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PERSPECTIVE

Priority Considerations for Medicinal Cannabis-Related Research

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Introduction and Rationale

The National Academy of Sciences, Engineering, and Medicine's 2017 publication *The Health Effects of Cannabis and Cannabinoids: The Current State of Evidence and Recommendations for Research* provided a significant contribution by synthesizing the existing evidence base for the therapeutic use of cannabinoids. With the tremendous interest and early data surrounding cannabinoid therapeutics, what remains is a strong need for systematic guidance regarding research priorities and future directions within this space.

This document focuses on priority areas for medicinal cannabis-related research. The authors, an international group of cannabis experts, have compiled this list, based on their extensive cannabinoid research experience. For clinicians to have confidence in recommending medicinal cannabis, anecdotal reports, however extensive and/or remarkable, are not sufficient. Evidence-based research is required.

This white paper provides an overview of current research gaps, while offering recommendations for studies that may serve to advance existing science within each area. In compiling this list of research recommendations, extensive reviews of the existing evidence (both basic and clinical) were conducted for the following conditions: Alzheimer's disease and other dementias, amyotrophic lateral sclerosis, autism spectrum disorder, cancer, depression/anxiety/posttraumatic stress disorder, epilepsy, glaucoma, hepatitis and other liver disorders, HIV/AIDS, Huntington's disease, inflammatory bowel disease, multiple sclerosis, muscular dystrophy, nausea, pain, Parkinson's disease, schizophrenia and other psychoses, and sickle cell disease. This list was compiled based on the legislative actions of various U.S. jurisdictions in enacting medicinal cannabis laws.

In the review of the above-noted conditions, a number of common themes emerged that both highlighted existing gaps in the literature and pointed to important future directions. Rather than focus on each disease/disorder, we chose to focus this review on the overarching themes that were observed across the literature. Each section that follows was authored primarily by one or two of the authors who have particular expertise in the pertinent space.

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Research Consideration #1: Routes of Administration

The pharmacokinetics (absorption, distribution, metabolism, and elimination) of a drug—in this case, cannabis—administered as pharmacotherapy or for recreational use varies significantly as a function of the route of administration. These pharmacokinetic differences influence the onset, peak, and duration of effects (also known as cannabinoid pharmacodynamics). These characteristics can help determine whether the drug dose delivers the expected/desired effect, the occurrence of adverse side effects, and interactions with other drugs or medications. Brief descriptions of cannabinoid pharmacokinetics and pharmacodynamics are described below for the variety of methods in which cannabinoids are administered.

Intravenous

The intravenous (IV) route offers advantages of 100% bioavailability (dose precision) and rapid onset of effects; however, disadvantages include higher abuse liability and increased potential side effects. Cannabinoids are poorly soluble in aqueous solutions and typically are not administered by the IV route, except in limited research settings. In one such study, Δ-9-tetrahydrocannabinol (THC), the principal psychoactive compound in cannabis, was slowly infused IV over 25 min (4–5 mg THC) into seven adults yielding mean peak plasma concentrations (C_{max}) of 62 μg THC/L, 3 μg 11-OH-THC/L (25 min), 4 μg 8β-OH-THC/L, and 14 μg 11-nor-9-carboxy-THC (THCCOOH)/L,[1] with T_{max} of 2.5–3 h. The authors reported that little THC-conjugate was quantified in blood compared with free THC. The elimination half-life ($T_{1/2}$) of THC in occasional cannabis users ranged from 18 to 57 h,[1–3] with similar THC time/concentration curves following IV or smoked cannabis administration. Kelly and Jones administered 5 mg THC IV to frequent and infrequent cannabis users and reported terminal elimination plasma half-lives for free THCCOOH (5.2–6.2 days) and for THCCOOH-glucuronide (3.7–6.8 days).[4]

Inhalation

Inhalation (via smoking or vaporization) is the most common route of cannabis administration, volatilizing the cannabinoids and many other compounds present in this heterogeneous drug. During cannabis smoking, THC and other cannabinoids are rapidly absorbed into the blood from the lungs and quickly distributed to the brain. Cannabinoid bioavailabilities are lower due to loss in side stream smoke and from pyrolysis. THC distributes into highly perfused tissues, including the liver, the primary site of metabolism. One of the important factors about inhalation is that individuals can titrate their THC dose due to the immediate onset of cardiovascular and subjective drug effects during and immediately after each inhalation. In a controlled research study, after six participants smoked a 3.55% THC cigarette using a paced smoking design, mean peak plasma concentrations of total THC, 11-OH-THC, and THCCOOH were 162 (range 76–267), 7.5, and 54.0 μg/L, respectively.[5] THC levels peaked before the end of smoking. Improvements in liquid chromatography-tandem mass spectrometry (LC-MS/MS) technology have resulted in the ability to directly quantify both free and glucuronidated cannabinoids.

Following *ad libitum* smoking of 50.6 mg THC, mean peak blood cannabinoid concentrations in μg/L (T_{max} hours) for THC, 11-OH-THC, THCCOOH, and THCCOOH-glucuronide in 11 frequent smokers were 151 (0.12), 9.0 (0.21), 23.5 (0.28), and 25.8 (1.1), respectively, and in 9 occasional users 51.6 (0.11), 2.8 (0.22), 8.4 (0.31), and 19.4 (2.1).[6] With chronic frequent medicinal or recreational cannabis intake, THC accumulates in the body's fat tissues and can be found in blood, oral fluid, and urine for 30 days or longer after last use.[7] Following acute dosing, cannabidiol (CBD) had peak blood concentrations μg/L (T_{max} hours) of 3.6 (0.11) in frequent and 1.8 (0.09) in occasional users.[8]

Cannabinol (CBN) and cannabigerol (CBG) are useful markers of recent cannabis intake in both occasional and frequent cannabis users as their detection windows were less than 1.5 h with a 0.3 μg/L limit of quantification (LOQ). Johansson et al. determined the terminal plasma elimination half-life of THC in chronic frequent users following smoking of 56 mg deuterium-labeled THC.[9] The mean THC plasma elimination half-life was 4.3 days when concentrations were followed for 10–15 days. Inhalation of combusted plant material is not an optimal 21st century drug delivery system; fortunately alternative modes of delivery are becoming increasingly available.

Vaporization is another form of inhalation that is becoming popular for cannabis delivery. The advantage of vaporization is volatilizing cannabinoids at a lower temperature, which reduces inhalation of polyaromatic hydrocarbons and other toxic pyrolysis compounds that directly result from combustion when cannabis is smoked. Abrams et al. investigated vaporization as

an alternative means of delivery for inhaled *Cannabis sativa*.[10] Subjects inhaled three strengths of cannabis (1.7%, 3.4%, or 6.8% THC) as smoked cigarettes and three as vaporized cannabis using the Volcano® device. One strength of THC and the delivery system were randomly assigned for each of six inpatient study days. Peak plasma concentrations and 6-h area under the plasma concentration/time curve of THC were similar for both delivery systems, and carbon monoxide levels were reduced with vaporization.

Newmeyer et al. compared peak blood THC, 11-OH-THC, THCCOOH, and THCCOOH-glucuronide concentrations and T_{max} by vaporization, smoking, and oral administration of the same 50.6 mg dose.[6] For frequent smokers following cannabis vaporization, mean peak blood concentrations were lower than those following smoking, while for occasional users, concentrations were similar. T_{max} was similar in both groups and for all constituents. Median CBD C_{max} were 2.9 and 2.8 μg/L, respectively, after smoking and vaporization in frequent cannabis users and 0.9 and 1.5 μg/L in occasional users. Median CBN C_{max} were 9.1 and 6.4 μg/L, respectively, after smoked and vaporized cannabis in frequent smokers and 3.1 and 4.1 μg/L in occasional users.

