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Review

Cannabis and epilepsy: An ancient treatment returns to the fore

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ABSTRACT

Cannabis has been associated with the treatment of epilepsy throughout history, and if ancient Assyrian sources referring to "hand of ghost" are considered credible, this relationship may span four millennia. A tradition of usage continued in Arabic medicine and Ayurvedic practice in India, which led, in turn, to early experiments in Europe and North America with "Indian hemp." Lack of standardization, bioavailability issues, and ultimately prohibition were all factors in cannabis-based medicines failing to maintain mainstream usage in seizure treatment, but investigation was resumed in the 1970s with interesting signals noted in both laboratory and clinical settings. Early case studies showed promise, but lacked sufficient rigor. Resumption of research coupled with mass experimentation by families of epilepsy patients has led to intense interest in cannabis-based medicines for its treatment once more, with greatest focus on cannabidiol, but additional investigation of tetrahydrocannabinol, tetrahydrocannabinolic acid, and other phytocannabinoids.

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1. Introduction

Epilepsy has afflicted mankind from a time before recorded history, and has figured in the earliest writings of ancient peoples, along with their varied interpretations of its meaning, significance, and treatment. While many of the early interventions would seem magical, superstitious, or worse to modern practitioners, these interventions often included elaborate recipes of herbs, some of which would be recognized today as pharmacologically active. Noteworthy among these was cannabis, either as a simple (sole agent) or *theriac* (complex mixture). It was only in the 19th century that more formal observations of cannabis with presumably THC-predominant preparations as an anticonvulsant were undertaken, and only in the last few years that rigorous clinical trials have been initiated with the seemingly more versatile, less controversial cannabidiol (CBD).

1.1. Ancient Asian sources and sorcery

The strongest evidence for use of cannabis comes from Mesopotamia, that area of the Fertile Crescent that lies at the crossroads of history, and has seen countless dominant cultures over time. Its ancient *materia medica* was best preserved in the mound of Kouyunjik in Nineveh, on the Tigris River near modern Mosul, Iraq. For some five decades, Reginald Campbell Thompson studied Assyrian medical texts from the Royal Library of Ashurbanipal, who ruled 668–626 BCE. Six hundred-odd broken tablets compiled the writings of the much earlier Akkadian and Sumerian cultures dating to the second millennium BCE [1–3].

While it may be impossible to guarantee the identity of medicinal plants in the tablets with assurance, some 30 references to *azallû* in Akkadian (Ancient Assyrian), and A.*ZAL.LA* in Sumerian were felt to clearly point to cannabis, as summarized in an examination of its synonyms [4](p. XVIII):

> *Sami nissati* 'a drug for sorrow', coupled with the property of spinning and making a cable, makes 'hemp', *Cannabis*, the Indian *bhang*, *binj*, certain, which is further borne out by the Persian *gargarinj*, *Cannabis sativa*, L. (the *–nj* is a frequent termination). *GAN.ZI.GUN.NU* is one of the most interesting words in cuneiform; we have already seen that *GAN.ZI.SAR* is *kanasu*, a narcotic 'like mandragora', presumably opium; *GUN.NU* is the equivalent of some form of *burrumu*, originally apparently 'to twist, weave' as well as 'to be two-coloured'. Consequently the word = *GAN.ZI* + "weave", i.e. the weaving narcotic, and there is great philological similarity between this and the Hindustani *ganjha* (cannabis), —.

These assignations have been disputed [5], but as discussed in greater detail in a prior publication [6], many of Thompson's contemporaries and successors accepted Thompson's interpretations, and no alternative identities would come close to fitting the descriptions of a plant that suggested

Abbreviations: CBD, cannabidiol; CBDA, cannabidiolic acid; CBN, cannabinol; ED_{50}, effective dose in 50%; THC, tetrahydrocannabinol; THCA, tetrahydrocannabinolic acid; THCV, tetrahydrocannabivarin.

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psychoactivity, was a source of fiber, was insecticidal, and could be delivered by fumigation, orally, cutaneously, or per rectum. The plant in question was pounded and filtered as is done with hashish to this day, and its seed, stem, leaf, and flower were all employed. Indications described for this medicinal plant included: amorous aid, erectile dysfunction, neuropathic-type pain, tonic benefits, urinary stones, lung congestion, possible spasticity, anxiety, grief, and depression.

