



American Herbal Pharmacopoeia®

Cannabis Therapeutic Compendium

Introduction

In 2014, the American Herbal Pharmacopoeia (AHP) released *Cannabis Standards of Identity, Analysis, and Quality Control*. It was the first such monograph of its kind published ever and has become one of the primary authoritative reference standards for the regulation of cannabis in many states. AHP's *Therapeutic Compendium* will provide a detailed and critical review of the therapeutics and safety of the medical use of cannabis including clinical and pre-clinical uses and pharmacology, dosages, preparations used, routes of administration, side effects, contraindications, interactions, and toxicology. The recreational use of cannabis will be briefly addressed but the focus of the *Therapeutic Compendium* is on the appropriate medical uses. The development of AHP's *Therapeutic Compendium* will be guided by Ethan Russo, MD, one of the world's leading authorities on the medical use of Cannabis. Findings thus far strongly suggest that the current scheduling of cannabis as having no medical benefit is unwarranted.

Evidence regarding the following therapeutic categories will be presented primarily for crude cannabis preparations. Each section has been written and reviewed by acknowledged experts in the field of cannabis medical research and will represent one of the most comprehensive, critical, and unbiased reviews of the medical cannabis literature in any language. Writers and reviewers include Raphael Mechoulam, Benjamin Whalley, Amanda Reiman, Vincenzo DiMarzo, Eduardo Muñoz, Clare Fowler, Giovanni Appendino, Pal Pacher, Donald Abrams, Manuel Guzman, Franjo Grotenhermen, Melanie Kelly, Mark Ware, and Ryan Vandrey to name a few. The *AHP Therapeutic Compendium* will be released early in 2017. Participants in the *Cannabis Academy Training Program* are being given this early access to all the completed *Executive Summaries* to date and will receive the full publication when it is released. Additionally, two full sections regarding the use of cannabis in cancer care and seizures are presented. These sections will be updated prior to formal publication.



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CANNABINOIDS AND CANCER: A SCIENTIFIC REVIEW

Authors

Donald Abrams MD
University of California–San Francisco
San Francisco, CA

Andrew Weil MD
Arizona Center for Integrative Medicine
University of Arizona
Tucson, AZ

Manuel Guzman PhD
Complutense University
Madrid, Spain

Editors & Reviewers

Ethan Russo MD
Phytects, International Cannabis Research Society
Seattle, WA

Marilyn Barrett PhD
Pharmacognosy Consulting Services
Mill Valley, CA

Dwight McKee MD
Aptos, CA

AMERICAN HERBAL PHARMACOPOEIA®
PO Box 66809
Scotts Valley, CA 95067 US
www.herbal-ahp.org
ahp@herbal-ahp.org

Potential Anticancer Effects of Cannabis

Historically, cannabis has been used to treat various types of cancers (see Russo 2007a), particularly topical application of the leaves, roots, or oil for definable tumors (Camerarius 1626; Parkinson 1640; Reymond 1976). More recently, cannabis has primarily been used for palliative relief of symptoms associated with cancer, predominantly nausea and vomiting, appetite stimulation and wasting, and pain control. The benefits of cannabis for these indications are well established (see Effects of Cannabis on Nausea and Vomiting; Effects of Cannabis on Pain). Anecdotal reports of direct anticancer effects of cannabis are plentiful. However, to date, only a single human pilot study (Guzman et al. 2006) and a large-scale cohort study (Thomas et al. 2015) have investigated the direct anticancer potential of cannabis. The pilot study examined the use of THC for refractory glioblastoma (Guzman et al. 2006). The cohort study attempted to evaluate the association between cannabis exposure and the incidence of bladder cancer (Thomas et al. 2015). In addition, there are a few published (Foroughi et al. 2011; Singh and Bali 2013), and unpublished (Valiente-Pedraza 2011) case reports indicating a possible benefit of cannabis oil preparations for cancer treatment.

Pre-clinical studies indicate in-vitro and in vivo anticancer potential of Δ^9 -THC (THC) and cannabidiol (CBD), as well as cannabigerol (CBG), another non-psychoactive cannabinoid. These studies indicate a direct anticancer activity via modulation of numerous mechanisms including key cell-signaling pathways, inducing direct growth arrest and tumor cell death, as well as by inhibiting tumor angiogenesis and metastasis (Blazquez et al. 2003; Vaccani et al. 2005). Further, it is suggested that cannabinoids are selective antitumor compounds as they kill tumor cells without affecting their healthy counterparts (Galve-Roperh et al. 2000; Sanchez et al. 1998; 2001). The results of these mechanistic studies for antitumor activity are promising, indicating the need for human clinical studies (Velasco et al. 2012). For a more complete review of the direct anti-cancer potential of cannabis and the underlying mechanism of cannabinoids, see De Petrocellis et al. 1998; Guindon and Hohmann 2011; Pisanti et al. 2009; Hermanson and Marnett 2011; Velasco et al. 2014.

Human Studies and Case Reports

There are no clinical studies conducted using cannabis for the treatment of malignant disease. There is a single study that investigated the effect of local administration of THC intracranially through an infusion catheter on the growth of recurrent glioblastoma multiforme (Guzman et al. 2006). The patients had previously failed standard therapy (surgery and radio/chemotherapy) and had clear evidence of tumor progression. The primary endpoint of the study was to determine the safety of intracranial THC administration. Additional parameters included length of survival of patients and various tumor cell parameters. A dose-escalation regime for THC was employed with total doses ranging from 0.08 to 3.29 mg for 10–64 days. No significant alterations in physical, neurological, biochemical and hematological parameters could be ascribed to THC in any of the patients. One patient experienced mild psychotropic effects, but otherwise the treatment was well-tolerated. Median survival of the cohort from the beginning of cannabinoid administration was 24 weeks (95% CI: 15–33). Decreased tumor cell proliferation (as determined by Ki67 immunostaining) and increased tumor cell apoptosis (as determined by active-caspase 3

immunostaining) was observed in tumor biopsies obtained from the only two patients in which sampling was feasible.

A case report of treatment of acute lymphoblastic leukemia (a cancer of white blood cells) indicated a promising reduction in blast cell count following intake of a preparation of hemp oil (Singh and Bali 2013). In this case report, a 14-year-old girl failed to respond to treatment with chemotherapy followed by a bone marrow transplant, and was then treated by her family with a cannabis preparation. Two oz of a *Cannabis indica* strain known as “Chronic Strain” was extracted using 1.2 liters of 99% isopropyl alcohol in a rice cooker yielding 7.5 mL of oil. The patient was administered a single drop of hemp oil in honey (amount not disclosed), with a dose starting at once per day, increasing to three times daily by day 15. The patient’s blast cell counts were 228,000 on day zero, increasing to 344,000 on day 5 and decreasing to 61,000 on day 15. At that time the original hemp oil batch had been consumed, and sequential batches (2–5) were made with different plant materials. Decreases in blast cell counts were observed with batches 1, 2, and 5, but not with batches 3 and 4. In spite of the promising effects of several batches of hemp oil, the patient succumbed to her illness. The authors indicated that clinical studies are warranted to further investigate these effects and to determine the most effective cannabinoid profile, dose, and method of administration. Clearly, isopropyl alcohol is not an appropriate solvent for orally consumed preparations.

A large-scale cohort study (the California Men's Health Study [CMHS]) regarding the use of cannabis and incidence of bladder cancer was conducted. The subjects (all male; aged 45–69) were followed for 11 years. In total, 82,050 subjects were tracked. In total, 279 developed bladder cancer. Of those who reported use of cannabis, 89 (0.3%) developed bladder cancer compared to 190 (0.4%) who did not report cannabis use ($P < 0.001$). Of subjects reporting the use of tobacco only, there was a significant increase in the incidence of bladder cancer (HR 1.52, 95% CI 1.12–2.07). In contrast, in subjects reporting use of cannabis only, there was a significant 45% reduction in bladder cancer (HR 0.55, 95% CI 0.31–1.00) (Thomas et al. 2015). While causality could not be ascertained, the results are suggestive of a potential protective effect of cannabis on the incidence of bladder cancer. The researchers posit that an anticancer effect may be due to the activation of specific g-protein-coupled receptors normally bound by endogenous cannabinoids. Pre-clinical studies demonstrate that cannabinoid receptor agonists (such as CBD and THC) exhibit a dose- and time-dependent inhibition on the growth of human (Yamada et al. 2010) and murine bladder cancer cell lines (Thomas et al. 2010).

