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ADVANCEMENTS IN CANNABINOID RESEARCH, PRODUCT OFFERINGS AND PATIENT ACCESS

A SUMMARY OF AVICANNA'S 3rd ANNUAL SYMPOSIUM - MEDICAL CANNABIS 2.0

HELD VIRTUALLY ON JULY 21st, 2020

Prepared By:
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AGENDA

Welcome Remarks and Introduction

Karolina Urban, Vice President Medical Programs, Avicanna Inc. (Moderator of Virtual Symposium)

Cannabis Pharmacology

Dr. Ruth Ross, PhD, Professor and Chair, Department of Pharmacology and Toxicology, Faculty of Medicine University of Toronto.

Medical Cannabis 2.0 & Avicanna's RHO Phyto Product Offerings

Dr. Justin Grant, PhD, MBA. Executive Vice President of Scientific Affairs, Avicanna Inc.

Developing Advanced Cannabinoid Formulations

Department of Pharmaceutical Sciences, Leslie Dan Faculty of Pharmacy, University of Toronto.

Anxiety, Depression and other Co-morbidities in Patients to be Treated with Cannabinoids: Implications for Optimal Care

Dr. Amza Ali, Chief Medical Officer, Avicanna Inc.

Real World Evidence and the Future of Medical Cannabis- Cannabinoid Medicine for Pain Management

Dr. Hance Clarke, Director of Pain Services, Toronto General Hospital, University Health Network.

Medical Cannabis by Shoppers

Neil D'Souza, Senior Manager, Operations, Shoppers Cannabis Care Centre.

Panel Discussion - Current Gaps and the Evolution of the Cannabis Sector

Patt McCutcheon, CEO MediPharm Labs; **Kaveh Kahen**, CEO Sigma Analytics; **Aras Azadian**, CEO Avicanna Inc; **Al Harrington**, Founder Viola Inc.

BACKGROUND & KEYNOTE REMARKS

Avicanna's 3rd annual Medical Symposium, "Medical Cannabis 2.0: Advancements in Cannabinoid Research, Product Offerings, and Patient Access", was held virtually on the 21st of July, 2020.

The purpose of the Symposium was to highlight the current state of advancements in the medical cannabis industry in Canada and abroad as well as underlining the key areas of research and product development. In addition, the speakers address patient access for medical cannabis products currently being offered on the market. This event brought together more than 1,000 participants including clinicians, researchers, regulatory affairs specialists, investors, members of the pharmaceutical industry and key representatives in the Canadian cannabis field.

This year's Symposium highlights opportunities in the cannabis industry from listening to patient and healthcare practitioner's (HCPs) needs and expectations as a result of changes in the regulatory landscape. In response, the industry began evolving a new standard to create better products, novel delivery forms, and higher quality standards, with a greater interest to develop more data. A wide range of topics were covered during the virtual event including critical considerations in drug development, product quality, new regulations allowing for optimization of new products with the patient perspective in mind, and the continued education for HCPs. This symposium provided insights into the clinical understanding of cannabinoid use for specific medical conditions, including common mental health comorbidities. Also, individual approaches to patient care are viewed as critical in determining the dosage and delivery form as well as the cannabinoid ratio. Lastly, the discussions of how clinicians are currently working with industry partners to evaluate products and the role of cannabinoids in pain management were described.

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CANNABIS PHARMACOLOGY

Dr. Ruth Ross, PhD

Professor & Chair, Department of Pharmacology & Toxicology, Faculty of Medicine University of Toronto; The Director of the Centre of Collaborative Drug Research at the University of Toronto; and Senior Scientist at the Centre for Addiction and Mental Health

Components of a pharmacological system include natural activators (agonists), receptors for these natural compounds, and enzymes that degrade these compounds. Cannabis contains many constituents (minor cannabinoids) that comprise a novel pharmacological system. Much of the mechanism of action and function of these minor cannabinoids remains unknown. The endocannabinoid system (ECS) is a really important multi-faceted system involved in brain function, learning and memory, stress, pain, mood regulation, cardiovascular, digestive, ocular pressure, and liver effects to name a few. Tetrahydrocannabinol (THC) is a partial agonist for the CB1 receptor in the central nervous system and the CB2 receptor mainly expressed in cells of the immune system. The main psychoactive effects of THC are mediated though cannabinoid receptor activation resulting in decreases of cAMP though adenylate cyclase inhibition. THC can act as a CB1 activator mimicking endocannabinoids, and it can act as a CB1 blocker and inhibit endocannabinoids. The effect of THC can be hard to predict since it is dose dependent and dependent on endocannabinoid tone and the role of the endocannabinoids in various disease states. Prior studies have shown that Δ9-THC suppressed the migration of natural killer (NK) cell migration induced by 2-AG[1], and that Δ9-THC acts as an antagonist toward the CB2 receptor[2]. Noticeably, several investigators have demonstrated that Δ9-THC suppresses various immune responses in vivo; for example, the administration of Δ9-THC to experimental animals results in a decreased resistance to viral and bacterial infection[2]. Taken together, it is plausible that Δ9-THC interferes with the action of 2-AG, such as the migration of NK cells, thereby inducing the suppression of innate and adaptive immune responses. These results are summarized in Figure 1.

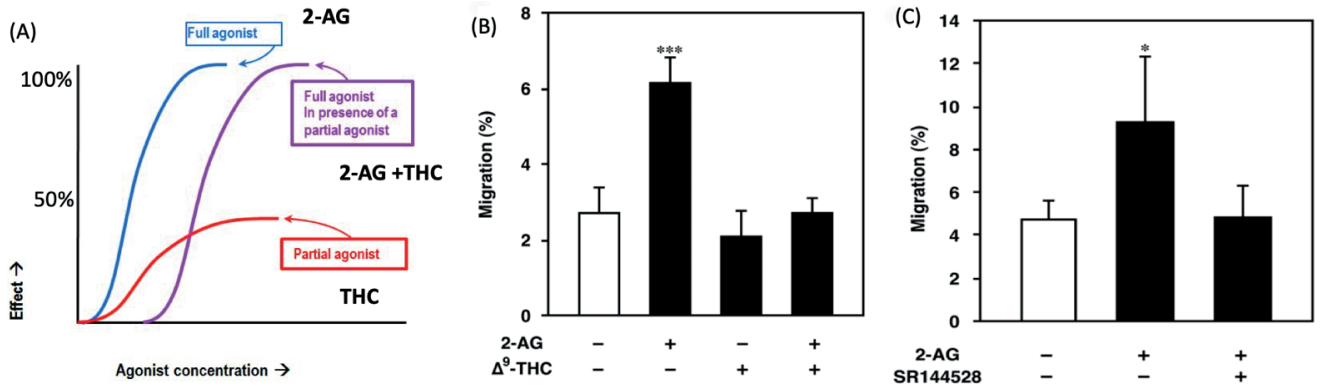


Figure 1: (A) Dose response curve of THC showing how it acts as a partial agonist, a full agonist and an antagonist. When you have a lower efficacy agonist, then THC is competing and shifts the curve of 2-AG to the right (like an antagonist), therefore the effects of THC can be harder to predict in certain disease states and in certain brain regions. (B) Effect of Δ9-THC on 2-AG–induced migration of leukemic natural killer (NK) KHYG1 cells. The migration of cells from the upper to lower compartment in response to 2-AG (1 μM) or Δ9-THC (1 μM) or 2-AG plus Δ9-THC (1 μM each). (C) Effect of 2-AG on the motility of human peripheral blood NK cells. Images adapted from Kishomoto et al., 2005 Journal of Biochemistry (137)2:217-23.

