Highs, Lows & Don't Knows

With attitudes towards cannabis softening, legalization in Canada and an ever-expanding list of potential medical uses, we review some key facts and research to help Life underwriters navigate this period of change.

Find out: Are cannabis, hemp and marijuana the same thing? What are THC and CBD? Are the medicinal benefits of cannabis true? What are the health risks? And as of now, is there enough data to assess the mortality impact?

Cannabis forms: hemp vs marijuana

Hemp and marijuana plants are members of the genus *Cannabis*. Both contain the chemical compounds[1] tetrahydrocannabinol (THC) and cannabidiol (CBD).

THC has psychoactive and neurological effects, providing intoxicating (a "high") and proposed therapeutic/analgesic properties.

CBD is non-psychoactive. It has the proposed therapeutic and analgesic properties of THC, but no intoxicating effects.

Marijuana and hemp plants are cultivated to have different concentrations of THC and CBD. The hemp plant contains mainly CBD, and very little THC. Its uses are industrial (e.g. for paper, rope, fabrics and insulation) and potentially medicinal/therapeutic.

In this report, "marijuana" refers to a cannabis product (the plant in its natural state or processed into various forms) containing intoxicating levels of THC. Marijuana products are used for these intoxicating properties, and some limited therapeutic indications. "Hemp" refers to non-intoxicating cannabis products with low levels of THC and higher levels of CBD. Hemp products are proposed to have industrial, medicinal and therapeutic properties. "Cannabis" refers to either marijuana or hemp products.

Shifting regulation

Cannabis has been used and consumed in varying forms in the United States (US) and Canada since the 1600s. In 1619, Virginia required that hemp be grown on every farm and it was even used as currency in several colonies. Smoking marijuana was not uncommon in the 1800s.

Over time, perceptions about its use and risk changed. The 1923 Canadian Narcotics Drug Act Amendment Bill and the 1937 US Marihuana [*sic*] Tax Act outlawed all cannabis consumption and forms. In 1970, the Controlled Substances Act banned cannabis of any kind in the US, and made it a Schedule 1 drug (no useful medical indication, high potential for abuse).

Jump forward several decades.

Canada has offered medical marijuana since 2001, and legalized recreational cannabis nationwide in 2018. The Canadian Food Inspection Agency (CFIA) regulates the import, export and grading of cannabis seed.

The 2018 US Farm Bill legalized the growing and possession of non-intoxicating hemp and hemp products that contain less than 0.3% THC. These non-intoxicating products are now legal in all 50 states, unless a state specifically outlaws its use. Hemp is now considered to be an agricultural product.

In contrast, marijuana remains illegal under US federal law. Since 1996, however, all but three US states and one US territory[2] have legalized cannabis for medical and/or recreational uses.

1 Known as cannabinoids.
2 Idaho, Nebraska, South Dakota, and the territory of America Samoa.

> [In 2016,] Cannabis was used by approximately 192 million people worldwide, 4% of the world's population."

Softening attitudes

Adults who felt that marijuana posed a "great risk" fell from 50% in 2002 to 33% in 2014; "no risk" increased from 6% to 15%[3]. A 2018 CDC report of 26,900 working adults in Colorado found that, during 2014-2015, 14.6% had used marijuana in the past month[4]. Marijuana use was highest in persons aged 18–25 years (29.6%) and lowest in those ≥35 years (11.0%). Use was higher among men (17.2%) than women (11.3%). A 2018 study into 2016 prior-year use, found that cannabis was used by approximately 192 million people worldwide, 4% of the world's population[5].

The many forms of cannabis

Dried marijuana includes the flower and leaf of the marijuana plant. This form is most commonly smoked, but can also be consumed orally.

Concentrates are cannabis products made via a variety of extraction processes that separate the THC and CBD cannabinoids from the plant. Some concentrates contain only THC, while others contain mostly or all CBD.

Hash is produced by using ice water and compression to extract THC from the marijuana plant into a resin. Rosin hash uses heat, while hash oil uses chemicals to extract the THC. THC–CO_2 oil is produced using CO_2 and pressure to extract THC, while butane hash uses solvents. Hash and oils are typically vaporized, or mixed with marijuana leaves and smoked. Tinctures are alcoholic extracts of the marijuana plant; liquid tinctures are taken sublingually (dissolved under the tongue).

THC can also be absorbed orally via food and drink infused with the marijuana plant, oils, hash or tinctures. Similarly, creams or lotions infused with THC allow topical application.

CBD can be concentrated or extracted from the hemp plant as described above for THC and marijuana, and can be administered through inhalation, oral or sublingual ingestion, or via topical creams and lotions.

A reliable label?