There were several limitations to the study acknowledged by the investigators, not the least of which was the inability of the researchers to establish that tobacco use alone was associated with a higher incidence of bladder cancer, an association that is clearly established in the literature (Bofetta 2008; Brennan et al. 2000; Freedman et al. 2011; Gandini et al. 2008). As a prospective observational study, the findings are limited by lack of controls regarding reporting, response bias, and the lack of evaluation of other potential risk factors for bladder cancer.

There is a published case report by Foroughi et al. (2011) suggesting that smoked cannabis may have played a role in the regression of tumors in two children with pilocytic astrocytoma. In one subject, an undisclosed amount of cannabis was smoked an average of three times per week for approximately three years. In the second subject, a growth of a residual tumor was observed at three and eight months post-operatively. The subject was further monitored for six years. At post-operative year three, a slight regression in tumor volume (3.3 cm^3 at 18

months versus 0.28 cm³ at six years) was observed. This subject reported cannabis use on an “almost daily basis” for three years. Neither patient received any formal follow-up medical treatment for the tumors and the authors report that the time frame of smoking coincided with the radiologically confirmed tumor regression.

Animal and In Vitro Studies

Numerous mechanistic studies demonstrate that select cannabinoids can affect the viability and invasiveness of multiple different cancer cell types through a variety of mechanisms including antiproliferative effects, apoptosis, inhibition of invasiveness, and inhibition of metastasis and angiogenesis (Calvaruso et al. 2012). Antiproliferative effects of cannabinoids were originally reported by Munson et al. (1975), who demonstrated that Δ^9 -THC, Δ^8 -THC, and cannabidiol inhibited Lewis lung adenocarcinoma cell growth in vitro as well as in mice. There was no follow-up of these findings until the late 1990s, when investigation was continued by scientists in Spain and Italy (De Petrocellis et al. 1998; Sanchez et al. 1998). The primary research regarding the direct anticancer potential of cannabis and its derivatives continues there today (e.g., Bifulco and DiMarzo 2002; Bifulco et al. 2006; Guzman 2003, among others).

Since the late 1990s, several plant-derived (THC and cannabidiol), synthetic (WIN-55,212-2 and HU-210), and endogenous cannabinoids (anandamide and 2-arachidonoylglycerol) have been shown to exert antiproliferative effects on a wide variety of tumor cell lines in culture systems. Tumor cells that have been shown to be sensitive to cannabinoid-induced growth inhibition include glioma (Sanchez et al. 1998, 2001; Vaccani et al. 2005; Velasco et al. 2004), thyroid epithelioma (Cuzzolino et al. 2009), leukemia/lymphoma (McKallip et al. 2002), neuroblastoma, and skin (Casanova et al. 2003), uterus (Contassot et al. 2004), breast (Ligresti et al. 2006; McAllister et al. 2007), gastric, colorectal (Patsos et al. 2005), pancreatic (Carracedo et al. 2006), and prostate (Olea-Herrero 2009; Ruiz et al. 1999; Sarfaraz et al. 2005) carcinomas.

More compelling than in vitro cell bioassays are a number of animal studies showing that cannabinoid administration slows the growth of various tumor xenografts including lung (Munson et al. 1975), skin (Casanova et al. 2003), and colon (Romano et al. 2014) carcinomas, thyroid epitheliomas (Bifulco et al. 2001), pancreatic carcinomas (Carracedo et al. 2006), lymphomas (McKallip et al. 2002), and gliomas (Gomez et al. 2002b; Sanchez et al. 2001).

Cannabinoids may exert their antitumor effects by a number of different mechanisms including direct induction of transformed cell death, direct inhibition of transformed cell growth, and inhibition of tumor angiogenesis and metastasis (Blazquez et al. 2003; Vaccani et al. 2005). The antitumor effect of cannabinoids is associated with CB₁ and/or CB₂ receptor agonist activity and has been shown by various biochemical and pharmacological approaches. The cumulative effects of CB signaling in the control of cell fate are expected to have important implications in the potential of cannabinoids for regulating tumor cell growth. For example, activation of CB receptors can lead to apoptosis mediated by the activation of caspase activity. Alternatively, cannabinoids may interact with the transient receptor potential channels of the vanilloid type-1 (TRPV1), causing activation of the mitochondrial apoptotic pathway.

More recently, Scott et al. (2014), investigated the in vitro and in vivo tumoricidal effects of the

combination of CBD and/or THC alone and in conjunction with radiation therapy in orthotopic murine glioma cell lines. Both pure (96%) CBD and THC, as well as extracts of either CBD- or THC-predominant strains (provided by GW Pharmaceuticals) were used. The CBD botanical extract contained 63.5% CBD, 3.6% THC, 1.1% CBG, 5.2% CBC, 1.3% CBDV, 0.4% CBDA, and 0.1% CBD. The THC drug strain contained 65.4% THC, 0.4% CBD, 1.3% CBG, 1.8% CBC, 0.9% THCV, 0.4% THCA, 2.0% CBN, and 0.2% CBO. In vitro concentrations of CBD or THC of 0.1–100 $\mu\text{mol/L}$ were used (equal total volume of 60 μL across the plates). For in vivo experiments, both cannabinoids were administered in combination in their pure form at a final concentration of 200 $\mu\text{mol/L}$ (4 mg/kg/mice), made up from 100 $\mu\text{mol/L}$ CBD and 100 $\mu\text{mol/L}$ THC. Significant ($P < 0.01$) dose dependent reductions in cell numbers were seen for both pure CBD and THC with cell death due predominantly to autophagy and minimally to direct cytotoxicity. CBD was observed to be more active when used in its pure form, suggesting that other compounds (e.g., CBC, THC, and CBG), in the CBD predominant cannabis extract inhibited activity. In contrast, THC was more effective when used as a whole cannabis extract, suggesting that other compounds (e.g., CBC, CBG, CBN) in the THC-predominant cannabis extract enhanced activity. Minimal and selective (U87MG cell lines) synergism was observed when CBD and THC were combined. When combined with radiation therapy, CBD and THC together produced greater cell death. Interestingly, pre-treatment of cells with the cannabinoids slowed DNA repair of irradiated cells. A similar significant enhancement of tumor regression was observed in vivo with the combination of the cannabinoids and radiation ($P < 0.01$). These and other mechanisms of tumor cell death have been recently reviewed (Calvaruso et al. 2012; Cridge and Rosengren 2013; Velasco et al. 2012; Velasco et al. 2014).

A desirable property of antitumor compounds is their preferential targeting of malignant cells. Cannabinoids appear to selectively kill tumor cells, but do not affect their non-transformed counterparts (Guzman 2003) and may even protect normal cells from cell death. This is best exemplified by glial cells. Cannabinoids have been shown to induce apoptosis of glioma cells in culture and induce regression of glioma cells in mice and rats. In contrast, cannabinoids protect normal glial cells of astroglial (Gomez et al. 2002a) and oligodendroglial lineages (Molina-Holgado et al. 2002) from apoptosis mediated by the CB_1 receptor.

The first indications of the ability of cannabinoids to inhibit tumor angiogenesis come from immunohistochemical and functional analyses in mouse models of gliomas (Blazquez et al. 2003) and skin carcinomas (Casanova et al. 2003). In these studies, cannabinoid administration altered the vascular hyperplasia characteristic of actively growing tumors into a pattern characterized by small, differentiated, impermeable capillaries, thus thwarting angiogenesis. This effect was accompanied by a reduced expression of vascular endothelial growth factor (VEGF) and other pro-angiogenic cytokines, as well as of VEGF receptors. Activation of cannabinoid receptors in vascular endothelial cells inhibited cell migration and survival, also contributing to impaired tumor vascularization. Cannabinoid administration to tumor-bearing mice decreased the activity and expression of matrix metalloproteinase 2 (MMP-2), a proteolytic enzyme that allows tissue breakdown and remodeling during angiogenesis and metastasis (Blazquez et al. 2008a, 2008b). Together these data support the inhibitory effect of cannabinoids in inhibiting tumor invasion in animal models.