Pertinent to the subject of epilepsy, numerous passages in the Kouyunjik cuneiform refer to treatment of a condition labeled "hand of ghost." One example is cited twice (K. 2448 + 6836 and K. 2615) [7] (1, 4, 4) and (99, 2, 4), transliterated [8](p. 524), "A.ZAL.LA U.HI.A *sindi sa qat etemmi*" and translated [9](p. 21), "Root of caper which is on a grave, root of acacia, right horn of an ox, left(?) horn of a kid that has been covered, seed of tamarisk, seed of laurel, *Cannabis*; these seven drugs area cataplasm for the hand of a ghost, with which to bind his temples." A similar account appears elsewhere (K. 7642) [7] (102, 39).

> Another passage is noted (K. 6261) [7] (89, 1, 5) translated [9] (p. 22):
>
> —[*Calendula*], *Chrysanthemum segetum*, lupins, asa(dulcis), *IR.KULLA*-plant, *EL.KULL.LA*-plant, —*Crataegus Azarolus*(?), tamarisk, seed of tamarisk, –tragacanth, the plant *Alasara*(?), black [alum], white alum, nitre, *AZAG.PAD*-salt, roses, *Cannabis*, fir-turpentine, pine-turpentine, *nuhurtu*-asafoetida, root of *nuhurtu*-asafoetida, the plant *kansam*, mustard, shoot of *Conium maculatum*, rue, fennel, mint, Amni, hellebore, asafoetida. Thirty-two drugs for removing sorcery, either in wine or in beer in *GIS.LIS* of tamarisk he shall drink.

An additional example is (K. 8127 + 8438) [7](90, r.20), translated [9] (p. 25), surmising this to be a "neuralgia" [7]:

> —that "stoppage of Life" [which besets(?)] that man should not draw nigh his body — hellebore, seed of *Cannabis*, mint, the *azallu*-plant, seed of *Solanum*, seed of daisy, together three grains each in honey of the mountains, oil and *kurunnu*-beer thou shalt mix, let it stand under the stars, in the morning before the sun he shall drink, stand on bitumen, look on lapis, cinnabar (carnelian, gold, silver, and he shall be freed.)

"Hand of a ghost" also appears in the prescription (K. 2477) [7] (94, 2, ii, 12), translated [10] (p. 804), "—and talks much—the hand of a ghost,–*Cannabis*, styrax, oak, *Ricinus*, *Oenanthe*, linseed, kelp (?), myrrh, wax of honey, *lidrusa*-plant, sweet oil, together thou shalt mix, anoint him therewith in oil."

In an article on diseases of the ears (K. 3486) [11] (97, 6), this account is found, "Lupins, *Calendula*, *Chrysanthemum segetum*, mustard, hellebore, seed of [tamarisk(?)], —*Cannabis*, *Asa foetida* (*nuhurtu*), *Asa foetida* (*tiatu*), mint, twelve drugs for [the hand of a ghost(?)]."

"Hand of ghost" was apparently also treated internally by cannabis [3] (p. 221) [7] (K. 4609.8) (76, 1, 21), and [8] (p. 524), "A.ZAL.LA —*ina sikari* NAG.MES-*ma ina'es* he drinks in beer [cannabis] (among 12 herbs for the 'hand of a ghost'.)" Such administration would certainly increase the likelihood of actual true pharmacological effects in epilepsy for seizures.

Finally, fumigation was also employed for this affliction [7] (K. 8867) (99, 3, r.4), supporting the concept of a parenteral administration of the drug for an acute benefit on seizures.

Thompson never identified the diagnostic entity "hand of ghost" definitively, but later work by an Assyriologist/neurologist team seems to have settled the issue [12], as this syndrome clearly was one associated with epilepsy. Their treatise, based on translation of Neo-Assyrian tablets dating from 718 to 612 BCE, unmistakably describes the various attributes of seizure disorders (auras, tonic extension, absence, complex partial and even gelastic spells) in striking variety (p. 187):

> We may say a few words about the "ghosts"— without perhaps straying too far down the dark alleyways of strange arguments. Ghosts roam at night, or may do so, and it is directly clear from the text itself that *sibit etmmi*, "seizure by a ghost", and *qat etemmi*, "hand of a ghost" were (or, more accurately, could be) the ancient terms for nocturnal epilepsy.
>
> Also noted [12] (p. 187):
>
> Similarly, the observation of TDP 34, 13: "If his forehead is 'seized' and pains him without appeasement from sunrise to sunset, it is 'hand of ghost'", will suitably refer to nocturnal (or, specifically, early morning) epilepsy, with severe headache, as commonly, continuing thereafter throughout the day.

