Review

Medical marijuana in cancer: harmful or harm reduction?

Alexandra Thielmann[1] & Paul J Daeninck*[2,3,4]

Practice Points

- There is a long history of cannabis use for a variety of purposes, and cannabis and cannabinoids have been used medicinally for centuries.
- Cannabis was deemed illegal during early 1900s with little scientific proof. Recent reviews and patient demand have forced reassessment of its legal status.
- Cannabinoids were discovered in cannabis products. Endogenous cannabinoid receptors and ligands were isolated and, from this, pharmaceutical cannabinoids have been developed.
- Randomized trials show a benefit of cannabinoids for use in cancer pain, nausea and vomiting and cachexia. There is less literature support for unfractionated cannabis use, with studies still emerging.
- In Canada, access regulations were developed for medical conditions due to patient demand. These do not legalize cannabis, but permit its use under specific circumstances.
- Recent legal challenges have led to an extensive review of the Canadian Medical Marihuana Access Regulations.
- The medicinal use of cannabis is associated with well-documented adverse effects; there is a danger of psychosis in those with family history or genetic predisposition.
- Cannabis use is associated with dangerous activities, including impaired driving.
- A paradigm shift is needed for a change from illegal drug to accepted medical therapy.
- There is emerging data on the benefits of cancer therapy with cannabis/cannabinoids.
- The risks need to be considered as policy/regulations evolve.

[1]Faculty of Medicine, 260 Brodie Centre, 727 McDermot Avenue, Winnipeg, Manitoba R3E 3P5, Canada
[2]St. Boniface Unit, CancerCare Manitoba, St. Boniface Hospital, LI 101-08, Block O, 409 Taché Ave, Winnipeg, MB R2H 2A6, Canada
[3]Department of Internal Medicine, Health Sciences Centre, University of Manitoba, Winnipeg, Canada
[4]WRHA Palliative Care Program, Winnipeg, Manitoba R2H 2A6, Canada
*Author for correspondence: Tel.: +1 204 235 3141; Fax: +1 204 237 6048; paul.daeninck@cancercare.mb.ca

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SUMMARY Marijuana (*Cannabis sativa*) has been a topic of much attention over several decades, initially as a herbal remedy for a variety of ills, then as a mild hallucinogen used by the 'counter culture' of the 1960s and more recently as a focus of increasing medical and scientific research. It also has become a popular alternative medication, and controversy continues to swirl around its indications, despite widespread anecdotal evidence. Cannabinoids, isolated from the plant as well as synthetically derived, have become a rapidly increasing area of research and clinical use in certain medical conditions, such as cancer and cancer treatment. Taken together, it becomes difficult for medical professionals to know whether these compounds can be used with caution or should be rejected outright due to the potential harms, which include the possibility of psychosis and driver impairment. Here, we explore the evidence for cannabis and cannabinoid use in supportive cancer therapy, as well as sift through some of the issues to be considered (including an explanation of the Canadian experience) as 'medical marijuana' becomes more widely available.

Cannabis has been used for thousands of years for both medicinal and recreational purposes; however, the evidence for cannabis use as a medical therapy has only become a topic of much controversy in the past 10–20 years. Cannabis is unique among plant-sourced drugs, given the social implications related to the complicated history and legal regulations surrounding its use. The cannabis plant can be processed into numerous products and drugs (collectively termed cannabinoids), including marijuana. Personal use of cannabis in the form of 'medical marijuana' is permitted in Canada under specific guidelines (the Medical Marihuana Access Regulations [MMAR]), which are detailed below. As with any potentially hallucinogenic drug, cannabis has both psychosocial and physiological benefits as well as real harms with use or misuse. It is these harms that have produced the most notoriety for cannabis, and have led to many social and legal barriers to its widespread acceptance. It is precisely these challenges that have prevented more in-depth clinical medical research from moving forward. Despite this, the public at large has embraced the idea of medical marijuana, especially when faced with serious and life-threatening diseases such as cancer or multiple sclerosis. In this article, we explore the possibilities of cannabis and cannabinoid use in cancer, reviewing the research available, as well as the barriers inherent in its acceptance as a mainstream supportive therapy.

