

## **The Marijuana Conundrum in North America**

### **A recognized deficiency: Inadequate protective protocols**

An evaluation of risk applied to marijuana products for medical purposes concludes that advanced mitigation strategies and new protective delivery protocols are necessary to adequately protect the public from harm. The Risk Evaluation and Mitigation Strategies (REMS) program is already an approved protocol in the United States (US) by the US Food and Drug Administration and in Canada a similar controlled distribution program is in place including RevAid®.<sup>1,2</sup> These programs are intended to assure patients are monitored to prevent or minimize major side effects and or reactions. There are a number of medications that fall into existing REMS restrictions include thalidomide, clozapine, isotretinoin, and lenilidomide. In both of these programs only prescribers and pharmacists who are registered or patients who are enrolled and who have agreed to meet all the conditions of the program are given access to these drugs.<sup>1,2</sup>

### **Current Government-approved Cannabinoid Products**

Dronabinol (Marinol®, generic), nabilone (Cesamet®, generic) are synthetic cannabinoids to mimic delta-9-THC and nabiximols (Sativex®) is a combination of delta-9-THC and cannabidiol. They all lack the pesticides, herbicides and fungicides placed on marijuana plants during growth.

The longest approved agents, dronabinol and nabilone are indicated for short term use in nausea and vomiting due to chemotherapy and appetite stimulation.<sup>3,4</sup> Nabiximols is used as a buccal spray for multiple sclerosis and as an adjunct for cancer pain.<sup>5</sup> The maximum delta-9-THC strengths available are 10 mg for dronabinol and 2.7 mg/spray of nabiximols.<sup>3,5</sup> Cannabidiol (CBD), a non-psychoactive compound, is one of many cannabinoids found in marijuana. CBD is currently available for free from the U.S. National Institute of Health in government-sponsored clinical trials as potential treatment of resistant seizures (Dravet's Syndrome and Lennox-Gastaut Syndrome).<sup>6</sup>

## **“Medical” Marijuana products**

All marijuana products, including marijuana for medical purposes, fit the prerequisites for a REMS program. The average potency of marijuana more than doubled between 1998 and 2009.<sup>7</sup> In 2015 common leaf marijuana averaged 17.1% THC in Colorado.<sup>8</sup> Examples of oral marijuana products contain 80 mg of THC in chocolates, cookies and drinks and even 420 mg of THC in a “Dank Grasshopper” bar.<sup>9</sup> Butane hash oil (BHO) is a concentrated THC product used in water bongs and/or e- cigarettes and contains upwards of 50 – 90% THC with a Colorado average of 71.7 % THC.<sup>8</sup> One “dab” (280 mg) of 62.1% BHO is equal to 1 gram of 17% THC in marijuana leaf form.<sup>8</sup> These extremely elevated levels of THC make true scientific research with these products incapable of passing Patient Safety Committee standards.<sup>10</sup>

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## **The Thalidomide Parallel**

The risks are so severe for thalidomide, in terms of use in pregnancy that a special protocol that educates, evaluates, mitigates and monitors has been made obligatory.<sup>11</sup>

Thalidomide (Contergan®) was developed by a German company, Chemie Gruenthal, in 1954 and approved for the consumer market in 1957.<sup>12</sup> It was available as an over-the-counter drug for the relief of “anxiety, [insomnia](#), [gastritis](#), and tension” and later it was used to alleviate [nausea](#) and to help with [morning sickness](#) by pregnant women. Thalidomide was present in at least 46 countries under a variety of brand names and was available in “sample tablet form” in Canada by 1959 and licensed for prescription on December 2, 1961. Although thalidomide was withdrawn from the market in West Germany and the UK by December 2, 1961, it remained legally available in Canada until March of 1962. It was still available in some Canadian pharmacies until mid-May of 1962.<sup>12</sup>

## **Canada had permitted the drug onto the Canadian market when many warnings were already available**

An association was being made in 1958 of phocomelia (limb malformation) in babies of mother's using thalidomide. A trial conducted in Germany against Gruenenthal, for causing intentional and negligent bodily injury and death, began in 1968 ending in 1970 with a claim of insufficient evidence. Later, the victims and Gruenenthal settled the case for 100 million dollars.<sup>11</sup>

In 1962 the American pharmaceutical laws were increased by the *Kefauver-Harris Drug Amendment* of 1962 and proof for the therapeutic efficiency through suitable and controlled studies would be required for any government approved medication.<sup>13</sup> According to paragraph 25 of the Contergan foundation law, every 2 years a new report is required to determine if further development of these regulations are necessary.<sup>13</sup>

In 1987 the War Amputations of Canada established The Thalidomide Task Force, to seek compensation for Canadian-born thalidomide victims from the government of Canada.<sup>12</sup>

In 1991, the Ministry of National Health and Welfare (the current Health Canada) awarded Canadian-born thalidomide survivors a small lump-sum payment.<sup>12</sup>

In 2015 the Canadian government agreed on a settlement of \$180 million dollars to 100 survivors of thalidomide drug exposure and damage.<sup>14</sup> Through Rona Ambrose, in her capacity as the Health Minister for the government of Canada at the time of the negotiations, an attempt was made to involve the drug companies related to the thalidomide issue in the survivor's settlement agreement. Negotiations with the drug companies failed. The Canadian taxpayer alone paid to amend the survivors by way of monetary award.

