

Review

Historical perspective on the medical use of cannabis for epilepsy: Ancient times to the 1980s

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ABSTRACT

There has been a dramatic surge in the interest of utilizing cannabis for epilepsy treatment in the US. Yet, access to cannabis for research and therapy is mired in conflicting regulatory policies and shifting public opinion. Understanding the current state of affairs in the medical cannabis debate requires an examination of the history of medical cannabis use. From ancient Chinese pharmacopeias to the current Phase III trials of pharmaceutical grade cannabidiol, this review covers the time span of cannabis use for epilepsy therapy so as to better assess the issues surrounding the modern medical opinion of cannabis use.

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1. Introduction

In order to understand the current state of medical cannabis use fully, it is essential that the historical context of cannabis be explored. The use of cannabis whether for recreational or therapeutic purposes is a polarizing concept enshrouded in myth and misconceptions. There is now a fundamental reconsideration of the medical uses of cannabis and epilepsy finds itself in the center of this argument. This paper seeks to trace the evolution of perceptions on cannabis as a medical therapy from its early medical uses 2700 BCE in Asia to the current patient-driven uses as a potential treatment for drug-resistant epilepsy (Fig. 1).

2. Ancient times

Cannabis is perhaps one of the oldest plants cultivated for human use. Archeologic evidence suggests that it was grown for use as fiber and rope as early as 12,000 BCE in central Asia [1] and artifacts that included hemp cloth or depicting hemp fiber dating back several millennia BCE have been discovered in many parts of China [2]. The first writings describing the use of cannabis for the treatment of human disease appear in Chinese pharmacopeias from the 2nd century BCE and credit Emperor Shen Nung who lived around 2700 BCE and is

recognized as the father of Chinese medicine for his systematic exploration of herbal remedies [3]. In the Middle East, Ancient Sumerian and Akkadian tablets reference the use of a medicinal plant that is most likely cannabis for a host of ailments including nocturnal convulsions around 1800 BCE [4]. Ancient Egyptian papyri also describe its use for numerous afflictions including infections, analgesia, and vaginal contractions from approximately this same time period [4]. Around 1500 BCE, Vedic texts from India note anxiolytic effects of cannabis [5]. By the first and second century CE, cannabis is noted in medical texts of civilizations throughout Asia and north Africa for many different ailments. Building on prior traditions, Islamic medicine in the Middle East, Spain, and North Africa incorporated cannabis into its armamentarium. Specific mentions of the treatment of epilepsy are found in the 11th century writings of the Arabic physician al-Mayusi who advocated the use of extracts of cannabis through the nose [6].

3. Victorian era

In the early 19th century, the Irish physician William O'Shaughnessy traveled to India to study its medical traditions and returned to Europe, along with a large supply of cannabis, to promote the therapeutic potential for "tincture of Indian hemp" [7] and published his own case reports and studies in dogs for disorders such as "rheumatism," tetanus, cholera, and "infantile convulsions" [8]. He wrote a vivid description of a 40-day-old baby girl who developed nocturnal convulsive episodes that progressed to "attacks [that] were almost unceasing, and amounted to regular tetanic paroxysms." Typical treatments such as leeches, purgatives, opiates, and warm baths were "without the

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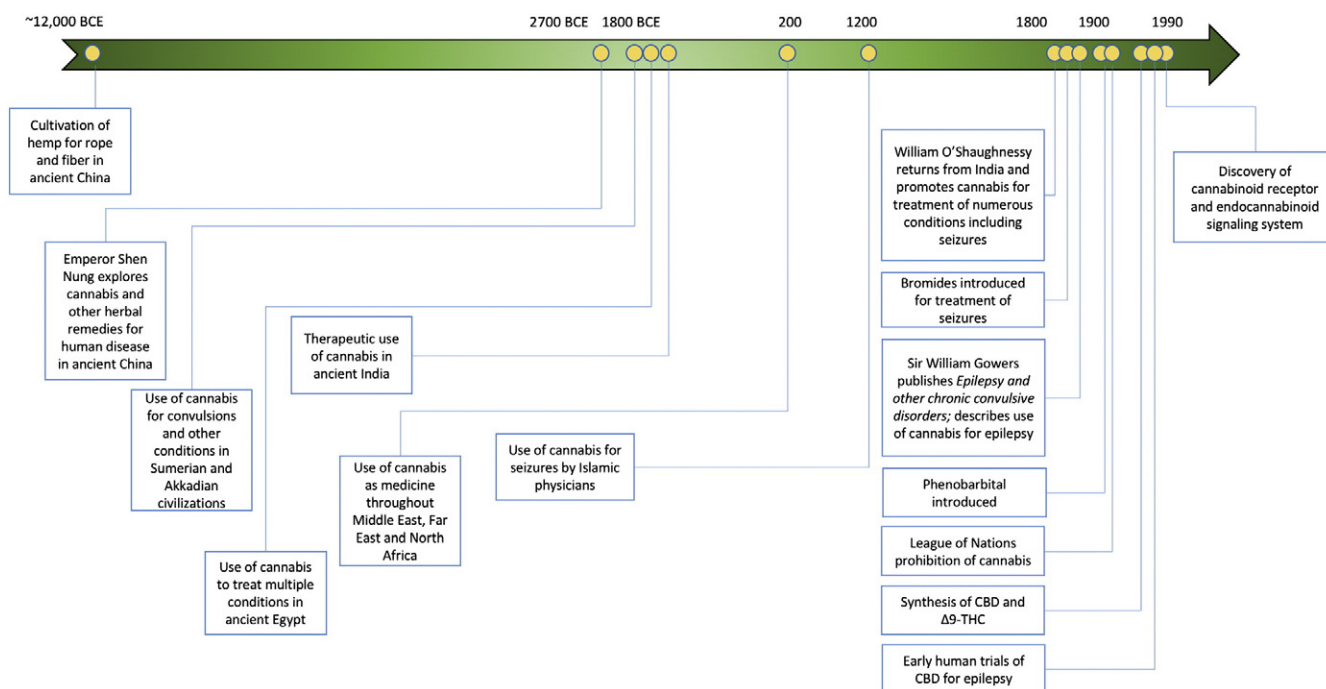