Some important requirements for a novel medicine relate to therapeutic targets (e.g., in pain relief), in selectivity, suitable pharmacokinetics (PK), metabolic stability, good bioavailability, reliability, with clinical efficacy and lastly with safety and the absence of any serious unwanted side-effects. Multiple clinical evidence in the effectiveness of cannabis have found positive results with pain in MS with both THC and CBD, with nausea and vomiting using THC, and in epilepsy with CBD, whereas other illnesses require more evidence. One of the most recent scoping reviews of systemic reviews on the benefits and harms of medical cannabis concluded that the results were mixed, with most reporting an inability to draw conclusions due to inconsistent findings and a lack of rigorous evidence. Mild harms were frequently reported, with possible harms of cannabis-based medicines outweighing benefits[3]. In addition, when developing a new medicine, tolerance to THC and acute classic cannabimimetic effects and chronic dose dependent effects should be accounted for when optimizing dosing regimens. Prior investigations have shown that tolerance can develop in some brain regions and not in others[4] which opens up an opportunity for future research to understand why there are regional brain difference in CB1 receptor tolerance. Other considerations for the creation of novel medicine include the dose, components, route of administration, frequency of use, intensity and timing, age, gender, genes, and the medicinal effect. Prevention of unwanted side effects (for example with THC) include psychoactive effects, risks of schizophrenia in vulnerable individuals, postural hypotension, increased heart rate, risk of cancer when smoked, dependence and withdrawal, and impairment with driving and certain jobs.

The pharmacological challenges of understanding the implications of how the endocannabinoid system (ECS) can be both down and upregulated needs to be considered for drug development. The ECS may be upregulated in a disease state and may be upregulated to produce an auto protective effect as exemplified in pain relief and can be upregulated to auto impair or exacerbate symptoms such as in fatty liver disease or obesity. In addition, the dysregulation of the ECS may exacerbate symptoms in some other illnesses, including chronic stress or Post Traumatic Stress Disorder (PTSD). When considering the development of medical cannabis, the effects in all these scenarios may be very different. If an investigator would want to tune up a system that is down regulated, then THC may be helpful. However, if the ECS is already ramped up to produce a protective effect, and a partial agonist is added, then the outcome may be more like that of an antagonist. Future studies would need to assess this outcome. Moreover, when considering cannabis as a medicine, good evidence of clinical efficacy where the benefits outweigh the risks, are of importance. More data is required on the effects of chronic use of Cannabidiol (CBD). It still remains unclear how CBD works and its poly-pharmacology. In addition, CBD is a potent inhibitor of Cytochrome P450 enzymes that are responsible for inactivating many prescription drugs. CBD may increase serum concentrations of SSRIs, tricyclic antidepressants, antipsychotics, beta blockers and opioids (including codeine and oxycodone). It is therefore important to assess CBD with drug to drug interactions.

To summarize the complex pharmacology of cannabis, THC is a partial agonist at the CB1 and CB2 receptors and can also function as an antagonist and there are regional brain differences for the development of tolerance. There is a difference in endocannabinoid 'tone' in various diseases that can be auto-protective or auto-impairing. In addition, there is a mix of THC, CBD and other minor cannabinoids and components where CBD has effects on the metabolism of THC and of other medications. As the ECS regulates the body's homeostasis, we need to understand how the exogenous administration of cannabinoids can affect the body. A number of considerations are required when evaluating medicinal cannabis that include; dose, its constituents, route and frequency of administration. In conclusion, we need more evidence for the medicinal effects and measurement of side effects in specific illnesses. There is a need for more data, research and education on the potential harms to the public of recreational cannabis use. Lastly, there is a need to design and implement placebo-controlled, randomized, double-blind clinical trials for safety and efficacy[5].

MEDICAL CANNABIS 2.0
& AVICANNA'S RHO PHYTO PRODUCT OFFERINGS

Dr. Justin Grant, PhD, MBA
Executive Vice President of Scientific Affairs
Avicanna Inc.

There are many clinical indications for medical cannabis and as of July 2020 nearly 1,000 clinical trials are listed on clinicatrials.gov with 72 of these clinical trials are being held in Canada on 117 conditions. The National Academy of Sciences, Engineering, and Medicine (NASEM), published a report in 2017 that reviewed nearly 10,000 abstracts on many clinical conditions and looked at the evidence of cannabis linked to these indications or symptoms. This list was updated in 2018 and published in the European Journal of Internal Medicine that found conclusive and substantial levels of evidence of medical cannabis for the following indications: Chemotherapy-induced nausea and vomiting (CINV), chronic pain, epilepsy, and in spasticity symptoms associated with multiple sclerosis (MS). Moderate evidence was found in glaucoma and sleep disturbances associated with chronic pain, MS, fibromyalgia, and sleep apnea. Limited evidence remains for indications surrounding anxiety disorders, appetite and weight loss with HIV/AIDS, dementia, Parkinson's Disease (PD), PTSD, Schizophrenia, Tourette Syndrome, and with Traumatic Brain Injury (TBI). Lastly, insufficient evidence to support or refute medical cannabis were found in abstinence, amyotrophic lateral sclerosis, cancer associated anorexia, cachexia, anorexia, chorea and neurological symptoms associated with Huntington's Disease (HD), dystonia, Irritable Bowel Syndrome (IBS), and with PD. Many of the trials that had conclusive or substantial evidence used products such as oils and sprays instead of smokable products, which is a trend that is currently increasing in the industry.

The evolution of medical cannabis in Canada has had a significant rise in interest amongst healthcare practitioners and patients in recent years. Sixteen million Canadians (17%) currently use cannabis, 39% of users are registered and are seeking guidance from HCPs. According to Health Canada, the number of active medical registrants has substantially increased over time with over 370,000 patients currently registered as federal license holders. In addition, 75% of medical cannabis users prefer smokeless and non-inhalable products. The largest category of growth for medical cannabis use has been found among seniors due to their increased number of comorbidities and they often seek natural alternatives.

There are a number of industry gaps for medical cannabis products. Although there is a trend moving away from cannabis inhalation and smokable products, there are currently only a few non-inhalable alternatives for patients. In addition, there is a lack of product stability requirements that may result in poor dose accuracy, consistency, and efficacy. Other industry gaps surround the paucity of research and development (R&D) of advanced formulations resulting in simple formulations that are not optimized for increased efficacy. There is a lack of delivery forms and cannabinoid profiles resulting in a limited variety of products to address specific patient needs. Lastly, these products are expensive, primarily those that contain high levels of CBD that could lead patients to choose illicit markets and self-medicate. Although industry gaps remain, Health Canada amended regulations in the Cannabis Act in October 2019 to introduce more advanced products and various drug delivery forms that include: vaporizers, edibles, extracts, topicals, sprays, capsules, oils, creams, and gels. These new regulations also include the ability to utilize advanced formulations and increased quality controls. Extracts may contain flavoring agents for improved taste and additives to increase quality and preserve the product and cannabinoid stability. Lastly, regulations have expanded on analytical testing as cannabinoid doses must be within 15% of the product label, microbial, chemical and solvent residue testing for these new products, and dissolution or disintegration testing are required for some products.

Edibles

- 10mg THC per package
- No vitamins or minerals
- Natural caffeine (<30mg)
- <0.5% w/w ethyl alcohol

Topicals

- 1000mg of THC per package
- "Hot List" of prohibited or restrictive ingredients

Extracts

- 10mg/unit, 1000mg/package THC
- No vitamins or minerals
- Max 7.5 g if contains ethyl alcohol
- No sugars, sweeteners, sweetening agents or colouring

General

- No health, dietary or cosmetic claims
- No nicotine or alcohol
- Not appealing to youth
- Must be Child resistant

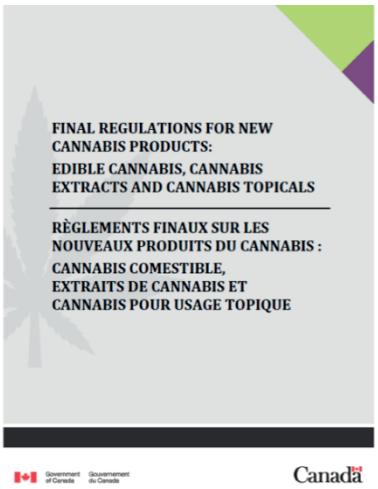


Figure 2: Examples of the new guidelines, restrictions and limitations for new cannabis products from Health Canada.