History

Cannabis use has been documented for thousands of years around the globe. It has been used as food and medicine, as well as in creating textiles and even pottery [1]. Cannabis in the form of hemp was grown for its versatility as ropes and cordage on ships used by world explorers, as well as navies from around the world [101]. Cannabis in several forms has historically been used by various religions as a means of attaining higher spiritual experiences [1]. In the early 1900s, cannabis (including marijuana, hashish and other products) use, possession and distribution became illegal in the USA and this was followed by Canada. Marijuana and other hallucinogenic products of the cannabis plant were classified as dangerous and controlled drugs along with narcotics such as cocaine and heroin [1], despite a lack of evidence to support this contention. Even with these restrictions in place, marijuana continues to be among the top three most used drugs in the world along with alcohol and aspirin [1]. Since the 1960s, when cannabis use was embraced by the younger counter-cultural generation, medical and socially progressive legislative committees in several jurisdictions have produced reports exploring the use of marijuana/cannabis and its social and societal implications [2]. The overwhelming majority recommended that marijuana use alone is not indicative of potential criminal behavior, and that it be decriminalized [1]. Many of these reports, despite their blue-ribbon credentials, were ignored or highly disputed in the political realm [1]. However, research into the benefits of medicinal marijuana began to accelerate. In several countries, the personal use of marijuana is tolerated, although distribution and sales remained illegal. As the costs of law enforcement

grew and the numbers of people jailed for simple possession of marijuana exploded, several countries have debated legalization and regulation [3]. By the year 2000, a few European countries had legalized possession, Canada proposed the MMAR [102] and several American states set up similar regulations governing medical marijuana use [4,5].

Current use in cancer patients

Cannabis use in cancer patients has many desirable outcomes. Some potential clinical uses include anti-inflammatory, analgesic, antinausea, antiemetic, anti-ischemic and antiepileptiform effects [2]. Furthermore, although the bulk of clinical observational studies report propsychotic and anxiogenic effects of marijuana, other preclinical research suggests possible anxiolytic as well as antidepressant properties [6–8]. Preclinical studies have also shown some benefit in conditions such as malignancy [9], immunologic and rheumatic diseases [10], chemotherapy-induced pain [11,12] and multiple sclerosis [13]. As such, the active components of cannabis have great potential use, and many people for centuries have been using it for treatment of almost any disease and disease symptoms. Research into these effects in part led to the current recommendations and guidelines from Health Canada.

The active chemical components in cannabis are called cannabinoids and function at a variety of receptors identified within the nervous system and beyond (see below). Delta-9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) are the most studied cannabinoids, however there are upwards of 70 different cannabinoids present in cannabis [2]. In most studies employing cannabis, tetrahydrocannabinol (THC) activity has been the main focus and cigarettes containing only or predominantly THC have been used. Only recently has the activity of CBD been recognized, and cannabis extracts containing both have been employed in clinical studies [14]. It is difficult to comment on the benefits of cannabinoids found in unrefined or 'street' cannabis. When the product comes from a central lab or regulated grower (often appointed by government agencies), the amounts and ratio of THC and CBD can be proscribed as part of the regulations. However, the cannabis available to the vast majority of medicinal users is unregulated, not tested and, in fact, may contain much higher amounts of THC and/or CBD than is commonly accepted by the scientific community. There must be an acceptance that the dispensaries and 'underground' suppliers have successfully developed and grown cultivars of cannabis that have varying amounts of active cannabinoids. The commercial products of Bedrocan® (The Netherlands' medicinal marijuana program official supplier) are an example of 'designer' cannabis (highly regulated and tested) supplying a recognized need, with several cannabis products available containing varying amounts of cannabinoids [103].

