Thai Journal of Obstetrics and Gynaecology
October 2018, Vol. 26, No. 4, pp. 206-216

SPECIAL ARTICLE

Cannabis (Gan-ja): Relevant Issues in Obstetrics and Gynecology

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ABSTRACT

Medical benefits of cannabis have become widely accepted. In Obstetrics and Gynecology, it was reported to be useful to alleviate nausea and vomiting from morning sickness in pregnant women and in gynecologic cancer patients who received chemotherapy. It has also been used as a pain killer during labor and menstruation. Some also claimed that the cannabis may also prolong life of cancer patients or even cure cancer. Owing to the illegalization of the cannabis in many countries for a long time, there has been no evidence-based data from clinical study to support the use of cannabis for those aforementioned conditions except for chemotherapy induced nausea/vomiting. Systematics reviews confirmed that cannabis was significantly more effective than placebo and at least as effective as various conventional antiemetics. However, due to the availability of many potent new standard antiemetics (5-HT3 receptor antagonists, and neurokinin-1-receptor-antagonists) without psychotropic effects, cannabis is not recommended as a first-line antiemetic agent. The exception is when the new standard antiemetics cannot adequately control nausea and vomiting from chemotherapy. The cannabis is contraindicated in pregnant women or lactating mother because of the possibility of adverse fetal and neonatal outcomes. Once cannabis is legalized for medical use in more countries, its efficacy in those aforementioned conditions can be tested and confirmed in randomized controlled trials.

Keywords: cannabis, marijuana, obstetrics, gynecology, pregnancy, cancer.

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Why should we know about cannabis?

Although cannabis is considered an illegal drug in Thailand due to its possible harmful effects on health, its medical benefits are widely accepted. At present, medical cannabis is legal in many countries and possibly in Thailand in 2019.

Cannabis, generally known as “marijuana” or local name “gan-ja”, has long been used for recreational and medical purposes. The Ancient Greeks used cannabis to dress wounds. Dry leaves of cannabis were used to treat nosebleed and its seeds were used to expel tapeworms[1]. Queen Victoria of Britain was also

claimed to have been prescribed cannabis for her menstrual pain and during childbirth[2].

Cannabis is one common ingredient in many Thai traditional medicine recipes as written in King Narai Pharmaceutical textbook and on the stone at Wat Phrachetupon Wimonmangkararam (Wat Pho). In the past, Thailand was famous for having the best strains of cannabis and as one of the top exporters of cannabis in the world[3].

In Thailand, cannabis has been grouped in category 5 narcotics under Narcotics act 1979. The production, sale or possession of any form of cannabis is illegal. The punishment varies from fine to imprisonment. This act results from the international drug control treaty as a part of the World War I peace treaties in 1912, which led to the national drugs control acts in most countries[4].

Since the early 20th century, advance in medical knowledge about cannabis makes the legal status of cannabis change rapidly. As of now, many countries have legalized the medical use of cannabis (such as Australia, Canada, Chile, Colombia, Germany, Greece, Israel, Italy, Netherlands, Peru, Poland, etc.). Moreover, some countries (Uruguay, Canada, Spain, etc.) have also legalized cannabis for recreational use.

In the United States of America, although whole or crude marijuana is not approved by the US Food and Drug Administration (FDA) for any medical use, pharmaceutical forms of cannabis product are approved by the FDA to treat some conditions[5]. Besides, medical marijuana is legal under state laws in around 30 states all over the country, such as California, New York, Illinois, Maryland, Massachusetts, Pennsylvania, Washington DC, etc. On the other hand, recreational marijuana is legal in around 10 states including California, Massachusetts, Washington DC, etc[6].

In Thailand, the narcotic law has been under revision process. Once this new regulation is approved (may be early next year; 2019), cannabis will be allowed for medical use in humans. As of now, Thailand's Governmental Pharmaceutical Organization (GPO) is contemplating researches to develop medicines from cannabis. A project to develop a special greenhouse to grow the premium-grade cannabis for researches is underway. They are waiting for the legalization to do the research of medical cannabis in humans.