The treatise also included prognostic features associated with epileptic variants. Then, as now, the outcome was sometimes fatal [12] (pp. 189):

> 9–10. [if an] epilepsy demon falls again and again upon him, his eyes are suffused with blood—R: and he blinks his eyes;—if his lower (*var.*: his upper) cheek areas twitch and his hands and feet are extended; if when the exorcist comes to see him *hope is perishing* that he will ever regain consciousness, —hand of the ghost of a murderer. (He will die).

An additional citation adds more detail [12] (p. 190):

> 16. If at the end of his fit when his limbs become relaxed again his bowels are sometimes seized and has a motion, it is "hand of ghost" (nocturnal epilepsy).
> 17–18. If at the end of his fit his limbs become paralysed, he is dazed (or dizzy), his abdomen is "wasted" (*sc.*, as of one in need of food) and he returns everything which put into his mouth———, —hand of a ghost who has died in a mass killing, He will die.

Another detailed passage indicates [12] (p. 191):

> IV NOCTURNAL EPILEPSY
>
> 27. If his seizure (or Possession) always takes place in the evening, it is the seizure of a ghost (nocturnal epilepsy).
>
> a) *Two symptom entries*
>
> 28. If ditto, he has a feeling of distention in his epigastrium and "his legs are lifted up" (i.e., he sits motionless(?)), —seizure by a ghost.
> 29. If ditto, he has a feeling of distention in his abdomen and is restless until the middle of the night (sc., when "relieved" by hi fit), seizure by a ghost.
> 30. If ditto, his eyes become cloudy and his ears hiss, seizure by a ghost.
>
> b) *One symptom entries*
>
> 31. If ditto, and his ears hiss, ——seizure by a ghost.
> 32. If ditto, and his ears (or, hearing) become "paralysed", —seizure by a ghost.
> 33. If ditto, and his forehead aches, seizure by a ghost.
> 34. If ditto, and at the time of his possession he is hot and from the evening watch until the middle watch he remains awake, (waiting) for him, —seizure by a ghost.
> ——————————
> 46. If his possessing demon begins to possess him in the late afternoon, and that the time of his possession he has ——, his forehead and his eyes oppress him and he has internal (or, stomach) pains, —hand of ghost.

Cannabis has an ancient history in ethnobotanical usage in India, as well [13]. Cannabis was one of the primary agents employed for rejuvenation and as a synergist in combination with other herbs [14], to promote health, and to prevent disease. Its primary indications were ordered as follows: sprue syndrome, sterility, impotency, diarrhea, indigestion, epilepsy, insanity, and colic pain.

1.2. Arabic and Islamic medicine

Indalecio Lozano published an early account of the use of cannabis to treat epilepsy allegedly attributed to Abu Bakr Muhammad ibn Zakariyya al-Razi (known in the West as Rhazes), an eminent Persian physician (865–925), in a passage translated from the original Arabic text [15] (p. 84–85, and translated, in turn, from Spanish by EBR):

> Wherein one relates how Ali ibn Makki cured the epilepsy of Zahir al-Din with hashish and music
> Razes says when discussing the treatment of epilepsy that the cannabis leaf is one of the medications which, because of its properties, cures this disease in an immediate manner. I —relates Razes— have proven this on various occasions. The last time was when I was trying to treat Zahir al-Din Muhammad ibn Isma'il ibn al-Wakil, son of the registry chamberlain of Baghdad under the Abbasid powers. Melancholy moods had seized Zahir al-Din, since becoming sick. So, they locked and chained him in his house. He used to suffer a seizure attack every week, and doctors were treating him for approximately six months, without cure. Then, brought before him for examination was 'Ali ibn Makki, a person of very great skill in playing the lute and tambourine, and composing poetry. His father, Makki, was a poet in the days of al-Nasir Li-Din Allah, among whose chamberlains his son ibn Makki was counted. He began to talk to Zahir al-Din to distract him, and suddenly, in a rapture, he began singing, and his song touched the emotions of the sick patient. When Ibn Makki realized this, he drew one of the sleeves of his gown a little hashish and placed it in front of him, offering it to him. Zahir al-Din refused to take it, having never tried it before. Ibn Makki reassured him to get him to eat it; then he played the lute and sang delicate poems to him. Just one hour had elapsed when Zahir al-Din noticed the effects of the hashish on his spirit and his senses. Then, he recovered his reason and bitterly regretted the calamitous state in which he had been found while he was sick. All this happened the day of the week in which he suffered the seizure.
> One historian reports that Zahir al-Din then applied himself assiduously to hashish consumption and never again abandoned it for a moment […].