Endogenous cannabinoids, such as anandamide and 2-arachidonoylglycerol (2-AG), function both centrally at predominantly cannabinoid type 1 (CB_1) receptors and peripherally at mainly cannabinoid type 2 (CB_2) receptors. Cannabinoids in marijuana interact with these receptors leading to antinociception, hypoactivity, euphoria and hypothermia [2]. Since THC was discovered, various synthetic drug forms have been produced in an attempt to reproduce the above-mentioned effects. Drugs that have been marketed and used clinically in North America include dronabinol (Marinol®, Abbott Laboratories, IL,USA), nabilone (Cesamet®, Valeant Canada LP, QC, Canada) and nabiximols (Sativex®, GW Pharmaceuticals PLC, Salisbury, UK) [14]. Many users find these drugs helpful for symptomatic relief, yet many people still prefer to inhale or ingest the actual cannabis product as demonstrated by Engels *et al.* who, in 2007, found that only a small proportion of patients resorted to physician-prescribed cannabis [15]. Modes of administration of cannabis include smoking, oral ingestion through 'butter' or baked foods, oral sprays and vaporization [14].

Benefits on disease state

Although the medical literature examining the effects cannabinoids have on cancer symptom management has focused on synthetic cannabinoids (see above), the public and media persist in their focus on medical marijuana/cannabis. Thus, a full discussion for practitioners requires both to be addressed, or there is a risk of not having enough information or inaccurate information when advising patients. The discussion that follows will include the available literature on the synthetic cannabinoids, but focus on medicinal cannabis, as there continues to be a lack of high-level information that practitioners

can readily use with their patients. Medical marijuana use will be discussed in the context of specific symptoms related to cancer and chemotherapy, including pain, nausea/vomiting and cachexia. This is meant to provide an overview of the various benefits that cannabis may have on a single disease state (cancer) and does not consider the many other roles that cannabis may play in other diseases.

Pain

The analgesic property of cannabinoids in cancer patients is currently of great interest, given that cancer-associated pain is common and can be difficult to control, especially in those patients that have advanced cancer. In support of the analgesic effects of cannabinoids, several studies document the analgesic properties of cannabis, as well as the presence of cannabinoid receptors at various levels of pain pathways [16], which suggest a physiological basis for the success of cannabis in treating pain.

Trials looking at cannabis use in pain control for cancer patients are very limited in number as a result of legislation against marijuana, as well as the unclear effects of marijuana on cancer progression [9]. Despite this, there are a number of studies investigating various cannabinoids, as well as newer synthetic drugs that utilize the endocannabinoid system.

Two trials by Noyes *et al.* in the 1970s demonstrated significant improvement in pain control, and also commented on the various side effects at high doses [17,18]. They concluded that the levels required for significant pain control were also high enough doses to cause heavy sedation and mental clouding [17], and also found that THC was comparable in effect to codeine, however the higher dose of THC induced undesirable side effects, including somnolence, dizziness, ataxia and blurred vision [17]. These studies demonstrate that although THC is effective in treating cancer pain, the high doses present difficulties with frequent and unwanted side effects.

More recent studies published in the past decade investigating the role of THC and CBD extracts in cancer-related pain provide further support for the analgesic benefits of cannabinoids. These newer trials attempt to establish a purpose for cannabinoid medication in conjunction with opioids, as well as define their safety and tolerability. In a review in 2009, Farquhar-Smith concluded that although cannabinoids in combination with opioids do seem to improve refractory cancer pain, specific cannabinoids targeting peripheral CB_2 receptors in order to avoid central side-effects may be required [19].

In 2010 Johnson *et al.* published a multicenter, double-blind, randomized, placebo-controlled, parallel-group study comparing THC to nabiximols (THC plus CBD extract; Sativex). They concluded that nabiximols was significantly better in reducing refractory cancer pain when used in addition to the baseline doses of opioids. In addition to efficacy, they investigated safety and tolerability of each extract, and found that patients experienced similar side effects to those already published (somnolence, dizziness and nausea), and that all adverse events except one episode of syncope were not related to the study drugs. However, they did find that nabiximols was associated with an increase in nausea and vomiting, yet the THC-only extract was not [20].