Similar peak CBG plasma concentrations of 5.1 and 2.9 μg/L were quantified in frequent cannabis users' blood, and 2.0 and 1.7 μg/L in occasional users' blood. Low median Δ9-tetrahydrocannabivarin (THCV) C_{max} ranged from 1.2 to 2.8 μg/L after smoking and vaporization in both groups of cannabis users. All of the minor cannabinoids, CBN, CBG, and THCV, were shown to be good markers of recent cannabis use with detection windows shorter than 0.5 h with a 0.3 μg/L LOQ. CBD is not a marker of recent cannabis use. Following inhalation, by either smoking or vaporization, peak drug effects occur immediately, with a gradual reduction in drug effects over the course of 2–4 h.

Oral

Oral administration has become an increasingly popular route of cannabis administration. Ingested cannabis products (aka "edibles") account for a large portion of sales in the legal (state) cannabis retail marketplace. Also, both dronabinol (Marinol®) and nabilone (Cesamet®) are Food and Drug Administration (FDA)-approved oral synthetic cannabinoid medications prescribed for nausea and vomiting reduction in cancer chemotherapy and for appetite stimulation in AIDS patients. In Newmeyer et al., 50.6 mg THC was ingested in a brownie by 11 frequent and 9 occasional cannabis users.[7] Mean peak blood concentrations of THC, 11-OH-THC, THCCOOH, and THCCOOH-glucuronide in frequent cannabis users were 15.3, 7.3, 36.4, and 53.0 μg/L, respectively. Occasional users' mean peak values were 10.3, 5.5, 39.8, and 124 μg/L. Time to maximum for all constituents occurred from 2.3 to 4.7 h. Of note are the later T_{max}, lower THC concentrations, and higher 11-OH-THC/THC ratio than following the inhalation routes.

Oral administration of medicinal cannabinoids avoids the toxicity of smoked drugs. However, in view of the delayed onset and prolonged kinetics, oral administration appears to be associated with a greater risk of dysphoric effects from "overdosing." The onset of subjective drug effects typically occurs 30–60 min after ingestion, with peak effects lasting from 90 to 180 min postconsumption, and a total duration of about 6–8 h.[11]

Oromucosal

Sativex® is a cannabis plant extract with a 50:50 mixture of THC:CBD approved in Canada, and multiple European and South American countries to treat neuropathic pain, spasticity, and overactive bladder associated with multiple sclerosis. It is administered as an oromucosal spray. Doses of 16.2 mg THC and 15 mg CBD yielded median peak plasma THC concentrations of 11.2 μg/L and for CBD, 3.7 μg/L.[12] THC T_{max} was 3.4 h and for CBD 4.5 h. Oromucosal delivery reduces psychoactive THC effects and improves cannabinoid bioavailability by bypassing first pass metabolism in the liver.

Transdermal

In vitro studies of Δ8-THC, CBD, and CBN absorption through human skin were conducted to determine whether skin patches could be exploited for treatment of nausea. In guinea pigs, 4 μg/L Δ8-THC blood concentrations were achieved in 1.4 h and maintained for 48 h after a patch containing 16 mg/mL Δ8-THC was applied.[13] Cannabinoids penetrated the skin, with CBD and CBN permeability 10-fold higher than for Δ8-THC.[14] A multitude of transdermal products exist in the retail cannabis marketplace, but no published studies examining human pharmacokinetics or associated pharmacodynamics have been published. This is an area where additional research is needed.

Rectal

Rectal cannabinoid administration has the advantages of absorption into the blood without first pass metabolism in the liver and provides a suitable route of administration for patients with upper gastrointestinal (GI)

or vascular issues. While THC itself is not absorbed from suppositories, THC hemisuccinate administered as a suppository had bioavailability of 13.5% in monkeys (which expelled most of the suppository)[15] and >60% in dogs trained to accept suppositories.[16] Blood levels and biological evaluation were carried out in humans.[17–19] Two patients had blood THC concentrations of 1.1–4 μg/L 2–8 h after rectal administration of 2.5–5 mg THC-hemisuccinate.[19]

In summary, cannabis/cannabinoids can be administered across a variety of administration routes, and, except for IV administration, products formulated for each route are sold in retail outlets where cannabis has been legalized. IV, smoked, and vaporized routes of administration produce immediate drug effects that are dose dependent and fairly short lasting. In medicinal use situations, these routes of administration are best suited for treating transient symptoms, or transient changes in symptoms that may benefit from large bolus doses to be delivered. Because these routes of administration are associated with immediate, large, and shorter lasting drug effects, they are also more prone to abuse.

Oral, sublingual, rectal, and transdermal routes of administration would be best suited for sustained management of stable health conditions/symptoms. Among these, sublingual and rectal administrations would likely result in a faster onset of drug effects because they bypass the GI tract and first pass metabolism associated with oral ingestion. Transdermal absorption and duration of effects would depend on characteristics of the vehicle used and the type of application (e.g., patch, gel, and cream).

Unfortunately, most controlled research on route of administration has been limited to smoked cannabis that has had up to 6% THC and is low in other cannabinoids. Research priorities in this area are to extend our understanding of cannabis pharmacokinetics and pharmacodynamics when administered via vaporization, oral ingestion, rectal, and transdermal routes of administration. Within all routes, there is a need to understand the impact, if any, of chemical variation in cannabis products (i.e., cannabinoid and noncannabinoid profile), the extent to which cannabinoids interact with other medications metabolized via the cytochrome P450 metabolic pathway, and the impact of cannabis tolerance on both pharmacokinetic and pharmacodynamic end-points.

Much less is known about the metabolism of CBD. CBD is metabolized in the liver and intestine by cytochrome P450 (CYP) CYP2C19 and CYP3A4, and 5′-diphospho-glucuronosyltransferase (UGT) UGT1A7, UGT1A9, and UGT2B7 isoforms, mainly producing hydroxylated and carboxylated metabolites.[20] CBD increased barbiturate-induced sleep duration in mice by inhibiting barbiturate metabolism, and also phenazone hepatic metabolism[21] due to inhibition of CYP3A and CYP2C microsomal enzymes.[22] Other research suggested that CBD also induced hepatic CYP3A, CYP2B, and CYP2C.[23] Later, CBD was shown to inhibit THC metabolic hydroxylation in humans. CBD administration before THC dosing, potentiated the effects of THC, which might be explained by THC and CBD pharmacokinetic interactions.[24] It is essential that CBD pharmacokinetics be determined to harness its therapeutic potential and understand its adverse events and drug/drug interactions.

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Research Consideration #2: Cannabinoid Concentrations

It is neither easy nor simple to describe the effects of cannabis. Each patient is an individual, and the concentrations of cannabinoids providing relief to one patient are not necessarily helpful to another. The many known compounds in cannabis that can exert differing biodynamic actions in the human body include (at last count) 262 terpenes, 120 cannabinoids, 62 ferments, 58 polyphenols, 58 steroids, 49 flavonoid glycosides, 27 amino acids and peptides, 26 metals and elements, 19 flavonoids, 17 vitamins, and 14 spirans. We lack detailed studies concerning interactions among these substances.[1–3] Recently, ~100 additional cannabinoid compounds, mostly cannabinoid acids, have been identified, which could constitute yet another set of compounds with medicinal potential.[4,5] In addition, selective breeding can be used to generate cannabis chemotypes (sometimes called chemovars) that overexpress certain compounds or groups of compounds that are believed to be associated with desired pharmacodynamic effects.