Although this account deals with recognized historical figures, the provenance of the story is certainly open to question [16,17]. The text itself derives from "Solace of the spirit in hashish and wine," a work of the 14th-century Damascene authority Taqi al-Din al-Badri from Arabic manuscript number 3544 in *Bibliotheque National de Paris*, *Kitab Rahat al-arwah fi l-hasis wa-l-rah* [15] (and Indalecio Lozano, personal correspondence, 2016). The uncertainty in its veracity derives from the loss of key manuscripts, and a contemporaneous literary tradition in which repetition (and sometimes embellishment) were the sincerest form of flattery. It certainly requires emphasis that this "cure" necessitated regular administration of hashish, as one might expect as a necessity in treating a chronic affliction.

An additional formal attestation is found in the Arabic literature [18,19], wherein Ali ibn al-Abbas al-Mayusi circa 1100 CE prescribed insufflation of cannabis leaf juice for seizure disorders. A translation of the text reads (translation, EBR): "The juice of the leaves of cannabis instilled in the nostril serves to treat epilepsy." Such a parenteral route of administration may have been an advantage in acute attacks wherein the oral route would be impractical or dangerous. It also suggests the likelihood that tetrahydrocannabinolic acid (THCA) was the active agent, rather than decarboxylated THC.

1.3. Medieval herbalists and European hemp

Interestingly, the European literature prior to 1840 has little to say on the issue of cannabis to treat seizures, with one notable exception. In 1557, Pietro Matthioli referred to the use of a decoction of hemp seed to treat epilepsy [20], implying that the treatment worsened the condition: "For whose doctrine I never consider those silly women, who give decoction of cannabis seed to children, who are epileptic, because of the harm added." John Parkinson in 1640 cited Matthiolus [21] (p. 598), "-but as Matthiolus saith, the women in Germany went a wrong course, to give their children the decoction of Hempe seede for the falling sickness, which it did rather augment, than helpe to take away—." A virtual lack of supportive literature from the Renaissance herbalists might indicate that low doses of hemp strains with available cannabidiolic acid (CBDA), if administered without heating, or cannabidiol if decarboxylated (but devoid of tetrahydrocannabinol) offered little therapeutic benefit.

1.4. Indian hemp and Western medicine

The advent of scientific examination of Indian hemp in 1840 allowed the first modern investigations of this indication as William O'Shaughnessy, an Irish physician in service to the British Crown in India, investigated the indigenous uses of cannabis by Ayurvedic practitioners, experimented on animals in turn, and then his patients [13,22]. O'Shaughnessy successfully treated a 40-day-old infant with convulsions with heroic doses of cannabis tincture to control the spells [23]. Interestingly, no sedation was observed despite the treatment. After 20 days, he observed, "The child is now (23rd November) in the enjoyment of robust health, and has regained her natural plump and happy appearance." The same indication for infantile convulsions appears even to modern times in Indian books of *materia medica* [24].

O'Shaughnessy lectured in Britain in 1842 on his therapeutic successes with Indian cannabis, and subsequently W. Ley reported similar success in abrogating spasmodic seizures in a 9-month-old infant [25], and in a wide variety of other spastic and arthritic conditions. He agreed with O'Shaughnessy's assessment (p. 409), "that in hemp the profession has gained an *anti-convulsive remedy* of the greatest value."

A few years later in his reference text, Robert Christison observed [26] (p. 974), "Indian hemp has been used as antispasmodic in hydrophobia, tetanus, malignant cholera, and infantile convulsions, with marked relief in repeated instances."