Canada has a federal agency which oversees cannabis products; Health Canada is responsible for accessing and monitoring the quality, safety and efficacy of all drugs and products that contain marijuana or hemp.

The US Federal Drug Agency (FDA) is not yet involved in the regulation of cannabis content or efficacy, and states which have legalized medical or recreational marijuana do not have the resources to provide these consumer protections. The FDA recently announced that it will intervene to prevent claims of medical efficacy unless there is sufficient data to support such claims.

> 70% of CBD products tested did not contain the amount of CBD extract promised on the label."

Due to the lack of uniform standards and testing, there remains significant variance in THC and CBD concentrations in different products, as well as inconsistency within single product lines. One study[6] reported that 70% of CBD products tested did not contain the amount of CBD extract promised on the label (40% had less than on the product label, while 26% contained too much). The study also found that 20% of marketed CBD products contained more than 0.3% THC, and thus were potentially intoxicating.

In addition, oral and topical products have variable absorption and bioavailability (proportion that reaches the circulation); typically less than 20% of the THC or CBD on the label is absorbed orally.

Medical uses

THC and CBD have been proven to be effective in the treatment of nausea and vomiting due to chemotherapy[7]. There is evidence which supports their use in adults with chronic pain, and in reducing spasticity in multiple sclerosis, though the effects are modest.

In Canada, the CFIA has approved two prescription products. Marinol® (which is no longer available) contained THC and was used for chemotherapy-related nausea and vomiting. Sativex® contains THC and CBD, and is approved for cancer pain and multiple sclerosis-related spasticity.

There are only two FDA-approved cannabis products in the US. Marinol®, also sold as Syndros®, can be prescribed in the US. Epidiolex®, which contains CBD, has recently been approved for the treatment of seizures associated with Lennox-Gastaut and Dravet syndromes, both of which present with recalcitrant infantile seizures.

Other proposed uses are based on the anti-inflammatory, neuroprotective and antidepressant properties of cannabis. Marijuana is marketed as a treatment of various diseases and disorders, including Alzheimer's disease, Crohn's disease, epilepsy, glaucoma, muscle spasms, nausea unrelated to chemotherapy, post-traumatic stress disorder, schizophrenia, and wasting syndrome (see **table 1**). The evidence to support these indications has, however, not been consistent[7].

> Some studies indicated that marijuana reduces the severity of opioid withdrawal symptoms."

Special mention is warranted in the recent proposed use of CBD to decrease the use of opioid medications, or in the treatment of opioid addiction.

3 Compton W, et al. Marijuana use and use disorders in adults in the USA, 2002-14: analysis of annual cross-sectional surveys. Lancet Psychiatry 2016; Lancet Psychiatry 2016; Published Online August 31, 2016.
4 Smith R, et al. Current Marijuana Use by Industry and Occupation-Colorado, 2014–2015 MMWR Weekly 2018; 67(14); 409–413.
5 United Nations Office on Drugs and Crime. World drug report 2018. Vienna 2018.
6 Bonn-Miller, et al. Labeling accuracy of cannabidoil extracts sold online, JAMA 2017; 318(17)1708-09.
7 National Academies of Sciences, Engineering, and Medicine. 2017. The health effects of cannabis and cannabinoids: The current state of evidence and recommendations for research. Washington, DC: The National Academies Press 10.17226/24625.

Cannabinoid and opioid receptors are distributed in the same areas in the brain. Some studies[8] indicated that marijuana reduces the severity of opioid withdrawal symptoms[9,10]. That said, these studies also suggest that marijuana increases the reward properties of opioid use, and prolongs the length of withdrawal symptoms.

Because CBD is neither intoxicating nor rewarding, the use of CBD to inhibit opioid craving has greater therapeutic potential than marijuana. Pilot clinical studies have shown that in individuals recently abstinent from heroin, CBD reduces the intensity of heroin craving[11]. However, the use of CBD prolongs the duration of withdrawal symptoms. There is no conclusive evidence that CBD is of benefit in the treatment of opioid withdrawal.

For sufferers of chronic pain, CBD may also be utilized to prevent the development of opioid addiction. When given access to cannabis, those currently using opioids for chronic pain decrease their use of opioids by 40–60%, and report that they prefer cannabis to opioids[12,13]. CBD and opioids appear to have a synergistic effect when given together. Pain control, even anesthesia, can be accomplished by combining low doses typically ineffective if used alone. Medical marijuana and CBD have consistently reduced the opioid dose needed to achieve desirable pain relief[14,15]. These observations may help overprescribing and dose escalation commonly associated with opioid addiction.