What are cannabis and cannabinoid?

Cannabis is a kind of plant that has 2 major active components: tetrahydrocannabinol (THC) and cannabidiol (CBD). THC has psychoactive effect while CBD has anti-inflammatory, antioxidant, and neuroprotective effect. Cannabinoid is a group of chemical compounds that either are derived from the cannabis plant (phytocannabinoids), are synthetic analogues (synthetic cannabinoids), or occur endogenously (endocannabinoids). Synthetic cannabinoids that are currently in clinical use include Dronabinol (oral synthetic THC) and Nabilone (oral synthetic THC).

Cannabis is a flowering plant in the family Cannabaceae. It is originated in Central Asia, but now is cultivated worldwide, including Southern Asia, India, Middle East, Africa, Europe, Canada and the Americas. The main species are Cannabis sativa, followed by Cannabis indica, and Cannabis ruderalis.

The term 'cannabis' is a scientific term or generic term that encompasses the compound as used in its herbal form, resin form, and in various derived or synthesized cannabinoid products[7]. Cannabis has many names such as marijuana (or marihuana), ganja (ganga), herb, bud, grass, pot, dope, Mary Jane, hooch, weed, hash, joints, brew, reefers, cones, smoke, mull, buddha, hydro, yarndi, Purple Haze, Northern Lights, charas, skunk, resin, heads and green[8-10]. Marijuana is usually referred to dried flowers and leaves of the cannabis plants[8], while other names are the slang names which in part reflect variations in genetics, growing conditions, processing, and constituent cannabinoids and other chemical compounds in different strains of the plants[10].

Endocannabinoids are fatty-acid cannabinoids produced naturally in the body[11]. The endocannabinoid system (ECS) is a physiologic system which regulates

various basic functions in human body, such as appetite, metabolism, sleep, mood, immune function, inflammation, neuronal development and protection, digestion, reproduction, memory, and learning, etc[12]. Cannabinoids interact mostly at cannabinoid receptors, but might have cross activity with opioid receptors[13]. Currently, two cannabinoid receptor subtypes have been identified: cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2)[11]. CB1 functions to modulate neurotransmitter activity in the brain, which can influence nausea, muscle spasticity, seizures, and psychoactivity[11]. CB2 receptors are expressed mainly outside the brain such as in cells and organs of the immune system and their regulatory functions[11].

Phytocannabinoids are cannabinoids that occur naturally in the cannabis plant. Two major active cannabinoids are Δ9 - tetrahydrocannabinol (THC) and cannabidiol (CBD)[10]. The THC can acutely impair learning and produce euphoria (high), schizophrenia-like symptoms, and anxiety[14], whereas CBD can enhance learning and has anti-inflammatory, antioxidant, neuroprotective, antipsychotic and anti-anxiety effects[15-17]. When taken together, the CBD may counteract and decrease adverse effects of THC[18]. Nabiximols and Epidiolex are the pharmaceutical products from cannabis plants that are currently, in clinical use.

Nabiximols (Sativex), an oromucosal spray containing THC and CBD in a 1:1 ratio, is an extract of cannabis used to treat cancer pain as well as muscle spasms and pain from multiple sclerosis[5,19].

Cannabidiol (Epidiolex), an oral solution CBD made from cannabis, is licensed for the treatment of two forms of severe childhood epilepsy, Dravet syndrome and Lennox-Gastaut syndrome[5].

Synthetic cannabinoids are cannabinoids that are synthesized in a laboratory. Synthetic cannabinoids that are currently in clinical use included Dronabinol and Nabilone[5,19].

Dronabinol (Marinol), an oral capsule containing synthetic THC, is licensed for treatment of anorexia as well as weight loss in patients with AIDS and chemotherapy induced nausea and vomiting[5,19].