Synergistic pharmacological interactions among the components of cannabis—one definition of the entourage effect—can certainly exist, although this concept has been largely overinterpreted, both in its original meaning (i.e., endocannabinoid-like molecules modulate the biological activity of endocannabinoids) and especially upon extrapolation to the plant (i.e., non-THC cannabinoids and terpenes modulate the therapeutic activity of THC). We do not have much good empirical data on this topic and need more, which should come from a combination of pre-clinical studies evaluating binding assays of different combinations of cannabinoids to see whether they displace each other or otherwise alter pharmacology of one another, to evaluate dose effects on pharmacology, to look at behavioral effects of cannabinoid interactions as well as THC-terpenoid interactions, and finally to perform comparative behavioral pharmacology studies in humans with isolated compounds as well as with boutique chemovars (chemically distinct plant entities with minor genetic and epigenetic changes with little or no effect on morphology or anatomy) to empirically test these entourage hypotheses.[6,7]

Most of the classical therapeutic activities of (THC-rich) cannabis extracts in the mammalian body (except for some restricted CBD-driven effects such as inhibition of seizures and psychoses) are conceivably due to the THC-evoked activation of CB_1 receptors.[8–12] These include, for example, inhibition of nausea and vomiting, stimulation of appetite, attenuation of cachexia/energy expenditure, analgesia, and reduction of spasticity. Nonetheless, the notion that CBD may make cannabis extracts safer is becoming widely accepted, and so, THC/CBD balanced preparations could have a wider therapeutic window than high-THC/low-CBD preparations.[13] The use of cannabis that does not contain CBD[14,15] may cause acute psychotic and anxiety episodes,[16] which is why CBD can be a valuable modulator of THC-potent agents.[17]

CBD could conceivably modulate the THC effect via a cytochrome p450 3A11 isoform interaction, although the pharmacodynamic process is not known. Does THCV or another phytocannabinoid component impact the activity of THC? These are research priorities.

We do not have enough knowledge concerning interactions and biodynamic effects caused by most cannabinoids, terpenes, and terpenoids.[18,19] We need to further validate the toxicity and potential health risks of terpenes and/or terpenoids. For example, limonene and linalool are prone to oxidation, and behave as dermal allergens.[20,21] Myrcene, limonene, and linalool can generate methacrolein and benzene as degradation products due to their oxidative liability when heated, potentially resulting in dangerous pyrolytic compounds.[22,23]

We need to conduct pre-clinical testing with multiple doses of pure compounds alone and in combination and create isobolograms that can inform dose and combination selection for clinical studies based on animal models of disease. Systematically testing THC:CBD ratios in clinical trials is a challenging undertaking. The

impact on measured outcomes would likely be small, so very large sample sizes would be needed. As an example, the initial clinical studies of nabiximols resulted in a "compromise" THC:CBD ratio of 1:1. For this product, mean maintenance doses of about 8 sprays (~22 mg THC and 20 mg CBD) per day have been shown to be effective for neuropathic pain and spasticity indications. Other THC:CBD ratio recommendations have been based on anecdotal reports.[24]

Another open question is whether the use of whole plant material, plant-based extracts, or synthetic cannabinoids is better for therapeutic treatment. Of course, for isolated pure phytocannabinoids this should not matter (i.e., pure Δ^9-THC is a unique molecule, with the same stereochemistry whether it is isolated from cannabis or produced in a test tube). Nonetheless, there might be some differences between plant-derived and synthetic cannabinoids. Nabilone, a synthetic THC derivative, has high agonistic potency on cannabinoid CB_1 receptors, a narrow therapeutic window, and erratic digestive absorption. These issues have prevented it from becoming widely accepted, relative to dronabinol, nabiximols, or crude cannabis preparations.

Admixtures of cannabis components originating during synthesis (and optical impurity of the initial products) can have a significant impact on the final product. Studies have found that (+)CBD and its derivatives bind to the cannabinoid receptors. Differences between (+) and (–)CBD have not been pharmacologically defined. If natural (isolated from the plant) or synthetic (–)CBD, as initial products, is used for this synthesis and is not optically pure, synthetic (–)CBD may include small amounts of the (+)isomer that can pharmacologically influence the effect of (–)CBD.[25–27]

According to many Internet claims, often based on overinterpreted pre-clinical murine studies, CBD has been touted as a "magic drug." However, there is limited clinical evidence of CBD's activity in humans, except for some specific conditions such as pediatric[28] and adult[29] epilepsies, and to a degree in schizophrenia[30] and social anxiety.[31] Clearly, clinical trials of CBD, including differences in the effects between (–)CBD and (+)CBD, are warranted for a range of medical and psychiatric conditions.

It is difficult to envisage large clinical trials that examine different isolates/extracts/ratios for many different conditions. These are out of reach in terms of money, time, and human resources. Thus, there may be parallel, nonmutually exclusive paths. Clinical trials with isolates could provide data on efficacy and safety, including particular doses, times, and pharmacokinetic (PK) characteristics.

We can follow traditional drug development methods here; start with basic chemistry/characterization, identify candidates based on pharmacology, screen with pre-clinical models of disease, and then carry forward promising candidates (whether single molecules or combinations) to human trials based on pre-clinical data. Additional observational studies of extracts could provide "signs/hints" of whether extracts are better tolerated and/or have higher efficacy than isolates.

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Research Consideration #3: Dosing of Cannabis and Cannabinoids

Guidance regarding dosing of cannabis/cannabinoids is a somewhat complex proposition. A drug dose refers to the precise amount of one or more substances to be taken at one time for a desired therapeutic effect. Traditionally in medicine, therapeutic agents, most often singular chemical entities, are developed for a target indication and for specific clinical populations. Through the process of evaluation in clinical trials, target doses that best balance therapeutic efficacy with safety and adverse events are identified. In following this model, the best information on dosing recommendations for cannabinoids is derived from cannabinoid medicines that have been developed through the clinical trial process and have been formally approved as medicine by regulatory bodies such as the U.S. FDA or Health Canada.

For example, the recommended dose of THC as dronabinol for appetite stimulation is 2.5 mg twice daily 1 h before lunch and dinner.[1] For chemotherapy-induced nausea and vomiting, the recommended dronabinol dose is 5 mg/m^2 1 to 3 h before chemotherapy and then every 2 to 4 h as needed for a total of four to six doses. Dronabinol is available in 2.5, 5.0, and 10 mg dosage formulations. Nabilone, a synthetic analogue of THC that has increased potency and oral bioavailability compared with dronabinol, is available as a 1 mg capsule in the United States, and as 0.25 and 0.5 mg capsules in Canada, with a recommended dose of 1 or 2 mg twice daily in the treatment of adverse side effects of chemotherapy, but should not exceed 6 mg.[2]

Nabiximols is a whole cannabis plant extract product that contains both THC and CBD.[3] It is delivered as a sublingual oromucosal spray. Each 100 μL spray contains 2.7 mg of THC and 2.5 mg of CBD. The manufacturers suggest that "the number of sprays each day depends on the individual." It is recommended that sprays should be dosed at least 15 min apart with an average daily dose of 1–12 sprays per day. In a chemotherapy-induced nausea and vomiting trial, 4.6 sprays a day of nabiximols in addition to standard antiemetics improved outcomes more than placebo.[4] This would be the equivalent of 12.4 mg of THC.