The treatment soon spread to North America, where R.R. McMeens employed a tincture of *Cannabis indica* successfully in four children, notably in a 7-week-old infant who had multiple daily seizures for over two weeks [27] (p. 329):

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

The rather comprehensive McMeens Report of 1860 on cannabis described the above success in pediatric epilepsy and added documentation of excellent control in three of four cases of chronic epilepsy in adults [28].

The previous year, Willis touted *Cannabis indica* as a versatile anticonvulsant [29] (p. 176), "I was led to the use of hemp in puerperal convulsions, having also seen its beneficial effects in convulsions in general, after all the common remedies had been tried without relief."

The eminent Sir John Russell Reynolds was one of the greatest 19th-century authorities on clinical cannabis, and personal physician to Queen Victoria. In an 1868 publication [30], he presented three case studies in epilepsy (two adults, one child), with benefits of varying degree in each. The descriptions are sufficiently lucid to leave no doubt as to accurate diagnoses. In a subsequent publication in 1890 [31], he seemed to reject cannabis for epilepsy treatment, but a close

reading reveals nosological confusion, and a ringing endorsement for some conditions that we would recognize today as seizure disorders, particularly those in children.

Cannabis remained in the pharmacopoeias of Western nations well into the 20th century, but its use for seizures was particularly impacted by the extreme pharmacological variability of its preparations, and eventually by its political prohibition.

1.5. Modern studies of cannabis and cannabinoids as anticonvulsants

In a 1974 letter, it was reported that a cannabidiol intravenous infusion in an epileptic patient aggravated pre-existing spike-wave activity. However, no actual seizures resulted [32]. As a general observation, attempted correlations of EEG severity to clinical efficacy of medication are quite risky. Similarly, it should be mentioned that electroencephalographic measures have generally been of little value in relation to cannabis effects. This topic was previously reviewed in some detail in Russo et al. [33]. It is well demonstrated that cannabis produces an increase in low voltage fast activity in the beta range of the EEG. However, it is not usually productive of epileptiform activity per se, or other pertinent changes, as demonstrated in numerous chronic use studies in the USA, Jamaica, Greece, and Costa Rica [34–37].

In 1975, a case report was published describing one adult who habitually employed phenobarbital and phenytoin treatment, but only attained complete control of seizures when concomitantly employing smoked cannabis [38].

Experiments in mice in the 1970s demonstrated the relative anticonvulsive potencies of various cannabinoids in maximal electroshock and bar-walk tests [39]. These were listed in order of potency of ED_{50}: 11-hydroxy-THC (14 mg/kg) > Δ^8-THC (83 mg/kg) > Δ^9-THC (101 mg/kg) > CBD (118 mg/kg) > CBN (230 mg/kg). Overall, a "protective index" was felt to be highest with CBD, and comparable to the (then) popular anticonvulsant, phenobarbital. Consroe et al. in 1977 studied a subpopulation of rabbits susceptible to seizures induced by THC at low doses [40]. CBD was effective at preventing convulsions when co-administered with THC, but not when administered before THC. In subsequent study, THCA showed anticonvulsant properties only at 200–400 mg/kg [41]. The following year, a prescient observation was made [42] (p. 639):

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

Subsequently, a great deal of clinical work in humans was pursued in Brazil particularly with cannabidiol [43,44]. Fifteen patients with frequent attacks of unresponsive "secondarily generalized epilepsy" (seizures of partial onset with secondary generalization), aged 14–49, were treated with CBD vs. placebo in double-blind fashion. Three of eight treated patients had complete seizure control with 200 mg of CBD per day, and a fourth with 300 mg per day. One was improving, but moved away and was unavailable for follow-up. One other was markedly improved, two somewhat, and one not at all. Neither laboratory changes, nor major adverse effects were noted; merely some somnolence in four subjects.

Another double-blind placebo-controlled study of CBD in South Africa with similar dosages in 12 subjects was published only in abstract form [45], and failed to demonstrate any benefit on their seizures.

Consroe reviewed the contradictory data in animals on the anti- and pro-convulsant effects of THC [46]. Some of these deleterious effects, including those with CBD occurred with near lethal dosages. It should be mentioned that while there are claims of seizure exacerbation in humans by THC, these are isolated occurrences with no correlation to dosage, timing of administration, etc.

A double-blind clinical trial was performed in the state of Maine [47] over a two-year period in which each patient served as their own control and revealed no effect of supplemental CBD on seizure frequency at doses of 300 mg/d in 10 subjects over six months. Serum CBD levels of 2–15 ng/ml were documented. One additional subject showed no response with CBD doses of 900–1200 mg/d.