Further support of the antiproliferative and antiangiogenic effects of THC comes from studies in human non-small cell lung cancer cell lines that over-express epidermal growth factor receptor, in which Δ^9 -THC (5 mg/kg for 28 days) inhibited epidermal growth factor-induced growth, chemotaxis, and chemoinvasion (Preet et al. 2008). In subsequent in vivo experiments, subcutaneous tumors were generated by inoculating severe combined immunodeficient (SCID) mice with the same lung cancer cell lines. Tumor growth in the THC-treated animals was significantly inhibited by 60% compared with vehicle-treated controls. The inhibition was significant for both the subcutaneous xenograft as well as the number and weight of lung metastases (Preet et al. 2008). Another study administered THC (15 mg/kg/d) with and without CBD injected peritumorally for 14 days alone or in conjunction with the chemotherapeutic drug temozolomide (TMZ; 5 mg/kg/d) to glioblastoma multiforme xenografts in nude mice. The combined treatment resulted in increased autophagy and apoptosis and reduced growth of glioma xenografts. Most notably, this effect was observed on both TMZ-sensitive and TMZ-resistant cells and the effects of the combined therapy was greater than either agent alone, reaching supra-additive (synergic) levels (Torres et al. 2011).

Another potential anticancer and particularly anti-metastasis mechanism for cannabinoids, the modulation of DNA-binding/differentiation inhibitory transcription factors (helix-loop-helix proteins [Id proteins]), has also been identified. Id helix-loop-helix proteins control processes related to tumor progression (McAllister et al. 2007). Reducing Id-1 using antisense technology led to significant reductions in breast cancer cell proliferation. Reductions of invasiveness were also observed in in vitro models and metastases in mice. However, reducing Id-1 expression with antisense technology is not a possible intervention in humans with breast cancer at this time, because the methodology is still in its infancy regarding human use, safety concerns, lack of selectivity toward the cancer cells, little efficacy in the long term, etc. Cannabidiol has been demonstrated to downregulate Id-1 expression in aggressive human breast cancer cells. Underlying this activity is the ability of CBD to upregulate extracellular signal-regulated kinases (ERKs), a protein kinase intracellular signaling molecule involved in the regulation of the metastasis-specific inhibition of the Id-1 transcription factor. The investigators suggest that cannabidiol represents the first nontoxic exogenous agent that can significantly decrease Id-1 expression in metastatic breast cancer cells leading to the downregulation of tumor aggressiveness. Another study demonstrated the ability of cannabidiolic acid (CBDA) to inhibit the migration of the highly invasive MDA-MB-231 human breast cancer cell line through a mechanism involving inhibition of cAMP-dependent protein kinase A, coupled with activation of the small GTPase RhoA (Takeda et al. 2012).

Two additional potential mechanisms of anticancer activity have been suggested. Cannabinoids, both plant-derived and endogenous, are believed to have anti-inflammatory effects. Inflammation is being increasingly linked to the development of various malignancies. Perhaps one of the most obvious associations is the development of colorectal carcinoma in patients with inflammatory bowel disease. A mouse study demonstrated that signaling of the endogenous cannabinoid system is likely to provide intrinsic protection against colonic inflammation (Massa et al. 2004). This led to the development of a hypothesis that phytocannabinoids and endocannabinoids may be useful in the prevention and treatment of colorectal cancer (Patsos et al. 2005). In addition, a mouse study demonstrated the

effectiveness of a standardized extract high in cannabidiol content to reduce azoxymethane-induced preneoplastic lesions and polyps as well as tumor growth in a xenograft model (Romano et al. 2014).

A group of investigators has demonstrated that Δ^9 -THC is a potent and selective antiviral agent against Kaposi's sarcoma-associated herpesvirus (KSHV), inhibiting KSHV replication through the activation of cannabinoid receptors (Medveczky et al. 2004). The authors concluded that further studies on cannabinoids and herpes viruses are important as they may lead to development of drugs that inhibit reactivation of these oncogenic viruses. Kaposi's sarcoma-associated herpesvirus/Human herpesvirus-8 (KSHV/HHV-8) and Epstein-Barr virus (EBV) are related and implicated in the cause of a number of malignant diseases including Kaposi's sarcoma, primary effusion lymphoma (KSHV), Burkitt's lymphoma, primary central nervous system lymphoma, Hodgkin's disease, and nasopharyngeal carcinoma (EBV). Contrary to these findings, however, is the recent suggestion that Δ^9 -THC may actually enhance KSHV infection and replication and foster KSHV-mediated endothelial transformation (Zhang et al. 2007). The latter investigators caution that use of cannabinoids may thus place individuals at greater risk for the development and progression of Kaposi's sarcoma, although epidemiologic data have not supported these in vitro findings.

Antitumor activity has also been demonstrated for cannabidiol (CBD), which is a non-psychoactive cannabinoid. CBD has a low affinity for cannabinoid receptors and appears to have antitumor activity that is independent of CB₁ and CB₂ receptors. The mechanism by which CBD promotes apoptotic death of cancer cells is being explored, but appears to result in an increase in reactive oxygen species inside tumor cells (Velasco et al. 2012).

Several reviews of the antitumor activity of cannabinoids have been published (e.g., Caffarel et al. 2012; Guidon and Hohmann 2011; Velasco et al. 2012). In particular, a connection between the endocannabinoid system and antitumor actions (inhibition of cell proliferation and migration, induction of apoptosis, reduction of tumor growth) of the cannabinoids in different types of cancer has been explored (Guidon and Hohmann 2011). In particular, these researchers focused on the treatment of breast, prostate, and bone cancers. Another review focused specifically on the potential for the treatment of breast cancer with evidence for the treatment of 3 main subtypes of breast cancer: hormone receptor-positive, HER2-positive and triple-negative tumors (Caffarel et al. 2012).

Conclusion

To date, data supporting direct anticancer effects of cannabis and cannabinoids in humans is very limited. There is historical precedent for the use of cannabis, predominantly topically, in the treatment of some cancers. Evidence is accumulating from cell culture and animal models that indicate the anticancer potential of Δ^9 -THC and CBD, as well as endogenous cannabinoids (e.g., anandamide and 2-arachidonoylglycerol). Preclinical studies have explored anti-proliferative, pro-apoptotic, antimigratory, and anti-invasive actions in a wide spectrum of cancer cells in culture. Perhaps of most promise is that tumor growth, angiogenesis, and metastasis are inhibited by cannabinoids in xenograft-based and genetically engineered mouse models of cancer. The therapeutic potential for crude cannabis and THC as therapies is limited by their psychoactive effects. However, these effects may be within the boundaries of tolerance compared to the toxicity profiles of cytotoxic chemotherapeutic and targeted small molecule therapies

widely used in oncology and should not be an impediment to further study. There is a potential for the development of non-psychoactive cannabis drugs based on CBD for anticancer therapies. There is considerable anecdotal data on the putative efficacy of cannabis in various types of cancer but this evidence is not well articulated or documented. Whether using THC or other cannabinoids, human clinical trials are required to determine the direct anticancer potential of cannabis.

Cannabis and cannabinoids are widely used in the management of symptoms associated with conventional cancer therapies including for pain, depression, coping with end-of-life care, nausea, appetite stimulation, and wasting. There is a strong body of scientific research supporting efficacy in these uses.

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

Author

Benjamin J Whalley PhD
School of Pharmacy
University of Reading, Whiteknights
Reading, Berkshire, United Kingdom

Editors

Lyle Craker PhD
University of Massachusetts Amherst
Amherst, MA

Mahmoud A ElSohly PhD
The University of Mississippi
National Center for Natural Products Research
University, MS

Aviva Romm MD, Herbalist, Midwife
Medical Director
American Herbal Pharmacopoeia®
Lennox, MA

Ethan Russo MD
GW Pharmaceuticals
Salisbury, United Kingdom

Roy Upton RH, DipAyu
American Herbal Pharmacopoeia®
Scotts Valley, CA

AMERICAN HERBAL PHARMACOPOEIA®
PO Box 66809
Scotts Valley, CA 95067 US
www.herbal-ahp.org
ahp@herbal-ahp.org

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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.

