



Medicinal Cannabis for Chronic Pain: A Tale as Old as Time

Lady Christine Ong Sio^{1*}, Dani Lapreze², Alexander Bautista¹

¹Department of Anesthesiology and Perioperative Medicine, University of Louisville, USA

²Department of Health Sciences Library, University of Louisville, USA

ABSTRACT

The understanding of the history of medicinal cannabis is important to successfully understand its integration to modern health care. According to the World Health Organization (WHO), the most widely cultivated, trafficked, and abused illicit drug is cannabis. With the growing use of cannabis in pain management, its legalization in more states, and advances in research about its safety profile, we aim to illustrate the beginnings of cannabis as an adjunct to the treatment of pain and its future role as part of the armamentarium in pain medicine.

Keywords: Cannabis; Cancer pain; Chronic pain; Endocannabinoid

INTRODUCTION

About 147 million people, roughly 2.5% of the world's population, consume cannabis, compared with 0.2% consuming cocaine, and 0.2% consuming opiates [1,2]. According to the 2016 National Survey on Drug Use and Health (NSDUH), 10.6% of people aged 12 years or older used illicit drugs in the past month, and 7.5% had a substance use disorder in the past year [3].

Cannabis, also known as marijuana, is a psychoactive drug that has been used for recreational and medical purposes. It belongs to a genus of flowering plants in the Cannabaceae family. There are three species identified thus far: *Cannabis sativa*, *Cannabis indica*, and *Cannabis ruderalis*. Cannabis is also known as hemp, hashish, dagga, bhang, loco weed, and grass. The cannabis plant has several active compounds including cannabinoids and terpenes, which are the most active compounds found to have therapeutic potential in conditions such as metabolic disorders, neurodegenerative disorders, movement disorders, anorexia, nausea, and pain management after chemotherapy in cancer patients [4].

According to the Centers for Disease Control (CDC), the prevalence of chronic pain among U.S. adults in 2019 was 20.4%, with 7.4% experiencing high impact chronic pain. Chronic pain

and its multidimensional impact in patients are among the most common reasons adults seek medical care and are associated with decreased quality of life, opioid dependence, and poor mental health [5]. Treatment is oftentimes refractory to traditional medications and requires comprehensive medical and psychosocial approaches. The utility of cannabis as part of chronic pain management has been controversial with conflicting literature regarding its use.

ANCIENT HISTORY OF CANNABIS

The earliest record of man's use of cannabis comes from Taiwan, where archaeologists unearthed an ancient village site dating back over 10,000 years to the Stone Age [6]. Studies have also shown that cannabis had been present during the Holocene Epoch, about 11,700 years ago, in the territories of Central Asia. From an etymological standpoint, the radix "*kan*" means cane, a long hollow woody stem with joints, and suffix "*bis*" means perfumed and good scented [7]. Cannabis was one of the staple crops of ancient China, valued not only for food, fiber, oil, and paper, but also as medicine [8].

Dating back to as early as 1000 B.C., the use of cannabis has been documented in the Chinese *Pen-ts'ao Ching*, the world's oldest pharmacopeia. Cannabis is regarded as a first class herb

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Corresponding author Ong Sio LC, Department of Anesthesiology and Perioperative Medicine, University of Louisville, USA, E-mail: lady.ongsio@louisville.edu.

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and a preparation made of female cannabis flowers is believed to be rich of *yin* and useful in conditions associated to *yin* loss, such as rheumatic pain, constipation, malaria, beri-beri and gynecological disorders [7]. In traditional Ayurvedic medicine, cannabis has been used as a sleep medication as well as an excitant, appetite stimulant, digestive aid, analgesic, aphrodisiac, intoxicant and *elixir vitae* [8,9]. In Persia, cannabis was used as treatment for gout, edema, infectious wounds, and severe headaches [10].

Cannabis use during surgical procedures dates to the second century A. D. when the famous Chinese surgeon Huan T'o (110-207 CE) performed organ grafts, bowel resections, laparotomies, and thoracotomies, and were rendered painless using ma-yo, an oil made from cannabis resin, *Datura*, and wine [6,7].

CANNABIS IN THE 19TH CENTURY

The introduction of cannabis into Western Medicine was around 1839 when William O'Shaughnessy, an Irish physician who experimented with the use of medical cannabis, published his work. Following this, cannabis use as medicine was adopted throughout Europe and America in the mid-nineteenth and early twentieth centuries. It has been noted to have the therapeutic effects of opium and may be a substitute for narcotics [9].

In 1860, the Committee on Cannabis Indica of the Ohio State Medical Society reported success for the use of cannabis to treat many ailments including gonorrhoea, asthma, rheumatism, and intense stomach pain. Cannabis' use in medicine continued to grow, peaking in the late 18th and early 19th centuries, when it could be readily found in over the counter pharmaceuticals such as "Piso's Cure for Consumption" and the "one day cough cure" [10].

CANNABIS IN THE 20TH CENTURY

Following the rise of its use in the 1900s, cannabis use began to decline due to a variety of factors. Vaccines such as tetanus made cannabis' previous role in treating these diseases obsolete. The development of synthetic analgesics such as chloral hydrate, antipyrine, and aspirin filled some of the demand for analgesics, reducing the need for cannabis. The development of the hypodermic needle and its application to opiates could be considered the greatest factor to the decline of cannabis use [10].