Condition	Mechanism of action/observations
Alzheimer's disease	Anti-inflammatory, antioxidant, antiapoptotic in in vitro and in vivo models of Aβ-evoked neuroinflammatory and neurodegenerative responses
Parkinson's disease	Attenuation of the dopaminergic impairment in vivo; neuroprotection; improvement of psychiatric rating and reduction of agitation, nightmare and aggressive behavior in patients
Multiple sclerosis	Improved elasticity in mice, anti-inflammatory and immunomodulatory properties
Huntington's disease	Neuroprotective and antioxidant in mice transgenic models; no significant clinically important differences in patients
Hypoxia-ischemia injury	Short term neuroprotective effects; inhibition of excitotoxicity, oxidative stress and inflammation in vitro and in rodent models
Pain, headache	Analgesic effect in patients with neuropathic pain resistant to other treatments
Psychosis	Attenuation of the behavioral and glial changes in animal models of schizophrenia; anti-psychotic properties on ketamine-induced symptoms
Anxiety	Reduction of muscular tension, restlessness, fatigue, problems in concentration, improvement of social interactions in rodent models of anxiety and stress; reduced social anxiety in patients
Depression	Anti-depressant effect in genetic rodent model of depression
Cancer	Antiproliferative and anti-invasive actions in a large range of cancer types; induction of autophagy-mediated cancer cell death; chemopreventive effects
Nausea	Suppression of nausea and conditioned gaping in rats
Inflammatory diseases	Anti-inflammatory properties in several in vitro and in vivo models; inhibition of inflammatory cytokines and pathways
Rheumatoid arthritis	Inhibition of TNF-α in an animal model
Infection	Activity against methicillin-resistant Staphylococcus aureus
Inflammatory bowel disease	Inhibition of macrophage recruitment and TNF-α secretion in vivo and ex vivo; reduction in disease activity index in Crohn's patients
Cardiovascular diseases	Reduced infarct size through anti-oxidant and anti-inflammatory properties in vitro and in vivo
Diabetic complications	Attenuation of fibrosis and myocardial dysfunction

Table 1: Conditions and diseases for which CBD may have therapeutic benefits, and the proposed mechanisms of action. Note, evidence remains inconsistent; there is currently inadequate data and research to assess the full effects of these indications[7]. Source: Modified from Pisanti, et al[16].

Current lack of data

Because cannabis was categorized as a Schedule 1 drug in 1970, research in the US has been limited. Even in states that have legalized recreational cannabis, research institutions face federal legal actions and loss of federal research funding if marijuana is provided for study. These federal restrictions prevent large, blinded and controlled studies. Until recently, therefore, most published reports are small, uncontrolled, self-reported and retrospective. Comorbidities and other confounding variables are not noted or analyzed.

The 2018 US Farm Bill removed hemp from the Schedule 1 drug category. This will allow researchers to study hemp CBD without the previous federal restrictions.

The Canadian Mental Health Association (CMHA) recently recognized the lack of quality data, stating that "Given the uncertainties of cannabis use on health, CMHA hopes to see greater investments in research to establish more conclusive evidence on the harms and benefits of cannabis consumption over the life course and its impact on mental health for Canadians"[17].

Negative health issues

An extensive review and critical analysis of the available literature by the National Institute of Health (NIH) in 2017[7] currently provides the best overview of the health risks associated with cannabis.

8 Small animal and un-blinded human studies.
9 Lichtman AH, Sheikh SM, Loh HH, et al. Opioid and cannabinoid modulation of precipitated withdrawal in Δ9-tetrahydrocannabinol and morphine-dependent mice. J Pharmacol Exp Ther. 2001; 298:1007–1014.
10 Izzo AA, Borrelli F, Capasso R, et al. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009; 30:515–527.
11 Hurd YL, Yoon M, Manini AF, et al. Early phase in the development of cannabidiol as a treatment for addiction: opioid relapse takes initial center stage. Neurotherapeutics. 2015; 12:807–815.
12 Kral AH, Wenger L, Novak SP, et al. Is cannabis use associated with less opioid use among people who inject drugs? Drug Alcohol Depend. 2015; 153:236–241.
13 Bellnier T, Brown GW, Ortega TR. Preliminary evaluation of the efficacy, safety, and costs associated with the treatment of chronic pain with medical cannabis. Ment Health Clin. 2018; 8:110–115.
14 Reiman A, Welty M, Solomon P. Cannabis as a substitute for opioid-based pain medication: patient self-report. Cannabis Cannabinoid Res. 2017; 2:160–166.
15 Stith SS, Vigil JM, Adams IM, et al. Effects of legal access to cannabis on scheduled II-V drug prescriptions. J Am Med Dir Assoc. 2018; 19:59–64.e1.
16 Pisanti, S., et al, Cannabidiol: state of the art and new challenges for therapeutic applications. Phalmacol Ther 2017. 175: 133-150.
17 The Canadian Mental Health Association Mental Health and Legal Cannabis in Canada. Published online October 17, 2018 http://cmha.ca/news/mental-health-and-legal-cannabis-in-canada.