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AMERICAN HERBAL PHARMACOPOEIA®

PO Box 66809
Scotts Valley, CA 95067 US
www.herbal-ahp.org



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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 15th 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 Δ^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 Δ^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 Δ^9 -THC dose used was $\sim 6 \mu\text{g/kg}$. 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 amnestic 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 amnestic 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 Δ^9 -THC exhibited both pro- and anti-convulsant effects (see also below for Δ^9 -THC-specific effects) in a manner that may be seizure type- and/or species-dependent. For example, Δ^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 Δ^9 -THC (differences in pharmacological potency and molecular mechanisms between CBD and Δ^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 Δ^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 Δ^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 Δ^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 Δ^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 Δ^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 Δ^9 -THC daily. However, no data was presented for THC effects upon his seizures since concurrent changes to conventional antiepileptic medication made assessment of Δ^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 Δ^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 (≤ 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% Δ^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 Δ^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 Δ^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 Δ^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 Δ^9 -THC in various seizure models. In one of the earliest studies, Δ^9 -THC (2.5–10 mg/kg Δ^9 -THC 15 min prior to seizure trigger and 10 mg/kg Δ^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 Δ^9 -THC administered 15 min prior to the seizure trigger and 10 mg/kg Δ^9 -THC administered 15–45 min prior to seizure trigger significantly reduced the number of animals exhibiting seizure signs. Δ^9 -THC administration after priming had no effect upon seizures. Around the same time, the effects of Δ^8 -THC and Δ^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 ED₅₀ of

58 mg/kg and 72 mg/kg for Δ^8 -THC and Δ^9 -THC respectively, with Δ^8 -THC showing a marginally lower TD_{50} value (3.4 mg/kg vs. 4.3 mg/kg) assessed by the appearance of abnormal behaviors.

Thereafter, Δ^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 Δ^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, Δ^9 -THC (>160 mg/kg) protected against hind limb extension. Interestingly, although this study showed that oral Δ^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 Δ^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 Δ^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_{50} of phenytoin by co-administration of Δ^9 -THC (50 mg/kg po), with even higher reduction achieved by co-administration of Δ^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, Δ^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 Δ^9 -THC effect led the researchers to describe it as “*more active*.” Co-administration of Δ^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 Δ^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 Δ^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 Δ^9 -THC are comparable, yet, when co-administered with phenobarbitone,

their individual effects upon seizure differed significantly. In another investigation, Δ^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, Δ^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 Δ^9 -THC lowering threshold to seizure in the 6 Hz test (Karler and Turkanis 1980), confirming the differences in effects of Δ^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, Δ^9 -THC, and CBD were unchanged. Δ^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 Δ^9 -THC, no significant effects upon any seizure measures were seen following acute or chronic 20 mg/kg ip Δ^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 Δ^9 -THC, which may suggest a tolerance effect.

Interestingly, whilst many of the above studies reported anticonvulsant effects of Δ^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 Δ^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 Δ^9 -THC, which, together with the uncertain aetiology of the ‘polyspike’ discharges, hinders generalizable conclusions. Further to this apparently proconvulsant effect of Δ^9 -THC in rats, in 1976 a report described Δ^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 Δ^9 -THC doses as low as 0.5 mg/kg iv, which the investigators suggested reduced in frequency and severity with repeated Δ^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- Δ^9 -THC (0.5 mg/kg) and Δ^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 Δ^9 -THC (0.5 mg/kg; iv) in the same rabbit strain. Here, carbamazepine (ED₅₀: 2 mg/kg), diazepam (ED₅₀: 4.7 mg/kg), and phenytoin (ED₅₀: 10.9 mg/kg) were each found to inhibit Δ^9 -THC-induced seizures in these animals. Phenobarbital (ED₅₀: 56.9 mg/kg) and ethosuximide (ED₅₀: 306 mg/kg) were also found to inhibit seizures but only at doses that also produced toxic effects. Interestingly, CBD (ED₅₀: 19.7 mg/kg) also inhibited these seizures but only when given prior to (cf concurrently) Δ^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 Δ^9 -THC in models of seizure or epilepsy, per se, it is notable that prolonged (>6 months) treatment (Δ^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 Δ^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, Δ^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 Δ^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 Δ^9 -THC, which is in contrast to the generalized sedative-hypnotic, GABA-mediated action underlying chlordiazepoxide and phenobarbitone effects upon all barbitone 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 Δ^9 -THC that showed transient Δ^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 Δ^8 -THC and Δ^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, Δ^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 Δ^8 -THC was ineffective. At intermediate seizure stages three (head nodding) and five (clonic jumping) and at the endpoint of kindling, neither Δ^8 -THC nor Δ^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 Δ^9 -THC responses.

In prophylaxis experiments, cats received daily injections of Δ^8 -THC and Δ^9 -THC (0.5–2.5 mg/kg ip) during the kindling process (15 days). Δ^9 -THC, but not Δ^8 -THC, suppressed undeveloped after-discharges at the start of kindling, effectively preventing the manifestation of spontaneous seizures. This study supports the assertion that Δ^9 -THC effects upon seizure are highly dependent upon the state of disease progression in epilepsy. In the same period, the effects of Δ^8 -THC and Δ^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 Δ^8 -THC nor Δ^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 Δ^9 -THC exhibiting greater potency than Δ^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 Δ^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. Δ^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_{50} 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 Δ^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 Δ^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_{50} values or best estimate [indicated by *] are shown in parentheses): CBD (120 mg/kg), Δ^9 -THC (100 mg/kg), 11-OH- Δ^9 -THC (14 mg/kg), 8β -, but not 8α -OH- Δ^9 -THC (100 mg/kg*), Δ^9 -THCA (200–400 mg/kg), Δ^8 -THC (80 mg/kg), CBN (230 mg/kg), and 9-nor- 9α - or 9-nor- 9β -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 Δ^9 -THC in the MES test, such that, compared with mice (see above), Δ^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_{50} values obtained from these experiments and median toxic dose (TD_{50}) values derived from mice treated with the same drugs and subjected to a bar-walk test for neurotoxicity, the investigators derived protective indices ($PI = TD_{50}/ED_{50}$) for Δ^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_{50}) and protective index (PI) values (where available) for species examined for anticonvulsant effects of cannabinoids

Drug	Mouse		Rat	
	ED_{50}	PI	ED_{50}	PI
Phenytoin	9	6	5	5
Phenobarbitone	12	1.5	12	
CBD	120	1.5	50	60
Δ^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, Δ^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 Δ^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 Δ^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 ED₅₀ 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 Mg²⁺ ions ('Mg²⁺-free') from or by addition of a K⁺ channel blocker, 4-aminopyridine (4-AP), to the bathing solution. In the Mg²⁺-free model, CBD (100 μ M) decreased epileptiform LFP burst amplitude and duration despite an increase in burst frequency. In the 4-AP model, CBD (100 μ 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 CB₁ receptors in Wistar rat and found that CBD exhibited low affinity for CB₁ receptors with no agonist activity, which supports a CB₁-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^{2+} -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 abating 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_{50} : 0.42, 3.6 and 7.3 μ M, respectively) in transfected HEK-293 cells (De Petrocellis et al. 2011a; De Petrocellis et al. 2011b) but acts as a TRPM8 antagonist (IC_{50} : 0.90 μ M) 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_{50} : 16.6 μ M; 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_{50} : 16.6 μ M vs. brain levels of <10 μ M 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 CB₁ or CB₂ 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^9 -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^9 -THCV in vitro and in vivo (Hill et al. 2010). This compound ($>20\ \mu\text{M}$) reduced burst complex incidence and amplitude and frequency of paroxysmal depolarizing shift (PDS) induced by Mg^{2+} -free bathing solution used to maintain olfactory cortex slices. In the same study, Δ^9 -THCV also inhibited propagation of epileptiform activity in addition to significantly reducing burst complex incidence and PDS amplitude after pre-treatment ($10\ \mu\text{M}$) of the brain slices 40 min prior to seizure induction. Thereafter, Δ^9 -THCV ($0.25\ \text{mg/kg}$) 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 γS binding). Anticonvulsant effects of Δ^9 -THCV, alongside anticonvulsant effects of other, synthetic, CB_1 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_1 receptor antagonism at both GABA- and glutamate-ergic presynapses. However, if Δ^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 Δ^9 -THCV upon a given seizure state will rely upon the sub-population of neurons involved and their CB_1 receptor expression (Lutz 2004). Moreover, the recent finding that disruption of seizure states in vivo by CB_1 -receptor-agonist-mediated desynchronization of pathological neuronal firing (Mason and Cheer 2009) could also underlie CB_1 -receptor-antagonist-mediated effects, which is entirely consistent with the inhibition of the propagation of epileptiform activity by Δ^9 -THCV (Hill et al. 2010).