Thalidomide continues to be sold under the brand name of Immunoprin<sup>®</sup>, among others in a REMS program. It is an [immunomodulatory drug](#) and today, it is used mainly as a treatment of certain cancers (multiple myeloma) and [leprosy](#).<sup>11</sup>

**Question: If the drug thalidomide included psychotropic properties and offered the “high” of marijuana would it be prudent or responsible to allow it to be legally sold and marketed for non-medical purposes - acknowledging thalidomide’s record for toxicity in pregnancy?**

### **Marijuana Risk Assessment and Government Acknowledgement**

Risks demonstrated in the scientific literature include genetic and chromosomal damage.<sup>15, 16</sup>

When exposure occurs in utero, there is an association with many congenital abnormalities including cardiac septal defects, anotia, anophthalmos, and gastroschisis. Marijuana use can disrupt foetal growth and the development of organs and limbs and may result in mutagenic alterations in DNA. Cannabis has also been associated with foetal abnormalities in many studies including low birth weight, foetal growth restriction, preterm birth spontaneous miscarriage, spina bifida and others.<sup>15</sup>

Phocomelia has been shown in testing in a similar preclinical model (hamster) to that which revealed the teratogenicity of thalidomide.<sup>15</sup>

THC has the ability to interfere with the first stages in the formation of the brain of the fetus; this event occurs two weeks after conception. Exposure to today’s high potency marijuana in early pregnancy is associated with anencephaly, a devastating birth defect in which infants are born with large parts of the brain or skull missing.<sup>15</sup>

The existence of specific health risks associated with marijuana products are acknowledged by national and various local governments and a plethora of elected officials in both Canada and the United States.<sup>16, 17, 18</sup>

Warnings and the contraindications for use by specific populations and in association with identified conditions, have been publicized by the Federal

Government of Canada and the Federal Government of the United States of America through their respective health agencies.<sup>16, 17, 18</sup>

A government of Canada leaflet produced by Health Canada and updated in December 2015: Consumer Information – Cannabis (Marihuana, marijuana) reads<sup>19</sup>:

*“The use of this product involves risks to health, some of which may not be known or fully understood. Studies supporting the safety and efficacy of cannabis for therapeutic purposes are limited and do not meet the standard required by the Food and Drug Regulations for marketed drugs in Canada.”<sup>19</sup>*

*“Using cannabis or any cannabis product can impair your concentration, your ability to think and make decisions, and your reaction time and coordination. This can affect your motor skills, including your ability to drive. It can also increase anxiety and cause panic attacks, and in some cases cause paranoia and hallucinations.”<sup>19</sup>*

*“When the product should not be used: under the age of 25, are allergic to any cannabinoid or to smoke, have serious liver, kidney, heart or lung disease, have a personal or family history of serious mental disorders such as schizophrenia, psychosis, depression, or bipolar disorder, are pregnant, are planning to get pregnant, or are breast-feeding, **are a man who wishes to start a family**, have a history of alcohol or drug abuse or substance dependence.”<sup>19</sup>*

***“A list of health outcomes related to long term use includes the following: Increased risk of triggering or aggravating psychiatric and/or mood disorders (schizophrenia, psychosis, anxiety, depression, bipolar disorder), decrease sperm count, concentration and motility, and increase abnormal sperm morphology. Negatively impact the behavioural and cognitive development of children born to mothers who used cannabis during pregnancy.”<sup>19</sup>***

In Canada, the College of Family Physicians has issued guidelines for issuing marijuana prescriptions.<sup>20</sup>

*“Dried cannabis is not appropriate for patients who: a) Are under the age of 25 (Level II) b) Have a personal history or strong family history of psychosis (Level II) c) Have a current or past cannabis use disorder (Level III) d) Have an active substance use disorder (Level III) e) Have cardiovascular disease (angina, peripheral vascular disease, cerebrovascular disease, arrhythmias) (Level III) f) Have respiratory disease (Level III) or g) Are pregnant, planning to become pregnant, or breastfeeding (Level II)”<sup>20</sup>*