Fig. 1. A timeline illustrating highlights from the history of the medical use of cannabis with an emphasis on the treatment of seizures and epilepsy.

slightest benefit” and the family agreed to a trial of cannabis. O'Shaughnessy [8] wrote:

“A single drop of the spirituous tincture, equal to the one-twentieth part of a grain in weight, was placed on the child's tongue at ten, p.m. No immediate effect was perceptible, and in an hour and a half two drops more were given. The infant fell asleep in a few minutes, and slept soundly till four, p.m., when she awoke, screamed for food, took the breast freely, and fell asleep again. At nine, a.m., 1st of October, I found the child fast asleep, but easily roused; the pulse, countenance, and skin perfectly natural. In this drowsy state she continued for four days totally free from convulsive symptoms in any form. During this time the bowels were frequently spontaneously relieved, and the appetite returned to the natural degree. October 4. At one, a.m., convulsions returned and continued at intervals during the day; five drop doses of the tincture were given hourly. Up to midnight there were thirty fits, and forty-four drops of the tincture of hemp were ineffectually given.”

The child was treated repeatedly with various cannabis tinctures for the next few weeks until the convulsions stopped. Several months later, O'Shaughnessy noted that “the child is now in the enjoyment of robust health, and has regained her natural plump and happy appearance.”

By the mid-19th century, physicians in Europe and North America explored and wrote about extracts and tinctures of cannabis for treatment of various maladies, with perhaps the earliest reports pertaining to the treatment of migraine [4]. The eminent neurologist Sir William Gowers included several references to cannabis in his writings including its use in the treatment of migraines and tremors associated with Parkinson's disease [9]. He also wrote about the use of cannabis for the treatment of seizures in his monograph *Epilepsy and other convulsive disorders* [10]. In his book, he describes a case of a man with epilepsy resistant to bromides, the only known anticonvulsant at the time, treated successfully with cannabis:

The attacks ceased for a time on bromide, but recurred when he discontinued attendance. He came again in October, 1870; scruple doses of bromide of potassium three times a day had now no effect,

and the fits, at the end of 4 months' treatment, were as frequent as ever. Ext. cannabis indicae gr. (~9.8 g), three times a day, was then ordered; the fits ceased at once, “a wonderful change” the patient declared. He had no fit for 6 months, and then, having discontinued attendance, the fits recurred, but were at once arrested by the same dose of Indian hemp. He continued free from fits for some months, until, during my absence, bromide was substituted for the Indian hemp; the fits immediately recurred, and he left off the treatment. He returned to the hospital in 6 months' time, and on Indian hemp passed 2 months without an attack. In the third month another fit occurred, and the patient again ceased to attend, and did not return.

The use of cannabis for the treatment of epilepsy, typically as an adjunct to bromides, was also mentioned in the writings of Gower's mentor, Sir John Russel Reynolds, another prominent British neurologist of the Victorian era [11].

4. The twentieth century

By the late 19th and early 20th century, references to cannabis and cannabis extracts/tinctures appear in many pharmacopeias in Europe and North America [12]. However, in the early 20th century, the use of cannabis for treatment of disease began to fall out of favor as Western medicine began to focus on isolated chemical entities, often synthetic, for pharmacotherapy. This soon was followed by international prohibitions of cannabis and cannabis trafficking [13]. Both occurred at the beginning of the era of the scientific study of therapeutic claims and the first controlled clinical trials, relegating the evidence for cannabis as an anticonvulsant to the realm of anecdote and small clinical studies.