In an investigation that also examined CBD and Δ^9 -THC effects (see above for experimental details), cannabidiol (CBD) ($150\ \text{mg/kg}$ and $50\text{--}200\ \text{mg/kg}$ 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 Turkanis 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 Δ^9 -THC cannabinoids. Although the underlying mechanism for these effects may be multifactorial, in the case of Δ^9 -THC, part of the antiepileptic action is most likely due to effects at central CB₁ 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 Δ^9 -THC but, compared with Δ^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 Δ^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 Δ^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 Δ^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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History and Traditional Indications of Cannabis

Cannabis is one of the most widely used botanical drugs in history. Its use as a medicine extends to the most ancient medical writings of Asia and Egypt, through a plethora of cultures, to its inclusion in the most established systems of botanical medicine in the world, its use by the primary medical authorities throughout the ages, and the plant's inclusion in the materia medicas and official pharmacopoeias from the 1st to the 20th century.

The oldest Egyptian record of a medicinal use of cannabis is contained in *Papyrus Ramesseum III* (~1700 BCE). The medicinal use of cannabis was reported in the earliest materia medica of China, the *Shen Nong Ben Cao Jing*, compiled by various writers between the first and 5th century. *De Materia Medica* of the Greek physician Dioscorides (~65 CE) is possibly the earliest surviving account of the medical use of cannabis in the Greek record. The medicinal use of cannabis was reported by the Roman physician Pliny the Elder around the 1st century, and by the Roman Physician Galen in the second century. The 9th-century Nestorian Persian physician Sabur ibn Sahl cited the use of cannabis various times in his dispensatorium, *al-Aqrabadhin al-Saghir*, the earliest known compendium of pharmacology in Arabic. In Ayurveda, reference to cannabis as a medicinal substance is found in *Vangasena's Cikitsāsārasamgraha* (around the 11th–12th centuries CE), and in the *Anandakanda* (~1200 CE). The noted physician and philosopher Paracelsus (1493–1541) described cannabis in a number of his many works. Noted Swedish botanist Linnaeus wrote a little-known *Materia Medica* (1749), in which he described the actions of cannabis.

Cannabis appeared in the first book on pharmaceutics in the late 1700s, *Apparatus medicaminum tam simplicium quam praeparatorum et compositorum* (1776–1789), a work that is regarded as the most important and best of its time and included 12 pages on cannabis. Cannabis herb was included in the 1st edition of the *British Pharmacopoeia* in 1864 (BP 1864), and the herb, extract, and tincture remained official in the *British Pharmaceutical Codex* until 1949. Cannabis was entered into the secondary list of the USP in the 3rd edition of 1850, and remained as a primary listing from the 4th entry of 1864 through the 11th edition of 1936. Various cannabis preparations were included in the *National Formulary* (NF), from the first edition in 1888 to the 6th edition in 1936, and cannabis occurred in many editions of the *US Dispensatory*.

From the earliest times to the more recent historical medical literature, the totality of evidence suggests that the most well established actions of cannabis are: anticonvulsant, antispasmodic, anesthetic, analgesic, appetite stimulant, anti-emetic, sedative, and antidepressant. Based on these actions, cannabis has been used for a wide array of medical conditions, including pain, migraine, headache, spasms, movement disorders, seizures, cough, insomnia, anxiety, depression, anorexia, nausea, and vomiting. Medical authorities throughout history used a wide array of cannabis preparations. As reflected in the historical medical literature, proper dosing of cannabis is considered to be of seminal importance for its safe use. Additionally discussed is the manner in which different individuals can respond to the same preparation very differently.

Wide variation in potency of cannabis, in conjunction with the social demonization of cannabis as a narcotic, led to the decline of the botanical as a medicine. However, despite national and international restrictions and prohibitions against cannabis, medical research continued in many countries and several cannabis-based drugs have been approved nationally and internationally (e.g., Marinol[®], nabilone, Sativex[®]). It appears clear that past social intolerances that inhibited investigations into the potential medical uses of cannabis are changing, though numerous challenges remain.



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The Endocannabinoid System

The identification of cannabinoid receptors, their endogenous lipid ligands, and the multitude of physio-pathological functions they regulate, has stimulated a plethora of studies that have explored the role of the endocannabinoid system (ECS) in health and disease and provides the basis for the therapeutic use of cannabis-based medicines. Mounting evidence has implicated the ECS in a growing number of activities, both in the central and peripheral nervous systems and in peripheral organs. This suggests that modulating ECS activity through the use of cannabis-based medicines holds therapeutic potential in a wide range of diseases.

The primary area of study of the ECS regards its modulation by Δ^9 -tetrahydrocannabinol (THC), the putative psychoactive constituent of cannabis. Studies of the biological effects of THC, and its synthetic analogs revealed strict structural selectivity as well as stereoselectivity, providing telltale signs of drug-receptor interactions. Conclusive evidence exists for a specific receptor for cannabinoids, named cannabinoid-1 receptor (CB₁ receptor) and a peripheral cannabinoid receptor, named CB₂. Although initially considered to be expressed almost exclusively in the brain and neuronal tissues, more recent studies identified CB₁ receptors in almost all peripheral tissues and cell types, albeit at much lower densities than in the brain. Similarly, CB₂ receptor expression at low yet functionally relevant levels has recently been demonstrated in specific regions of the brain and gut, myocardium, cardiomyocytes, endothelial cells, vascular smooth muscle, Kupffer cells, bone, exocrine and endocrine pancreas, reproductive organs/cells, and in various tumors. Cannabidiol (CBD), conversely, displays high potency as an antagonist of CB₁/CB₂ receptor agonists in CB₁- and CB₂-expressing cells or tissue. Other cannabinoids interact with cannabinoid receptors with varying levels of binding affinities, actions (agonist/antagonist), and in sometimes a biphasic dose-dependent manner.

The first endocannabinoids identified were anandamide (AEA) and 2-arachidonoylglycerol (2-AG). Anandamide is a partial or full agonist of CB₁ receptors depending on the tissue and biological response measured. 2-AG can stimulate CB₁ and CB₂ receptors. Both anandamide and 2-AG are putative retrograde neurotransmitters in the brain, involved in unique forms of synaptic plasticity. Numerous other endogenous lipids with endocannabinoid-like activity have been reported, but their biological effects, metabolic pathways or cellular transport have not been studied in much detail. Fatty acid amide hydrolase (FAAH) is the key anandamide degrading enzyme, the role of which has been studied extensively.

In the most basic terms, cannabinoids/endocannabinoids help us to eat, sleep, relax, forget, and protect. Cannabinoids stimulate neurogenesis in the hippocampus, which may be relevant for the treatment of depression. Cannabinoids may also be neuroprotective, attenuate chemotherapy-induced nausea and emesis, improve sleep cycles, and reduce nightmares. The activation of hypothalamic CB₁ receptors by endocannabinoids or phytocannabinoids increases appetite, a therapeutically relevant effect in wasting disorders. In the amygdala, activation of CB₁ receptors can help extinguish aversive memories, which could justify the therapeutic testing of CB₁ agonists or FAAH inhibitors in post-traumatic stress disorder (PTSD). Cannabis, endocannabinoids, and modulators of the ECS have been exploited to alter pain sensation and may also be of therapeutic value in neurodegenerative disorders such as multiple sclerosis, schizophrenia, obesity/metabolic syndrome, and glaucoma.



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Effects of Cannabis on Amyotrophic Lateral Sclerosis

Historical Data

Historical data on the use of cannabis for amyotrophic lateral sclerosis (ALS) is lacking. ALS is listed as a potential therapeutic use in Health Canada's information for health care professionals on cannabis and cannabinoids.

Clinical Data

Based on the well-known protective effect of cannabinoids against oxidative cell damage and excitotoxicity, combined with their anti-spastic effect in MS, the use of cannabis for the palliative management of ALS has been proposed. The potential benefits for ALS patients include muscle relaxation, analgesia, bronchodilation, saliva reduction, appetite stimulation, and sleep induction.

In an anonymous survey of patients with ALS who used cannabis, relief from weakness, drooling, shortness of breath, spasticity, appetite loss, depression and pain was reported. Limitations of this study included its small size, and lack of controls and information on products used, dosages, routes of administration, duration, and formal measures of improvement. In a pilot study of the safety and tolerability of synthetic THC (dronabinol) in ALS patients, improvements were observed for insomnia, appetite, and spasticity. Conversely, in a short 2-week randomized, double-blind, placebo-controlled crossover trial in ALS patients who received dronabinol, no changes in cramp intensity or frequency, intensity of fasciculations, as well as validated measures of quality of life, quality of sleep, appetite and depression were observed. There is a need for more clinical trials to better establish how cannabinoids may benefit patients with ALS, and longitudinal data to determine if there may be effects on disease progression.