Epidiolex®, recently approved by the U.S. FDA, is a plant-derived oral CBD preparation that has shown benefit in clinical trials in children with refractory seizure disorders.[5] The suggested dose in children is 10–20 mg/kg per day. It is recommended to commence at a dose of 2.5 mg/kg per day in two divided doses and increase to tolerance. Other trials of Epidiolex have investigated doses as high as 50 mg/kg daily.[6–9] Earlier CBD studies using preparations other than Epidiolex evaluated doses of 10 mg/kg in Huntington's disease,[6] 300 mg in Parkinson's disease,[7] 600 mg in social anxiety,[8] 400–800 mg in schizophrenia,[9] and 400–800 mg in opiate addiction,[10] but insufficient research has been conducted to establish specific dose recommendations for these health conditions.

The dosing of botanical cannabis is less clear, in large part, due to the variability in the chemical constituency of the plant and resultant products and variation based on different routes of administration.[11] Picking appropriate dosing has also been complicated by the availability of botanical cannabis for both medicinal and nonmedicinal purposes made possible through legislative action rather than through the conduct of traditional clinical trials. With respect to the chemical composition of a botanical cannabis product, the most common characteristics described are the THC and CBD content, often provided as a % of the whole product for raw plant material or highly concentrated extracts (e.g., wax, shatter), as mg per dose for "edibles," and as mg/mL for liquid solutions (aka tinctures).

For raw botanical products, it is important to note that the % THC or CBD concentration simply refers to the concentration of drug in that matrix, but the dose is determined by the amount that is consumed and the method of consumption. For example, a person

who inhales a 100 mL puff of smoked cannabis containing 5% THC receives the same THC dose as someone who inhales a 25 mL puff of smoked cannabis that has 20% THC. However, in this scenario, the dose of substances other than THC is likely to be different, and there are hundreds of known chemical constituents in the cannabis plant that have been hypothesized to modulate the effects of one another (i.e., the so-called entourage effect[12]). In another scenario, if two individuals inhale 100 mL puffs from the same cannabis, but one smokes and the other uses a vaporizer, the smoker will get a smaller THC dose because some of the THC will be lost during combustion.[13]

Several studies of botanical cannabis have been conducted to evaluate the therapeutic potential for a variety of health conditions, but the evaluation of cannabis to alleviate pain has been predominant.[14–17] Much of this research was done in laboratory studies in the United States using cannabis obtained from the National Institute on Drug Abuse (NIDA). The THC content of cannabis assayed in these trials ranged from 1.7% to 6% THC (equivalent to 17–60 mg of THC per 1 g cannabis cigarette). Canadian studies have used herbal cannabis products containing 9.4% to 12.5% THC. These studies have consistently demonstrated that cannabis can reduce neuropathic pain.[18–21] No clinical studies have explored the role of CBD in pain conditions.

Interestingly, variations in the potency of cannabis did not always produce variation in outcomes. In fact, in animal models, THC has been shown to have a biphasic effect, such as being anxiolytic in low dose and anxiogenic in higher concentrations.[22] In addition, research has shown that cannabis users will adjust the manner in which they smoke cannabis (e.g., depth or intensity of puffing) to compensate for differences in the potency of different varieties of cannabis as a means of titrating THC dose.[13,23]

The State of Colorado was the first to establish 10 mg THC as a "unit dose" for oral cannabis products not intended for medicinal use.[24] In controlled scientific studies, this dose of THC has been associated with discriminable and predominantly pleasant drug effects, with little impairment via oral and smoked routes of administration. However, the same dose via vaporization or doses of 25 mg THC or higher across other routes of administration have been associated with an increased likelihood of adverse effects such as nausea, dizziness, anxiety, paranoia, and sedation among infrequent cannabis users. This research was limited to cannabis that had a very low level of CBD, which has been hypothesized to mitigate some of the adverse effects of THC.[12,23] CBD is now being increasingly found in chemovars available in dispensaries and for research purposes; thus, the THC-modulating effects of concurrent administration of varying ratios of CBD will likely become clearer in the near future, but for now, no data exist to enable a provider to provide guidance with respect to the best ratio of THC:CBD to treat any health condition or to help reduce the likelihood or severity of unwanted side effects.

The actual THC content of a utilized botanical cannabis product depends on the concentration in the particular chemovar, which can vary considerably. Eighty percent of Israeli cannabis patients are licensed to obtain 20–30 g of cannabis monthly; 4% have allowances up to 150 g a month.[25] In Canada, there is no set limit to cannabis authorization, although possession limits are set at 150 g; however, the average amount reported by patients who are registered in the federal access program is less than 1 g daily.[26]

In starting a naive patient on a cannabis regimen, the current mantra is to "start low and go slow" (despite its grammatical incorrectness!).[23] One might start with a 2.5 mg THC equivalent dose at bedtime to limit adverse events and allow for the development of tolerance. Half that dose might be considered in the very young, the elderly, or people with cardiovascular health problems. Some would even advocate that patients consider starting with even lower doses (e.g., in the increasingly popular "microdosing"[27] range) down to as low as 1 mg. Ultimately, however, there is considerable individual variability in response to cannabis, and the "right" dose for a given individual at any one time will be dependent on his or her use history and the intent for the use at that moment.

To discuss optimal dosing of cannabis is akin to trying to describe the treatment of cancer. Just as there are hundreds of different malignancies, all requiring differing treatment interventions, so are there hundreds if not thousands of cannabis chemovars that will all have varying concentrations of cannabinoids and other bioactive chemicals. Hence, it is impossible to define a broadly applicable therapeutic dose of cannabis as these things need to be evaluated using defined and reliable formulations for specific therapeutic conditions. As the botanical is quite safe, the recommended patient-determined titration of dose until the optimal desired effect is the best that can currently be advised for an inhaled product.[11]

More guidance might be reasonable for orally ingested edibles or tinctures and oils, but again, individual

variability in response will preclude the ability to define a one-size-fits-all recommendation. Whether this is an area that is amenable to further research is difficult to assess as there are so many variables and moving parts that the effort seems Sisyphean.

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Research Consideration #4: Study Design

Research is needed to understand and characterize more fully the properties and potential utility of any drug substance, and cannabis is no different. The methods most appropriate for any given study will depend on the aims of the research. For example, research related to the study of cannabis can include therapeutic drug development, regulatory science, public health evaluation, economic impact, epidemiology, safety versus efficacy, or other issues. Within these broad research categories, research methods have been established to ensure scientific rigor and should be followed. Any research study that involves administration of an experimental drug must include administration of an appropriate control substance (placebo, vehicle, positive control). Furthermore, the use of validated and reliable measures is essential. Here we provide a general overview of research approaches that relate to cannabis and a discussion of relevant research methods with reference to more comprehensive guidelines.

Therapeutic drug development is the cannabis research area for which research methods are best established, and perhaps is of greatest interest at the moment. Governing bodies such as the U.S. Food and Drug Administration, Health Canada, or the European Medicines Agency oversee drug development and have well-defined requirements for establishing the safety and efficacy of a novel therapeutic. Internationally, there is wide agreement on what evidence is needed to approve a new drug for labeling and, thus, a standard approach to drug development research has been established. Initially, this process includes drug discovery, determination of the pharmacology, identification of a target therapeutic use, the conduct of pre-clinical toxicology and pharmacokinetic studies, and evaluation for a signal of therapeutic potential in pre-clinical models of human disease states. If this initial work suggests that a novel therapeutic agent appears safe and has therapeutic promise, then a progression of human clinical trials commences. Drug development with novel cannabinoid molecules would follow this trajectory as is.