The NIH concluded that marijuana can impair attention, concentration, episodic memory and motor coordination, and may have a causative role in chronic diseases.

It does not appear to increase the chances of developing depression, anxiety or posttraumatic stress disorder, but can increase the symptoms of bipolar disease.

THC appears to increase the risk of developing psychoses or schizophrenia, in a dose dependent fashion[18].

Heavy cannabis users are more likely to report thoughts of suicide than are non-users[7].

> "THC appears to increase the risk of developing psychoses or schizophrenia."

The NIH found that smoking cannabis is associated with chronic cough and phlegm production. This can cause microscopic lung and airway changes similar to those seen in tobacco smoking[19]; there are no additive effects from smoking both cannabis and tobacco[7]. Cannabis smoking cessation is associated with the resolution of these bronchitis symptoms. Data is not clear on whether smoking marijuana is associated with chronic obstructive pulmonary disease (COPD) or asthma. Long-term marijuana use is not associated with lung cancer or with head and neck cancer[7].

A large study (involving data from several countries) found that self-reported marijuana use is associated with a 20-30% increase in the rate of motor vehicle crashes[20]. In Canada, where medical marijuana has been legal since 2001, cannabis-associated incidents involved almost 7,800 people and 75 deaths in 2012[21]. In four US states that legalized marijuana between 2012 to 2017 – Nevada, Colorado, Washington and Oregon – car crashes rose by 6%[22].

However, to date there is no clear link between THC blood levels and impairment[23]. Testing drivers for THC is inconsistent and was rarely, if ever, done before 2012. Even today, if a driver tests positive for alcohol consumption, THC testing is not usually done[22], presumably due to the additional costs and lack of established legal limits.

The potential risk of long-term CBD use is less established than marijuana/THC use. The FDA found the safety profile of Epidiolex® to be acceptable. Since CBD has no intoxicating effects, there is no expectation of increased motor vehicle accident rates, as reported with products with intoxicating levels of THC.

CBD resins and oils may contain chemical by-products, but the long-term health effects of these contaminants is currently unknown.

Impact on mortality

The majority of the medical literature that addresses the associated mortality of cannabis is unreliable due to small size, short periods of study, selection bias, and a lack of control regarding co-morbid conditions.

The Institute of Medicine (IOM) and NIH reviewed available published data. The reported results were re-analyzed and validated. Independent, objective consensus opinions were reached by these agencies. Both the IOM and NIH concluded there is no increase in all-cause mortality associated with cannabis use[7, 24].

> "Both the IOM and NIH concluded there is no increase in all-cause mortality associated with cannabis use."

A similar exercise for CBD-specific literature has not been completed. There is no rationale or evidence that CBD has increased mortality implications as compared to cannabis use, which at present shows no increase. As such, it appears reasonable to assume that there is no proof of increased mortality associated with CBD.

Contact us

If you found this overview interesting, and/or have related findings or opinions to share, please contact us. We look forward to hearing from you.

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18 Scott JC, Slomiak ST, Jones JD, et al. Association of Cannabis With Cognitive Functioning in Adolescents and Young Adults: A Systematic Review and Meta-analysis. JAMA Psychiatry 2018; 75:585.
19 Roth M, et al. Airway inflammation in young marijuana and tobacco smokers. Am J Respir Crit Care Med 1998; 157: 928-937.
20 Rogeberg, O., and R. Elvik. 2016. The effects of cannabis intoxication on motor vehicle collision revisited and revised. Addiction 111(8):1348–1359.
21 Wettlaufer A. Estimating the harms and costs of cannabis-attributable collisions in the Canadian provinces. Drug and Alcohol Dependence 2017; 173:m185-190.
22 IIHS Highway Loss Data Institute. Legal pot: Crashes are up in states with retail sales, Status Report, Vol. 53, No. 6, October 2018.
23 Desrosiers, N. A., S. K. Himes, K. B. Scheidweiler, M. Concheiro-Guisan, D. A. Gorelick, and M. A. Huestis. 2014. Phase I and II cannabinoid disposition in blood and plasma of occasional and frequent smokers following controlled smoked cannabis. Clinical Chemistry 60(4):631–643.
24 IOM (Institute of Medicine). 1999. Marijuana and medicine: Assessing the science base. Washington, DC: National Academy Press.