Grinspoon and Bakalar presented three vignettes in their 1997 book documenting successful treatment of seizure disorders in humans with cannabis [48], including that of the well-known activist, Valerie Corral, a victim of post-traumatic seizures only controllable with cannabis. Numerous other anecdotal claims are posted on Grinspoon's website: http://www.rxmarihuana.com/_vti_bin/shtml.exe/search.htm by inserting search terms "epilepsy" or "seizures".

Petro described successful treatment of epilepsy in 11 additional self-selected cases of persons applying for legal medical exemption through the US Compassionate Use Investigational New Drug Program [49].

In Gieringer's survey of some 2480 clinical cannabis patients in Northern California, 25 or 1% employed cannabis as treatment for epilepsy [50]. Valerie Corral served as a provider for 3 epilepsy patients out of 77 total subjects in her survey, or 4% [51]. These patients completed weekly questionnaires from 1993 to 1997 with regards to their clinical status, reporting marked improvement in seizures ($p = 0.001$). In a 2003 German survey of medicinal cannabis users, 3/143 patients or 1.4% had seizure disorders [52].

Based on a review of available literature, the British Medical Association concluded in a 1997 report [53](p. 52), "With such scanty human data, the role of cannabinoids as possible therapeutic agents in epilepsy remains speculative. It is unlikely that psychoactive cannabinoids such as THC, which have dual convulsant-anticonvulsant effects, will be therapeutically useful." Similarly, in 1999 the Institute of Medicine in the USA concluded [54] (p. 1730), "Given the present state of knowledge, clinical studies of cannabinoids in epilepsy are not indicated." As late as 2001, in his last article before his death [55], Hollister categorized anticonvulsant properties of cannabis an indication with "sparse evidence of efficacy."

1.6. What is different now?

Some extremely important laboratory work in the interim has subsequently altered the landscape on this issue. Wallace et al. demonstrated in mice that seizure threshold was mediated by cannabinoid mechanisms, mediated by CB_1, and that this effect was blocked by the antagonist, SR141716A [56].

This work was expanded subsequently [57], employing a pilocarpine–induced seizure model in rats that mimics drug-resistant complex partial seizure disorders in humans, the most common type of seizures that fail to respond to conventional approaches. THC produced a 100% reduction in seizures, whereas phenobarbital and diphenylhydantoin did not. The animals demonstrated both acute increases in endocannabinoid production and a long-term up-regulation of CB_1 production as apparent compensatory effects counteracting glutamate excitotoxicity. The latter effect is common to stroke, head injury, and migraine. The implication is an improvement in plasticity, and neuroprotection. Although, THC was labeled "impractical" as an anticonvulsant by the authors, this contention is not necessarily supported by the evidence as, based on their own dosing, the anticonvulsant effect was active at sub-sedating levels.

While available clinical evidence provides little compelling support for THC having significant proconvulsant properties in humans, we must remain cautious, as animal data do raise the possibility that high-dose THC could have such an effect in certain patients. The situation may be analogous to that observed with other anticonvulsants. For example, carbamazepine can occasionally produce tonic convulsions when blood levels are excessive. Similarly, although sometimes clinically necessary, the combination of valproate and clonazepam may precipitate clinical absence status epilepticus.

Patients continue to tell us of the efficacy of cannabis for their seizures. In my own practice (EBR), I had several patients who claimed

markedly enhanced seizure control when cannabis was available, far in excess of that achievable with best available medical management with standard anticonvulsants. Some used solely cannabis, having abandoned conventional pharmacotherapy due to lack of efficacy or undesirable adverse effect profiles.

We know from older surveys of street cannabis in North America that virtually all strains were devoid of CBD [58] until recently. The same was found in European sampling, where various strains were tested by David Pate and David Watson at HortaPharm (Watson, personal communication, 2003):

> We GC tested all the entrees of two years of the High Times Harvest Cups, both hash imported and domestic, and all herbal cannabis. As well as one year, 31 different clones that were available in grow shops here. As well as our own collection of hybrid clones. They are all Western bred strains not just North America. It confirms what I say, Rob and I collected the samples and Dave Pate did the GC lab work. —We could also tell if the hash sample was domestic or imported just by cannabinoid profiles, all of the hash imports from the third world had CBD, none of the locally made domestic hash samples did.