Development of botanical cannabis, on the contrary, would be a little different because so much is already known about the toxicology, pharmacokinetics, and safety of cannabis. However, pre-clinical research could not be avoided entirely because, before the initiation of human research, the drug product must be very clearly defined and manufacturing methods must be established that meet regulatory requirements for human administration. Data are needed to demonstrate consistency and stability in the end product within and across multiple batches/lots of product. The route of administration and precision in dose delivery must also be demonstrated. These requirements are where therapeutic development of botanical cannabis poses unique challenges, given its incredibly diverse chemical profile and the heterogeneity in product that typically occurs both within and across harvests of cultivated plants.

Once a drug product has been defined and preclinical research conducted, a series of human clinical trials should follow. First, Phase 1 studies are conducted in healthy volunteers to establish the pharmacokinetics and pharmacodynamics of the drug in humans following acute and chronic dose administration. These studies are typically performed with small numbers of research volunteers (usually 8–14 per study), and always include a placebo control. Phase 1 studies can be designed to evaluate the effects of variations in dose, frequency of dosing, or perhaps different formulations of the drug. Phase 1 studies are used to define the bioavailability of the drug, type and time course of drug effects, and identification of potential adverse effects. Thus, end-points usually include the measurement of the drug and metabolites in blood/plasma, subjective drug effects, cardiovascular effects, and adverse events. These data are then used to inform dosing conditions for Phase 2 studies, which are the first studies evaluating the drug in a target clinical population. The primary aim of Phase 2 studies is to determine whether the drug is both safe and has the intended therapeutic effect in individuals who have a defined health condition for which the drug is believed to produce therapeutic benefit. In Phase 2 studies, a primary therapeutic end-point and relevant secondary end-points must be defined before study initiation, and sample sizes are calculated to determine how many people are needed to participate to detect a clinically meaningful effect on those outcomes.

Phase 2 studies typically include multiple dose regimens (vary in amount and/or frequency of drug administration) to identify the dosing scheme that maximizes clinical benefit while minimizing the frequency and/or severity of adverse effects. If a Phase 2 study demonstrates the drug results in significant improvement on clinically important end-points compared with placebo, then Phase 3 trials are initiated.

Phase 3 trials are required to demonstrate the safety and efficacy of a drug in large clinical populations that vary in sex, age, geographic location, and other important demographic characteristics, as appropriate, based on the target clinical indication. If there are other approved medications for the target clinical indication, Phase 3 studies often will include a direct comparison of the novel drug with the established standard of care. Typically, at this stage of development, a single dosing regimen was identified during Phase 2, but in some cases, two dose regimens may be evaluated in Phase 3 to better understand risk versus benefit in a larger population.

In parallel with Phase 3 trials, development of cannabis or any cannabinoid medication will also require a separate abuse liability evaluation. These studies involve administration of therapeutic and supratherapeutic doses of the agent being studied to individuals who currently use other drugs with known abuse liability for nonmedicinal purposes. Important end-points for abuse liability testing are subjective ratings of drug liking, willingness to take it again, valuation of the drug by the study participants, and self-administration behavior. If significant therapeutic benefit of the drug is demonstrated, and shown to outweigh the potential risks of use, then a drug may be submitted to the appropriate regulatory authorities for marketing approval. Outcomes of the abuse liability study will be used to determine regulatory restrictions placed on the drug if approved.

With all of that said, we now must address the fact that cannabis has been legislatively approved for both medicinal and nonmedicinal use widely. This has happened in the absence of much of the required research just described. Because of this, research on the safety and efficacy of cannabis at the patient level remains needed, but can be obtained via other methods. One approach is to conduct observational studies. Often referred to as Phase 4 or postmarketing surveillance research, observational studies do not include placebo groups, but rather record health-related and other specific information about individuals using a drug. In this case, individuals using cannabis can be recruited to provide information about the cannabis products

they use and validated health outcome assessments are obtained.

The impact of cannabis use in observational research can be enhanced by comparing cannabis users to individuals who do not use cannabis but are similar to the cannabis users with respect to demographic and relevant health characteristics and/or by evaluating the same individual over time and obtaining assessments during periods when cannabis is used and not used. It is also possible to obtain this type of data by evaluating patient medical records. The challenge of this approach is that medical records often do not include data on cannabis use due to it being an illicit drug historically, and when information on cannabis use is included, the requisite details needed to determine cannabis product type, dose, route of administration, and frequency of use are likely not provided.

In parallel to observational research on the impact of cannabis use at the patient level, public health research is needed to evaluate the impact of cannabis use at the population level. Public health and economic research relies on the collection of important data from large, representative samples of individuals in a defined geographic region. These data sets include national surveys and records of public health (across a number of domains), health care utilization, socioeconomic status, workplace and motor vehicle accidents, crime, community health and resources, unemployment, education, and measures of industry health and economics. These data sets are typically available either publicly or by request. Advanced training in biostatistics and/or economics is required to appropriately evaluate outcomes from these data. With the appropriate expertise, these data sets can yield highly important information about the impact of cannabis legalization and/or use on key public health and economic indicators.

A related and equally important area of research needed on cannabis and cannabinoids is regulatory science. Research here encompasses a variety of disciplines and methods. Due to this, we are unable to go into extensive detail on methodology for each topic, but rather highlight key needs and identify the relevant disciplines from which expertise is needed. First, analytical chemistry research is needed to establish standard methods for product test methods. Currently, testing of cannabis products varies and research has not been conducted to determine the validity and reliability of test methods being utilized. Plant science and toxicological research is needed to establish standards for the use of chemicals in cannabis cultivation and processing (e.g., pesticides, solvents). Pre-clinical and human behavioral pharmacology studies are needed to better understand the effects of individual chemical components of the cannabis plant and their interactions, as well as differences in use across various routes of administration and types of delivery devices. Behavioral and social science research is needed to establish regulations for cannabis product marketing, including both advertising and product labeling, to minimize cannabis misuse and harm.

Behavioral and toxicological research is needed to develop methods of reliably detecting whether an individual is acutely impaired. This is critical for enforcement of driving under the influence laws, maintaining safe workplaces and determining culpability in other accidents or criminal activity as there currently is no method for differentiating individuals who use cannabis in responsible versus irresponsible ways in situations where impairment poses a public health risk. Indeed, the research needs with respect to cannabis regulatory science reach far and wide, extend beyond the key areas broadly highlighted here, and deserve urgent attention.

Of note, the conduct of all of the studies described must be done in accordance with established international regulations for research. This includes both pre-clinical and clinical research. For reference, regulations for the responsible conduct of research with animals are provided here,[1,2] and guidance for human research is provided here.[3,4] A summary of additional guidance and regulations regarding the conduct of clinical trials for therapeutic drug development can be found here.[5–7] Approval from local regulatory agencies and ethics review boards must also be obtained before initiating any research studies involving living beings or identifiable personal health information. For those considering therapeutic development of cannabis, guidance on botanical drug development can be found here[8] (FDA botanical guidelines).

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Research Consideration #5: Long-Term Effects

Proponents of medical cannabis see its widespread acceptance as welcome news that is long overdue. At the same time, its opponents cringe at the risks that will be unleashed on an unsuspecting public. As more people use cannabis, the stakes of legalization are increasing rapidly. Every day, there are more people using medicinal cannabis to treat a wide variety of ailments and symptoms that include pain, anxiety, nausea, insomnia, posttraumatic stress disorder (PTSD), and depression. If cannabis is therapeutically effective, these patients are benefiting. However, if not, millions of patients are wasting their time, their money, and being exposed to health risks unnecessarily.

