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Societal issues and policy implications related to the use of cannabinoids, cannabis, and cannabis-based medicines for pain management

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1. Introduction

In many regions, local laws and regulations permit the use of cannabis for medicinal purposes in a manner that circumvents well-established procedures for assessing the efficacy, safety, manufacturing, and marketing of medicines. Moreover, the availability of recreational cannabis effectively allows bypassing of the regulatory protections placed on the use of medicinal cannabis products.

Cannabis has been used by humans for millennia, including for pain relief, historically described as a substance (*pharmakon*, in

Greek) that can be a remedy as well as a poison.^{54,72,81} Currently, cannabis is also the most commonly used illicit drug globally,^{6,22} with over 200 million users.⁴⁰ The use of cannabis among adolescents and young adults in the past decade has increased, with 11% of Americans aged 18 years or older, and 22% of Canadians aged 16 years or older reporting cannabis use in the past month, with 7% to 11% reporting daily or almost daily use.³³ In England and Wales, where recreational use is not legalized, an estimated 2.1 million people use cannabis, mostly obtaining it from illegal sources.⁴⁸ Although currently available data from randomized controlled trials neither support nor refute the safety and efficacy of cannabis, cannabinoids, or cannabis-based medicines (CBM) for managing pain,²⁸ it is clear that the use of cannabis is expanding globally.

The use of cannabis without proper regulation of manufacturing and supply, together with ready access to unregulated, and often illicit, markets of high-concentration products, can result in major societal risks and harms. This topical review, as a part of the work by International Association for the Study of Pain (IASP) Presidential Taskforce on Cannabis and Cannabinoid Analgesia, will focus on societal issues and policy implications related to use of cannabinoids, cannabis, and CBM for pain management.

2. Regulation of cannabis cultivation

Growing cannabis plants, and subsequent extraction or formulation processes, presents legal complexities and challenges due to a wide jurisdictional variability in laws and operational approaches. For example, within the European Union, growing cannabis plants that contain <0.2% Δ^9 -tetrahydrocannabinol (THC) (referred to as hemp) is legal, but there have been arrests in some European Union countries for the sale of hemp-based products if they contain any detectable amount of Δ^9 -THC.⁴² Being a plant, the growth and precise composition of cannabis, including its phytocannabinoid content, is subject to a wide variety of influences. These include, but are not limited to, plant genetics, lighting levels, temperature, humidity and water availability, soil composition, and nutrient availability. To best control these parameters, particularly for cannabis intended for medicinal use, indoor growing is typically favored over outdoor growing.

Over the past 4 decades, cannabis potency, indicated by the THC content in seized samples, has increased significantly worldwide,^{12,26,38,39} and has doubled in Europe over the past decade,³⁰ posing risks in the context of its unregulated use. Regulatory issues also exist with cannabidiol (CBD), a

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phytocannabinoid used as an individual compound, infused in food products, or in combination with THC. The U.S. Food and Drug Administration (FDA) and other regulatory bodies around the world have found that more than 90% of CBD products contained substantially less CBD than labeled, and some contained substantial amounts of THC.⁸ In addition to variability in phytocannabinoid composition, the presence of harmful contaminants, eg, pesticides, herbicides, molds, bacteria, metals, and solvents, are particularly concerning when used for medical purposes by vulnerable populations such as children, patients with malignancies or HIV, or those treated with immunosuppressants.^{49,64,67} However, major regulatory bodies such as the U.S. Environmental Protection Agency have not provided guidance on which cannabis-related exposures can be considered safe, or how to regulate contaminants. In the absence of universally accepted regulations, some countries and states have determined their own requirements, resulting in an incoherent global regulatory landscape of cannabis cultivation, which is far below standards compatible with pharmaceutical manufacturing of medicines for human use. The physical infrastructure and energy consumption, artificial light, irrigation, and temperature control associated with indoor cannabis growing, especially in areas with scarce water resources, should also be considered in the context of environmental sustainability and carbon footprint of cannabis cultivation.^{3,47} The expansion of outdoor cultivation for economic benefit (eg, in developing countries, to boost local economies) may divert the availability of soil and other natural resources from use for food production. Ensuring the security of the cannabis crop (particularly high THC content crops) in terms of access to nonauthorized individuals and children is another important regulatory consideration. Environmental impacts from cannabis cultivation and processing, such as the emissions of toxic air pollutants,⁶⁵ or occupational health implications of cannabis production, remain largely unexplored.⁴⁰