With all these regulations in mind, Avicanna Inc. developed the RHO Phyto line of products. These are phytotherapeutics with high quality natural cannabinoids such as CBD and THC in many ratios and dosage forms. RHO Phyto products are **discrete**, **odourless**, with **controlled dosing** and designed for easy titration. Products have been optimized with advanced formulations for **higher absorption, faster onset and long-term stability.**

Table 1: Avicanna's quality approach for RHO Phyto. Ideal properties of therapeutic agents.

	Accuracy of Dosing	Bioavailability	Onset of action	Stability	Reproducibility	Drug Delivery
Definition	How close the dosing unit is to the intended dose	The percentage of the dose absorbed into the bloodstream	Duration of time for the effects of a product to start working	A products ability to maintain its physical & chemical properties and concentration of cannabinoids over time	Degree to which the same drug and formulation properties are achieved over time	The dosage form and route of administration
RHO Phyto Approach	**Standardized methods to provide accurate cannabinoid concentration**	**Advanced formulations to increase absorption backed by preclinical studies**	**Optimized formulations for faster onset versus basic MCT oil**	**Formulations tested to ensure the stability of cannabinoids for extended period of time**	**Standardized operating and quality assurance procedures**	**Products delivered via oral, oromuscosal and topical methods**

The RHO Phyto product line includes products with various routes of administration such as oral (oil drops, capsules), oromucosal (sublingual sprays), and topical (creams and gels) and each delivery form has specific advantages. For example, oil drops allow the patient to titrate themselves providing both convenience and discreetness. Capsules have a predetermined dosage, easy to regulate and are a common form of medication that patients are comfortable with administering. Sublingual sprays offer faster onset compared to MCT oil and are convenient and discreet. Lastly, topical creams and gels are ideal for local or deep tissue delivery and have less systematic effects.

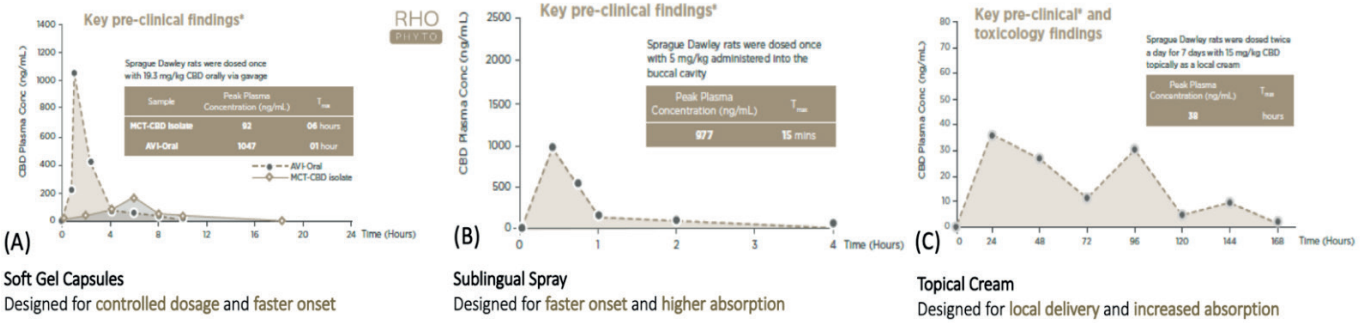


Figure 3: RHO Phyto preclinical research conducted at the University of Toronto in the Faculty of Pharmacy. (A) The soft gel capsule peak plasma concentration is ~1,000 ng/mL of CBD occurring within 1 hour of administration, whereas the MCT-CBD isolate oil's peak plasma concentration is ~100 ng after 6 hours. Thus, RHO Phyto's formulation was 10 times higher in plasma concentration and 6 times faster to reach peak plasma levels than MCT-CBD oil. This shows a higher bioavailability and faster onset for our capsules compared to simple formulations that are currently on the market. As a result, patients would see a more rapid onset of effects that may prevent potential overdosing. (B) The RHO Phyto sublingual spray also has higher absorption with a peak plasma concentration of ~1,000 ng/mL of CBD occurring at 15 minutes so the patient can have faster effects for acute conditions. (C) The topical cream for local delivery showed increased absorption when dosed 2x daily with a peak concentration at ~40 mg/mL (y axis: CBD plasma concentrations (ng/mL); x axis is time (hours).

Table 2: Risks associated with THC are important for patients and HCPs to understand. Individual patient needs and circumstances should be evaluated.

Risk	Description
Prescribing to those under 25 years of age	• The adolescent brain is still developing, therefore they may be more vulnerable to negative effects on brain structure and function. • Patients under the age of 25 are at greater risk for psychosocial harm related to cannabis use, including suicidal ideation, persistent psychosis, and illicit drug use.
Prescribing for older adults	• Older adult patients have an increased sensitivity to neurological and psychoactive effects of medical cannabis, particularly to that of THC, and can feel dizzy and lightheaded. This is evident in older adult patients with dementia and those who are prone to falls. • If considered appropriate and utilizing a medically supervised prescription, elderly patients should start at the low end of the dosing range.
Psychosis or other psychiatric conditions	• Cannabinoid preparations containing THC should not be used in patients with a family history or previous episodes of psychosis, psychiatric conditions or major depression.
Heart disease cardiac/ coronary conditions	• Cannabinoids can affect a patient's heart rate and blood pressure levels, which can cause cardiac ischemia. • Only under careful supervision by their HCP should patients use medicinal cannabis if they have a history of heart disease or are receiving heart medications.
Pregnancy and lactation	• Medical cannabis should not be prescribed prior to or during pregnancy as it could affect the development of the fetus. • Medical cannabis should not be used by patients who are breastfeeding.
Liver disease	• A high degree of caution should be placed on patients with liver disease, as they may have more difficulty metabolizing cannabinoids.
Addiction and anomalous prescribing	• Addiction to medical cannabis is not common. However, care should be taken if patients have prior history with problematic substance use. • Sudden treatment cessation may elicit withdrawal symptoms that can include restlessness, irritability, insomnia, vivid dreams, and decreased appetite.
Other medications	• Cannabis use can worsen the cognitive impairment caused by opioids, benzodiazepines, other sedatives, and alcohol.

Health Canada 2018 [Information for Health Care Professionals]

Lastly, Avicanna is committed to providing education for HCPs and patients. The Avicanna Academy provides resources including the Health Care Practitioner Guide, Patient Guide, publications, and other content focused on education. Avicanna's My Cannabis Clinic, a patient onboarding system, allows patients to have access to medical cannabis with guidance from a healthcare practitioner. Lastly, Avicanna provides webinars, symposiums, courses, and works with patient advocacy groups.

DEVELOPING ADVANCED CANNABINOID FORMULATIONS

Leslie Dan Faculty of Pharmacy, University of Toronto

Cannabinoids are challenging molecules to formulate. This can be partly attributed to their physiochemical properties as cannabinoids are hydrophobic, lipophilic and chemically sensitive to environmental factors such as air, heat, oxygen, and light. Cannabinoids are largely insoluble in water and are metabolized in the body by liver enzymes reducing their bioavailability[6,7,8]. These are important considerations when designing formulations since drugs need to be molecularly dissolved in order to permeate cell membranes or to bind to receptors to elicit their physiological response.

