Demystifying medical cannabis

Tilray, a Canada-based federally licensed medical cannabis producer, serves patients on four continents and shares its insights into the field

High drug prices, ageing populations, and public demand for alternatives to traditional pharmaceuticals are generating significant interest in medical cannabis on the world stage. Mounting evidence that cannabinoids, the active compounds in cannabis, can benefit patients suffering from a range of conditions has encouraged policy makers to legalise and regulate medical cannabis from Europe and Latin America to Australia and New Zealand.

The regulatory landscape

Currently, ten European Union member states authorise some form of cannabinoids or medical cannabis. Fledgling medical programmes in Croatia, Cyprus, Germany, Czech Republic, Italy and the Netherlands will soon be joined by those in Poland and Denmark, with Ireland, Spain and the United Kingdom currently navigating reform. More than 600 million people live in countries that have legalised medical cannabis and cannabis-derived medicines, with over 200 million of those people in the EU alone.

Despite these positive developments, having laws on the books is insufficient. Some EU countries allow the sale of medical cannabis flowers, but don't yet permit the standardised extract products sought by patients and doctors. While cannabinoid access is theoretically possible, few EU pharmacies carry cannabis products and fewer doctors prescribe it, leaving patients to rely on the unregulated black or grey markets for medicines. Proactive steps must be taken to ensure product safety, patient access and appropriate dosage forms.

The lack of adequate standards for medical cannabis products is a critical issue that needs to be addressed by regulations. A 2015 study by Vandrey *et al.* tested 75 products from dispensaries in three different US cities and found that over 80% of products were inaccurately labelled. In 2016, *The Globe and Mail* tested products from nine unregulated dispensaries in Canada and found that 66% of the products contained harmful contaminants.

Master horticulturists and meticulous care ensure the highest quality and consistency of Tilray products

Policy makers can avoid these challenges by enacting robust yet sensible regulations to enforce compliance standards and widen patient access. The EU requires medical cannabinoid products to be produced per the European Medicines Agency's (EMA) Good Manufacturing Practice (GMP) guidelines, the global pharmaceutical standard. Tilray, a federally licensed cannabis producer based in British Columbia, was the first medical cannabis producer in North America to become GMP certified, allowing it to become the first North American supplier of GMP-compliant cannabinoid products to patients in the EU, Latin America, Australia and New Zealand.

Meanwhile, medical cannabis producers have an obligation to contribute to the scientific body of knowledge surrounding cannabinoids, building the foundation for improved patient outcomes. Tilray's ability to produce investigational drug products according to ICH guidelines (The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use) allows it to partner with leading international universities for clinical trials. These trials generate critical safety, tolerability and efficacy data that can be used to inform patient treatment. Tilray also conducts rigorous observational and epidemiological research, including the largest cross-sectional examination of Canadian medical cannabis patients conducted to date, and a longitudinal study to examine the effects of medical cannabis on the substitution of prescription and illicit drugs.

Thus far, there is a lot to admire in the European approach to medical cannabis regulation. Some European policy makers and regulators are embracing medical cannabis products that are standardised, well-characterised formulations meeting strict product quality standards. Each EU member state has taken its own approach, though many would like pan-European regulations for these products. Germany – the world's second-largest market for pharmaceuticals, which legalised medical cannabis earlier this year and mandates insurers consider patient coverage – has completed a cannabis monograph that could become the template for regulatory agencies in other EU states if medical cannabis were added to the European pharmacopeia.

	NAT'L ACAD SCIENCE[1]	BARNES REPORT[2]	WHITING ET AL[3]
PAIN	Good	Good	Moderate
CINV	Good	Good	Low
SPASTICITY	Good	Good	Moderate
ANXIETY (CBD ONLY)	Limited	Good	Low
SLEEP	Moderate	Moderate	Low
APPETITE STIMULATION (HIV, CANCER)	Limited	Moderate	Low
TOURETTE'S SYNDROME	Limited	Limited	Low
GLAUCOMA	Limited - *ineffective*	Moderate	Low
DEPRESSION	Limited - *ineffective*	Limited	Low
PARKINSON'S	Insufficient	Moderate	Not Evaluated
HUNTINGTON'S	Insufficient	Limited	Not Evaluated
HEADACHE	Not Evaluated	Limited	Not Evaluated
DEMENTIA	Limited - *ineffective*	Moderate	Not Evaluated
POST-TRAUMATIC STRESS DISORDER	Limited	Moderate	Not Evaluated
CANCER	Insufficient	Limited	Not Evaluated

Fig. 1 Evidence for specific indications according to The Health Effects of Cannabis and Cannabinoids[1], the Barnes Report[2], Whiting et al.[3]

Regulators, lawmakers, medical professionals and industry must work in concert to provide optimum healthcare solutions in a timeframe that matters. The European Union should seize the opportunity to provide true leadership, bringing meaningful improvements to the lives of its 500 million inhabitants by enacting smart and effective regulations of cannabinoids and medical cannabis that harmonise national approaches and ensure patient safety and access.