For some symptoms, there is good evidence that medical cannabis is effective. However, for many symptoms and conditions, an adequate evidence base does not exist yet. We also know very little about the long-term risks of medical cannabis. Virtually all published studies about cannabis's risks, ranging from heart disease to schizophrenia, have been conducted in people using cannabis recreationally. Those people may use in very large amounts, over long periods of time. They may also combine cannabis with other drugs such as heroin and cocaine, in ways that most medical users do not. Thus, it is difficult to generalize observations of harms in that population to, say, someone who uses a square of cannabis-infused chocolate to sleep at night.

When most of us decide to use a medication, we do so with a good sense of its risks and potential benefits. We know what it is likely to do *for* us, and we are aware of what it might do *to* us. However, most people using medicinal cannabis now are doing so without enough knowledge to make informed decisions, because we just do not have the data.

The thin evidence base for cannabis has led to calls for more randomized controlled trials, and it is true that more high-quality trials are needed. However, those trials will take time, and we cannot afford to wait for evidence about its risks and potential benefits. People are using medicinal cannabis today, and we need more data, now.

Therefore, in addition to more—and better—randomized controlled trials, we need to further explore ways of crowdsourcing the science of medicinal cannabis. That is, we need to learn from people who are using medicinal cannabis today, and who could be teaching us about what it is doing for them, and to them. Specifically, we need registries that collect the experiences of large numbers of patients, as they use cannabis in real-world ways, over long periods of time. There are at least four ways that crowdsourced data could help to answer clinically important questions about medicinal cannabis.

First, crowdsourcing data are arguably the best way to provide long-term information about the benefits and safety of cannabis. Clinical trials in this field will likely never be large enough—or well funded enough—to follow patients for years. Longitudinal data about safety and efficacy will need to come from registries. In those studies, we will need to examine both well-understood risks, such as addiction and dependence, and suspected risks such as myocardial infarction, stroke, and schizophrenia. In particular, longitudinal registries are the only way to reliably identify risks that are rare and therefore are unlikely to be detected in small clinical trials that enroll a few dozen people.

The long-term longitudinal studies that registries make possible can also provide valuable insights into patterns of use and the susceptibility of symptoms over time. For instance, these sorts of data can help to define symptom rebound after prolonged use. Again, short-term randomized controlled trials are ill suited to answer such questions.

Third, large sample sizes of diverse patients in a registry are needed to answer pressing questions about interactions between cannabinoids and medications, as many patients are taking multiple medications, in varying combinations and at several doses. Large samples are needed for an analysis that can tease out side effects, interactions, and risk factors.

Registry data can shed light on the relative benefits of the wide variety of ways that cannabis is used in real-

world settings. For a given indication, patients might use varying combinations of cannabinoids, at different doses, by several routes of administration. Characterizing and testing each of those in a randomized controlled trial would be prohibitively time-consuming, and expensive. However, insights can be obtained, with a reasonable degree of accuracy, with the crowdsourced data that come from registries.

Although they are no substitutes for randomized controlled trials, registries are nevertheless a quick way of figuring out what types of trials we should be doing. They can tell us which symptoms might respond, and which doses might be effective. These data can also give us hints of risks that might exist.

An additional research methodology that is pertinent to this space is the open-label extension of randomized trials. Open-label extension studies typically follow a double-blind, randomized, placebo-controlled trial of a new drug. At the end of the double-blind phase, participants are invited to enroll in an extension study. The study will normally be longer than the randomized trial and often extends for a year or longer. All participants in the extension study are given the study drug, and both they and the investigators are unblinded to drug and dose. The objective is primarily to gather information about the safety and tolerability of the new drug in long-term, day-to-day use. In cannabis studies, the regulatory approval of this approach would have to be negotiated with the appropriate oversight agencies, but this "approximation" of real-world use could be valuable in adding to the evidence basis for cannabis/cannabinoid use.

At present, people are utilizing a wide variety of cannabis formulations for a multitude of medical indications. Sometimes it will work, and sometimes it will not. And—if we are being honest—sometimes people will *think* that it works when in fact the effects are driven by a placebo effect.

Nevertheless, we can harness these thousands of little experiments going on every day. We can get a sense of what could work, what might work, and what probably will not work. And—what is probably just as important—we can learn about whether cannabis is safe and what its long-term effects may be on medical conditions and symptoms.

Research Consideration #6: Effects of Drug/Drug Interactions

Knowledge of the pharmacokinetics and metabolism of cannabinoids, particularly THC and to a lesser degree CBD, in humans is fairly well established. However, not much is reported on the human metabolism of the majority of less predominant cannabinoids. The cannabinoids are metabolized by a series of enzymes in the gastrointestinal tract and liver that modify them (and other organic compounds) by adding chemical moieties that allow them to be secreted into the gut or through the urine. There are two main enzymatic systems that process these ingested (or injected, inhaled, etc.) products. These two enzyme structures are classified into Phase I and Phase II systems. Phase I enzymes typically add an oxygen atom to the exogenous organic compound. The cytochrome P450 enzymes (CYP450) are a set of proteins that perform this first step of metabolism. The second phase is performed by a group of enzymes called the uridine-diphosphate glucuronosyltransferases (UGTs). These enzymes typically link a glucuronide molecule to the exogenous structure. This sugar-like molecule allows the body to secrete the cannabinoid into the urine or bile.[1] This process can be inhibited by many different drugs, botanicals, or foods. Many of the cannabinoids modulate the activity of these CYP450 enzymes.

A full understanding of how individual cannabinoids interact with other drugs is vital if cannabis-derived medicinals are to be used more broadly in clinical care. There are good data that the CYP system is vital for metabolism of both CBD and THC.[1,2] Δ-9 THC is metabolized by both CYP1A2 and CYP2C9 into 11-OH-Δ-9-THC and 11-nor-9carbocy-Δ-9-THC and these are then glucuronided by the UGT system.[1] The same metabolic steps clear CBD.[1]

There is strong evidence that both CBD and THC inhibit different CYP isoenzymes resulting in effects of metabolism of other medications.[3,4] This is becoming a major issue for treatment of epilepsy, as patients with seizures are typically on multiple pharmacological agents that are metabolized by this system. This will also be an issue for treatment of psychiatric disorders (e.g., anxiety, PTSD) and cancer patients; both groups often are treated with multiple agents for their conditions. While there have been four large Phase 3 trials that have demonstrated efficacy for a purified CBD preparation (Epidiolex-Greenwich Pharma) and strong support of its efficacy from a number of open-label studies[5–8]—and in fact, Epidiolex has now received FDA approval—the question of the efficacy of CBD versus its role to lower the metabolism of other antiepileptic drugs continues to be raised.

Data from the Greenwich/GW trial of CBD for Dravet syndrome have provided evidence for alterations of at least one commonly used antiepileptic drug, clobazam.[9] Clobazam, metabolized by CYP2C19 and CYP3A4, is a novel benzodiazepine with 1–5 side chains on the main benzene ring of the molecule. Two studies[9,10] have demonstrated that there is a substantial increase in both clobazam and N-desmethylclobazam (the active metabolite of clobazam) upon treatment with CBD, although the range of elevation was highly variable (from 0% to 80% increase of clobazam levels to 150–600% increase of N-clobazam levels[9,10]) and with unclear relationship to CBD dosing or level, although this was not well analyzed in these articles. In addition, pediatric epilepsy studies utilizing CBD have presented data demonstrating an increase in liver enzymes (particularly aspartate transaminase and alanine transaminase) in patients taking valproic acid, but without comment on change in valproate levels. Clearly, these data demonstrate that there are important interactions between CBD and antiepileptic drugs metabolized by the CYP system, indicating that further study is needed.