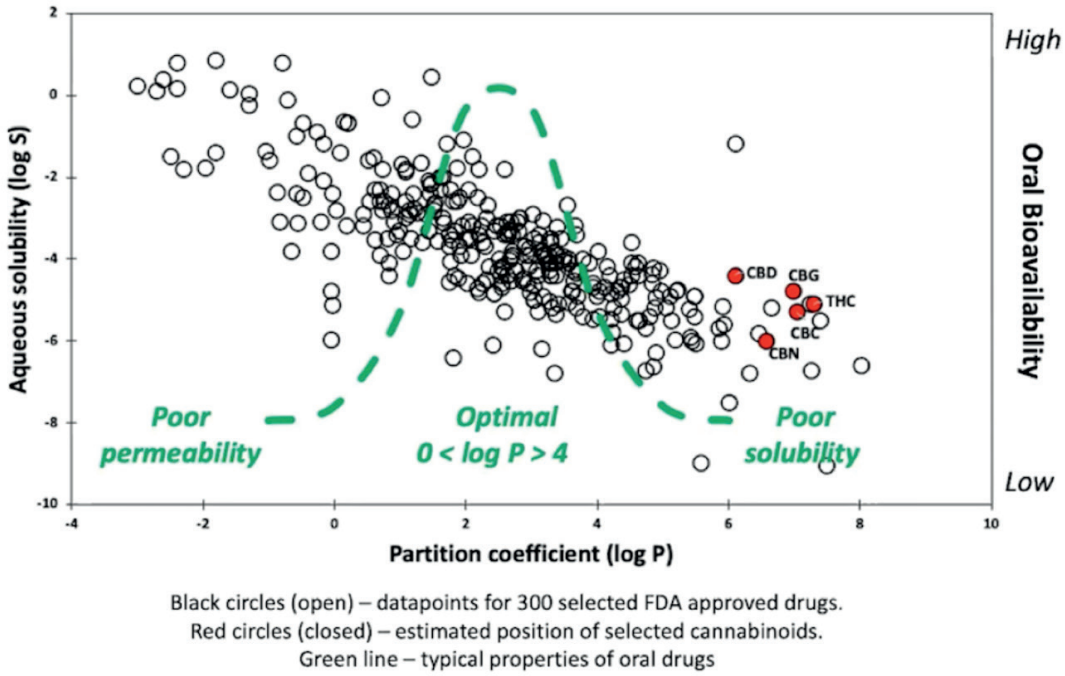


Figure 4: Properties of Cannabinoids in relation to other FDA approved drugs. This figure shows the relationship between solubility and lipophilicity for 300 FDA approved compounds. Estimated values of cannabinoids (red circles) were obtained from www.drugbank.com. The superimposed bell curve (in green), shows the typical properties of FDA approved oral drugs that have log P values ranging between 0 and 4. Generally compounds to the left of this curve will have poor permeability, and compounds to the right of the curve including cannabinoids have poor solubility. Increasing the solubility of cannabinoids can effectively move them to the center of the bell curve and make them better candidates for oral delivery.

Other challenging properties of cannabinoids is their chemical instability relating to photo, thermal and oxidative degradation[9,10]. Many of these studies have concluded that oxidative degradation is the most prolific cause of cannabinoid degradation, while exposure to light and higher temperatures tends to catalyze this degradation process. This sensitivity of cannabinoids to oxygen is reflected in their pharmaceutical products shelf-life. For example, the formulation tradenames Epidiolex and Sativex have shelf-lives of up to two years, but once these are open and exposed to air, their stability reduces to 12 weeks for Epidiolex and 42 days for Sativex from date of opening. This sensitivity to environmental factors is an important consideration when designing cannabinoid formulations. As a result, Avicanna's oil drop is formulated with natural antioxidant ingredients to enhance the stability of this product (See Figure 5).

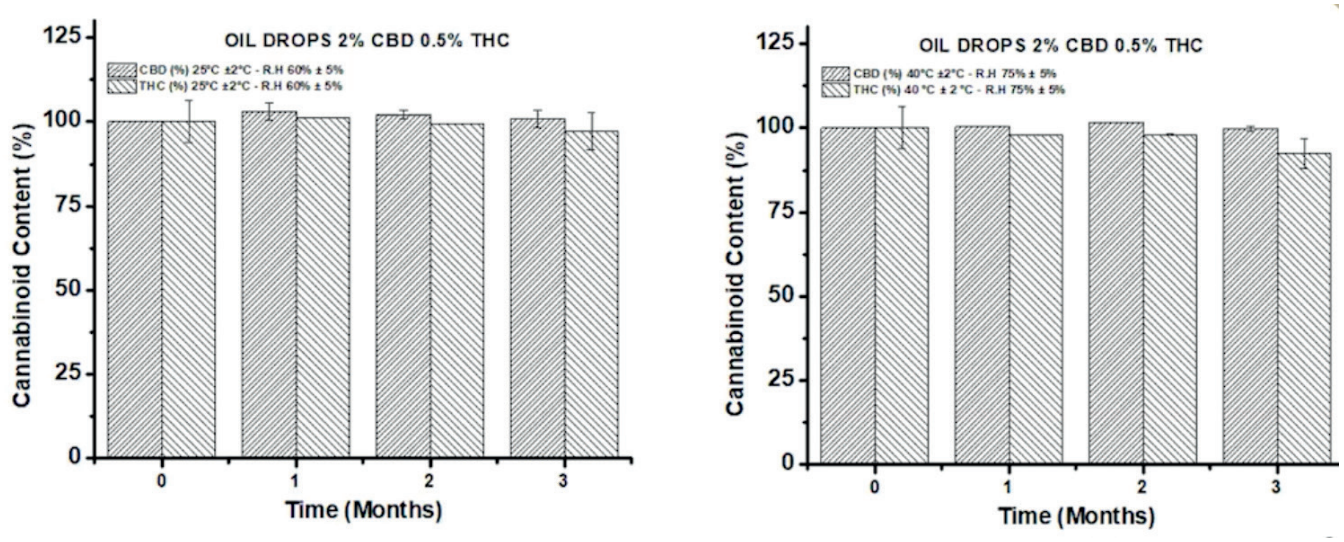


Figure 5: Stability of Avicanna's Oil Drops containing CBD and THC. Little to no loss of CBD and THC content was observed in the oil drop formulation over a 3 month period at 25ºC (left) and 40ºC (right). *Data provided from Dr. F. Le Devedec and Dr. L. Bracco.*

The following considerations should be considered when designing cannabinoid formulations: cannabinoids require solubility enhancing excipients or formulations (i.e. nanoparticles), and stabilizing agents such as antioxidants. First-pass metabolism may be reduced or avoided by sublingual administration of cannabinoids (i.e. sublingual spray). Avicanna uses an enhanced oral formulation that contains a self-emulsifying drug delivery system (SEDDS) to increase cannabinoid solubility[11]. This design was implemented to significantly increase cannabinoid absorption. In 2019, Avicanna conducted a pilot study on a CBD micelle-based formulation that yielded greater absorption of CBD compared to other competitor MCT based products (Figure 6a). In addition, a study was performed to optimize the release of CBD from a gelatin capsule in PBS buffer at 37ºC using a USP dissolution apparatus (100 rpm) (Figure 6b).