A clinical overview of cannabis

Cannabinoids and the endocannabinoid system

Cannabis *sativa* contains hundreds of cannabinoids. The two most well-studied and prevalent cannabinoids are tetrahydrocannabinol (Δ^9THC) and cannabidiol (CBD). Studies have shown that THC is responsible for the euphoric effect commonly associated with cannabis. While there is ongoing research on other minor cannabinoids present in cannabis, their physiological relevance is still largely unknown.

The endocannabinoid system (ECS) is a complex system of receptors, ligands and enzymes contained within the body. The ECS has been shown to play a role in fundamental biological processes such as pain modulation, movement control, energy balance, mood and memory.[4] The phytocannabinoids THC and CBD act within this ECS, such as on the CB1R and CB2R, but have also been shown to modulate the activity of receptors outside the ECS, such as GPR55, TRPV1 and GPR119.[5] As the body of research on the importance of the ECS grows, so does interest in developing novel chemical entities (NCEs) that target pathways involved in regulating fundamental processes modulated by the ECS. It is critical to note that these NCEs are distinct from the phytocannabinoids THC and CBD discussed in this article.

Cannabinoid Products

Typically, when we speak of drug therapy, we imply two factors. The first is a definition of the drug itself: a formulation with a defined active ingredient (or combination of active ingredients) shown to be responsible for a therapeutic effect. The second is clinical data to inform treatment with that drug product. Yet the term 'medical cannabis' has come to represent a range of products, from inhaled whole dried flower to orally administered pharmaceutical products containing defined doses of cannabinoids. This range in definition, understandably, creates significant confusion for prescribing physicians.

The most common methods of the administration of cannabinoids are via the lungs by inhaling or via the gut by swallowing oral solutions or capsules. Cannabis strains can vary dramatically in cannabinoid content and composition, resulting in a highly variable dose of the active ingredient. While there have been many published studies on inhaled cannabis flower, the results of these studies are difficult to interpret.

In the last 30 years, pharmaceutical drug products containing THC, or THC and CBD in combination, including Marinol (Dronabinol), Cesament (Nabilone), and Sativex (Nabiximols), have been approved for several indications. However, even in countries where federal health agencies have approved their use, these pharmaceutical cannabinoid medications are often rarely accessed by patients. In many EU countries, this is partly due to the onerous documentation requirements imposed on prescribing physicians and partly due to the high cost and non-reimbursable nature of the drugs.

Cannabinoid pharmacokinetics

Cannabinoid pharmacokinetics are highly influenced by the route of drug administration and the formulation of the drug product. Inhalation acts as an efficient and rapid method of delivery, whereas oral ingestion results in slower absorption with lower, more-delayed peak THC and CBD plasma levels. The variability of both THC content in plant material (0.3% to 30%) and inhalation dynamics leads to unpredictable plasma THC levels from smoking. Reported C_{max} and area under the curve (AUC) values of THC and CBD from inhalation are one to two orders of magnitude higher than via the oral route. T_{max} after inhalation is substantially shorter (0.14 to 0.26 hours) compared to oral administration. Bioavailability of THC and CBD is, on average, two- to three-fold higher upon inhalation than upon oral ingestion. Low oral bioavailability may be the result of variations in drug absorption and degradation resulting from different physiological states (full *vs.* empty stomach) and first-pass metabolism in the liver.[4]

One of the most critical issues facing the future of cannabinoid treatments is the development of formulations that do not require smoking or vaporisation. While cannabis has traditionally been ingested via pulmonary delivery, there are several disadvantages to this method. First, the chemical composition of whole cannabis flower varies widely and is rarely accounted for. Second, the patient is exposed to toxic by-products of combustion or potentially harmful additives found in cannabis concentrates processed for vaporisation. Third, pulmonary delivery has a specific pharmacokinetic profile that is not suited for many of the indications for which cannabinoids may be effective. If we are to develop best-in-class cannabinoid treatments, the pharmacokinetic parameters of investigational drug formulations must be considered.

Therapeutic *versus* medical use

Reports describing the effects of cannabis on various symptoms fall into two principal groups: those describing the effects of inhaled whole cannabis flower (or its preparations) and those using isolated cannabinoids. This distinction is critical since the former is closely linked to the historical use of cannabis as a herbal medicine. This use is still considered therapeutic in some communities and relies on the patient's ability – via trial and error – to discover products that relieve symptoms and establish the most effective use of those products. The physician is rarely involved in guiding the patient in this type of use. In contrast, the use of drug products containing defined doses of active ingredients is largely driven by conventional pharmaceutical development of specific cannabinoids such as THC or CBD. This truly medical use requires clinical data to assist the physician in guiding appropriate treatment: data such as a safe starting dose and titration schedule, side effects profiles, drug-drug interactions and efficacy for specific indications.

Clinical evidence

The medical cannabis literature is far from satisfactory. It contains many small-scale studies, open-label trials and case studies, but very few good quality, statistically significant placebo-controlled, blinded trials – the gold standard for proving efficacy. Clinical research on cannabinoids has been limited by the products available for research. Drawing solid conclusions from the literature can be difficult.