Animal and In Vitro Data

Elevated levels of cannabinoid receptors were measured in microglia of post-mortem human spinal cords of human patients with ALS. In an experimental animal model of ALS, levels of endocannabinoid components have been shown to be disrupted and up-regulated in the CNS. In this model, THC administered either before or after the onset of the disease delayed motor impairment and prolonged survival and potentially reduced oxidative and excitotoxic damage in spinal cord cultures in vitro. Cannabinol was also found to delay symptoms, but did not affect survival. However, a cannabinoid receptor agonist was found to prolong survival. A standardized cannabis extract, containing a combination of phytocannabinoids, has also been shown to alter the endocannabinoid system and course of disease in an animal model of ALS.



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Effects of Cannabis on Appetite—Executive Summary

Historical Data

Cannabis in its various forms has been known since antiquity for increasing appetite, particularly for palatable foods, and can also result in significant weight gain. There is a long litany of experiential reports of this effect of cannabis going back centuries in the historical literature, as well as in the 19th century medical reports of O'Shaughnessy. In Ayurvedic medicine, small doses of cannabis have been used to improve appetite, whereas overuse is believed to cause loss of appetite. The leaves of cannabis are included in the *Ayurvedic Pharmacopoeia of India* (2001) under the name *vijayā* where cannabis is recorded for *agnimāndya* (sluggishness of the digestive fire; often referring to dyspepsia and loss of appetite). Wasting syndrome (cachexia) and loss of appetite in AIDS and cancer patients as well as anorexia nervosa are listed as potential therapeutic uses in Health Canada's information for health care professionals on cannabis and cannabinoids. Similarly, according to the Office for Medicinal Cannabis (OMC) in the Netherlands, there is sufficient reason to believe that medicinal cannabis can help in cases of loss of appetite and weight loss due to cancer or AIDS. In Israel, cannabis prescriptions are available for AIDS wasting syndrome associated with AIDS and for HIV+ patients with significant loss of body weight. However, cannabis may not be as effective as standard medications for reversing wasting syndromes.

Clinical Data

Wasting conditions, partially due to appetite loss, such as that which occur with HIV, AIDS, cancer, or chemotherapy, are primary motivators for cannabis use among patients. There is experiential data on the appetite-stimulating effects of cannabis and cannabinoids in numerous clinical trials since the 1960s and a growing body of formal clinical evidence documenting the therapeutic effectiveness of oral synthetic THC (Marinol[®], dronabinol) and smoked cannabis for increasing appetite, caloric intake, and weight gain, and preventing weight loss in these conditions. Mixed results have been demonstrated for oral THC and a standardized cannabis extract (Cannador[®]), with some populations of patients responding and others not. Notably, increased appetite does not result in a reversal of wasting syndromes in all populations studied. Additionally, the potentially positive effects of cannabis may not compare favorably to standard medications (e.g., megestrol). According to the findings of many clinical studies, increasing the effectiveness of cannabis-based treatment for appetite stimulation needs to take into account the patient's concurrent therapeutic treatment(s), history of cannabis use (experienced or naïve user), the amount of drug administered, and the time and setting of the drug treatment.

Animal and In Vitro Data

Following the identification of THC as the main psychoactive principal in cannabis, the appetite-promoting effect from smoking could be attributed to THC, even before the identification of specific cannabinoid receptors. Numerous animal studies have articulated the pharmacology of the appetite-stimulating effect of cannabis. Studies have shown that THC-induced appetite stimulation is dependent on the route of administration, the dose used, the social environment, and satiety status. Preliminary research suggests that CB₁ receptors are predominantly responsible for these effects and has demonstrated a significant association between CB₁ gene (CNR1) polymorphisms and eating disorders.



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Effects of Cannabis on Epilepsy and Seizures

Historical Data

Historians have provided detailed accounts of cannabis as an anti-epileptic, anti-convulsant, anti-spasmodic, and in the treatment of seizure disorders. The use of cannabis for seizure control was described as long ago as 1100 AD by Arabic writer al-Mayusi, Ibn al-Badri in the 15th century, and by medical practitioners in the 1800s. In classical Ayurvedic and Chinese medicine texts, cannabis has been described as being used for convulsions. Currently, epilepsy is listed as a potential therapeutic use in Health Canada's information for health care professionals on cannabis and cannabinoids.

Clinical Data

The available data from small trials, case studies, and surveys on the use of cannabis and its constituents for the treatment of epilepsy and seizures in humans suggest that cannabis exerts an anticonvulsant effect, can reduce both the incidence and severity of seizures, can result in physical and behavioral improvements in children and adults, and rarely acts as a proconvulsant. 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. Additionally, CBD was well tolerated in pediatric subjects and exhibited no neurotoxic or motor side effects. In addition to a possible 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. More recent results employing cannabidivarin (CBDV), CBD's naturally occurring propyl derivative, suggest that it may be more efficacious than CBD. Notably, 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. Moreover, when considering the effects of cannabis on seizures, the potential for cannabis to cause effects outside of the central nervous system (CNS) should not be ruled out.

Animal and In Vitro Data

In preclinical research, anticonvulsive and anti-epileptiform effects of cannabinoids including THC, CBD, CBDV, and THCV have been reported. The consistently anti- and not pro-convulsant effects of CBD, as compared with THC, combined with the indication that its effects arise via mechanisms that are discrete from conventional anticonvulsants, support the potential clinical utility of CBD. Although the underlying mechanism for the anticonvulsant effects of cannabis may be multifactorial, in the case of THC, part of the antiepileptic action is most likely due to effects at central cannabinoid receptors. In the case of the non-THC plant cannabinoids, phenomenological evidence suggests that serotonergic and GABAergic mechanisms may be involved. Recent preclinical studies suggest that some of the effects of cannabis on seizures could be a consequence of blood flow modulation and not direct effects on central neuronal activity.



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Effects of Cannabis on Huntington's Disease

Historical Data

Historical data on the use of cannabis specifically for Huntington's disease is lacking. However, cannabis has been used extensively for spasms, and therefore may have applicability for movement disorders such as Huntington's disease. Huntington's disease is listed as a potential therapeutic use in Health Canada's information for health care professionals on cannabis and cannabinoids.

Clinical Data

Human trials on the effects of cannabis and cannabinoids in HD have shown improvements in chorea, motor function, cognition, mood, and behavior, and decreased anxiety and depression with the THC analogue nabilone or smoked cannabis. Differences in results across studies are apparent; however, these were all very small trials using different preparations and routes of administration. Preliminary evidence indicates that THC may be more effective than CBD for treating HD symptoms; therefore, the specific ratio of cannabinoids in cannabis varieties used is important. Because of the CNS pathology, an argument could be made that inhalation may be the best delivery route, compared to oral administration, for rapid delivery and loss of first-pass metabolism. There is a need to compare modes of delivery, and for whole plant studies in HD, comparing varieties with different CBD/THC ratios.

Animal and In Vitro Data

Pre-clinical studies in humans and animals suggest that the endocannabinoid system is involved in the pathogenesis and/or progression of HD, and that cannabinoid agonists and inhibitors of endocannabinoid transport could be of significant therapeutic benefit in HD due to their antihyperkinetic and neuroprotective effects. Studies have demonstrated that a decrease in cannabinoid receptor level and endocannabinoid signaling activity in the basal ganglia is one of the earliest changes in HD, preceding nerve loss and clinical symptoms, and likely contributes to the hyperkinesia associated with this disease.