3. Regulation of marketing and advertising of cannabis

The marketing of cannabis products as medicinal (as opposed to regulated CBM) is generally not regulated by agencies such as the FDA or the European Medicines Agency using standards set for pharmaceutical products, leading to reduced oversight of health claims made for medicinal or recreational cannabis products. A rapid growth of “expert cannabis clinics” is occurring, where patients, often with complex medical comorbidities, are treated predominantly with cannabis-based therapy, in lieu of a comprehensive treatment approach.⁴⁴ In addition, in contrast to pharmacies where medications are dispensed by trained and licensed professionals, most cannabis dispensaries are providing drugs and medical advice by nonmedical personnel.³⁶ These are important considerations in the context of a worldwide expansion of the for-profit cannabis industry. In the United States alone, the sales of cannabis are projected to increase from \$8.5 billion to \$75 billion by 2030.⁴ National and international cannabis brands are emerging, with marketing campaigns on social media, billboards, radio, and podcasts. Companies use slogans such as “Welcome to the new normal,” and promote claims that cannabinoids reduce anxiety, pain, and insomnia, improve skin, “and much more,” without any adequate description of health warnings or harms.⁴ When Canada legalized cannabis in 2018, one of the fundamental principles in the Canadian Cannabis Act was that cannabis should not be advertised or promoted in ways that increase consumption.¹⁷ The U.S. states that have legalized nonmedical cannabis vaguely prohibit advertising and

promotions that appeal to children. However, a large survey demonstrated that there is substantial exposure to cannabis advertising among adolescents and adults both in Canada and in the United States.⁶³

Greater exposure to cannabis advertising is associated with higher average use, intentions to use, and positive expectancies.^{21,57,63,79} Cannabis legalization and advertising has resulted in perceptual shifts among population in North America, so that 50% of high school students across the United States now endorse the belief that smoking cannabis regularly does not carry great risk.⁵¹ The consequences of cannabis advertising mirror those of alcohol and tobacco (ie, exposure to advertising increases use, particularly in adolescents), but without regulations of cannabis advertising in place.^{1,32}

4. Decriminalizing cannabis: harm vs harm reduction

The legal status of cannabis varies significantly around the globe. Although some countries have legalized recreational use (eg, Canada) or decriminalized personal use (eg, the Netherlands), many countries allow cannabis for medicinal use only, or do not endorse any legal status for cannabis.^{6,20,53} Under decriminalization, both production and sale remain illegal, but law enforcement does not prosecute individuals for the possession of small amounts of cannabis. Legalization, however, allows more stringent regulation and taxation.

Diverse sources of evidence have identified associations between administration of cannabinoids and development of psychosis, motor vehicle accidents, respiratory problems, cardiovascular problems, development of some cancers, and low fetal birth weight.⁵² Conversely, several factors have driven policymakers to increase access to cannabis. Cannabis legalization has been proposed as a solution to an overburdened law-enforcement system.^{55,56} For instance, the decrease in cannabis-related arrests in Washington state after cannabis legalization was shown to enable the police to reallocate resources to other divisions; reduction of crime rates, including rape, property crime, and theft, were observed,⁶ potentially attributable to cannabis legalization. Although cannabis legalization may lead to reduction in overall cannabis-related arrests, the effect of legalization on mitigating the substantial racial disparities that exist in cannabis-related arrests is unclear.^{27,73}