Nabilone (Cesamet), an oral capsule containing synthetic cannabinoid derivative mimicking THC, is approved for chemotherapy-induced nausea and vomiting that was not responded to conventional antiemetics[5,19].

What are the preparations and route of cannabis administration?

There are many forms of cannabis such as herbal form, resin form, tincture, oil and synthesized cannabinoid products. Herbal form varies greatly based on strain, growing conditions, and processing. Patients who use this form may have to titrate their cannabis intake. Cannabis can be used by smoking, vaporizing, oral intake, oral spray, oral drop, suppositories or topically use.

Cannabis in the raw plant is in an acid form - tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA) which do not interact with the human body. THCA and CBDA must be heated to decarboxylate the acid to THC and CBD to make them available for use in the human body[11].

There are many forms of cannabis such as herbal form, resin form, tincture, oil and synthesized cannabinoid products. The components of chemical compounds in cannabis plants vary greatly based on strain, growing conditions, and processing[10,11]. Besides, individual responses to cannabis may be different and unpredictable[20]. Each patient or consumer may prefer one form over another. Some patients may prefer synthetic cannabinoids because of their consistency whereas some may prefer cannabis plants. This may be because cannabis plant is a blend of many different natural cannabinoids and terpenes. Each compound has its own individual effects, but it may be more effective when work together (entourage effect). Hence, the patients who use natural cannabis plant for medical purpose may have to titrate their cannabis intake.

Cannabis can be consumed by several means: smoking, vaporizing, oral intake, oral spray or drop, suppositories or topically use[21,22]. The most common

of which are rolling it into cigarettes or putting it in a pipe or in a cigar for smoking. It can be mixed with food (such as brownies, cakes, butter, candy, ice cream, chewing gum, etc.), or made into tea, juice, smoothies, etc[21-23]. It can also be administered sublingually as spray or tincture drop[21,22]. It can be used as vaginal or rectal suppositories, which mostly made from cannabis-infused coconut oil or cocoa butter-base[11]. It can also be used as topical oil emollient on the skin. Of these, smoking provides most rapid onset of effects within minutes and lasts for 2-4 hours while the onset of oral intake is about 60 to 180 minutes and lasts for 6-8 hours[21].

Why should obstetricians and gynecologists know about cannabis?

Medical cannabis may be useful in both obstetrical and gynecological practices. It may be used as an antiemetic agent in gynecologic cancer patients receiving chemotherapy and in pregnant women for morning sickness, as pain killer for menstrual cramp and labor pain. However, one important caveat of cannabis use in pregnant women is the adverse effect on fetus.

The use of cannabis in obstetrics and gynecology has been recorded as early as 2737 BCE. It has been used for treatment of menstrual cramp, labor pain and even induction of labor. As of now, medical evidences have suggested the benefit of cannabis in relieving various symptoms of nausea/vomiting, chronic pain, spasticity in multiple sclerosis (MS), depression, anxiety disorder, sleep disorder, etc. However; according to a recent systematic review and meta-analysis by Whiting et al[9], there was only moderate-quality evidence to support the use of cannabinoids for the treatment of chronic pain and spasticity, and low-quality evidence suggesting the improvements in chemotherapy induced nausea and vomiting, weight gain in HIV infection and sleep disorders. At present, a few indications have been widely accepted, which include pediatric treatment-resistant epilepsy (especially Dravet syndrome and Lennox-Gastaut syndrome), pain syndromes associated with multiple sclerosis and chemotherapy-induced nausea[24].

Since medical evidences support the use of cannabis for pain and nausea, questions arise for its efficacy for nausea and vomiting from morning sickness syndrome and for labor pain. One precaution is when the cannabis is available as an over-counter drug or even with physician prescription; there may be more pregnant patients use them for leisure or recreation. Therefore obstetricians should know whether cannabis is safe for the fetus in utero. Gynecologists also should know whether cannabis could help women who suffer from menstrual pain or dysmenorrhea. Gynecologic oncologist should know whether cannabis products are better than standard antiemetics for gynecologic cancer patients who receive chemotherapy, and whether cannabis should cure cancer.