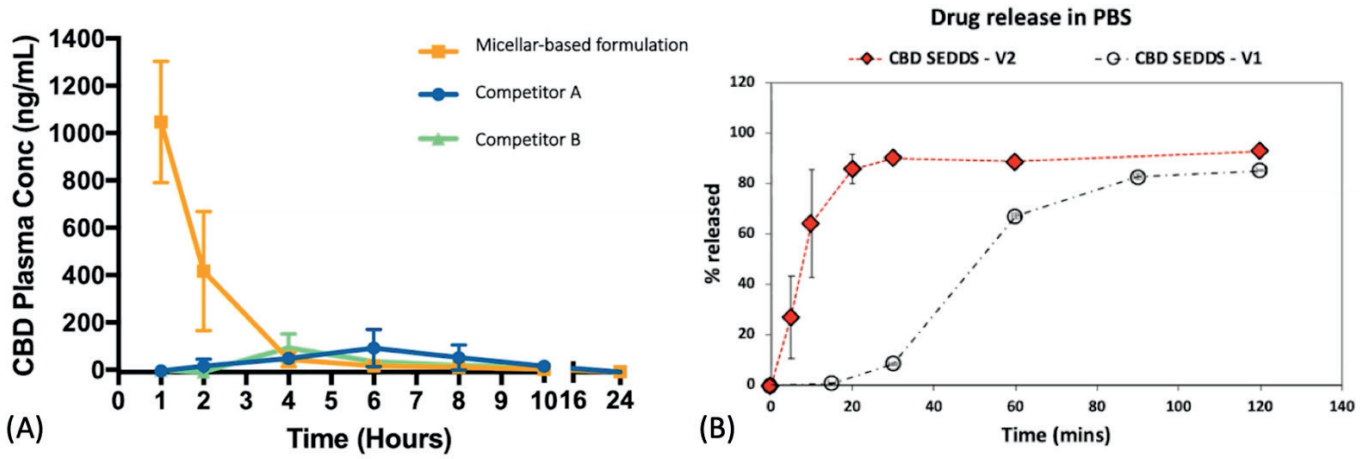


Figure 6: A pilot study on Avicanna's CBD oral delivery formulations s. (A) Plasma profiles of CBD over time in micellar CBD based formulations SEDDS (yellow) compared to competitor products that contain MCT CBD isolate (Competitor A - blue) and MCT CBD resin (Competitor B - green). The micellar based formulation showed a 10 fold increase in maximum plasma levels compared to controls. (B) An optimized capsule formulation containing CBD SEDDS (v2-red diamonds) demonstrated increased drug loading with an antioxidant agent and had a faster release profile, which may provide higher bioavailability.

Epidermolysis Bullosa (EB) is a rare genetic skin disorder that causes severe skin blisters in children and adults. There is currently no cure for EB, although there is some anecdotal evidence that CBD can be used to control its symptoms[12]. Avicanna has designed and optimized a topical CBD formulation for the treatment of EB and is pursuing Phase II/III clinical trial testing.

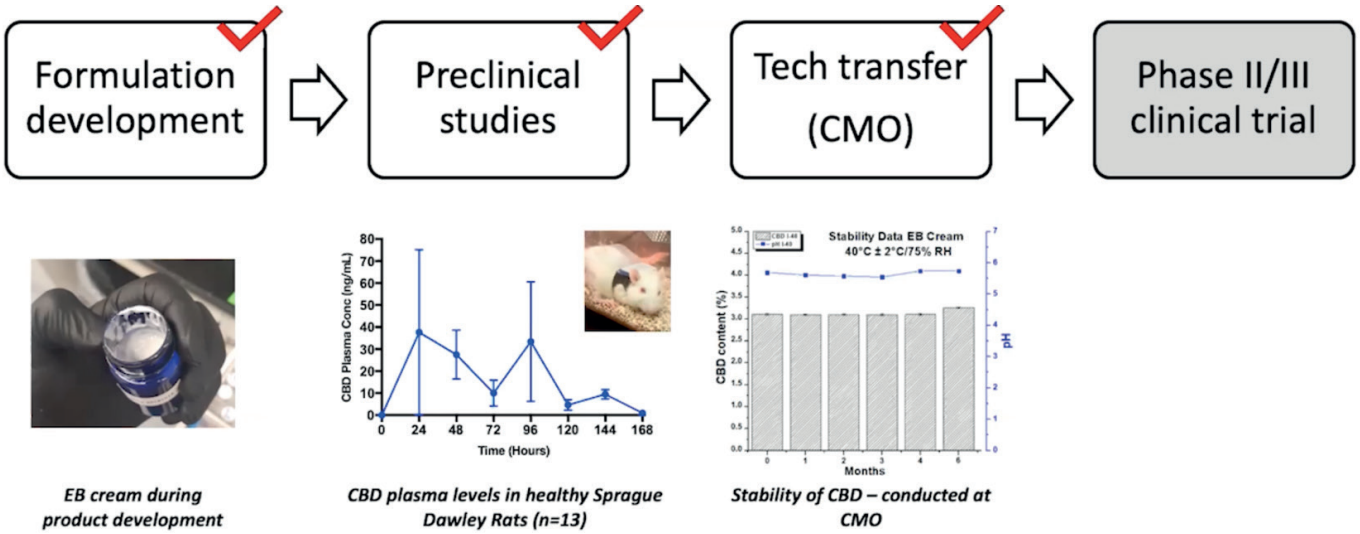


Figure 7: Stages of development for Avicanna's topical CBD cream for the treatment of Epidermolysis Bullosa.

Current work in engineering nanotechnology formulations of cannabinoids for treatment of COVID-induced lung inflammation is underway. Many COVID-19 patients have demonstrated symptoms of the 'cytokine storm' and have been associated with acute respiratory distress syndrome (ARDS)[13,14]. Prior studies have shown that CBD reduces the expression of cytokines in rodent models of lung-injury[15]. Based on this evidence, CBD and other cannabinoids may reduce the expression of pro-inflammatory cytokines and as a result, may offer therapeutic benefits in preclinical models of COVID-19. In collaboration, Avicanna aims to develop an intranasal formulation of cannabinoid nanoparticles as a safe and effective treatment of COVID-19 related inflammation.

In conclusion, cannabinoids are challenging molecules to formulate, advanced formulations such as SEDDS have demonstrated increased loading and enhanced absorption in comparison to existing MCT based oil formulations. Preclinical characterization of cannabinoid formulations are important to ensure the safety, stability, and efficacy of the products. Preclinical data on Avicanna's topical cream formulation was used to support a CTA application to Health Canada for the dermatology condition EB. Lastly, we are developing cannabinoid formulations that may have potential for treating symptoms associated with COVID-19 lung inflammation.

ANXIETY, DEPRESSION AND OTHER CO-MORBIDITIES IN PATIENTS TO BE TREATED WITH CANNABINOIDS:

IMPLICATIONS FOR OPTIMAL CARE

Dr. Amza Ali, MBBS, DM, MSc, FRCP, FACP, FAAN, FAES, MBA
Chief Medical Officer
Avicanna Inc.

A comorbidity can be defined as any additional condition co-occurring with a primary index condition. These conditions can often be behavioral, or a mental health disorder. Common comorbidities include anxiety, depression, anorexia, and sleep dysfunction. Comorbidities are often mental health disorders especially when the primary condition is neurological. They are associated with worse health outcomes, more complex clinical care, increased health care costs, and may even be worse for the patient than their index condition. When we focus on only the index condition, we miss an opportunity to provide optimal care to patients. Models have been developed that characterize the relationships of health burdens to quality of life (QoL), but also include considerations of economic, sociocultural, environmental, and patient behaviour factors. Disease factors interact with social and economic factors to make management more challenging, time-consuming, and resource intensive. Untreated comorbidities may lead to worsening of the primary index condition, resulting in a decline of QoL. In addition, the patients' perspectives of how multiple conditions affect their health and well-being are highly relevant to the constructs of comorbidity. The temporal sequence of comorbidities and their timing in relation to the index condition should be taken into consideration, instead of only looking at it cross-sectionally.