In the 1930s and 40s, chemists began isolating the tetrahydrocannabinoids (THC) found in cannabis [12]. Soon after, a small and poorly described study using “THC isomers” in 5 institutionalized children with epilepsy and intellectual disability reported seizure freedom in 1 child and significant improvement in another [14]. In the early 1960s, the molecular structure of the major phytocannabinoids, cannabidiol (CBD) and Δ9-THC, was elucidated by Mechoulam and his colleagues [15,16] allowing for further investigation of structure–function relationships and

pharmacological actions though much of early research was on the adverse and psychoactive aspects of cannabinoids. More widespread use of recreational cannabis in the 1960s and 1970s allowed clinicians to observe and report effects of smoked cannabis on seizures. Some case reports described worsening of seizures with cannabis use [17] while others reported dramatic improvements [18]. The variable effects of smoked cannabis on seizure control were also reported in subsequent surveys of patients with epilepsy [19–21]. Epidemiological studies in the 1980s also suggested a potential anti-seizure effect of smoked cannabis; a case-control study of illicit drug use in new-onset seizures presenting to an urban emergency room suggested that men who used cannabis within 3 months of admission were at lower risk for seizures [22].

There was early recognition that the psychoactive effects of Δ^9 -THC limited its therapeutic potential and some researchers looked to CBD, the most abundant nonpsychoactive phytocannabinoid, as a potential anti-seizure treatment after promising results in animal models of seizures (reviewed in [23]). The first reported human use was in a single patient with probable generalized (“centrocephalic”) epilepsy in whom an intravenous infusion of 40 mg of CBD did not alter the frequency of epileptiform discharges on the EEG [24]. Subsequently, there were four small prospective controlled studies of CBD for epilepsy performed in the 1970s and 80s. The first study [25] assigned 4 adults with treatment-resistant epilepsy to 3 months of 200 mg/day of oral CBD and 5 to placebo. Details on baseline seizure rates are scarce but two patients in the CBD group were seizure-free and one showed partial improvement whereas no change was reported in the control group. Another study examined 200–300 mg/day of oral CBD in teenagers and adults with treatment-resistant “convulsive” seizures [26]. In this study, 4 of 8 patients in the CBD group and 1 of 7 in the placebo group were seizure-free at the end of an 8–18 week observation period though investigators were not blinded to treatment assignment. A subsequent study was performed in institutionalized adults with intellectual disability and epilepsy and reported no difference in seizure control between the 6 patients assigned to 200–300 mg/day of CBD and 6 patients assigned to placebo [27]. Finally, the only trial that was double-blinded was a 6-month cross-over study in twelve adults with treatment-resistant epilepsy which found no difference in seizure frequency during placebo and 300 mg/day CBD exposure [28]. All of the studies were small, underpowered, and had methodological problems that limited the interpretation of results [29].

Despite an accumulation of anecdotal and pre-clinical evidence suggesting anticonvulsant effects of various cannabinoids, scientific exploration was hampered by the lack of a clear central nervous system target of action. This changed in the late 1980s and early 1990s with the discovery of the cannabinoid receptor [30] and endogenous cannabinoid receptor ligands [31], sparking a renewed interest in the understanding of the therapeutic potential of cannabinoids and modulation of the endocannabinoid system.

5. Conclusions

In their assessment of the evidence of the potential anticonvulsant actions of cannabis in 1978, Feeney and colleagues [32] opened with the following quote attributed to the 19th century British physician Sir Edward Seivking: “There is not a substance in the materia medica, there is scarcely a substance in the world, capable of passing through the gullet of man, that has not at one time or another enjoyed a reputation of being an anti-epileptic.” This statement reflected their dour assessment of the state of the evidence for the anti-convulsant properties of cannabis at the dawn of the 1980s and poor scientific quality of the literature supported their views. Case reports and anecdotes, no matter how ancient or how many, cannot support evidence-based medical practice. However, they can present hypotheses to be rigorously tested in the laboratory and in the clinic. Since the 1980s, the historical literature presented in this review has been used to justify many claims

about the potential therapeutic benefits of cannabis in epilepsy by advocates of “medical marijuana.” However, it has also served as the rationale for careful animal experiments (reviewed in [33]) and multiple ongoing randomized, adequately-powered, controlled trials of specific cannabinoids (e.g. NCT02224560, NCT02224690, NCT02318537, NCT02091375, NCT02369471). These trials, once completed, could hopefully provide the highest levels of evidence regarding the anti-seizure effects of cannabis constituents and determine if they will benefit the 1/3 of people with epilepsy who cannot get adequate seizure control with currently available treatments.

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