A recently published Phase IIb study examined the benefit of nabiximols use in escalating doses in patients with severe, intractable cancer pain [21]. Again, use of the drug was shown to reduce the intensity of cancer pain, without excessive side effects. A secondary benefit of reduction in sleep disruption was also found.

Currently, in Canada, nabiximols (Sativex) is the only cannabinoid with labeled indications for adjunctive use for pain relief in cancer patients [104]. The MMAR also permits the use of cannabis as an analgesic for patients with cancer-related pain who have not benefited from other treatment options [102].

Using cannabis for cancer-related pain has not gained widespread acceptance in the scientific community, and thus has not resulted in published trials. We can extrapolate from other recent trials using cannabis for pain relief that benefits may be seen, especially if the mechanism of pain is similar [22,23]. Another area of interest lies in the combination of cannabis with other commonly used analgesics. Abrams *et al.* published a study intended to evaluate the safety of cannabinoid use in chronic opioid users, specifically those using morphine and oxycodone [24]. Overall, they found a statistically significant reduction in pain after 5 days of combined opioid and vaporized cannabis use. They report no effect on opioid metabolites and no effect on oxycodone kinetics, however they did note

a decrease in maximal morphine concentration. It was not clear as to the causes of pain in these patients, so potentially some patients with cancer-related pain may have been enrolled. This study supports the safety of augmenting opioid use with cannabis, and suggests promising possibilities for chronic pain control.

Nausea & vomiting

Many patients with cancer experience nausea and vomiting related to cancer treatments, such as chemotherapy (chemotherapy-induced nausea and vomiting [CINV]) and radiation, and can be difficult to treat with commonly used antiemetics [25]. Several commonly used drugs such as dopamine antagonists and serotonin (5-HT_3) antagonists function at specific receptors effectively preventing vomiting, although they are much less effective in decreasing or alleviating the perception of nausea [26]. This suggests that another class of drugs targeting different receptors may be successful.

In the 1970s researchers began investigating the effectiveness of cannabinoids in the treatment of CINV, partially based on anecdotal reports [27] as well as historical documentation (some centuries old) of control of nausea using cannabis (e.g., reports of use by Queen Victoria [1]). Research eventually led to the production and use of nabilone, a synthetic form of THC, which is currently specifically indicated in Canada for nausea and vomiting associated with cancer therapy. Several studies employed nabilone for CINV, most with positive results, demonstrating that oral THC was at least equivalent to other existing medications [28]. Another derivative from cannabis, Δ^8-THC, was used successfully as an anti-emetic in CINV in eight children [29]. The researchers followed each child over a period of 2 years and found complete resolution of symptoms, including delayed nausea and vomiting, using Δ^8-THC during chemotherapy, regardless of antineoplastic protocol. The benefits of cannabinoids in CINV were confirmed by a systematic review of 30 papers comparing the use of cannabinoids to available therapy of the time, but the authors noted that no comparison had been published using cannabis [28]. A search of the literature for smoked marijuana/marijuana cigarettes and chemotherapy produced only three reports. The earliest article reported smoked cannabis used as a rescue drug in case of vomiting episodes [30], and a later paper documented an uncontrolled study of cannabis use for chemotherapy [31]. Another report, only in abstract form, employed cannabis compared with THC as a treatment for CINV [32]. In all of these papers, cannabis was found to be beneficial, but (when used as a comparison) was not superior to the study medication [32].

The use of the cannabinoids for CINV or anticipatory nausea may hold promise. A preclinical study using a shrew model of CINV demonstrated the benefits of cannabinoids versus ondansetron (a 5-HT_3 antagonist), and the total abolition of vomiting using the agents in combination [33]. In a 2007 double-blind placebo-controlled trial, Meiri *et al.* compared the effectiveness of dronabinol with the newer anti-emetic drug ondansetron [34]. They concluded that dronabinol alone was equally effective as ondansetron alone in treating both nausea and vomiting. Interestingly, the combination of ondansetron plus dronabinol was not more effective than either drug alone.