Leveraging some preclinical and clinical data suggesting opioid-sparing effects of cannabinoids, legalization of cannabis has been promoted as an attractive avenue to address the opioid overdose crisis in the United States.⁶ A decriminalized or legalized cannabis market also offers new sources of revenue for state governments through taxation.^{13,45,56} However, some government employees and politicians involved in cannabis legislation have come under increasing scrutiny with regards to non-disclosure of conflicts of interests with the cannabis industry.^{9,35}

An important consideration in the debate of cannabis legalization is the potential increase in cannabis sales on the black market, as a result of price differentials between the legal (taxed) and illegal markets. Diverting legally sourced cannabis for sale on the black market negates some of the economic benefit to local governments. Recent estimates suggest that California’s illicit cannabis market is worth approximately 4 times the size of its legal market.⁶

With emerging data on increased postlegalization societal harms such as increased rates of psychiatric disorders, and increased rates of hospital emergency department visits for cannabis-related symptoms and toxicity presentations,⁶ the benefits and harms of cannabis regulation should be carefully considered and monitored.⁷⁵

5. How will legalizing unregulated recreational cannabis affect medicinal cannabis use?

Laws governing recreational use affect medicinal cannabis use by changing supply and demand, costs, taxation, purity, and potency. Studies have shown that medicinal cannabis users are different from those who use cannabis recreationally, with the former reporting more medical problems, pain, and poor function.⁶² This suggests that medicinal users of cannabis consume cannabis for symptom management more so than for recreation.

With the potency of cannabis increasing,^{26,58} there is concern that recreational legalization will lead to medicinal cannabis users bypassing medical advice on dosing, resulting in worse outcomes. Nonregulated cannabinoid products with high THC concentration (eg, 14% THC in “skunk” in the United Kingdom, and up to 90% in “shatter” and “wax dabs” products in Colorado) pose significant risk to consumers, as evidenced by increased risk of psychosis in areas where such products become available.^{23,48}

Due to the availability of a wide variety of regulated and unregulated cannabis products, and the high prevalence of their consumption in patients who are prescribed medicinal cannabis, clinicians often struggle to discuss proper use of cannabinoids with patients.⁶⁶ Beyond general education focusing on harm reduction, clinicians often cannot access reliable information on the particular product a patient proposes to obtain and use. Although many healthcare professionals support the principle of using medicinal cannabis in certain patient populations (particularly cancer patients and hospice patients),¹⁶ there is a widespread lack of self-perceived knowledge surrounding all aspects of medicinal cannabis use among clinicians.³¹ In contrast to pharmaceutical products, the information provided by cannabis manufacturers and their representatives is not regulated, and thus, is highly variable.^{8,29} Organized and transparent regulatory policies, as well as standardized prescribing and monitoring protocols, mirroring those of pharmaceutical products, can greatly benefit the prescription and monitoring of medicinal cannabis products to improve patient safety.

6. Changes in cannabis policy and opioid use patterns

The legalization of cannabis in the midst of the “opioid epidemic” in various jurisdictions created important research opportunities. Studies reported that legalization of *both* cannabis use *as well as* cannabis dispensaries (but not decriminalization of cannabis alone) has been associated with subsequent reduction in rates of opioid prescriptions, hospital admissions for opioid use disorder and overdose (9%-28%), as well as in opioid deaths (16%-24%).^{5,10,59,68,77} With a shift in U.S. opioid overdose deaths from prescription opioids to heroin and synthetic opioids such as fentanyl, however, the effects of cannabis legalization on opioid overdose and deaths decreased, with some studies showing a negative trend of more opioid overdoses.⁶⁹ In one study of people living with HIV and chronic pain, cannabis use was not associated with lower odds of opioid initiation or higher odds of opioid discontinuation.⁵⁰ However, in another recent survey of opioid substitution among people who have used cannabis, 41% of opioid users reported a decrease or cessation of opioid use due to cannabis use.⁴³ A systematic review assessing the relationship between cannabis use and decriminalization with opioid-related outcomes provided mixed results.⁷⁸

