

Medicinal cannabis in Thailand: 1-year experience after legalization

Nantthasorn Zinboonyahgoon^{a,*}, Sahaphume Srisuma^{b,c}, Wirun Limsawart^d, Andrew S.C. Rice^e, Chuthamane Suthisisang^f

1. Introduction

Cannabinoids, cannabis, and cannabis-based medicines (CBM) have been used for medical purposes for a variety of conditions, including chronic pain, neuropathic pain, and cancer pain.^{13,16–18,25,30,42} Nevertheless, the clinical application remains controversial due to the limited evidence of benefit, potential harm, and legal/regulatory issues around the world.^{11,14,24,26,33,41}

The public's interest in cannabis products has risen globally and has been accelerated by legalization for medicinal and recreational purposes in many countries.³² In Thailand, cannabis was categorized as a controlled substance since the early 1930s. Nevertheless, by the rapid promulgation of new regulations in February 2019, the country became the first and only nation in South East Asia that legalized medicinal cannabis.^{6,32,38}

Regardless of the controversy of the medical indications, the effort to put forward the “liberalization” of medicinal uses of cannabis has led to a complex situation that impacts the public and the healthcare system. This review describes the unique experience, 1-year after the legalization of medicinal cannabis in Thailand.

2. Medicinal cannabis: pharmacology and clinical efficacy

Cannabis contains more than 500 compounds, including 2 important cannabinoids; tetrahydrocannabinol (THC) and cannabidiol (CBD). *Cannabis sativa*, the species commonly grown in Thailand, has a quite high concentration of Δ^9 -tetrahydrocannabinol (Δ^9 -THC), which binds with high affinity to CB1 and CB2 receptors and provides analgesia, appetite stimulation, and antiemetic effects.^{2,19} However, by binding to CB1 receptors in

the central nervous system, Δ^9 -THC can induce drowsiness, decrease alertness, impair short-term memory and executive functions, alter judgment, impair psychomotor task performance, psychosis, and exacerbate psychotic episodes.^{5,33} Moreover, THC also induces cardiovascular adverse effects, including cardiac arrhythmia, hypertension, coronary spasm, orthostatic hypotension, and transient ischemic attack.²⁸ Unlike THC, CBD elicits its pharmacological effects (anxiolytic, analgesic, and anticonvulsive effects) without exerting significant activity on CB₁ or CB₂ receptors. Cannabidiol is not associated with the above-mentioned neurological and cardiovascular effects,^{2,19} abuse, or dependence.⁴⁴

The clinical data regarding the analgesic efficacy of cannabis products in chronic pain are still controversial due to limitation of high-quality evidence.^{1,11,15,36} The recent meta-analysis by the IASP Presidential Task Force on the use of cannabinoids, cannabis, and CBM for pain management showed no strong evidence to support the analgesic benefit of CBM.^{11,24} In addition, the defined type, optimum dose, and route of administration of CBM products for each condition are still unknown.³³ Finally, even if death from respiratory depression directly from medicinal cannabis has not been reported, the death from cardiovascular disease, death from car accidents, long-term neurological and psychological sequelae, and Cannabis use disorders have been concerning.^{9,33}

3. Medicinal cannabis in Thailand before legalization

In Thailand, the cannabis plant or *ganja* had been a part of traditional materia medica for centuries.⁸ As in the early 19th century, many countries began to ban the plant; it was first criminalized in Thailand in 1934 by the Marijuana Act.¹⁰ This law was later combined into the Narcotics Act (1974) in which “marijuana” is classified as a Category V narcotic in Section 7.²⁰ As a signatory of the 1961 Single Convention on Narcotic Drugs,²⁷ which includes the control of misuse of cannabis,⁴³ Thailand abides by the international standard.