Is cannabis useful in nausea/vomiting of pregnancy (morning sickness to hyperemesis gravidarum)?

There has been no evidence-based data of cannabis as an antiemesis in nausea/vomiting of pregnancy. To date, only some case reports and survey studies claim its effect in nausea/vomiting of pregnancy and even hyperemesis gravidarum.

Historically, cannabis has been utilized as a treatment for morning sickness[25]. There were few case reports and survey studies that reported the use of cannabis in treatment of nausea/vomiting of pregnancy and even hyperemesis gravidarum. A case study by Curry[26] demonstrated that nausea and vomiting of pregnancy may be relieved by smoking cannabis in very small amount (1-2 puffs, 1-2 times a day). In 2009, Westfall et al[27], reported his survey of 79 female users of medicinal cannabis who had experienced pregnancy. Of those 40 who used cannabis to treat nausea and/or vomiting of pregnancy, 37 (over 92%) rated cannabis as extremely effective or effective.

To date, there has been no study actually assessed its efficacy for this indication. Prospective studies or good clinical trials are needed to confirm its

effectiveness and safety in early pregnancy.

What is cannabinoid hyperemesis syndrome in pregnancy?

Though cannabis has antiemetic effect, chronic cannabis user may develop cannabinoid hyperemesis syndrome (CHS) during pregnancy. This syndrome is characterized by cyclic intractable nausea/vomiting and abnormal bathing behaviors. CHS is usually resistant to standard antiemetics and subsides only with cannabis abstinence.

Cannabinoid hyperemesis syndrome (CHS), was first described in chronic cannabis user by Allen et al[28] in 2004. It is characterized by cyclic intractable nausea/vomiting with abdominal pain, and abnormal bathing behaviors (for example showering in hot water for hours each time and multiple times per day). CHS is often resistant to standard antiemetics and subsides only with cannabis abstinence. Hot showers and baths were also reported to be effective in relieving symptoms[29-31].

Obstetricians may be familiar with antiemetic properties of cannabis, but may not be aware of its paradoxical reaction. Hence, in pregnant women who have severe nausea and vomiting which are not relieved by antiemetics, obstetricians should be aware of CHS by inquiring about cannabis use and bathing behaviors.

Should cannabis be used to support pregnant women who have labor pain?

No clinical study has supported the use of cannabis for labor pain. However, in the lay press, many pregnant women had reported their positive experiences from cannabis during their final stage of pregnancy.

Cannabis has been reported to be associated with the improvement of chronic pain in many studies, though with only moderate-quality evidence[19]. Considering labor pain, no evidence in the medical literature supports its uses. However, in the lay press, pregnant women had reported their positive experiences with CBD and THC during the final stage of pregnancy[32,33]. They believed that CBD in conjunction with THC can decrease labor pain and speed up contractions[33]. Some also questioned whether cannabis may replace oxytocin and epidural block or other conventional labor pain medications[33]. The advantage of using cannabis instead of oxytocin is that cannabis has no hyper-stimulation effect[33].

Methods of self-cannabis treatment in final stage of pregnancy include bath bombs, cervical ointments, tinctures, distillate pills, etc.[33].

Is there any adverse outcome in pregnant women who used cannabis?

The results from previous reports are still conflicting. Nevertheless, one meta-analytic study demonstrated a higher rate of low birth weight, neonatal intensive care unit admission and maternal anemia. Until more data are available to support its safety, women should be advised not to use cannabis during pregnancy or while lactating.

With the legalization for medical use of cannabis, it is possible that cannabis use in pregnant women may increase. In animal, there is evidence that THC can cross the placenta although at low level[34]. Hence, obstetricians should know whether cannabis use in pregnancy will cause any adverse fetal and also maternal outcomes.