Although some preclinical and clinical evidence suggest opioid-sparing effects of cannabinoids, or analgesic synergy between the 2 classes of drugs,^{18,41,76} one concern is that people merely substitute one addictive substance with another.¹⁴ In addition, despite pharmacological differences between opioids and cannabinoids (notably overdose risk), there are nevertheless concerning similarities between the economic forces and public health messaging of perceived safety that fueled the opioid epidemic in North America, and those that drive the global expansion of medicinal cannabis use, without the appropriate evidence of long-term efficacy and safety.²⁸

The relationship between access to cannabis and opioid prescription rates remains circumstantial, and the clinical relevance of synergistic analgesia is currently conjectural, requiring further data at the population level.⁷⁸ Moreover, the safety of concurrent use of opioids and cannabis is unknown. There is lack of consensus in policies at the hospital and physician level regarding the importance of opioid tapering in patients with concurrent use of cannabis,⁷⁰ given the potential for drug interactions and ongoing substance use.

7. Driving and operating machinery

Systematic reviews show consistent evidence that use of cannabis impairs cognitive and psychomotor ability and impairs driving skill.¹⁵ Effects are mainly acute but can last for 24 hours. This is consistent with an association between acute cannabis consumption and an approximate doubling in risk of motor vehicle collision.² Pilots accustomed to smoking cannabis and trained in simulator tasks also have impaired function up to 24 hours after smoking. Despite these data, 1 in 5 teenagers has reported driving under influence of cannabinoids,⁷¹ and chronic pain patients treated with medical cannabis admit driving under the influence of cannabis.⁷ Due to the risk of impaired attention, memory, decision-making, and executive function with cannabis use,^{19,61,80} there are also concerns about people in occupations that require unimpaired cognitive abilities, such as clinicians in acute care settings, and operators of heavy machinery.

8. Vulnerable populations

Certain populations may be more vulnerable to undesirable effects of cannabinoids. Daily use of cannabis, particularly with high THC content, is associated with about 50% risk of increased depression, doubling the risk of psychosis or schizophrenia, and a risk of developing cannabis dependence.⁴⁰

There are substantial data showing psychological and cognitive vulnerabilities in *adolescents* with heavy or daily use of cannabis,^{24,34,60} including higher levels of depression, risk of psychosis, and poorer cognition and educational achievements.

Edible cannabis products have been associated with accidental poisoning in *children*,^{11,46,79} including a small mass-casualty event caused by supplying of gummy candy containing THC at a child’s birthday party.⁷⁴ Trends to make cannabis-based edible products more attractive to the consumer may increase poisoning risk to children.

Cannabis use during *pregnancy* has been associated with negative maternal outcomes such as preterm delivery and preeclampsia, as well as neonatal outcomes such as anemia, lower birth weight, and placement in neonatal intensive care.^{37,49} Despite these data, nearly 70% of cannabis dispensaries in Colorado reported recommending cannabis products for the treatment of nausea in the first trimester of pregnancy.²⁵

These risks must be carefully assessed and weighted against possible benefits or widespread use of cannabinoids, including for pain management.

9. Future steps in policy for reducing societal harms

As summarized in **Table 1**, major concerns remain over how recreational laws will affect medicinal cannabis use, including in people with pain. Changing supply and demand, taxation,

potency, and marketing and advertising of cannabis are major factors that affect public health. The presence of chemical and microbial contaminants in cannabis products also pose increased health risks, particularly in immunocompromised patients. As the content of THC in cannabis is known to be increasing in several countries, there is a concern that legalization of recreational use will lead to medicinal users bypassing medical advice on dosing, resulting in adverse outcomes.

Table 1
Key societal issues and policy implications related to the use of cannabinoids, cannabis, and cannabis-based medicines in the context of pain management.