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Cannabis and Mental Health

Historical Data

There are numerous historical accounts on the use of cannabis in various mental illnesses. In traditional Chinese medicine, the *Běn Cǎo Gāng Mù* (1596 CE) notes that cannabis can be used for the “hundred diseases of wind-withdrawal,” a reference to mental disorders. In Ayurvedic medicine, the *Rajanighantu* of the 13th century characterized cannabis as *medhakaritva* (inspiring of mental power). Ancient Assyrian medical texts included anxiety and depression as indications for cannabis preparations. In the 19th century, French psychiatrist Jacques Joseph Moreau de Tours believed that hashish was the supreme medicament for use in psychiatry and his book *Du Hachich et de l’aliénation mentale* is considered a foundational work of experimental psychiatry and psychopharmacology. In 1890, the British physician JR Reynolds summarized 30 years of experience with *Cannabis indica*, recommending it for patients with “senile insomnia,” providing a classic description of “sun-downing” in incipient Alzheimer’s disease. Indications recorded for the first formal pharmaceutical preparations of cannabis introduced to the German market in the late 1800s included depression and psychosis. Conversely, there is a plethora of historical literature that describes the detrimental effects of indiscriminate, excessive, and prolonged use of psychotropic cannabis preparations, with many accounts reporting mental dullness, lack of motivation, confused thinking, and dependence. Alzheimer’s disease, dementia, anxiety, depression, schizophrenia, and psychosis are listed as potential therapeutic uses in Health Canada’s information for health care professionals on cannabis and cannabinoids.

Clinical Data

Cannabis may provide some benefit for various mental disorders; however, consistent supportive data from rigorous clinical trials on the use of cannabis or phytocannabinoids specifically as a treatment are lacking. Both positive and negative effects are well established for cannabis. Paradoxically, cannabis can cause mental disturbances and, in some situations and individuals, be used in the treatment of the same mental disturbances it causes. Some preliminary research suggests that cannabis use by itself is not a sufficient cause of mental disorders, but rather that it acts as a component cause of these disorders, in that it interacts with other factors, such as dose, duration of exposure, and age of first exposure, to increase the risk in individuals with certain genetic, environmental, or situational vulnerabilities.

The most extensively investigated phytocannabinoid for potential psychiatric applications is cannabidiol (CBD). In studies involving healthy human subjects, CBD decreased THC-induced anxiety, significantly reduced post-THC paranoia and the likelihood of positive psychotic symptoms, and significantly improved memory. In a study with cannabis-naïve patients with generalized social anxiety disorder, CBD reduced anxiety compared to placebo, and was associated with a pattern of induced brain activity compatible with anxiolytic-like activity. CBD has been shown to reduce THC-induced impairment of binocular depth perception, a feature of schizophrenia. Some of the most persuasive human evidence for the antipsychotic potential of cannabis comes from a double-blind, four-week parallel group comparison of CBD with amisulpride in patients with acute schizophrenia. Both treatments produced a convincing

and significant improvement in psychotic symptoms from baseline, however there were significant advantages for CBD in terms of adverse events.

Animal and In Vitro Data

The activity of the endocannabinoid system within the central nervous system is essential for mental health. A ‘cannabinoid hypothesis’ for the pathogenesis of schizophrenia has been suggested that involves increased density of CB₁ receptor binding, increased cerebrospinal fluid levels of the endocannabinoid anandamide, and evidence of a functional interaction between endocannabinoid and dopaminergic systems. The role of endocannabinoid signaling in depression and depression-like behaviors has been described. Overall, impaired endocannabinoid signaling appears to be associated with greater vulnerability to stress, anxiety, and depression. Chronic stress significantly lowers endocannabinoid activity, leading to depression and anxiety behaviors in animals, which has been shown to be reversed following exogenous cannabinoid administration in these animals. Preclinical data suggest that increasing endocannabinoid signaling exerts antidepressant effects through mechanisms similar to those of conventional antidepressant drugs. Analysis of human *post-mortem* Alzheimer’s disease brains has revealed some alterations in ECS composition and signaling. Neuronal damage may increase endocannabinoid production, which has been proposed as a potential defense mechanism against toxicity.

Recent studies demonstrate that phytocannabinoids, including THC, CBD, and CBC, exert antidepressant-like actions in animal models of behavioral despair. CBD has been reported to have anxiolytic effects and to be effective in reversing social withdrawal in rats. Mice and humans share a similar mechanism of anxiolytic effects of cannabinoid receptor stimulation, and induced anxiety when cannabinoid receptors are blocked with a synthetic drug. CBD has been shown mechanistically to work via serotonin receptors. In addition, antioxidant and anti-inflammatory properties of CBD were shown in preliminary research and have been proposed to account for its neuroprotective actions.

Several mechanisms of action underlying cannabinoid neuroprotection against amyloid- β (A β) have been proposed. In N2a-variant amyloid- β protein precursor (A β PP) cells, THC was shown to be effective at lowering A β levels, as well as both total glycogen synthase kinase-3 β (GSK-3 β) levels and phosphorylated GSK-3 β , at low concentrations in a dose-dependent manner. THC directly interacted with A β peptide, thereby inhibiting aggregation. CBD has been shown to prevent cognitive deficits in A β -injected rats.



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Effects on Nausea and Vomiting—Executive Summary

Historical Data

In a review of ancient Arabic medicine, the therapeutic action of cannabis as an anti-emetic has been described. Cannabis has also been used for vomiting in Ayurvedic medicine. In the *Cincinnati Lancet and Observer* of 1862, a case history of the successful treatment of a severe near fatal case of *Hyperemesis gravidarum* was reported using an orally administered extract of cannabis.

According to the Office for Medicinal Cannabis (OMC) in the Netherlands, there is sufficient reason to believe that medicinal cannabis can help in cases of nausea due to cancer or AIDS as well as nausea and vomiting associated with chemotherapy or radiotherapy used in the treatment of cancer, hepatitis C or HIV infection and AIDS. Chemotherapy-induced nausea and vomiting (CINV) is listed as a potential therapeutic use in Health Canada's information for health care professionals on cannabis and cannabinoids. Similarly, in Israel, cannabis prescriptions are available for vomiting associated with chemotherapy for cancer.

Clinical Data

According to a number of scientific reviews, the current data supports the use of cannabis or its isolated constituents for nausea and vomiting due to chemotherapy or radiotherapy of cancer. In various clinical trials, cannabis (both inhaled and oral THC) has been compared to some traditional anti-emetics and was reported to be an effective anti-emetic treatment for patients experiencing CINV, with generally mild side effects, and in some trials, was effective in patients previously unresponsive to other, more conventional anti-emetic medications.

Clinical trials provide evidence that the inhalation of THC may be more effective than administering oral THC in preventing CINV. Smokeless inhalation devices (i.e., vaporizers) for delivering THC have been developed, and have been demonstrated to increase tolerance for inhaled cannabis due to decreased bronchial irritation.

Anecdotal evidence suggests that THC also alleviates anticipatory nausea, which often develops over the course of repeated chemotherapy. Additionally, there is some preliminary clinical evidence that cannabis-based medicines may be effective in treating the more difficult-to-control symptoms of nausea and delayed nausea and vomiting in children receiving chemotherapy.

Animal and In Vitro Data

Animal and mechanistic data suggests that the potential benefit of cannabis, cannabinoids and cannabis-based preparations in CINV is explained by the role of the endocannabinoid system in the control of nausea and vomiting. The role of both central and peripheral mechanisms as well as the interaction of the cannabinoid system with the serotonergic system has been implicated in the anti-emetic effects of cannabis. Animal research has also supported anecdotal reports that cannabis and cannabinoid compounds may attenuate anticipatory nausea. Both CBD and THC appear to be associated with these effects.



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Effects of Cannabis on Tourette's Syndrome

Historical Data

Historical data on the use of cannabis for Tourette's syndrome is lacking, though the long-term use of cannabis as an antispasmodic suggests a potential benefit for relieving some Tourette's symptoms. Tourette's syndrome is listed as a potential therapeutic use in Health Canada's information for health care professionals on cannabis and cannabinoids, and by the Office for Medicinal Cannabis (OMC) in the Netherlands.

Clinical Data

The majority of information regarding the use of cannabis for reducing symptoms associated with Tourette's syndrome comes from case reports and 2 small randomized placebo-controlled trials. Patient reports indicate that self-administered smoked cannabis is effective for some symptoms of Tourette's syndrome, predominantly tics and behavioral disorders such as attention deficit hyperactivity disorder (ADHD) and obsessive compulsive behavior (OCB). Orally administered THC appears to be similarly effective in some patients for some symptoms. In the 2 available randomized placebo-controlled trials evaluating orally administered THC in Tourette's syndrome, significant tic improvement was reported, as well as significant OCB improvement in some patients. Additionally, a trend toward significant improvement of immediate memory span was reported. A Cochrane review of these 2 randomized placebo-controlled trials concluded that there is an association with oral THC administration and tic reduction and weak evidence for improvement in OCB.

