg/kg i.p.) model of acute generalized seizure in adult Wistar rats and using the same study drug dosing regime, CBDV significantly reduced seizure severity (200 mg/kg) and mortality (100–200 mg/kg) whilst significantly increasing the number of animals remaining free from any sign of seizure (100–200 mg/kg) and the latency to first sign of seizure (200 mg/kg). In additional experiments using the same PTZ model, the investigators demonstrated that CBDV (200 mg/kg) was not only well tolerated when co-administered with conventional anticonvulsants (sodium valproate or ethosuximide) but retained its own anticonvulsant effects (i.e., acted additively). When the effects of CBDV (50–200 mg/kg ip; 60 minutes before convulsant challenge) alone were examined in the, often intractable, acute pilocarpine-induced model of temporal lobe seizures and *status epilepticus* in adult Wistar rats, it was found to exert no statistically significant effects upon any of the parameters measured. However, in subsequent experiments using the same model that examined CBDV (200 mg/kg) effects when co-administered with the conventional anticonvulsants, sodium valproate or phenobarbitone, and where larger group sizes received CBDV treatment, not only were significant anticonvulsant effects attributable to CBDV alone found, but a degree of anticonvulsant synergism with phenobarbitone revealed. Moreover, the investigators also

established the anticonvulsant efficacy of CBDV when administered orally in the PTZ model of generalized seizure, showing that 400 mg/kg CBDV (p.o.; 3.5 hours before convulsant challenge) significantly reduced seizure severity. Finally, CBDV (50–200 mg/kg ip; 60 minutes before testing) was shown to be very well tolerated since it produced no significant effects in the standardized static beam and grip strength motor and neurotoxicity assays, whilst the same doses of sodium valproate used above in seizure models caused significant adverse effects in both assays.

With regard to CBDV's possible mechanism(s) of anticonvulsant action, little is known about its pharmacology. To date, two reports have described differential effects of CBDV at transient receptor potential (TRP) channels, although the role of TRP channels in epilepsy is not known, which prevents meaningful mechanistic inferences from in vitro results at the channels. However, in the interest of completeness, CBDV is an hTRPA1, hTRPV1 and hTRPV2 agonist (EC<sub>50</sub>: 0.42, 3.6 and 7.3 μM, respectively) in transfected HEK-293 cells (De Petrocellis et al. 2011a; De Petrocellis et al. 2011b) but acts as a TRPM8 antagonist (IC<sub>50</sub>: 0.90 μM) in transfected HEK-293 cells (De Petrocellis et al. 2011a). Besides activity at TRP channels, CBDV has been reported to inhibit diacylglycerol lipase-α (IC<sub>50</sub>: 16.6 μM; in vitro), the primary synthetic enzyme of the endocannabinoid, 2-arachidonoylglycerol (De Petrocellis et al. 2011a). However, not only is a role for diacylglycerol lipase-α in epilepsy yet to be determined, but the physiological relevance of this finding (IC<sub>50</sub>: 16.6 μM vs. brain levels of <10 μM after 200 mg/kg ip dosing in rats; Hill et al. 2012) is unclear. Finally, in a recent publication that reported significant anticonvulsant effects in animal models for a CBDV and CBD-rich cannabis extract, results were also presented that showed that CBDV did not exert these effects via modulation of CB<sub>1</sub> or CB<sub>2</sub> receptors (Hill et al. 2013). As such and given the wide range of cellular systems targeted by plant cannabinoids, it would be erroneous to conclude at this stage that CBDV exerts its significant and broad anticonvulsant effects via TRP or diacylglycerol lipase-α modulation.

### *Other Cannabinoids*

Whilst many cannabinoids have been identified in cannabis (ElSohly and Slade 2005), few have experienced the concerted attention such as received by Δ<sup>9</sup>-THC and CBD in studies of seizures and/or epilepsy. However, a few reports exist of the effects of “minor” cannabinoids upon seizures.

Anti-epileptiform and limited anticonvulsant properties were demonstrated for Δ<sup>9</sup>-THCV in vitro and in vivo (Hill et al. 2010). This compound (>20 μM) reduced burst complex incidence and amplitude and frequency of paroxysmal depolarizing shift (PDS) induced by Mg<sup>2+</sup>-free

bathing solution used to maintain olfactory cortex slices. In the same study,  $\Delta^9$ -THCV also inhibited propagation of epileptiform activity in addition to significantly reducing burst complex incidence and PDS amplitude after pre-treatment (10  $\mu$ M) of the brain slices 40 min prior to seizure induction. Thereafter,  $\Delta^9$ -THCV (0.25 mg/kg) significantly reduced seizure incidence in the pentylenetetrazol model of acute generalized seizures, albeit failing to affect other commonly employed measures (e.g., no agonist stimulation of guanosine-5'-O-(3-thio)triphosphate [ $^{35}$ S]GTP $\gamma$ S binding). Anticonvulsant effects of  $\Delta^9$ -THCV, alongside anticonvulsant effects of other, synthetic, CB<sub>1</sub> receptor antagonists (Echegoyen et al. 2009; Kozan et al. 2009), do not lend themselves to a straightforward interpretation, as it is impossible to predict the overall consequence of broad CB<sub>1</sub> receptor antagonism at both GABA- and glutamate-ergic presynapses. However, if  $\Delta^9$ -THCV exerts preferential effects at GABAergic synapses in hyperexcitability states, as has been shown in the cerebellum (Ma et al. 2008), it is clear that the overall consequences of  $\Delta^9$ -THCV upon a given seizure state will rely upon the sub-population of neurons involved and their CB<sub>1</sub> receptor expression (Lutz 2004). Moreover, the recent finding that disruption of seizure states in vivo by CB<sub>1</sub>-receptor-agonist-mediated desynchronization of pathological neuronal firing (Mason and Cheer 2009) could also underlie CB<sub>1</sub>-receptor-antagonist-mediated effects, which is entirely consistent with the inhibition of the propagation of epileptiform activity by  $\Delta^9$ -THCV (Hill et al. 2010).