*“Dried cannabis should be authorized with caution in those patients who: a) Have a concurrent active mood or anxiety disorder (Level II) b) Smoke tobacco (Level II) c) Have risk factors for cardiovascular disease (Level III) or d) Are heavy users of alcohol or taking high doses of opioids or benzodiazepines or other sedating medications prescribed or available over the counter (Level III)”<sup>20</sup>*

In February 2013 The College of Family Physicians of Canada issued a statement advancing the position that physicians should sign a declaration rather than write a prescription as the potential liability, as well as the ethical obligations, for health professionals prescribing marijuana for medical purposes appears not to have been adequately addressed by Health Canada.<sup>21</sup>

*“In our view, Health Canada places physicians in an unfair, untenable and to a certain extent unethical position by requiring them to prescribe cannabis in order for patients to obtain it legally. If the patient suffers a cannabis-related harm, physicians can be held liable, just as they are with other prescribed medications. Physicians cannot be expected to prescribe a drug without the safeguards in place as for other medications – solid evidence supporting the effectiveness and safety of the medication, and a clear set of indications, dosing guidelines and precautions.”<sup>21</sup>*

Representatives of the government of the United States held a press conference at the Office of National Drug Policy (ONDCP) in 2005. Mental health experts and scientists joined high-ranking government officials to discuss an emerging body of research that identified clear links between marijuana use and mental health disorders, including depression, suicidal thoughts and schizophrenia.<sup>22</sup>

The US Substance Abuse and Mental Health Service Administration (SAMHSA) report about the correlation between age of first marijuana use and serious mental illness; and an open letter to parents on "Marijuana and Your Teen's Mental Health," signed by twelve of the Nation's leading mental health organizations, ran in major newspapers and newsweeklies across the country.<sup>23</sup>

Included were the following announcements:

*“Regular use of the drug has appeared to double the risk of developing a psychotic episode or long-term schizophrenia.”<sup>23</sup>*

*“Research has strongly suggested that there is a clear link between early cannabis use and later mental health problems in those with a genetic vulnerability - and that there is a particular issue with the use of cannabis by adolescents.”<sup>23</sup>*

*“Adolescents who used cannabis daily were five times more likely to develop depression and anxiety in later life.”<sup>23</sup>*

In 2016 the Obama Administration steadfastly opposes legalization of marijuana and other drugs because legalization would increase the availability and use of illicit drugs, and pose significant health and safety risks to all Americans, particularly young people.<sup>24</sup> The US government still maintains marijuana is classified as a [Schedule I drug](#), meaning it has a high potential for abuse and no currently accepted medical use in treatment in the United States.<sup>17, 18</sup>

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## **Risk Evaluation and Mitigation Strategy for Marijuana Products**

The dispensing of marijuana for medical purposes must follow a strict dispensing and monitoring protocol; no less arduous than that used for the delivery of drugs such as thalidomide.

**Recommendation** - The implementation of a REMS for marijuana products (REMSMP).

1. The first order for a government is to protect the public. As such, it befits a government approving marijuana for medical purposes to implement a REMS program.
2. Medical cannabis/marijuana dispensaries/stores/delivery systems will be required to comply with all necessary components of a rigorous REMS program prior to selling and dispensing marijuana products.
3. Governmental regulatory organizations must be responsible for the cannabis/marijuana for medical purposes programs and obtain the required evaluations [(i.e. laboratory tests (pregnancy, HCG, etc.), physical and mental health examination documentation], signed patient consent, provider contract and education forms - performed in the required time frames both before initiation, during and after continued usage of marijuana products for medical purposes.
4. Quarterly audits will be performed, by the government regulatory organization, on each medical marijuana/cannabis dispensary for compliance. Failure to comply with the REMSMP program will result in fines and other appropriate penalties to the marijuana dispensaries.

## **A REMS for Marijuana Product Potential Framework:**

### **EMBRYO-FETAL TOXICITY & BREASTFEEDING**

- Marijuana causes DNA damage in male and female patients.<sup>15</sup> If marijuana is used during conception or during pregnancy, it may cause birth defects, cancer formation in the offspring, Downs Syndrome or embryo-fetal death.<sup>15, 16, 18</sup>
- Pregnancy must be ruled out before the start of marijuana treatment. Pregnancy must be prevented by both the male and female patients during marijuana treatment by the use of two reliable methods of contraception.
- When there is no satisfactory alternative treatment, females of reproductive potential may be treated with marijuana provided adequate precautions are taken to avoid pregnancy.