The social movement for liberalization of cannabis use in Thailand was taken up by a political party and became a government policy after the 2018 general election. Rapidly implemented by the newly elected cabinet, the policy led to the promulgation of the Narcotic Act (No. 7, 2019) in February 2019 to legalize the use of cannabis for medicinal purposes.^{6,21} The act included in Section 22 a window of opportunity for people possessing marijuana for medicinal uses with a ninety-day amnesty, from February 27 to May 21, 2019.³⁹ Tens of thousands of people requested the amnesty through the Food and Drug Administration of Thailand (Thai FDA), which affords evidence that the illegal use of marijuana in Thailand was already widespread.⁴

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^a Department of Anesthesiology, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, ^b Ramathibodi Poison Center, Faculty of Medicine Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, ^c Division of Clinical Pharmacology and Toxicology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand, ^d Society and Health Institute, Health Technical Office, Office of the Permanent Secretary, Ministry of Public Health, Thailand, ^e Pain Research, Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, United Kingdom, ^f Department of Pharmacology, Faculty of Pharmacy, Mahidol University, Bangkok, Thailand

*Corresponding author. Address: Siriraj Pain Management Center, 1st Floor, 10th BLDG, Siriraj Hospital, Siriraj, Bangkoknoi, Bangkok, Thailand 10700. Tel: +6624197842. E-mail address: nantthasorn@gmail.com (N. Zinboonyahgoon).

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In addition, there was reported uses of marijuana for indications other than currently recommended,^{3,35} such as headache, insomnia, cancer, cardiovascular disease, and diabetes mellitus (this information was presented by K Tontisirin, a Thai FDA officer, in a conference on medical cannabis and cannabinoids at Siriraj Hospital, Bangkok, Thailand on January 16, 2020, attended by N.Z.). Moreover, there was evidence that illegal cannabis-based products could be harmful because seized illegal marijuana was found to be contaminated with heavy metals, pesticides, and fungi.⁷

4. The situations after the legalization

4.1. Legalized preparations and guided uses

To ensure appropriate implementation of the 2019 changing in legislation and to mitigate against potential adverse outcomes, the Thai government established a multilevel system of safeguards, which included implementation of standards around manufacture and prescribing, and a system for monitoring and evaluation. To ensure product safety, the Thai FDA and the Ministry of Public Health (MOPH) worked with many stakeholders to develop a safe “supply chain” of CBM, from growing the crop to the utilization by patients (this information was presented by the director of MOPH’s Medical Cannabis Institute, in a meeting at the MOPH on February 7, 2020, attended by W.L.).

There are 3 categories of cannabis-based products legalized for medicinal purposes in Thailand. The first, launched in June 2019, are medicinal-grade CBMs produced by 2 official producers (Government Pharmaceutical Organization and Chao-phraya Abhaibhubejhr Hospital, a public hospital that is a center of integration between western medicine and Thai traditional medicine [TTM]) in 3 formulae (1) High THC that contains 13 mg/mL THC, (2) High CBD that contains 100 mg/mL CBD, and (3) the THC:CBD 1:1 mixture that contains 27 mg/mL THC and 25 mg/mL CBD). The second category relates to TTM products that contain cannabis as an active ingredient. There were 16 formulae selected by the Department of Thai Traditional and Alternative Medicine (DTAM) based on the TTM manuals, proposed for a variety of conditions including insomnia, stroke, muscle spasm, poor appetite, and chronic pain⁸ (Table 1). Although the composition of cannabis in TTM formulas was claimed to be minimal, there was apparent batch-to-batch variability in Δ^9 THC content, implying that stricter oversight of manufacturing quality control was required. Finally, the third group is folk medicine products prepared by registered folk healers. In the first year after legalization of CBM, however, this third group still awaited development (this information is from the observation of W.L., who worked in the Ministry of Public Health’s research project to evaluate the implementation of medical cannabis policy in 2020). Nevertheless, people still had continued to access cannabis-based products from folk healers and underground markets^{12,40} as they were widely used before the legalization^{22,40} and limited availability of the authorized products and prescribers.