CANNABIS IN THE 21ST CENTURY AND BEYOND

With the development and popularity of synthetic pharmaceuticals such as opioids, nonsteroidal anti-inflammatory agents, and barbiturates, the use of cannabis preparations began to decline in the 1930s, following federal restrictions and taxation [9]. The Marihuana Tax Act was passed in 1937, and cannabis preparations were removed from the United States Pharmacopeia in 1941 [8,10]. Over the next couple decades, cannabis use in medicine was essentially non-existent, and it was not until the 1970s that medical interests were revived [10].

ENDOCANNABINOID SYSTEM

In the late 1980s, a new radiolabeling technique led to the discovery of high affinity binding sites of cannabinoids or receptors in rat brain membranes. Now known as the endocannabinoid system, it is so named because it was first identified as activating the same receptors as cannabinoids [11]. The cannabinoid 1 (CB1) receptor binds tetrahydrocannabinol (THC) and is thought to produce the "high" of marijuana. There has been evidence suggesting that genetic variation in the endocannabinoid system is associated with substance use disorders [12]. CB1 is found at high levels in the neocortex, hippocampus, basal ganglia, cerebellum, and brainstem. Cannabinoid 2 (CB2), encoded by the gene CNR2, is found mainly on immune cells and in the central nervous system, mostly associated with inflammation, addiction, and synaptic plasticity [12].

In the United States, cannabis is classified as a schedule 1 drug under the Controlled Substances Act, indicating it has a high potential for abuse and no accepted medical use. However, at the state level, policies on the medicinal and recreational use of cannabis vary greatly, and in many states, conflict significantly with federal law. In 2014, Colorado legalized the recreational use of cannabis followed by Washington, California, and Alaska. At the present, the recreational use of cannabis is legal in 18 states, the District of Columbia, the Northern Mariana Islands, and Guam. The medical use of cannabis is legal in 36 states with doctor's recommendation. Twelve other states have laws limiting THC content. Although cannabis remains a schedule 1 drug, the Rohrabacher Farr Amendment prohibits federal prosecution of individuals complying with state medical cannabis laws [14]. Although the use of cannabis remains federally illegal, some of its derivative compounds have been approved by the Food and Drug Administration (FDA) for prescription use. Among these are THC, nabilone, and cannabidiol (CBD).

The use of cannabis for cancer pain management has been purported in several studies. A preliminary study conducted by Noyes et al [15], demonstrated an analgesic effect of the drug in patients experiencing cancer pain.

In a double blind study, placebo and 5, 10, 15, and 20 mg THC were administered to 10 patients, with pain relief significantly superior to placebo demonstrated at high dose levels (15 and 20 mg). At these levels, substantial sedation and mental clouding were reported [15]. In a double blind, randomized, placebo controlled study on the efficacy, safety, and tolerability of THC:CBD extract in patients with intractable cancer-related pain and patients with advanced cancer and inadequate analgesia, despite chronic opioid therapy by Johnson et al, demonstrated that THC:CBD extract was a useful adjunct treatment for relief of pain. Further research is needed to establish the efficacy of medical cannabis, either as an alternative to opiates or as an adjunctive therapy, and to identify the most appropriate methods of administration to achieve optimal therapeutic efficacy with minimal side effects [15].

The burgeoning body of literature for non-cancer related use of cannabis led to legalization of cannabis to allow permissive access. According to a recent review, approximately 15% of patients suffering from pain in Canada and Australia self-medicate with cannabis to treat their conditions [17]. Several studies from the United States, Israel, and the United Kingdom have

shown that 30%-87% of patients in different patient populations claim to use cannabis for medicinal purposes, and report pain or chronic pain relief as the reason for use [18].

There are several randomized controlled trials of smoked cannabis, all showing efficacy in chronic pain and spasticity [18], however, longer duration trials, as well as larger sample sizes, are lacking. The study Cannabis for the Management of Pain: Assessment of Safety Study (COMPASS) is a multicenter cohort study evaluating the long-term safety issues in patients using cannabis as part of their pain management regimen. This study showed that the most common adverse effects include headache, nasopharyngitis, nausea, somnolence, and dizziness, and the use of medical cannabis had a higher rate of developing non-serious respiratory adverse events. There was, however, no significant effect on medicinal cannabis with regards to hematological, biochemical, liver, renal and endocrine function. As a secondary outcome measure, pain intensity and physical dimension of quality of life over one year among cannabis users are significantly improved [19].

IMPLICATION OF MEDICINAL CANNABIS IN THE FUTURE

As the paradigm of managing chronic pain is changing, medical marijuana can be a viable adjunct or alternative to oral opioids for the treatment of cancer and non-cancer pain. Under federal law in the United States, marijuana remains to be illegal. Currently, there are 20 states that permit the sale of marijuana for medicinal use, and 2 FDA-approved medications that are available on the market, Marinol (dronabinol) and Cesamet (nabilone). There remains a large gap in education regarding its use and effects. Robust research and strong governance are needed to settle controversial issues regarding marijuana legalization.

CONCLUSION

The medical community should work on comprehensive educational programs, not to placate the stigma and misinformation regarding medical marijuana, but rather to assist in its safe and effective integration into medical practice, especially for chronic pain patients.

CONFLICT OF INTEREST

The authors have no conflict of interests to disclose and the manuscript has been read and approved by all authors.

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