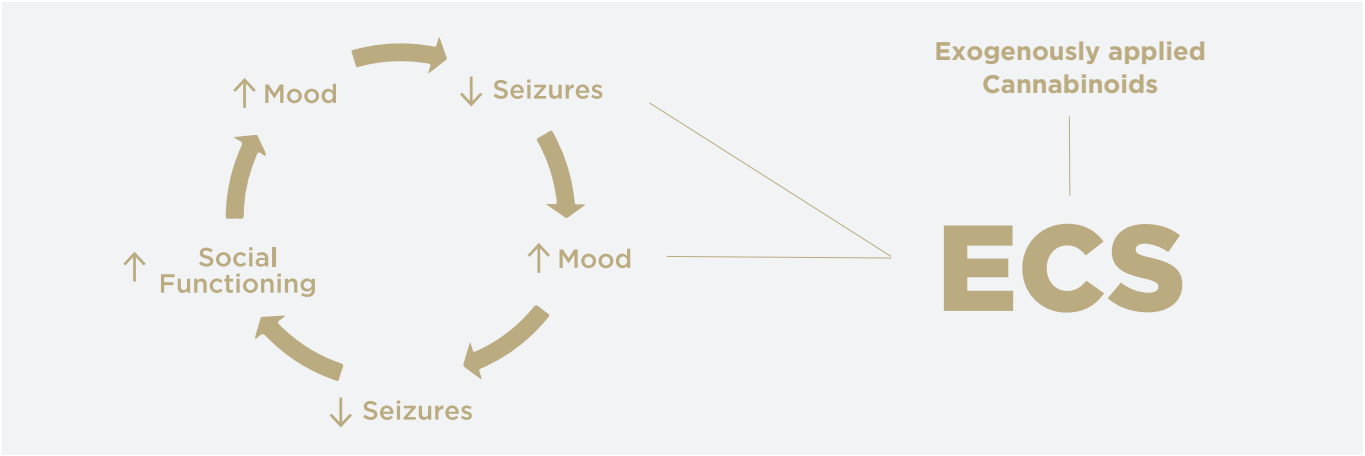
In order to understand why one may develop unwanted health comorbidities alongside index conditions, a better understanding about the limbic and endocannabinoid systems is helpful. **The limbic system (LiS)** is a system seated deep inside the brain and is responsible for elaborating mental health comorbid conditions in patients with primary conditions. It is responsible for our emotional lives but also many higher mental functions, such as learning and formation of memories, The LiS is comprised of the amygdala (emotion centre of the brain), hippocampus (formation of new memories), thalamus and hypothalamus (involved in changes with emotional reactivity, basal ganglia (involved in habit-learning and motor behaviour), and the cingulate gyrus (places an emotional content to our memories). There is a particularly high density of CB1 receptors in the limbic system involved in epilepsy and mood dysfunction.

The endocannabinoid system (ECS) is a homeostatic system widely distributed throughout our body with a close interface with the LiS. Anandamide (bliss chemical) AEA, and 2-arachidonoyl glycerol (2AG) are two endocannabinoids that are produced by our body and interact with receptors to produce changes in function with different organ systems and that are degraded enzymatically by the ECS. For example, the ECS heightens our sense of smell and augments taste when hungry, to change behaviour to seek food and enjoy it more. In regulating the LiS through the ECS, we may improve not only the primary condition (e.g. epilepsy) but also the comorbidity itself as well as lessen the impact of the comorbidity on the primary condition. Endocannabinoids have been found to be involved in an "on

demand" protective mechanism against seizures[16], wherein lower levels of cerebral spinal fluid (CSF) AEA levels in patients with epilepsy were found[17]. In addition, a strong negative correlation was found between serum AEA content and Hamilton ratings for anxiety[18].

What is important to note is that worsening of the comorbidities can worsen the index condition creating a vicious spiral of unwanted health outcomes. For example, prior studies showed that the effect of depression doubles the risk of seizures[19]. Seizure frequency and depression are the most important predictors of quality of life in epilepsy patients. The management of patients with epilepsy should not only be aimed at just preventing seizures but the treating clinicians should also be cognizant about depression which itself can significantly affect the quality of life of patients[20].

One route of treatment to correct the endocannabinoid-LiS balance is with **exogenous cannabinoids** to improve not only for example, seizure control, but to also improve the associated mental health comorbidities that were themselves worsening seizure control. Therefore, manipulating the ECS can positively influence the multiple functions of our LiS.



However, using exogenous cannabinoids for treatment of both index conditions and comorbidities is not straightforward. Success depends on a number of factors some of which include: what the specific index condition is, which cannabinoid and in what combination it is used, what and how many comorbidities exist and the possibility that the exhibited cannabinoid could help or worsen one or more of the associated comorbidities. Drug interactions may occur with other drugs patients are taking particularly if they share the same liver-enzyme based metabolic pathway, and conversely that these drugs may potentially also have an impact on the pharmacokinetics of the cannabinoid and thus the risk of side effects from cannabinoids.

When treating patients" comorbidities with cannabinoids, a pan-holistic approach is needed including non-pharmacological options, understanding the relationships between primary index condition and comorbidities, monitoring the effects of cannabinoids on the comorbidities and the medications being used for these, as well as determining the potential impact of co-administered drugs on the effect of the prescribed cannabinoids.

In summary, the close relationship between two ancient systems, the limbic system, which is responsible for our emotional state, and the endocannabinoid system may provide a unique opportunity with use of exogenous cannabinoids to influence not only the primary medical condition but also the associated mental health comorbidities, which contribute profoundly to a patient's quality of life when living with a chronic condition.

REAL WORLD EVIDENCE AND THE FUTURE OF MEDICAL CANNABIS

CANNABINOID MEDICINE FOR PAIN MANAGEMENT

Dr. Hance Clarke, MD, PhD, FRCPC
Director or Pain Services – Toronto General Hospital, University Health Network

When we look at products that we can use from a pharmacological standpoint, the following Table 3 lists prescription DINs for cannabinoids that HCPs can prescribe to individuals like Nabilone (a synthetic THC drug), and Sativex (an oromucosal spray with a 1:1 THC to CBD ratio).

Table 3: Prescription DINs of Cannabinoids

Name	Description	Approval status
Nabilone (Cesamet)	Oral capsule (0.25–1.0 mg)	Approved in Canada for **chemotherapy-induced nausea and vomiting**
Nabiximols (Sativex)	Oromucosal spray (2.5 mg THC + 2.7 mg CBD/mL)	Approved in Canada for **MS-associated neuropathic pain, spasticity and advanced cancer pain**
Dronabinol (Marinol)	Oral capsule (2.5–10 mg THC)	**Not available in Canada**
Epidiolex	Oromucosal spray (98% pure plant-derived CBD)	FDA-approved for **drug-resistant epilepsy**; only available in Canada via study protocols

The statistics of cannabis use have increased over the past years. 40% of Canadians have admitted to cannabis use in their life, and 10% have used for symptom management. Since October 2018, at the turn of legalization, the numbers started to rapidly increase and have reached over $180 million in sales per month as of April 2020 in Canada. In addition, a survey for over 600 orthopedic surgery patients at Toronto Western Hospital found that approximately 20%, or 1 in 5 patients were using a cannabis product to manage their musculoskeletal (MSK) related arthritis pain.

It is important to know what types of cannabis products patients are consuming. This can be accessed by conducting a real-world evidence (RWE) clinical trial. A RWE trial is a study in which a HCP authorizes a patient with a medical document for a validated strain of a cannabis product where all the constituents are thoroughly known and can only be obtained from 1 of 12 licensed producers. Data is collected at baseline, 3 week, 1 month and 6 month time points to look at patient pain-related outcomes, anxiety, depression, overall satisfaction, and quality of life outcomes. Adults aged 19 or more with a valid medical document provided by their HCP virtually or on paper, can register with Medical Cannabis by

Shoppers and would need to provide informed consent. Moving the cannabis industry into an area of validation reliability allowed for programs like TruTrace Technologies to emerge as a master registry and "Smart Hub" for testing, product verification and quality assurance ensuring that patients and prescribers have confidence in the medicine being prescribed and for cannabis product tracking. The Centre for Cannabinoid Therapeutics at the University Health Network (UHN) in Toronto has established a virtual way for patients to be engaged while collecting outcome information utilizing patient apps, that become summarized into clinically meaningful reports and questionnaires completed prior to visits where progress and patient outcomes monitored remotely via a virtual portal. Patients wanting to take part in RWE trials can access the RWE microsite: www.MCRWE.ca that also contains training videos for HCPs. This is an excellent educational source for Canadian patients and HCPs.

The highest risk for poor outcomes in patients over the next 5 years are patients on **high dose opioids**[21]. Opioid weaning is important as millions of North Americans are on doses greater than 90mg /day. Tapering the dose can be difficult, as patients fear a return to a state of overwhelming pain. Several factors can increase the likelihood of success: the patient's readiness for change, psychological support, pharmacological support, and careful monitoring[21]. Opioids and cannabis have inter-related pathophysiology. Interplay between opioid and cannabinoid receptors have been described as having overlapping neuroanatomical distribution of receptors, particularly at the dorsal horn, locus ceruleus, and dorsal striatum. Co-activation of CB1 and mu/kappa opioid receptors may also play a role in the exogenous opioid sparing effect of medical cannabis. Studies looking at opioid weaning with cannabis are currently underway to assess the relationship between cannabinoids and weaning patients off of opioids. Preclinical studies have demonstrated robust evidence for opioid sparing effect of cannabis, however, human data is lacking and more research is needed.