In human studies, the results of neonatal outcomes from cannabis use in pregnancy are conflicting. Many studies have shown associations between cannabis use and preterm labor[35,36], low birth weight[37,38], neonatal intensive care unit admissions[35], and stillbirth[39], while others have found no impact on birth outcomes[40-42]. However, the meta-analytic study by Gunn et al[43] which included 24 studies, reported that infants exposed to cannabis in utero had higher rate of low birth weight (OR=1.77: 95% CI 1.04 to 3.01; mean difference of birth weight = 109.42 g: 38.72 to 180.12) and neonatal intensive care

unit admission (OR = 2.02: 1.27 to 3.21) compared with infants of the non-users. This meta-analysis also demonstrated that women who used cannabis during pregnancy had an increase rate of anemia (OR 1.36: 95% CI 1.10 to 1.69).

Can cannabis help with dysmenorrhea?

There has been no evidence from clinical study to support the use of cannabis for menstrual pain. However, in the lay press, various forms of cannabis were claimed to reduce or even eliminate the menstrual pain.

People use cannabis for menstrual pain relief for a long time. Queen Victoria was also said to use cannabis for this purpose. However, from the literature review, there is only one clinical study reported about the use of cannabis for menstrual pain[44]. In that study (reported in 1847), the patient received the tincture of the Cannabis indica with unfavorable results[44].

Though there is no formal clinical study support the use of cannabis for menstrual pain or dysmenorrhea; pharmacologically, cannabis should have benefits for menstrual pain because CBD may provide pain relieve while both CBD and THC have muscle relaxant effects that can reduce the spasms associated with menstrual cramps. Moreover, THC will provide anxiolytic effect and euphoria mood[45]. At present, there are lots of cannabis products in many forms such as bath salts, body balm, vaginal cream, vagina supossitory, tincture, eatable cocao, butter, etc[46,47]. Russel[47] reported in 2016 that she had tried 7 cannabis products and found that all helped her severe menstrual cramp, but her favorites were vaginal suppository and the CBD tincture. For vaginal suppository, her whole painful pelvis was suddenly unlocked after insertion around 10-15 minutes. For CBD tincture, which has a 15:1 ratio of CBD to THC, her pain was eliminated around five minutes after she had a couple drops under her tongue.

In some states of America, lawmakers are pushing to add menstrual pain to the list of conditions that justify the medical use of cannabis[46].

Should cannabis be used as antiemetics in gynecologic cancer patients who received chemotherapy?

Both herbal cannabis and synthetic cannabinoids are not recommended as a first-line antiemetic because new standard antiemetics (5-HT3 receptor antagonists, and neurokinin-1-receptor-antagonists) are potent and without any psychotropic effects. However, cannabis may be useful in those cancer patients whose nausea and vomiting cannot be controlled by the new standard antiemetics.

Herbal cannabis has been claimed to have benefit in chemotherapy induced nausea and vomiting (CINV). However, most of the published studies are only observational or uncontrolled study without any randomized controlled trial. Besides, there is still lack of standardization regarding dosing and potency in their uses[48]. Hence, herbal cannabis, at present is not recommended for CINV[49].

On the other hand, synthetic cannabinoids [nabilone (Cesamet- a synthetic analog of THC) and dronabinol (Marinol-synthetic THC)], or whole plant extract (e.g. nabiximols) were tested in lots of controlled clinical trials.

In early 1980s, nabilone was licensed for CINV while dronabinol was also licensed as antiemesis in 1985[50]. Considerable systematics reviews confirmed that these synthetic THC and whole plant extract (e.g. nabiximols) were significantly more effective than placebo and at least as effective as various conventional antiemetics such as prochlorperazine, metoclopramide, chlorpromazine, thiethylperazine, haloperidol, domperidone, or alizapride[23, 51]. However, most evidences had only moderate quality[49]. From subgroup analysis, patients receiving cannabinoids had better control in those who received moderate emetogenic chemotherapy regimens but had similar efficacy in those who received a low or highly emetogenic chemotherapy regimen[23]. Despite this result, one drawback was the significant more adverse events observed among those who received

cannabinoids[23]. These adverse events included sedation, drowsiness, euphoria, dizziness, dysphoria, depression, hallucinations, paranoia, and hypotension[23].