In terms of prescription safety, the Department of Medical Service (DMS) launched the first version of its guidance for medicinal cannabis use³⁴ on April 30, 2019 (there are later versions of the guideline, the latest one was published in January 2020 [as of February 2020]). The DMS later revised the document in response to emerging concerns, including those healthcare professional communities (the latest version is shown in Table 1).³⁵ The Thai Association for the Study of Pain (TASP)³⁷ published a statement on medicinal cannabis use, in response to that indicated by DMS in November 2019³⁷ (Table 1). Both

organizations were in broad agreement for the indication for cancer pain, neuropathic pain, and pain from multiple sclerosis, but not for headache.

The new regulations permit western medicine professionals to dispense the approved medicinal-grade CBMs, and registered traditional medicine practitioners to administer the TTM formulae. There was a rapid implementation strategy, that by February 2020, 11,250 providers were trained and certified to ministry of health standards to dispense medicinal cannabis (Table 1). Of these, 5920 (52.6%) were western medicine professionals (medical doctors, pharmacists, and dentists) and 5330 (47.4%) were traditional medicine practitioners.²³ Consultations visit and prescriptions for medicinal cannabis, monitored by the MOPH, have been increasing. The data from June 2019 to February 2020 revealed 10,230 consultations and 6452 prescriptions for cannabis-based medicinal products²²

As part of their strategy, the MOPH and Thai FDA set up a reporting system for monitoring and evaluation of the services and recording of adverse events.^{12,22} Records must be completed at the first and every subsequent visit to the clinic and sent weekly to the MOPH.

4.2. Patients’ perspectives

A survey of 118 patients at the Pain Clinic at Siriraj Hospital in Bangkok was conducted in January 2020 (the survey was conducted by providing patients, who visited the Siriraj Pain Clinic in January 2020, with questionnaires. Each participant responded anonymously. This survey is a part of the study conducted by N.Z. and ethically approved by Siriraj Hospital’s IRB [Code of Ethics No: SI172/2020]). The anonymous responses revealed that approximately 20% of patients report use of cannabis products for medicinal purposes (5% are still using, 7.5% used once and stopped, 7.5% have applied for a period, but already stopped). The reasons stated for continuing use includes for cancer pain, appetite stimulation, sleep aid, and treatment of cancer. Thirty percent of the patients obtain the legalized CBMs, two-thirds of which were medicinal-grade products prescribed by western medicine professional and one-third were TTM formulae prescribed by TTM practitioners. Seventy percent of the patients possessed unapproved cannabis-based products, obtained through online sources or from neighbors and friends. The price of unapproved products is estimated to be about 0.6 to 10 times that of medicinal-grade products.

Despite the high incidence of use, there is still a lack of understanding of medicinal cannabis among patients. Twenty percent of the patients in this survey believe cannabis can cure cancer, whereas 47% and 22% of the sample believe cannabis can alleviate cancer pain and chemotherapy-induced nausea and vomiting, respectively. Only 28% of the patients believe they have enough understanding to use cannabis-based products. This finding is supported by another survey of 106 doctors who attended a medicinal cannabis training (the survey was done by providing the doctors, who attended the medicinal cannabis conference at Siriraj Hospital on January 16, 2020, with questionnaire. Each participant responded. This survey is a part of the study conducted by N.Z. and ethically approved by Siriraj Hospital’s IRB [Code of Ethics No: SI172/2020]). Only 11% of the doctors felt the patients have adequate comprehension of the safe medicinal use of cannabis-based products. A survey on public awareness of medicinal cannabis in Thailand was

Table 1
Comparison of the guidelines from the Thai Ministry of Public Health (The Department of Medical Service [DMS]'s guidance for the use of cannabinoid products and the Department of Thai Traditional and Alternative Medicine [DTAM]'s guidance for the use of Thai Traditional Medicine [TTM] formulas) and Thai Association for the Study of Pain (TASP).