Meta-analyses and commissioned reports have attempted to bring some order to the chaos by categorising existing trials by methodological validity. For this article, results from one published meta-analysis and two major reports, commissioned by national public institutions, are included (Fig. 1). Each of these reports graded existing trials using all types of medical cannabis products according to methodological validity – rating randomised placebo-controlled clinical trials (RCTs) as the most robust and open-label trials and case studies as the least robust. A range of indications were evaluated.

Whiting *et al.* published a meta-analysis reviewing 79 trials (screened from an initial 505 identified studies).[3] GRADE (Grading of Recommendations Assessment, Development and Evaluation) was used to rate the overall quality of the evidence for risk of bias, publication bias, imprecision, inconsistency, indirectness and magnitude of effect. The indications reviewed by Whiting *et al.* were prespecified by project funder the Swiss Federal Office of Public Health.

A 2016 report was commissioned by the All-Party Parliamentary Group (APPG) for Drug Policy Reform in the UK, wherein the goal was to 'to assess the evidence and bring a dispassionate view of what is known about current and potential applications of cannabis-based treatments' (Barnes Report, 2016).[2] The authors of this report summarised the clinical evidence from ~120 studies, culled from over 2,200 initially identified, adopting the grading system used by the American Academy of Neurology.[7]

Early this year, a group of leading researchers in the field were tasked with conducting a comprehensive review of current evidence on the health effects of cannabis and cannabinoids by the US National Institutes of Science, Engineering and Medicine.[1] In addition to summarising the evidence for the therapeutic potential of cannabis, this report also lays out the potential harmful health effects of use.

The strongest clinical evidence for efficacy appears to be for the treatment of various types of pain, nausea and vomiting associated with chemotherapy, spasticity associated with multiple

sclerosis (MS), and anxiety. It is important to note that, for anxiety, products containing only CBD are indicated; THC can cause an increase in anxiety in ~10% of the population. Of note, the National Academies report found that there is some evidence on a lack of efficacy for both glaucoma and depression, whereas the other two reports found evidence in support of efficacy, illustrating the difficulties in interpreting small-scale clinical studies with different formulations of the active ingredient/s.

New evidence since the publication of these reports indicates that CBD may be effective in treating some seizure types. Recent data published in the *New England Journal of Medicine* indicates that an investigational drug product containing the single active ingredient CBD (Epidiolex®; GW Pharma) results in a statistically significant reduction in seizure frequency.[8] The data on combination drug products containing CBD and THC for epilepsy are thus far inconclusive, though there are widespread reports of artisanal cannabis preparations in use for the treatment of seizures. One of the most critical areas of investigation remains the study of combination THC/CBD drug products in the treatment of specific seizure types.

Common reported side effects associated with cannabinoid use were dizziness, dry mouth, nausea, fatigue, euphoria, vomiting, disorientation, drowsiness, confusion, loss of balance, and hallucination. Most side effects were reported to be mild at low doses, increasing in severity and frequency as doses escalated, and resolved upon discontinuation of the study drug.

Cautions and risks

The Barnes and the National Academies reports suggest that there is some evidence for a causal link between cannabis use and schizophrenia, particularly in those individuals with a genetic predisposition to psychosis or among the most frequent cannabis users. Thus, caution is recommended when prescribing cannabinoid medicines for such individuals. There is a small dependency rate with cannabis – at around 9% – which warrants caution. This compares to a 15% dependency rate for alcohol and 32% dependency rate for tobacco. The evidence for cognitive impairment for long-term use is not clear, especially in the developing brain. As with all prescription drugs, a careful risk-benefit analysis is warranted, taking into account the severity of symptoms being treated by the drug and its side effects. Finally, the effects of THC on driving must be studied so that informed policies can be put in place to ensure public safety.

Therapeutic doses of cannabinoids are significantly lower than the amounts traditionally associated with recreational use. Thus, the assessment of potential long-term harmful physiological effects and risks on public health should focus on therapeutic doses of medical cannabis preparations as opposed to commonly used recreational doses.

Conclusion

There is considerable literature demonstrating the efficacy of cannabinoid therapy for various types of pain, chemotherapy-induced nausea and vomiting, spasticity associated with MS, and anxiety. There remains a great need for larger, adequately powered and controlled studies evaluating the efficacy of cannabinoids for other indications. As the field moves forward, particular attention must be paid to the specific composition of the active ingredient/s best suited to treat specific symptoms, as well as the pharmacokinetic profile of the drug product. Further studies on the potential risks and health hazards associated with cannabis use are critical so that vulnerable patients can be protected, particularly from longer-term negative effects. These studies will be facilitated by the legalisation of cannabinoids for medical indications in strictly controlled circumstances with the development of quality-controlled products.

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Brendan Kennedy, Global President
Catherine Jacobson, PhD, Director of Clinical Research
Sean Carney, Director, Europe

+420 776 012 709

sean.carney@tilray.com
www.tilray.com