In the United Kingdom, in the GW Pharmaceuticals database, according to Helen Adams (personal communication, 2003):

> We have 69 (4000 + total) patients registered on the GW patient contact database who have epilepsy. Out of these 69, 34 have used cannabis medicinally and found benefit. 22 out of the 34 felt the cannabis worked better than prescribed medicine. 3 of the 34 said prescribed medication worked better than cannabis. 8 felt it was impossible to tell any difference. 1 person thought cannabis & prescribed meds worked the same. These patients took their own supply of cannabis and obviously we have no way of knowing the individual chemical makeup. [But unless they were using imported hashish, it is highly likely that no CBD was present-EBR]

A subsequent formal survey of 2969 returned questionnaires in the United Kingdom in the period 1998–2002 reported that 24 (1.12%) utilized cannabis for epilepsy [59].

In an abstract from Italy [60], a case series of 18 children with drug-resistant epilepsy were treated with low-dose CBD in corn oil (? 25–27.5 mg). They noted improvements in seizure frequency and severity as well as cognition in most, including two with Lennox-Gastaut syndrome, but only half continued treatment due to high costs (300 Euros/month).

In Germany, Lorenz published in-depth case reports employing dronabinol (synthetic THC) in a dose range of 0.04–0.12 mg/kg/d in eight children neurologically affected with degenerative diseases, seizure disorders, or post-traumatic and hypoxic encephalopathy [61]. Benefits of the treatment included reduced seizures, muscle spasms, increased sociability, and palliative effects in those who succumbed to their illnesses. A latter case series corroborated these findings [62]. THC with an average dose of 0.2 mg/kg/d was utilized in 13 similarly affected children aged 7 months–17 years with improvement in spasticity and pain in the entire cohort (100%), and better sleep in 10 (77%), without dose tolerance or dose escalation, over the course of five years. Additionally, he observed no withdrawal effects even when undertaken abruptly. No control groups were present in either case series, and ascertainment bias in seizure reporting cannot be ruled out (vide infra).

More recently, the extensive basic science investigation of anticonvulsant properties of cannabidiol, summarized in [63], led to extreme public interest in utilizing it to treat epilepsy. This progress was publicized online by Project CBD (https://www.projectcbd.org/) in California, and enormous attention developed to the case of Charlotte Figi and other children with Dravet syndrome [64], especially after broadcast of the Cable News Network TV documentary "Weed" (https://www.bing.com/videos/search?q=CNN+Weed+Documentary&&view=detail&mid=98E4A417E38B9D094AE398E4A417E38B9D094AE3&FORM=VRDGAR).

However, this evidence of the anticonvulsant efficacy of cannabidiol remained anecdotal, although bolstered by a survey of families with affected children [65], and the open-label reports on Epidiolex® administration [66,67]. Scepticism continues in some circles, and certainly may be supported by marked differential responses in parental improvement reported in families using CBD preparations who were native to Colorado (22% responder rate) vs. those moving to the state for such treatment (47% responder rate) [68]. These reports have been followed by Phase II and III clinical trials of Epidiolex that seem to support benefit of CBD, at least according to press release data.

Many issues remain. Among them are the question of cannabinoid monotherapy versus polypharmacy. Anecdotal information from at least one clinician with a large epilepsy client base [69] supports the contention that inclusion of THC with CBD allows seizure control with much lower doses of the latter (e.g., 16.5 mg/kg/d maximum, as compared to 25 mg/kg/d in Epidiolex clinical trials). This contention of benefit to combining THC and CBD has yet to be tested in formal clinical trials, and such synergy has neither been confirmed in patch-clamp or animal testing. Additionally, although Karler observed only a weak anticonvulsant effect of THCA at 200–400 mg/kg/d in animal experiments [41], the possibility of effective control with very low doses has been supported by clinical experience with quantitative assays of the specific preparations, suggesting a possible multiphasic dose response effect for THCA (Dustin Sulak, DO, 2016, personal communication).

It is highly likely that the suggestion of any cannabis-based therapy for epilepsy will remain controversial, even for non-psychoactive preparations, but it is hoped that formal clinical trials with proper methodology will elucidate remaining issues and offer safe and effective for treatment of intractable epilepsy.

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