In an investigation that also examined CBD and  $\Delta^9$ -THC effects (see above for experimental details), cannabidiol (CBD) (150 mg/kg and 50–200 mg/kg by oral gavage) had no significant effect upon chemically or electrically induced seizures in mice (Chesher and Jackson 1974). Cannabichromene (CBC) was also examined in a study described above (Karler and Turkianis 1978), although the anticonvulsant effect reported therein was tempered by the investigators' observation that this effect occurred at higher, potentially toxic, doses and, as such, was unlikely to be a true anticonvulsant effect.

## *CONCLUSION*

The available literature (case studies, surveys, and pre-clinical data) on the use of cannabis and its constituents for the treatment of epilepsy and seizures in humans suggests there is a general consensus that cannabis exerts an anticonvulsant effect and rarely acts as a proconvulsant, although both findings are based predominantly on subjective evidence. Most of the available human evidence suggests that both a reduction in incidence and severity of seizures, as well as physical and behavioral improvements in children and adults treated with either cannabis or its

preparations (e.g. CBD solution), can be achieved. Most notably, limited data from case reports suggest that CBD can be effective in the treatment of symptomatic seizures that are resistant to standard antiepileptic medications, and its lack of psychoactive effects renders it more attractive than THC cannabinoids. Although the underlying mechanism for these effects may be multifactorial, in the case of THC, part of the antiepileptic action is most likely due to effects at central CB<sub>1</sub> receptors. In the case of the non-THC plant cannabinoids, phenomenological evidence suggests that serotonergic and GABAergic mechanisms may be involved, but modern, molecular-level studies are required to properly determine whether this, or as-yet-unidentified targets (e.g. effects upon cellular calcium release and sequestration, neuroendocrine modulation, etc.), is the case.

When one considers the highly variable, typically idiopathic and/or cryptogenic nature of epilepsy, the variable starting phytocannabinoid composition of the cannabis used, the variable routes of administration, and the presence of complicating concomitant disease and drug states, it is therefore unsurprising that a single, coherent conclusion describing cannabis' effects on seizures cannot be drawn. On the basis of extant evidence from a variety of acute models of seizure, CBD not only represents the most widely investigated phytocannabinoid after  $\Delta^9$ -THC but, compared with  $\Delta^9$ -THC, exhibits the most reliable anticonvulsant effects, exhibiting clinically beneficial effects in epileptic children resistant to antiepileptic medications. For this specific patient population, whilst high CBD and low THC strains — usually consumed orally in children — appear to be effective, their long-term efficacy and safety have not yet been properly demonstrated in well-controlled clinical trials. Since the published evidence describes pro- and anti-convulsant effects of THC-containing treatments in both humans and animals, use of such treatments, particularly in critically ill children, warrants significant care and caution.

Additionally, in contrast to clinically used anticonvulsants, CBD was well tolerated in pediatric subjects and further exhibited no neurotoxic or motor side effects, as assessed by standard rotarod tests (Consroe et al. 1981; Jones et al. 2012; Martin et al. 1987). In addition to a potential effect in epilepsy, CBD has been proposed as having potential for use in the treatment of tonic-clonic, cortical focal, and partial, but not absence, seizures (Karler and Turkanis 1981). However, it is notable that no repeated-dosing, longitudinal studies employing CBD have been undertaken in spontaneously epileptic animal disease models. Such studies represent a crucial requirement for the assessment of the compound's potential for successful translation into clinical use. More recent results employing CBDV, CBD's naturally occurring propyl derivative, suggest that it may be more efficacious than CBD, although a direct side-by-side comparison is

required to definitively answer this question, mostly likely in multiple animal models but ideally in the human clinical trials now under way (GW Pharma 2013).

Moreover, when considering cannabis effects upon seizures, the potential for cannabis to cause effects outside of the central nervous system (CNS) that consequently affect CNS function/dysfunction should not be ruled out. For example, recent studies using positron emission tomography (PET) methods revealed that the effects of cannabis smoking increased regional cerebral blood flow (rCBF) in paralimbic (mesocortical) regions, while reducing rCBF in the temporal, parietal, and frontal lobes and the thalamus (O'Leary et al. 2000; 2002), the latter being seizure-susceptible areas. Consequently, some cannabis effects upon seizures could be a consequence of blood flow modulation and not direct effects upon central neuronal activity.

Despite the potentially beneficial effects of cannabis and its constituents in the management of epilepsy, psychotropic effects of  $\Delta^9$ -THC limit or prohibit its widespread therapeutic use, particularly as an anticonvulsant where regular, repeated doses throughout a patient's lifetime are necessary. However, it is also notable that not only are all currently approved anticonvulsant drugs associated with some significant motor and/or cognitive side effects (Fisher 2012), many epilepsy patients are unable to drive motor vehicles or maintain employment because of either these side effects, the symptoms of the disease, or a combination of the two (Besag 2001). If  $\Delta^9$ -THC exhibited anticonvulsant effects and its side effects were less as compared with the side effects of conventional anticonvulsants or with disease symptoms, there would be stronger justification for its use. Moreover, if anticonvulsant effects can be confirmed for crude non-psychoactive Galenical preparations (standard tinctures), this may offer an alternative to psychoactive cannabis preparations and standard medications. In either case, an understanding of the effects of isolated  $\Delta^9$ -THC and CBD in disease models better informs the results of the studies presented above that examined effects of whole cannabis on seizures.

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