Despite this promising research, a review published in early 2012 in the *Journal of the National Comprehensive Cancer Network* states that although cannabinoid derivatives have been shown to be beneficial in treating CINV, the current standard of care is 5-HT_3 antagonists, as they are more efficacious and afford greater safety [35]. Cannabinoid derivatives are, for now, reserved for patients with symptoms that are difficult to treat with the standard 5-HT_3 receptor antagonists.

Currently the MMAR outlines the use of cannabis for cancer-chemotherapy related nausea and vomiting in patients that have not benefited from using other treatments [102]. Various other methods of cannabinoid administration, including inhalation, are less well studied, but intrinsically make sense, as nausea and vomiting often prevent the administration of oral agents. Given that Musty and Rossi, in a review of US state clinical trials states that many patients report preference for smoking marijuana [36], perhaps future research may reveal a more effective cannabinoid for use in CINV.

Cachexia

Cachexia, or muscle-wasting syndrome, is especially difficult to prevent and treat in cancer. It has been widely reported anecdotally that cannabis use can stimulate appetite and thereby prevent and treat cachexia [37].

The role of cannabis and weight gain is not as well studied in cancer patients as it is in HIV/AIDS patients. There are currently no studies using cannabis in cancer-related anorexia/cachexia. Studies using cannabinoid extracts or pharmacologic cannabinoids pertaining to cancer patients are somewhat mixed, despite early trials investigating oral THC (dronabinol) showing increased appetite and weight gain [37]. In 2006, one multicenter Phase III randomized controlled trial compared the effects of cannabinoid extract (THC) versus placebo on both appetite and quality of life [38]. They reported that, although the drugs were well tolerated by patients, they did not find an improvement in quality of life or appetite. A recent Canadian study demonstrated improvement in taste sensation leading to an increase in appetite and calorie intake [39]. Despite this lack of convincing evidence, the MMAR currently permits the use of cannabis for cancer-related cachexia where other agents have failed [102].

Access to medical marijuana in Canada

The use of medical marijuana was first regulated by Health Canada in 2001. The MMAR define under which circumstances and by what method marijuana may be used for medical purposes. This document does not legalize marijuana or permit the prescribing of marijuana by physicians; rather it specifies how people suffering from grave and debilitating illnesses may gain access to marijuana seeds or dried marijuana [102]. The patient is then exempted from federal laws regarding possession. Otherwise marijuana possession, use and distribution for recreational purposes remain a criminal offense in the Canadian legal system.

Patients, with the help of a licensed physician, may apply to Health Canada for authorization to possess and use marijuana, as well as the ability to grow limited amounts of marijuana for personal use. Medical marijuana is currently available only to individuals with debilitating symptoms, including severe pain, persistent muscle spasms, seizures, cachexia, weight loss and anorexia [102]. Specific medical conditions that cause many of these symptoms are outlined in the regulations, and include cancer as well as multiple sclerosis, spinal cord injury, spinal cord disease, HIV/AIDS, severe forms of arthritis, and epilepsy. Other conditions may lead to similar or equally debilitating symptoms, therefore these applicants are also considered for authorization [102].

Since the creation of the MMAR, there have been several legal challenges to various sections of the regulation, as well as criticism in the media regarding the implementation and 'product' (cannabis) of the program. In response to criticism towards the court-ordered authorizations through the MMAR, Lucas published an article in 2012 summarizing an attempt to understand patient needs, challenges and experiences through an online survey [40]. He found that up to 72% of respondents were unsatisfied with the MMAR, and suggested that Canada's current policies are not meeting the needs of this patient population. Although the number of patients using medical marijuana is increasing, this report highlights the potential for further improvement in safe, reliable access to marijuana such as through community-based dispensaries, as well as more effective policies. As of the writing of this article, Health Canada has undertaken a complete review of the MMAR program, including consultation with experts and clinical providers to help understand their education needs in providing marijuana for medicinal purposes [Kalant H, Pers. Comm.].