There are two questions that the interaction data raise. First, what is the best approach to performing clinical trials with cannabis preparations? Should medications with known interactions be excluded from use during trials or should detailed pharmacokinetic interaction studies be performed? The Epidiolex CBD data do not show a clear 1:1 relationship between increasing clobazam (or N-clobazam) dose and outcome. Many patients were able to be weaned off or decrease the dose of clobazam, while still experiencing good efficacy. This raises the suggestion that the effect of CBD may not be only on metabolism or pharmacokinetics but at the target of the medicine as well. Hence, removing these medications from clinical trials would limit the trials and prevent "real-world" clinical experiences from moving forward. Moving forward with trials that allow all typical concomitant medications into the trial would be prudent, but ensuring that thorough analysis of the drug/drug interactions and genetics of the CYP system is obtained is needed to both understand the potential nuances of the interactions and to potentially predict how any individual would respond.

The second question the interaction data raise relates to the efficacy of cannabis as a stand-alone agent or as an adjuvant to other compounds. Is there a need for THC or CBD to modify the activity of other drugs (or even each other)? Studies that are powered to detect the role of cannabis to be effective as a solo agent or with other drugs are needed. Designing studies that require controlling for these types of factors lead to difficulty in enrolling patients and powering appropriately. Generation of data that support the important interaction and efficacy information needs to be considered when any study is designed.

It is known that foods and other botanicals also can interact with the P450 system. Many people interested in natural remedies are apt to use cannabis products as part of their care plan. These individuals are then also at risk for interactions between pharmaceuticals and botanicals or nutraceuticals that could be dangerous. Studying these interactions would also be important for future trials, particularly ones outside the pharmaceutical realm where these issues will be more likely to be considered.

Overall, there are many therapeutic areas for which cannabis may or may not show efficacy. As studies emerge that report on the dosage and efficacy of cannabis, further studies on the pharmacodynamic interactions between cannabis and other drugs and nutraceuticals are needed. These studies should both measure levels of parent compound and metabolites and how these interact with each other. This field should also appeal to individuals who are interested in pharmacogenomics as correlating polymorphisms in the CYP and UGT system with level of metabolism and interactions between cannabis and drugs could provide a path forward that allows a cleaner and individualized approach to treatments.

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Research Consideration #7: Individual Variability in Cannabinoid Effects

Cannabis is a plant of a complex chemical profile with more than 500 identified compounds, of which 120 are cannabinoids.[1,2] Although they have close chemical structures, cannabinoids have different pharmacological effects from other compounds. THC and CBD are the most pharmacologically studied cannabinoids with different biological effects. Moreover, the same dose of cannabinoids affects individuals differently. This individual variability of cannabinoid effects may be attributed to one or more of the following factors: genes, gender, and/or metabolism.

Since the major activity of cannabis (mainly THC-rich) is mediated through the cannabinoid receptors CB1 and CB2, it follows that variability in the genes controlling these receptors in different people would be a factor in the reason for the variability in individual responses to cannabis and cannabinoids. Cannabinoid receptor CB1 variants in drug users have been associated with substance use disorder[3–11] and cannabis dependence (CD).[12,13] Furthermore, the gene controlling the endocannabinoid system enzyme fatty acid amide hydrolase (FAAH) has shown an association with CD phenotypes. FAAH is the enzyme expressed in the brain and liver that inactivates anandamide (an endogenous CB1 agonist). Covault et al. and Filbey et al. studied and characterized the neural mechanisms that underlie the effects of the cannabinoid receptors 1 (CNR1) and FAAH genes on CD.[5,14]

Individuals with certain disease conditions such as irritable bowel syndrome (IBS), migraine, and fibromyalgia responded positively to exogenous cannabinoid treatment, possibly due to clinical endocannabinoid deficiency.[15] However, objective proof and clinical data are lacking. Also, high doses of CBD, which elevates the level of anandamide (centrally acting endocannabinoid), were shown to provide significant improvement in schizophrenic patients.[16] This indicates the involvement of the endocannabinoid system and that agents inhibiting anandamide deactivation (such as CBD) are of significant clinical utility.

Many reports indicate that cannabis acts differently in men and women. Frattore and Fratta published a comprehensive review on the importance of sex differences in cannabinoid action in humans and animals.[17] They reported the biological and behavioral differences of cannabinoids between males and females. Females are more susceptible to cannabis abuse and dependence than men, with greater tendency to relapse.[18] Female sex hormones, especially estrogen, may play a role in the CB1 receptor densities.[18–20] Estrogen may modulate the activity of FAAH, which may affect the endocannabinoid activity.[21] All these are factors that may explain the gender differences in the response to cannabis and cannabinoids. A greater understanding of the mechanistic reasons for these differences will improve the development of sex-specific ways to treat CD and the use of cannabis-based therapeutics.

Perhaps the most obvious reason for individual variability in cannabinoid effects is the metabolic differences among individuals. Fast metabolizers will convert Δ^9-THC to its inactive metabolite Δ^9-THC-9-COOH, resulting in low levels of Δ^9-THC in their circulation. It follows that the higher the circulating Δ^9-THC or the active metabolite 11-OH-Δ^9-THC, the higher the psychological effects. Measuring the CYP450 activity might be an important clinical test to define a safe and effective dose of cannabinoid (more for THC than CBD).

The following are areas that need to be explored (Table 1).

Table 1. Areas for Future Research

Study of gene/gene interactions and the relationship between genes and endocannabinoids
Determination of the level of circulating endocannabinoids in patients using cannabis or cannabinoid treatment
Effects of cannabis extract/cannabinoids on people with different health conditions, such as irritable bowel syndrome, migraine, fibromyalgia, and cancer
Effects of cannabinoids on patients who suffer from kidney, liver, and heart diseases
Relationship, if any, between male sex hormones (androgens) and the human endocannabinoid system; differential metabolism of cannabinoids in male vs. female
Effect of differences in individual levels of hepatic metabolic enzymes (such as cytochrome P450) and the resultant effect on cannabinoid action
Interactions between cannabis and other medicines
Interaction between cannabis and food

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Research Consideration #8: Comparative Efficacy

There are several therapeutic areas where the efficacy of cannabis or cannabinoids has been compared head to head with other agents in randomized controlled trials. These studies are valuable to examine because they offer an insight into the use of other drug products as active controls, and they also allow some perspective on how cannabinoids measure up when tested directly against existing therapies in controlled experimental settings.

A qualitative and limited review of PubMed was conducted using keywords cannab* and (*appetite* or *nausea* or *pain* or *sleep* or *anxiety*) and trial. Abstracts in English were searched for comparative trials. Only studies of therapeutic efficacy were included (e.g., treatment of cannabis use disorder was excluded). Only studies using clinically available cannabinoids were included (e.g., levonantradol was excluded). No attempt was made to identify unpublished data.

The conditions for which comparative studies of cannabinoids have been conducted include pain, sleep, nausea, appetite, and asthma. The studies dated from as early as 1979.