Ministry of public Health's guidelines	TASP's statement on medical cannabis use ³⁷
<p>DMS's guidance for the use of cannabinoids product³⁵</p> <p>Medical cannabis benefits for six conditions include: neuropathic pain, chemotherapy-induced nausea and vomiting, intractable epilepsy, spasticity from multiple sclerosis, AIDS-related cachexia, and palliative care conditions</p> <p>May be beneficial for conditions including generalized anxiety disorder, Parkinson disease, Alzheimer disease, and demyelinating disease</p> <p>Might be beneficial for cancer treatment, but more information and research are needed</p> <p>DTAM's guidance for the use of TTM formulas³</p> <p>The indications for the use are:</p> <ul style="list-style-type: none"> Insomnia Stroke Muscle spasm Poor appetite Chronic pain Others (as indicated for each particular formula) 	<p>Cancer pain: There is low to moderate quality of evidence showing that medical cannabis products (MCs) are better than placebos. However, MCs are not better than opioids, and side effects increase with higher doses.</p> <p>Palliative care patients: There is low-quality evidence showing symptom improvement for increasing appetite and weight gain, but no difference for sleep, depression, or quality of life. Side effects such as dizziness, sedation, and confusion, which may impact patient quality of life, should be a concern.</p> <p>Neuropathic pain: There is not enough evidence showing MCs are better than the current standard treatment. MCs have more significant side effects. TASP does not recommend MCs use over the standard treatment.</p> <p>Headache: There is not enough evidence showing MCs alleviate headaches. TASP does not recommend MCs for headaches.</p> <p>Pain from multiple sclerosis (MS): There is evidence showing MCs improve spasticity and pain from MS; however, TASP does not recommend MCs as the first option. MCs may be considered if standard treatment fails or is associated with intolerable side effects. Prudent evaluation and close monitoring are needed.</p> <p>Musculoskeletal (MSK) pain: MSK pain usually responds to the standard guidelines for treatment. The fibromyalgia, however, does not respond well to the treatment. The evidence of benefit and risk of MCs for fibromyalgia is still unclear; further information from future studies is needed. In addition, the interaction between MCs and other analgesics, such as tramadol, nonsteroidal anti-inflammatory drugs, and selective serotonin reuptake inhibitors, should be a concern.</p>

conducted by the National Institute of Development Administration. Out of 1257 people, 17.5% were interested in information about the cannabis situation, 35% were not interested at all, and the rest showed some degree of interest.²⁹

4.3. Reports of untoward effects

Although DMS began the training for medical professionals and launched the first guidance for medicinal cannabis use on April 30, 2019, the Government Pharmaceutical Organization distributed standard cannabis oil products later in June 2019.^{22,34} Therefore, the utilization of medicinal cannabis before the training can be regarded as a lack of medical supervision. Similarly, the cannabis oil preparations used before June 2019 are illegal products, obtained from underground market.

Ramathibodi Poison Center, which provides a national 24-hour toxicology consultation service, reported a total of 302 cases with adverse effects from cannabis-based product exposures between January 2018 and May 2019.³¹ The incidence of reported adverse effects of cannabis oil increased in the 2 to 3 months before the change in the law and continues to increase thereafter (Fig. 1). The Center's data suggest that the most frequently used cannabis-based products are oil (79.5%) and smoking (12.6%). Frequently reported effects are tachycardia (44.0%), palpitations (36.4%), high blood pressure (36.4%), dizziness (35.1%), nausea (25.2%), vomiting (24.8%), agitation (16.2%), dry mouth (15.6%), and central nervous system depression (14.2%). Four cases of seizures (1.3%) and 4 cases of coma (1.3%) were reported. Twenty-one cases (8.8%) underwent brain imaging (CT scan or MRI brain) due to alteration of consciousness. Four cases (1.3%) underwent tracheal intubation for ventilatory support, but no mortality has been reported. Reported indications for the use of cannabis oil (240 cases) were insomnia (18.8%), trying without any illness (13.3%), pain control (11.7%), cancer treatment

(8.3%), cancer prevention (5.0%), food supplement (5.0%), and treatment of diabetes mellitus (5.0%).