Since most of these studies were conducted before the emergence of 5-HT3 receptor antagonists and neurokinin-1-receptor-antagonists (NK-1 antagonists), which are the standard anti-emetic agents at present[52]. As of now, there has been no published randomized controlled trial comparing cannabinoids with NK-1 antagonists. Only one published randomized controlled trial, that compared dronabinol alone and in combination with ondansetron versus ondansetron alone in patients receiving moderately to highly emetogenic chemotherapy, was available[53]. This study concluded that dronabinol or ondansetron was similarly effective for the treatment of CINV. Combination therapy with dronabinol and ondansetron was not more effective than either agent alone.

For the reason that 5-HT3 receptor antagonists (such as ondansetron, granisetron, dolasetron, etc.) are potent and do not have psychotropic effects[52], synthetic cannabinoids are not recommended as first-line antiemetics. Nonetheless, they may be useful in some cancer patients whose nausea and vomiting can not be controlled by 5-HT3 receptor antagonists or by NK-1 antagonists.

Can cannabis cure cancer?

Lots of evidences from preclinical studies showed that cannabinoids had antitumor effect. Clinically, most case reports were only in lay press. To date, there is not enough data to confirm their effectiveness as therapeutic agents for cancer.

Cannabinoids are well-known of their palliative effects on some cancer-associated symptoms such as cancer-related pain, chemotherapy-induced nausea and vomiting, and anorexia. Moreover; in preclinical studies, lots of evidences show that these molecules may have antitumor effects. The anticancer mechanisms of cannabinoids included antiproliferative, anti-metastatic, antiangiogenic, and proapoptotic effects[54,55]. Adding, cannabis extracts with a variety of chemotherapy in vitro and in animals models demonstrated synergism in reducing tumor cells[54]. Despite these evidences, some studies reported discordant results that antitumor effect of cannabinoids was demonstrated only with higher drug doses whereas their lower doses would stimulate cancer proliferation[54].

Besides these preclinical studies, most of the clinical reports which claimed that cannabis can treat human cancer were in the lay press, especially the internet and mostly with anonymous authored. Here are a few stories of those who believed that they had advantage from cannabis as cancer treatment.

Sharon Kelly, a 54- year-old Australian woman had posted on youtube that she had successfully treated her stage IV lung cancer with lymph node metastasis by using cannabis oil. She had cancer free after only 7 months on cannabis.

Rick Simpson had successfully treated his basal cell carcinoma by topically applying concentrated cannabis oil which he named it “Rick Simpson oil”[56]. He had written a book of 129 pages entitled “Phoenix Tears Rick Simpson Oil Nature’s Answer For Cancer”[56]. In this book he described how to make the oil, and conditions that could be improved or cured by using his oil. For skin cancer, he suggested the oil application to the cancer area and cover it with a bandage, then reapply fresh oil and a new bandage every three or four days and the cancer should soon disappear (mostly within 3 weeks)[56].

In Thailand, Buntoon Niyamapa, had made cannabis oil according to Simpson technique and reported that it helped his sister to remain cancer-free after treatment of uterine cancer by surgery and radiotherapy. He was then well known for his oil, lots of cancer patients came to see him for cannabis oil. He claimed that his oil can prolong life in cancer patients and can cure in some cases. Although some patients were not cured, they were less suffering from their cancer related symptoms[57].

Since most of the case reports were in the lay press. At present, there is not enough data to confirm their effectiveness as therapeutic agents.

Is cannabis addictive?

Tetrahydrocannabinol has the potential

additive effect but not in the same extent as other drugs whereas cannabidiol has no any abuse or dependence potential.