- Females of Reproductive Potential: Must avoid pregnancy for at least 4 weeks before beginning marijuana therapy, during therapy, during dose interruptions and for at least 3 months after completing therapy.<sup>25</sup> Females must commit to either abstain continuously from heterosexual intercourse or use two methods or reliable birth control as mentioned. They must have two negative pregnancy tests prior to initiating marijuana therapy and monthly pregnancy test with normal menses or two months with abnormal menses and for at least 1 month after stopping marijuana therapy.
- Males (all ages): DNA damage from marijuana is present in the semen of patients receiving marijuana.<sup>15</sup> Therefore, males must always use a latex or synthetic condom during any sexual contacts with females of reproductive potential while using marijuana and for up to 3 months after discontinuing marijuana therapy, even if they have undergone a successful vasectomy.<sup>25</sup> Male patients using marijuana may not donate sperm.
- Blood Donation: Patients must not donate blood during treatment with marijuana and for at least 1 month following discontinuation of marijuana because the blood might be given to a pregnant female patient whose fetus should not be exposed to marijuana.
- Marijuana taken by any route of administration may result in drug-associated DNA damage resulting in embryo-fetal toxicity. Females of reproductive potential should avoid contact with marijuana through cutaneous absorption, smoke inhalation or orally.
- If there is contact with marijuana products topically, the exposed area should be washed with soap and water.
- If healthcare providers or other care givers are exposed to body fluids of a person on marijuana, the exposed area should be washed with soap and water. Appropriate universal precautions should be utilized, such as wearing gloves to prevent the potential cutaneous exposure to marijuana.
- Several psychoactive cannabinoids in marijuana are fat soluble and are found to concentrate in breast milk. Nursing mothers must not be receiving marijuana.<sup>16</sup> Consult the primary care provider about how long to be off of marijuana before considering breast feeding.

#### NON-SEMINOMA TESTICULAR GERM CELL CARCINOMA

- Marijuana use is a known risk factor in the development of non-seminoma testicular germ cell carcinoma in males.<sup>26 - 29</sup>
- The presence of non-seminoma testicular germ cell carcinoma must be excluded before the start of marijuana treatment. The patient's primary care

provider must perform a testicular examination and review the patient's human chorionic gonadotropin (HCG) blood test before starting marijuana. Male patients must perform weekly testicular self-evaluations while receiving marijuana. They are also required to have their primary care provider perform a testicular evaluation and a HCG blood test performed every 4 months while receiving marijuana.<sup>30, 31</sup>

### MENTAL HEALTH:

- Short term high dose and chronic marijuana usage is a known risk factor for the development of multiple mental health disorders.<sup>16, 18, 20, 32 - 35</sup> Depression, paranoia, mental confusion, anxiety, addiction and suicide potential are all associated with acute and chronic exposure to marijuana.<sup>16, 18</sup> Decline in intelligence is a potential risk of adolescent-onset marijuana exposure.<sup>16, 18, 36</sup>

The presence of these mental health disorders must be evaluated by a licensed psychiatrist or psychologist by use of the Mini International Neuropsychiatric Interview or equivalent validated diagnostic instrument before marijuana is started. The diagnostic mental health evaluation tool will be completed every 1 month by an independent licensed psychiatrist or psychologist for a minimum of 6 months until unchanging and then every 4 months thereafter while receiving marijuana ending 4 months after the last exposure to marijuana.<sup>37</sup>

### PSYCHIATRIC EVALUATIONS:

History of Substance Abuse Disorder: As the prevalence of substance use disorders amongst those patients requesting medical authorization of marijuana products is known to be extremely high the patient population must be screened prior to dispensing marijuana products for risk of a substance use disorder. Substance use must be monitored prior to onset of marijuana with the World Health Organization, Smoking and Substance Involvement Screening Test (WHO-ASSIST, V3.0), and repeated at monthly intervals until unchanging and every 3 months thereafter while receiving marijuana, ending 6 months after the last exposure to marijuana.<sup>38</sup>

### Conclusion

The evidence that thalidomide and tobacco products were harmful was known to the manufacturers/distributors before government and the populous acknowledged these dangers. To date, there continue to be legal repercussions to said manufacturers/distributors/government for knowingly placing the public at risk. We believe that the same will happen for marijuana products and that it is our responsibility to assist the Canadian government to protect the public from a similar outcome. Since the government is fully aware of the marijuana harms, the government must not be complicit in risking Canadian health/lives, but rather must mitigate any and all such risk to current and future generations.<sup>39, 40</sup> The REMSMP program described assists in providing patient education, provider education and required patient monitoring before any marijuana products are allowed to be dispensed. The program also requires on-going data collection and analysis, to determine the actual hazards from marijuana use and whether the program should even continue. As the stewards of the country's human and financial resources, it is critical that government protect the public from potential irreversible harm and itself from litigation risk by harmed individuals knowing that, in the context of marijuana use, harm is not only possible but probable.

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