Harms & social implications

Medical marijuana research has focused on benefits in disease therapy, as well as investigated social implications and detrimental effects. The majority of harms associated with cannabis used strictly as medical treatment are undesirable side effects [41]. These include somnolence, dizziness, ataxia and blurred vision, as well as dysphoria, depression, hallucinations, paranoia and arterial hypotension. These could limit the use of even small doses of cannabis, depending upon the age and condition of the user. Certain unintended side effects may make cannabis a more appealing choice for antiemetic therapy in some cancer patients, despite the greater efficacy and recommended standard of care to use 5-HT_3 receptor antagonists. These effects include a sensation of euphoria or 'high', sedation and/or drowsiness [28]. These are often given as the reasons why cannabis is used as a recreational drug, which leads to the complicated politics surrounding the topic of medical marijuana.

At the turn of the century, the *Canadian Medical Association Journal* published a report

documenting self-reported medical marijuana use in Canada [42]. Approximately 2% of people interviewed had used marijuana for medicinal purposes in the previous year. Also noted was that, 'The use of marijuana for *any reason* [emphasis added] was associated with male sex, relative youth, cigarette smoking, heavy drinking, alcohol problems and cocaine use.' This report highlighted the necessity for a system to ensure access to quality-controlled marijuana for medical use, as well as the need for further research to determine what factors influence the choice to use medical marijuana, which may include alcohol and other drug use. This article also notes that although there are clearly documented benefits of medical marijuana, there are many societal influences regarding its use.

One much debated topic is the correlation between cannabis use and psychosis, specifically whether marijuana causes psychosis, or if those predisposed to psychosis are more likely to use marijuana. In 2010, Canadian authors Shapiro and Buckley-Hunter reviewed data on this subject, and concluded that cannabis is a significant risk factor in the development of psychosis, and that adolescents are more vulnerable due to their stage of mental development [43]. They recommend introducing policies that reduce the incidence of adolescent marijuana use, however, they acknowledge that current efforts to deter recreational marijuana use have not been as successful as hoped [43]. Further supporting this recommendation, Bossong and Niesink reviewed the literature and concluded that cannabis use during adolescence, specifically THC, does result in disturbances in prefrontal cortex development [44]. However, they note that the dose used, duration of exposure and timing are not known [44]. Recent work looking at pharmacogenetics has discovered a significant interaction between cannabis use and a specific AKT genotype on long-term changes in cognition, suggesting a possibility for genetic predisposition to deleterious psychotic effects of cannabis use [45]. Other studies investigating various genetic factors, such as neuregulin-1 collectively suggest the presence of a genetic predisposition to cannabis-induced psychosis during the critical period of brain development in adolescents [46].

A study by Moreno *et al.* evaluated impulsivity, sensation-seeking traits, impulsive decision-making and inhibitory control in young university adults either using recreational cannabis or binge-drinking [47]. They also assessed symptoms of depression, anxiety and psychosis in these groups. They found that both groups demonstrated increased impulsivity, however binge drinkers demonstrated increased impulsive decision-making only, while cannabis use was associated with deficits in inhibitory control leading to increased impulsive behaviour. Although they did not observe any symptoms of depression, anxiety or psychosis during this study, they recommend further research to assess long-term outcomes as well as possible psychopathological symptoms.

In 2010, a British Roadside Survey reported that 9.9% of drivers surveyed had been drinking and that 7.2% tested positive for drug use [48]. The majority of drivers testing positive for drugs had been using cannabis, which can impair driving skills, in keeping with increased impulsive behavior (consistent with Moreno *et al.* [47]), and increase the risk of crash. In comparison with the findings of Ogborne *et al.* [42], they found that although it was true that male drivers were more likely than female to test positive for cannabis, age had little predictive value. Drivers of all ages tested positive, with the majority between 45 and 54 years of age [48].

A recently published literature review in the *British Medical Journal* attempts to assess the outcome of acute consumption of cannabis on risk of motor vehicle collision (MVC) [49]. The basis for this study is the rising number of drivers using cannabis, and the effect of cannabis on driving performance. They found that acute cannabis consumption nearly doubled the risk of a driver being involved in an MVC, often resulting in serious injury or death. They note various limitations to their study, with most pertaining to varying legal drug thresholds and judgment of driver impairment across regions.