Most of the evidences suggest that THC has the potential additive effect but not in the same extent as other drugs such as opiate, met-amphetamine, cocaine, etc. In animal model, THC can induce animal to self-administer the drug, which suggested that it has additive potential[58]. Freeman and Winstock[59] reported that only a minority of cannabis users become addicted, while Hasin et al[60] reported that 30 % of those who used cannabis may have some degree of cannabis-related disorders.

Flórez-Salamanca et al[61] and Lopez-Quintero, et al[62], reported that lifetime cumulative probability of individuals with cannabis abuse that would evolute to dependence at some point in their lives were 8.9-9.4% which were lower than 15.6-20.9 % from cocaine, 22.7-26.6% from alcohol and 67.5% from tobacco.

Factors associated with vulnerability of cannabis addiction included male gender, young age, concurrent tobacco use, frequent (especially daily) and high-potency cannabis use[59,63].

CBD counter act THC indirectly by antagonist at CB1, CB2 and other orphan receptors. In humans, CBD exhibits no effect indicative of any abuse or dependence potential. People who smoked cannabis containing high levels of CBD were less prone to have their attention captured by cannabis-related stimuli than were those smoking cannabis with low CBD content. Several countries have modified their national controls to accommodate CBD as a medicinal product.

Are there any withdrawal symptoms in cannabis users?

The cannabis withdrawal symptoms such as irritability, sleep difficulty, depressed mood, decrease appetite may appear within 1-2 days after cessation in those with prolonged and heavy use. These symptoms are usually mild and can resolve within 1-2 weeks.

For cannabis user, withdrawal symptoms seldom represent a problem since they only ever occur in heavy users after abrupt cessation[63]. In heavy or prolonged cannabis use, these symptoms appear within 1-2 days after discontinuation and peak after 2-6 days[64]. Most symptoms are mild and mostly resolve within 1-2 weeks. Cannabis withdrawal symptoms include irritability, anxiety, muscle pain, chills, sleep difficulty, insomnia, nightmares, headache, decreased appetite, depressed mood, etc[64,65]. Unfortunately, antidepressants, anxiolytics, noradrenaline-reuptake inhibitors, and anticonvulsants have not been approved to alleviate cannabis withdrawal symptoms[10].

Is cannabis safe for medical use?

Although cannabis has lots of adverse events, most of these adverse events in the medical use are not serious. However, long-term treatment in children and adolescents should be cautious because of the much higher risk of cognitive impairments in these age groups.

No acute death has been attributed solely from cannabis consumption or treatment with cannabinoids[63]. However, there are lots of adverse effects reported in cannabis users. Most of these adverse effects were reported from studies of recreational users of cannabis. These adverse effects include impairment of memory, reductions in psychomotor and cognitive performance, euphoria, disorientation, drowsiness, confusion, loss of balance, and anxiety. Other frequent physical effects of cannabinoids are tiredness, dizziness, tachycardia, orthostatic hypotension, dry mouth, nausea, vomiting, fatigue, somnolence, reduced lacrimation, muscle relaxation, increased appetite, myocardial infarction, stroke, and transient ischemic attack[19,24,63]. Heavy or long-term use of cannabis is associated with chronic bronchitis and chronic psychosis-related health disorders, including schizophrenia and depression[24]. Myocardial infarction, stroke, and transient ischemic attack have also been associated with cannabis use[24].

Concerning the safety of cannabis in medical use, Wang et al[66] had performed a systematic review of medical cannabinoids from 31 published studies. They reported that 96.6% of all reported adverse

effects were determined by authors to be non-serious. The most common non-serious adverse event was dizziness (15.5%) whereas the most common serious adverse effects included relapsing multiple sclerosis (12.8%), vomiting (9.8%), and urinary tract infections (9.1%). However, the rate of serious adverse event was not significantly different from the control.

While medical cannabis seems to be safe, long-term treatment in children and adolescents should be cautious because the risk of cognitive impairments is much higher in these age groups[63].

Acknowledgement

The authors thank Prof. Dr. Siriwan Tangjitgamol for proofreading and editing our manuscript.

Potential conflicts of interest

The authors declare no conflict of interest.

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