Animal and In Vitro Data

Amongst other theories on the pathophysiology of Tourette's, it is thought that tics are associated with abnormal activity of the neurotransmitter dopamine. Preclinical experimentation suggests an interaction between exogenous cannabinoids, endocannabinoids, and dopamine.



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Effects of Cannabis on Urinary Function

Historical Data

In Ayurvedic medicine, cannabis was used to promote urination, alleviate pain in the kidney, and to ameliorate anuria caused by spasm of the urinary bladder. In traditional Chinese medicine, the seed and stalk of hemp strains were used to promote urination. Today, these are not common functions ascribed to cannabis in these systems. There is no or little other historical data suggesting that cannabis exerts a marked affect on urinary function.

Clinical Data

Clinical studies demonstrate that cannabis has clinically relevant effects on the bladder and that cannabinoid receptor agonists may effectively suppress symptoms of bladder overactivity, which may be applicable in common lower urinary tract disorders, including overactive bladder, bladder pain syndrome, and bladder outlet obstruction.

In patients with MS, improvement in bladder control was demonstrated with cannabis, a cannabis extract (Sativex®), and THC. Benefits reported included decreases in urinary frequency, nocturia, incontinence, urgency and hesitancy in initiating micturition. Clinical evidence appears to confirm that cannabinoid receptors are differentially expressed in neurogenic overactive bladders, and that cannabinoid agonists used for the treatment of symptoms of urgency and associated incontinence in patients with MS, act via bladder CB receptors. One large-scale human cohort trial reported an association between cannabis use and a significant reduction in the incidence of bladder cancer.

Some studies report an adverse effects profile that could be prohibitive for some patients (intoxication, hallucinations). The use of cannabidiol (CBD), when given alongside THC, has been shown to reduce the possible adverse effects seen when subjects are dosed with THC alone.

Animal Data

In animal models of bladder inflammation, endocannabinoid antagonists attenuated a referred hyperalgesia in a dose-dependent fashion, and after systemic application of a synthetic analogue of THC, bladder overactivity associated with inflammation was significantly attenuated.

In an animal model of partial bladder outlet obstruction, when a selective cannabinoid receptor agonist was applied, the number of non-voiding contractions decreased, while opening detrusor pressures and bladder compliance increased.

In Vitro Data

In the human prostate, there is evidence for the presence of cannabinoid receptors, which may be associated with prostatitis-like symptoms. Cannabinoid receptor-immunoreactivity was shown to be expressed on prostatic cholinergic nerves. A role for CB-mediated modulation of autonomic neurotransmission in the prostate has been proposed.



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Ophthalmic Effects of Cannabis

Historical Data

The earliest reference in the historical literature on the use of a plant believed to be cannabis for the eyes originates from ancient Egypt, where it was recorded as being used as an ingredient in an eyewash for the treatment of unspecified eye conditions. Visual effects are reported from the Chinese materia medicas, and it is believed that the Indian materia medicas recommended cannabis preparations for ocular conditions.

Glaucoma is listed as a potential therapeutic use in Health Canada's information for health care professionals on cannabis and cannabinoids, and by the Office for Medicinal Cannabis (OMC) in the Netherlands. In the United States, glaucoma is included as a medical diagnosis for Compassionate Investigational New Drug (IND) Program patients.

Clinical Data

The existing clinical data on the ocular effects of cannabis are limited, with methodological shortcomings including insufficient power, quality, and homogeneity. Various clinical studies show that cannabis and cannabinoids lower IOP. However, these IOP-lowering effects may not be sustained, no changes in the underlying pathological mechanisms of glaucoma are evident, and the psychoactive effects of cannabis constrain its therapeutic use. Additionally, malfunction of a component of the cannabinoid signaling system in the human eye has been shown to be strongly implicated in blinding disorders of the lens and retina. Few studies have explored the long-term ocular effects of cannabis and the question of other potential unpredictable effects and off-target risks in the eye has been proposed.

Larger, well-designed trials are warranted to accurately determine the comparative efficacy of cannabinoids relative to other commonly used therapeutics for ocular hypertension and glaucoma. Further research on the potential of behaviorally inactive cannabinoids, as well as refinement of topical formulations for behaviorally active cannabinoids to minimize psychoactivity, may also hold promise.

Animal and In Vitro Data

The endocannabinoid signaling system has been found to be abundant in the mammalian eye, with cannabinoid receptors present in every major ocular tissue. Animal research has demonstrated that cannabinoids act locally in the eye via activation of ocular cannabinoid receptors. However, other evidence in animals suggests that some cannabinoids, such as cannabidiol and non-psychoactive cannabinoids, such as CBG, can act at distinct non-cannabinoid receptor targets to reduce IOP. The use of genetic animal models demonstrated that cannabinoids may reduce IOP by acting as “indirect sympatholytics” and inhibiting the release of norepinephrine in the eye. Data from experimental studies indicates that cannabis and some cannabinoids may also have anti-inflammatory and neuroprotective effects in the eye and that in addition to glaucoma, may be useful in the treatment of other ocular pathologies, such as uveitis and ischemic eye diseases.



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Cannabis International Status

Internationally and domestically, there are varying levels of tolerance for use of cannabis, and regulations regarding its medical and recreational use are changing rapidly. In the US, cannabis is regulated under the *Controlled Substances Act* (CSA), which was designed to fulfill US treaty obligations under the United Nations' *Single Convention on Narcotic Drugs* (1961). This treaty restricts cannabis to appropriate medical use only, and places strict controls on cannabis cultivation in a manner similar to those imposed on opium poppies. In the US, individual states have enacted their own rights, regulations, and prohibitions regarding both medical and recreational cannabis use. This conflicts with federal law, which maintains cannabis as a Schedule I drug, which is defined as a drug or other substance that has a high potential for abuse; has no currently accepted medical use in the US; and lacks accepted safety when used under medical supervision; and conflicts with the UN Treaty.

A number of countries (e.g., the US, Canada, Israel, the Netherlands, and others) provide an official source of medicinal-grade cannabis to select chronically ill patients. Thus, approved medical use of cannabis in the US is starkly inconsistent with the scheduling of cannabis. Additionally, several countries (e.g., Canada, Denmark, Germany, Spain, New Zealand, and the United Kingdom) have approved pharmaceutical preparations made from cannabis extracts (e.g., Sativex®) as prescription-only medicines.

In North America, Canadians currently have access to the widest representative of cannabinoid drugs in the world, including dronabinol (Marinol®), nabilone (Cesamet®), nabiximols (Sativex®), and crude cannabis. In the US, synthetic THC (dronabinol, Marinol®) was rescheduled by the DEA to Schedule II in 1985, and Schedule III in 1999. In December 2013, Uruguay became the first country to legalize the growing, sale, and use of cannabis. In the European Union, the Netherlands represents the most liberal state in terms of access to cannabis for both medicinal and recreational use. In India, bhang (the dried leaf of cultivated or wild-collected *Cannabis sativa*), when used in traditional medicine preparations and products, is regulated as an active ingredient of traditional medicines used in the Indian Systems of Medicine (Ayurveda, Siddha, and Unani). Countries with the most severe penalties for cannabis possession, use, or trafficking include Indonesia, Iran, Malaysia, Saudi Arabia, Singapore, and the United Arab Emirates (UAE). Due to the rapidly changing regulatory environment, primary regulatory policies in various states and countries as well as expected requirements under international treaties should be referred to for the most current regulations.

Potential uses indicated by such agencies as Health Canada's information for health care professionals on cannabis and cannabinoids and the Office for Medicinal Cannabis (OMC) in the Netherlands, or medical diagnoses for Compassionate Investigational New Drug (IND) Program patients in the US include: chronic pain, glaucoma, chemotherapy-induced nausea and vomiting, Tourette's syndrome, multiple sclerosis, HIV/AIDS (including AIDS-associated nausea, loss of appetite, weight loss, and debilitation), cancer (including nausea, loss of appetite, weight loss, debilitation, wasting syndrome, and pain), asthma, inflammatory bowel disease, and Parkinson's disease. Other potential therapeutic uses, for instance those outlined by Health Canada include: Alzheimer's disease, dementia, musculoskeletal disorders, epilepsy, Huntington's disease, amyotrophic lateral sclerosis, palliative care, and psychiatric disorders.