Pain

Nabilone was equivalent to gabapentin in neuropathic pain.[1] Palmitoylethanolamide has been found to be superior to ibuprofen in patients with temporomandibular joint (TMJ), osteoarthritis, or arthralgia.[2] Dihydrocodeine was found to be superior to nabilone in patients with chronic neuropathic pain.[3]

Sleep

Nabilone was equivalent to amitriptyline in insomnia associated with fibromylagia.[4]

Nausea

Oral THC was compared to metoclopramide syrup and prochlorperazine tablets for nausea and vomiting in children undergoing chemotherapy[5] and has been shown to be equivalent to prochlorperazine in adults with chemotherapy-induced nausea and vomiting.[6] Oral THC has been shown to be equivalent to haloperidol[7] and superior to prochlorperazine.[8]

Nabilone has been shown to be superior to prochlorperazine in three studies for chemotherapy-induced nausea and vomiting[9–11] and to domperidone in one study.[12]

In a study of 61 patients with chemotherapy-induced nausea and vomiting, dronabinol or ondansetron (adjusted doses over the 5-day study) was similarly effective. Combination therapy with dronabinol and ondansetron was not more effective than either agent alone.[13]

Appetite

Cannabis extract (2.5 mg THC, 1 mg CBD) was not found to be different from pure THC or placebo in a large trial of 243 patients with cancer-related cachexia/anorexia syndrome.[14]

In 469 advanced cancer patients, megestrol acetate (800 mg/day) provided superior anorexia palliation compared with dronabinol (2.5 mg twice a day) alone.

Combination therapy did not seem to confer additional benefit.[15]

Asthma

Oral nabilone (2 mg) has been shown to be inferior to terbutaline for bronchial dilatation in asthma.[16]

Conclusion

The purpose of this short review was to explore the comparative efficacy of cannabinoids with other conventional therapies, and we have found that historically, some cannabinoids have been compared with a wide range of drugs in head-to-head trials. The studies were generally small, making it hard to draw strong conclusions about the relative efficacy of cannabinoids. We only focused on trials where cannabinoids have been directly compared with other conventional therapies, as opposed to extrapolating data from cannabinoid-only trials and comparing effect sizes with other medications. This would be a very complex undertaking.

While comparative work has been conducted for nausea, for example, in patients undergoing cancer chemotherapy—showing that cannabis can help with nausea equal to or better than older antiemetics—newer antiemetics may be more effective. Clinicians considering cannabinoid therapy expect to understand whether the efficacy is better than standard pharmacotherapy. While placebo-controlled trials are needed in many of the chronic diseases for which cannabinoids are purportedly used, several therapies already exist. Comparative trials will be needed in due course, and formulations need to be developed with this in mind (Table 2).

Table 2. Cannabinoids, Conditions, and Comparators

Cannabinoid	Condition	Comparators
Nabilone	Pain	Amitriptyline
Dronabinol/Δ-9-tetrahydrocannabinol	Sleep	Dihydrocodeine
Cannabis extract	Nausea and vomiting	Prochlorperazine
Palmitoylethanolamide	Anorexia	Gabapentin
	Asthma	Ibuprofen
		Haloperidol
		Domperidone
		Metoclopramide
		Terbutaline

See text for details of which drug has been compared with which comparator in which condition.

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Research Consideration #9: Need for Clinical Data

The legalization of cannabis and certain cannabinoid preparations (e.g., CBD oil) in many U.S. states for conditions ranging from Alzheimer's disease to migraines, and autism to PTSD, has created a situation where there is belief among medical patients that there are data to support such therapeutic use. In the majority of cases, such data are nonexistent. While the phrase "cart before the horse" has become cliché in the medical cannabis arena, it remains accurate.

We are in dire need of data to support or refute the clinical efficacy of cannabis and individual cannabinoid preparations for the vast majority of conditions for which it is currently used. The reason we know that a

purified plant-derived CBD extract (Epidiolex) at doses ranging from ~10 to 20 mg/kg in children with Dravet and Lennox/Gastaut syndromes is effective is due to a large amount of pharmaceutical funding for randomized controlled trials (RCTs). The same goes for data to support the use of a 1:1 ratio of THC to CBD (nabiximols) in multiple sclerosis, nabilone for nausea and vomiting induced by cancer chemotherapy, and dronabinol (THC) for chemotherapy-induced nausea and vomiting and anorexia associated with weight loss in adult AIDS patients.

The funding required to understand fully the effects of cannabis, or individual cannabinoid combinations, on clinical outcomes can be sizeable. While pharmaceutical companies have significantly contributed to our understanding of cannabinoid therapeutics, we cannot and should not rely on them to determine the efficacy of cannabis/cannabinoids for the litany of conditions for which they have been legalized in various U.S. jurisdictions.

There is a strong need for research to address, and support or refute, legislative actions. We need to conduct not just one, but many clinical trials of specific and well-defined cannabinoid preparations on state-approved medical conditions. These should include short- and long-term safety and tolerability studies, dose-finding studies, both small and large efficacy studies, and comparative efficacy studies. To say, for example, that medical cannabis is legalized in a given state for anxiety tells us nothing about clinical efficacy (for which there are very little data), what cannabis to use, and at what dose. In fact, studies have consistently documented anxiogenic effects of THC (particularly at high doses) and anxiolytic effects of CBD.[1,2] Only well-designed clinical trials can provide the evidence needed to properly care for those in need, while reducing the risk of serious adverse consequences associated with experimentation.

Some might argue that epidemiological data on the patterns of cannabis use among those already using state-sanctioned medical cannabis should suffice as a guide for product choice, dosing, and efficacy. Were product manufacturing regulated and human decision-making sound, epidemiological data could be sufficient. Unfortunately, we know that there is little oversight in the manufacture of cannabis products, leading to the sale of mislabeled and likely inconsistently manufactured THC and CBD preparations throughout the country.[3,4] We also know that many individuals with mental health conditions choose to use substances that are associated with long-term negative consequences (e.g., cocaine).[5] Therefore, in populations with PTSD, the use of high THC cannabis preparations, which we know to cause acute euphoria and may lead to dependence,[6] is extremely problematic.

Future research should start by examining the efficacy of cannabis/cannabinoid preparations for those conditions for which there are no good existing pharmacological treatments. It is for those populations that well-controlled studies that determine short- and long-term safety and efficacy, including dosing guidelines, are most needed. Studies should be adequately powered to detect hypothesized effects, and effect sizes and associated clinical significance should be thoroughly examined. Consistent with recent guidance from the Food and Drug Administration,[7] it is also important to integrate patient perspectives and needs throughout the clinical examination of potential therapeutic effects, including the identification of end-points and selection of outcome measures.

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Conclusions

The overall field of "cannabis medicine," in which the cannabinoids offer potential promise in the treatment of a myriad of disease states and symptom complexes, is one of the most vast and exciting areas of health care mankind has ever faced. The concept that a natural substance that has been cultivated and used for millennia can now be associated with specific biologic effects through an increasingly well-characterized diverse receptor system in the human body opens potential for improvement in quality of life and suppression of disease that perhaps no other group of compounds—natural or synthetic—can offer. Unfortunately, the social and political history of the index plant over the past century has greatly complicated our ability to perform

rigorous research in this potentially high-yield area. Studies of phytocannabinoids are exorbitantly expensive, and when funding is available, logistical and regulatory obstacles can delay study execution for months to years.

Many of these issues cannot be addressed by scientists, but are matters of public policy and market economics. This review has been intended to inform the interested researcher of where and how large the data gaps in this space lie, in the hopes that—whatever the obstacles—when funding and interest *are* available, the greatest possible impact can be made with the prosecution of rigorous, sound, biologically plausible research.

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Abbreviations Used

CBD = cannabidiol
CBG = cannabigerol
CBN = cannabinol
CD = cannabis dependence
FAAH = fatty acid amide hydrolase
FDA = Food and Drug Administration
GI = gastrointestinal
IV = intravenous
LOQ = limit of quantification
PTSD = posttraumatic stress disorder
RCTs = randomized controlled trials
UGTs = uridine-diphosphate glucuronosyltransferases
THC = Δ-9-tetrahydrocannabinol
THCV = Δ-9-tetrahydrocannabivarin