MEDICAL CANNABIS BY SHOPPERS

Mr. Neil D'Souza
Senior Manager, Operations, Shoppers Cannabis Care

Medical Cannabis by Shoppers in Canada is a new initiative to support patient access to medical cannabis via their online portal that launched on January 8th 2019 in Ontario, April 23rd, 2019 in Alberta, and on December 3rd in the rest of Canada. Patients can access medical cannabis by placing orders online through Shoppers' e-commerce site or they can call their call center. HCPs can access a portal on their site to find out more information and resources for continued education and clinical tools. A number of benefits for both patients and physicians choosing Medical Cannabis by Shoppers are highlighted in Tables 4 and 5.

Table 4: Benefits and Values of Choosing Medical Cannabis by Shoppers.

Convenience & Selection	Clinical Guidance	Offering Value
Patient have access to a **variety** of medical cannabis products	Highly trained **advisors & pharmacists**	**No dispensing fee** for medical cannabis products
Benefits for patients • No need to switch LP when a product is out of stock **Benefits for physicians** • No need to issue more than one medical document	**Provide support and guidance on:** ✓ Selecting **an appropriate product** ✓ Titrating the dose ✓ Preventing and **managing side effects** ✓ Reviewing concurrent **medications**	• **Telemedicine** • Direct billing for **Veterans Affairs** • Support for **private insurers** • **Compassionate pricing** for lower income households • *Free shipping until July 15th and same day for GTA

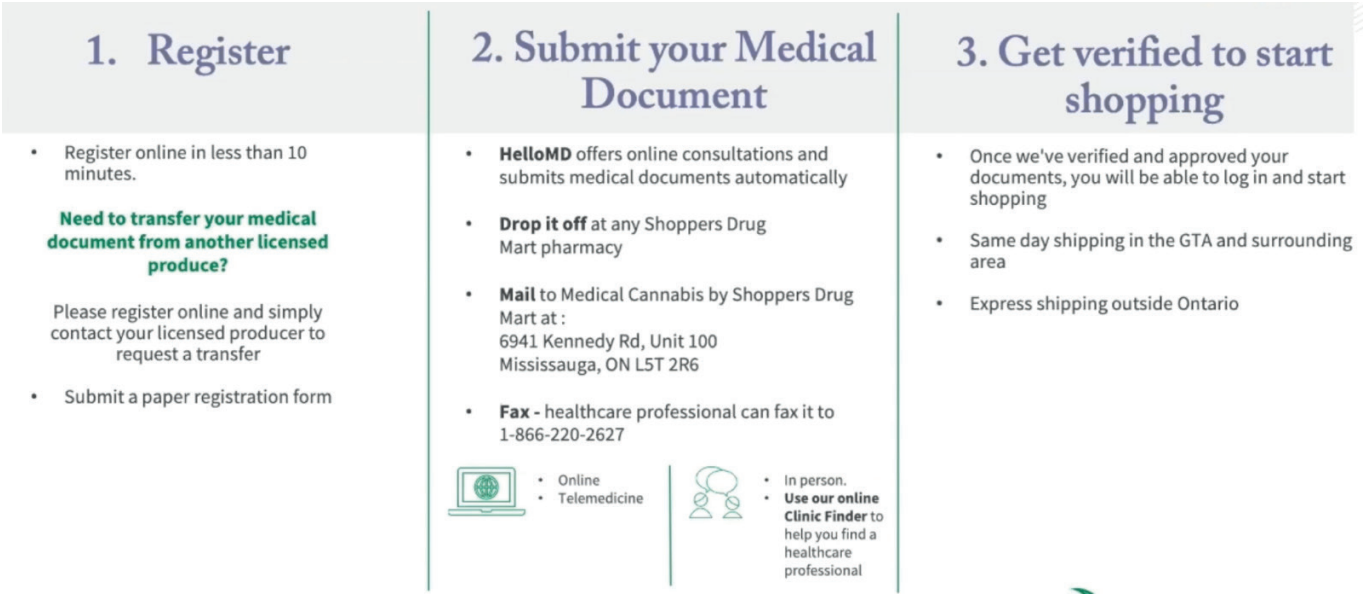
Table 5: Medical Cannabis by Shoppers is dedicated to providing high quality products and up to date information for patients and health care providers (HCPs).

High quality products		Up to date information	
Medical Cannabis	**Accessories**	**For Patients**	**For HCP**
✓ Capsules ✓ Dry Flower ✓ Cannabis Oil ✓ Vapes ✓ Topicals ✓ Edibles ✓ Sprays	✓ Vaporizers ✓ Infusers ✓ Storage Containers	✓ Shoppers Cannabis Care Team has Pharmacists and Advisors trained to help you choose what best suit your needs.	✓ Education ✓ Tools ✓ Free starter kit

The team at Shoppers Cannabis Care takes a traditional pharmaceutical approach similar to what is done in pharmacy. To begin, there is a detailed discussion with the patient to gather information and define clear treatment goals. The HCP recommends to 'start low and go slow' for cannabis-naïve patients, while ensuring that patients experience the therapeutic benefits of these products while minimizing any unwanted side effects. For more experienced patients, HCPs discuss using multiple-dose formats or 'as needed' dosing for help with their symptoms.

The Shoppers Cannabis Care team is made up of cannabis trained pharmacists and advisors that help patients navigate their journey with medical cannabis. The team is available to support patients with general inquiries, registration, product selection, technical support and with placing orders. Pharmacists are available to evaluate any clinical interactions with current medications, identify any potential side effects and provide follow up to ensure positive therapeutic outcomes. The patient process with registration is streamlined and exemplified in Table 6.

Table 6: Patient process and registration



Medical Cannabis by Shoppers is also collaborating with the University Health Network (UHN) for a real world evidence (RWE) study. The RWE is a research study to understand the effects of medical cannabis over a 6-month period in adult patients with chronic pain and associated issues with sleep, anxiety or depression. This study is the first of its kind in Canada and will include patients from across Canada and give researchers valuable information on the use of medical cannabis as a treatment option. Patients have access to strains of medical cannabis that have been genetically tested. Patients track their symptoms using standardized questionnaires. Shoppers created a partnership not only with UHN, but with TruTrace Technologies and qualified cannabis companies including Avicanna.

Patient support programs include direct billing services and insurance coverage is dependent on the patient's benefits provider. Insurance Coverage Suppliers include: Manulife, Great West Life, Johnston Group and WSIB to date. Prior authorization needs to be completed by the prescriber. If approved, the insurance company will notify the Shoppers Cannabis Care team directly. Alternative coverage options available include manual submission or utilizing Health Spending and Wellness Accounts. For veterans, Shoppers has created the Veterans Red Poppy Program. As part of this program, Shoppers will directly bill the Affairs Canada (VAC) for patients' claims. Patients do not have to pay out of pocket expenses. Medical Cannabis by Shoppers also offers the 'Good Faith Coverage' for the first 30 days (up to a

maximum of 90 grams) at no additional cost while VAC evaluates patients' application coverage. A compassionate program was initiated that provides patients who earn less than $30,000 annually to apply for 20% reductions on all products (stackable with price reductions). This emergency compassionate pricing is now available for individuals that have been affected financially due to COVID-19. Patients would need to call the Shoppers Cannabis Care team for approval. In addition, all patients over the age of 65 will qualify for an automatic senior's discount of 10% that's not stackable with compassionate pricing discount, and on the first Thursday of each month, seniors over 65 will receive a 20% discount on Seniors Day. Previously, free shipping was only offered on all orders exceeding 100$ before tax, however currently, free shipping is offered on all orders for all patients across Canada irrespective of price due to COVID-19.