These studies suggest that recreational use of cannabis has been linked to the emergence of psychosis in adolescents (specifically those who are at higher risk due to family history or genetic tendency), impairs inhibitory control thereby increasing impulsive behavior and is associated with increased risk of MVC. This information is important for the education of providers of medical marijuana, in that these patients should be screened carefully and the risks and benefits are clearly outlined to the

patient. It is likely that, although cannabis may one day be more widely available for medical use, its use for recreational purposes will remain illegal or highly regulated. Furthermore, these studies highlight the potential policy changes that will be necessary should medical marijuana become legal. For example, it is possible that regulations for cannabis use similar to alcohol use may need to be implemented, such as routine drug testing of drivers. Restrictions for specific patient populations would also need to be considered, given the potential harm to young patients, or perhaps the possibility of oversedation to high-risk patients like the elderly. Finally, the public perspective of marijuana use would require a paradigm shift from the perception of illicit drug to clinically prescribed therapy.

Future perspective

The major questions remaining to be answered relate to the potential uses of cannabis in disease therapy, and if various natural forms of the cannabis will become legal to prescribe. The public and political perspective of medical marijuana use will require a paradigm shift from the focus on illicit drug control to clinically proven and accepted medical therapy, supported by further research evaluating the safety and efficacy of cannabis and its derivatives.

In terms of cancer therapy, there is abundant preclinical data that shows possible beneficial effects of cannabinoids on malignant cell function, as well as having antineoplastic properties [50]. It has also been shown that the antineoplastic properties of cannabinoids are dependent upon the tumor cell expression of cannabinoid receptors [50,51], which will be important for optimizing efficacy of the cannabinoid therapy used. Emerging data has also shown that cannabis and cannabinoids do not negatively interact with presently used chemotherapeutics [52], which would also be an impediment to widespread use and acceptance by oncologists. To date, only one human study has been published describing treatment of cancer patients (glioblastoma multiforme) using THC [53]. As a pilot study, it demonstrated the safety in using cannabinoids as a cancer therapy and showed a mild benefit on the overall survival of the treated cohort (nine patients). However, it has set the stage for future trials in patients with CNS tumors. This information has also prompted other experts to advise inclusion of survival data in studies using cannabis or cannabinoids for palliative symptom control in patients with advanced malignancies [Ware M, Pers. Comm.].

An additional interesting area of research to watch relates to the ability of cannabinoids to interact with multidrug resistance (MDR) proteins, which can inhibit the effective functioning of antineoplastic medications. Plant-derived cannabinoids (THC, CBD and cannabinol) have been used *in vitro* to inhibit the function of a multidrug transporter, p-glycoprotein [54], as well as a member of a family of MDR proteins, ABCG2 [55]. Thus, cannabinoids can potentially play another important role in enhancing the treatment of certain cancers. This may be especially true in breast cancers, where the MDR protein ABCG2 has been shown to be most active [56].

Policy changes will also need to account for increased risk of adverse effects in specific populations, including young and adolescent patients. A recent Canadian study investigated the possibility that having relaxed medical marijuana laws may in fact lead to an increase in rates of marijuana use [57]. Interestingly, they found limited evidence supporting this hypothesis, and even suggest that adolescent usage rates may decrease where there are medical marijuana laws. They suggest further studies to help guide future policy changes. This and other similar data may aid in speeding the process of implementing better policies to improve patient access to medical marijuana.

As for future directions for policy implementation, further research is required to fully elucidate the negative and/or detrimental side effects of medical marijuana use before it becomes freely available to prescribe. Such research was not available to regulators when the MMAR was enacted. As with all other medications, rigorous scientific data are necessary to ensure patient safety and efficacy of drug therapy. Trials evaluating the usefulness of various cannabinoids isolated from cannabis have led to the production of increasingly successful cannabinoid preparations, which may indeed cause fewer side effects [14]. Cannabinoid research has been increasing over the past 50 years, but specific research into marijuana used for medicinal purposes is still scant, despite its documented use for thousands of years.

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