By contrast, the subsequent data of supervised prescriptions, monitored by the Thai FDA¹² after June 2019 to December 2019 (the report was concluded on December 5, 2019, we believed that the data collection started from June, when the supervised prescription was started) show the indications for CBMs prescribed by western medicine professional complied with the DMS's guidance (total 241 patients, top 5 indications include: palliative care [33%], intractable neuropathic pain [13.7%], cancer pain [12.5%], Parkinson disease [12.5%], and intractable epilepsy [3.7%]). Sixty percent of the patients in these group used medicinal-grade product, whereas 40% still used illegal product. Moreover, the reports on adverse effects of cannabis-based products are generally low (5%) and less severe (dry mouth and dry throat [4.2%], and abnormal renal function [0.8%]).¹² Similarly, the indications for TTM formulae abide by the DTAM's guideline (total 165 patients: insomnia [87%], stroke with motor weakness [6.7%], and musculoskeletal pain [2.4%]). Almost all patients in this group used a TTM formula approved by the DTAM.

While the Thai FDA monitored the use and adverse effects of patients receiving supervised prescriptions of CBMs, the Ramathibodi Poison Center recorded the adverse effects reported in patients with unsupervised uses of illegal cannabis products. The adverse effects reported by the FDA were of lower severity than those reported by the Poison Center. Although these data sets are obtained from different sources and periods, they illustrated potential benefit of regulated and supervised use of cannabis for medicinal purposes.

5. Conclusion

Although medicinal cannabis hitherto has limited evidence of effectiveness, it was introduced in Thailand. Monitoring has suggested that its use is associated with adverse effects,

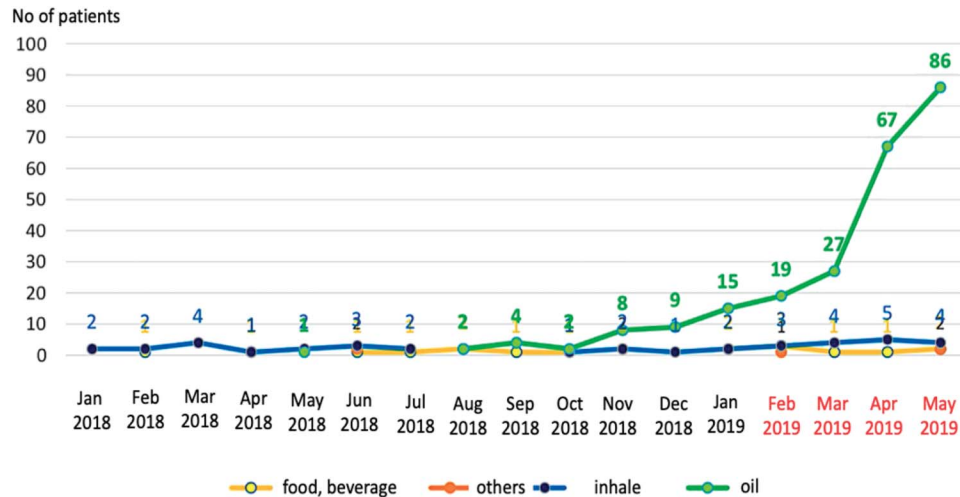


Figure 1. Number of patients reporting adverse effects from cannabis product exposures notified to Ramathibodi Poison Center, Thailand, between January 2018 and May 2019 (a period of 1 year before [in black letters] to 4 months after legalization [in red letters]).³¹

especially in the unregulated and unsupervised use arenas. The public understanding and awareness in Thailand about the benefits and harms of medicinal cannabis were not well developed and the rapid legalization was initially associated with significant reporting of adverse events. However, the subsequent supervision and prescribing by certified health providers and the availability of a more standardized product supply may have been associated with a reduction in the use of unregulated products and the perception of a reduction of the adverse events. Further experience is required before a definitive view can be given on this. The Thai experience may be helpful in informing cannabis-associated health care in low- and middle-income countries. It is clear that well-planned strategies, including education for medical professionals and patients, informing public awareness and an adequate quality-controlled supply of standard cannabis-based medicinal products are needed before the implementation. Because this article was only able to collect the opportunistic data during a period of significant and rapid change, long-term monitoring regarding efficacy, safety, and socioeconomic impacts of medicinal cannabis in Thailand are still required.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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