Area of risk	Examples and implications	Area of need
Regulation of cannabis cultivation	Inconsistent and unregulated supply Lack of standardization of allowable chemical and microbial contaminants, posing particular risks to vulnerable populations (eg, immunocompromised patients) Labeling often not reflecting composition Lack of regulated allowable THC content, resulting in extremely high-potency products Use of natural resources (eg, soil and water) and carbon footprint of cannabis cultivation is not accounted for	Adoption of strict policies on cannabis cultivation and quality control, to minimize harm Environmental implications need to be considered and mitigated
Testing for cannabis and cannabinoid safety and efficacy	Paucity of large, high-quality studies with cannabinoids in pain The freedom of manufacturers to sell cannabis without a proof of efficacy and safety minimizes their responsibility and motivation to conduct large, rigorous studies	Use taxation of recreational and unregulated medicinal cannabis, to fund large-scale rigorous studies on efficacy and safety of cannabis and cannabinoids in conditions such as chronic pain
Marketing and advertising of cannabis and cannabinoids	Cannabis and cannabinoid-containing products are widely advertised on a variety of platforms, including social media Little regulation exists over cannabis advertising; exposure to advertising of potentially addictive substances increases use and misuse, particularly among adolescents. Unregulated marketing and advertising of cannabis has increased adolescent cannabis use, and fueled the false perception that cannabis use is safe	Banning of advertising and promoting cannabis, to mitigate societal harms (particularly in children and adolescents) Tight regulation of health claims made for marketing Mandatory demonstration of efficacy in high-quality efficacy studies, to allow supporting health claims
Cannabis legalization and its effects on medicinal cannabis use	Availability of nonmedicinal cannabis (potentially at lower price and higher potency) will likely cause diversion to use cannabis without careful medical supervision, increasing the likelihood of adverse outcomes	Careful control of supply, quality, access, and pricing of medicinal cannabis to prevent adverse outcomes
Cannabis policy and opioid use	Possibility that opioid doses can be reduced by initiating cannabis Cannabis is being promoted as a solution for opioid overdose crisis The possible opioid-sparing effects of cannabinoids are unclear, and the safety of opioid and cannabinoid combination is not established	Careful experiments required to determine opioid-sparing properties of cannabis Safety of cannabinoid and opioid combinations needs to be determined in rigorous trials
Driving and operating aircraft and machinery	Cannabis impairs cognitive skills and reaction time, and doubles the risk of motor vehicle collision Consistent regulations on allowable use of cannabis (or blood levels of THC) compatible with driving are lacking	Clear and consistent guidelines need to be set regarding driving under cannabinoid influence, as well as fast and reliable methods of testing cannabis exposure
Cannabis legalization and its effects on vulnerable populations	Daily or almost daily use of cannabis, particularly high-potency, is linked with substantial increase in cognitive and psychiatric problems, particularly among younger adults and adolescents, and people with preexisting mental health problems Immunosuppressed patients are at higher risk of toxicity from potential chemical and microbial impurities and contaminants found in cannabis Edible cannabis products increase risk of accidental poisoning in children Cannabis use during pregnancy has been associated with adverse maternal and neonatal outcomes	Introduce strict regulation for adult-only use of cannabis (unless specifically prescribed by an expert clinician for a childhood disorder such as epilepsy) Properly educate and implement programs for minimizing exposure and use in high-risk populations

THC, tetrahydrocannabinol.

Adoption of strict governmental policies, at least those shown to mitigate tobacco- and alcohol-related harms, would be important.⁴⁰ Regulation of production, sales, and allowable THC contents of any product may increase cannabinoid safety. Complete banning of advertising and promotion, together with strong public education programs targeting vulnerable groups, can help mitigate some of the societal harms.

Implementation and strict reinforcement of evidence-based approaches for limiting driving under cannabinoid influence can help reduce the amount of motor vehicle accidents. Even stricter regulations should be implemented in the civil aviation and airline industry.

Current data may be insufficient to make evidence-based conclusions on each of these matters, but the speed at which cannabinoid markets are growing outpaces the speed at which high-quality data are generated. Measures to mitigate individual and societal harms should therefore be implemented rapidly.

Conflict of interest statement

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