PANEL DISCUSSION

CURRENT GAPS AND THE EVOLUTION OF THE CANNABIS SECTOR

Panelists:

Patt McCutcheon, *CEO MediPharm Labs*
Dr. Kaveh Kahen, PhD, *CEO Sigma Analytics*
Aras Azadian, *CEO Avicanna Inc.*
Al Harrinton, *Founder Viola Inc.*

What is required for the evolution of the cannabis sector is more data on unique formulations. The lack of data creates gaps for physicians who may not understand how the product should be used, at what dose, and how patients should be identified. The process is still cumbersome for physicians to write scripts for patients, in addition to being able to best identify which products would be most effective for a patient given their index health condition and comorbidities. More information needs to be relayed to physicians if the product is even available for purchase. This industry is moving towards a platform where a patient has: access to insurance coverage for different cannabis products, the option for a number of different cannabis products with data available to them, and lastly access to education both on their own and through their HCP and pharmacist.

Over the past century, due to the advancements in life sciences, we have seen a major boom in pharmaceuticals. In Canada under a Federally legalized system, we are able to expedite this process for research and development of cannabis products. The gap lies at the molecular level to obtain clear data and understand the exact interactions of cannabinoids with our receptors and understand and design proper dosages and formulations. Clinical trials have started, and once more are complete, we will hopefully end up with targeted formulations for very specific indications that are safe and show high efficacy.

Other gaps in this industry relate to separating particular formulations and product quality for a naïve versus more advanced user (or with medical versus recreational use). In addition, areas of research and development continue to look at controlled and consistent dosing, better titration, and with better education and training for physicians. By having these items in place with a data driven clinical approach, more substantial and accurate data will be obtained for better quality formulations and products.

Other gaps pertain to quality control (QC) testing and establishing Good Manufacturing Practice (GMP) standards as the minimum requirements for testing. The requirements for establishing a QC lab in Canada are ‘very light.’ All one would need is a room with a high-performance liquid chromatography (HPLC) system, security, and someone whose scientifically accredited to issue certificates for label claims. Although we are in the early days after legalizing, these can cause issues in the market, for example, inaccuracies in label claims resulting in recalls and lawsuits as well as labs inflating THC values in order to attract clients. However, there are clear pharmaceutical and food quality controls ensuring rigorous testing in labs with drug establishment licenses (DEL license), which is similar to GMP for QC. The market is currently, and will continue, to correct itself with migration to high quality labs and under Health Canada’s guidance to accelerate this process.

Further evolution in designing products with patient conditions in mind for efficacious outcomes is important. If one looks at pediatric populations, the product would require a high level of safety and

ease of use for a caregiver. For a palliative care patient, we need to have a product that gets quickly absorbed such as an inhaler or topicals for hip or knee pain that would need to be appropriately formulated for the target condition and health outcome. It's up to the cannabis industry, regulators, and companies to work better together to bring these medical benefits to patients.

CONCLUSIONS

The 3rd annual Avicanna Symposium highlighted the many opportunities and challenges that the medical cannabis field has to offer. The main conclusions from the symposium are as follows:

- Nearly 61% of people in Canada that are using medical cannabis for therapeutic indications are self-medicating. As an industry, we need to focus on education of both patients and HCPs who may not have all the access to training for understanding these products. Forums like this symposium and research publications are excellent resources for educating patients and HCPs.

- In the past, the benefits of cannabinoids were perceived to be derived from inhalation products, which was a huge misconception. Now, we have more evidence of the benefits in using non-inhalable delivery forms that patients and HCPs are learning about. For example, dermatology creams now provide relief with cannabinoids that have minimal systemic effects. These are alternatives that HCPs can prescribe without the adverse effects of inhalable or edible products.

- It is critical that there is a partnership between the patient and the HCP. It is only through a good rapport between patients and HCPs where patients reveal their perspective that could improve their quality of life.

- It is imperative that both HCPs and patients are educated on medial cannabis products. The variation in recreational cannabis lies between 10-12%. This is important since medical cannabis has to be standardized, verified, and tested to bring down this variability as the medical cannabis industry moves forward. Resources, education and more information on prescribing medical cannabis for physicians, researchers and for patients can be found at the Canadian Consortium for the Investigation of Cannabinoids (ccic.net) as well as the Medical Cannabis by Shoppers portal for HCPs.

- Canada was one of the first G7 countries to legalize medical cannabis use that allowed Canadians to set many of the testing standards early for product safety testing. Previously, Canada used a conservative approach to bring simple products to the market and now we are developing and producing more advanced products. With our approach, we are able to establish new IP on formulations and have opportunities for more clinical research to be conducted since they have been Federally approved for testing.

BIOGRAPHIES

Karolina Urban, MSc, PhD Candidate, *Avicanna Inc.*

Karolina is the Vice President of Medical Programs at Avicanna. Karolina is currently a PhD student in the Rehabilitation Sciences Institute and collaborative program in Neurosciences at the University of Toronto. As she is also a member of the Concussion Centre team, Karolina's research is focused on using various imaging techniques to explore brain alterations following pediatric concussion, including fNIRS and Magnetic Resonance Imaging (MRI). Karolina received her Bachelor's degree in the Faculty of Physical Health and Education with a minor in psychology from the University of Toronto. She then completed her MSc in Neurosciences from the University of Calgary while exploring brain function and communication using functional Near Infrared Spectroscopy (fNIRS) in pediatric concussion.

Dr. Ruth Ross, PhD, *University of Toronto*

Ruth Ross obtained a PhD in Pharmacology from The University of Edinburgh in 1990. In 2008 she became Chair in Molecular Pharmacology at The University of Aberdeen. In 2013 she relocated to The University of Toronto to take up the position of Chair of the Department of Pharmacology & Toxicology and Director of the Centre for Collaborative Drug Research. Dr Ross has been engaged in cannabinoid pharmacology research since 1994. Her research focuses on understanding the molecular pharmacology of the endocannabinoids, phytocannabinoids (cannabis) and new small molecules targeting the system. She has expertise in understanding the molecular pharmacology of endocannabinoids and phytocannabinoids including the physiological an pathophysiological role of the endocannabinoid system. This includes both the potential harms of recreational use and the safety and efficacy of cannabis as a medicine for the treatment of various illnesses. She is also the lead for the Ontario Consortium of Cannabinoids in Clinical Practice, an organization devoted to advancing evidence-based research and education of cannabis. Dr. Ross also co-leads the Toronto Consortium for Cannabinoids and Cannabis research (TC3), which is comprised of network of researchers at the University of Toronto and Toronto affiliated health services.

Dr. Justin Grant, PhD, MBA, *Avicanna Inc.*

Ruth Ross obtained a PhD in Pharmacology from The University of Edinburgh in 1990. In 2008 she became Chair in Molecular Pharmacology at The University of Aberdeen. In 2013 she relocated to The University of Toronto to take up the position of Chair of the Department of Pharmacology & Toxicology and Director of the Centre for Collaborative Drug Research. Dr Ross has been engaged in cannabinoid pharmacology research since 1994. Her research focuses on understanding the molecular pharmacology of the endocannabinoids, phytocannabinoids (cannabis) and new small molecules targeting the system. She has expertise in understanding the molecular pharmacology of endocannabinoids and phytocannabinoids including the physiological an pathophysiological role of the endocannabinoid system. This includes both the potential harms of recreational use and the safety and efficacy of cannabis as a medicine for the treatment of various illnesses. She is also the lead for the Ontario Consortium of Cannabinoids in Clinical Practice, an organization devoted to advancing evidence-based research and education of cannabis. Dr. Ross also co-leads the Toronto Consortium for Cannabinoids and Cannabis research (TC3), which is comprised of network of researchers at the University of Toronto and Toronto affiliated health services.

Dr. Amza Ali, MBBS, DM, MSc, FRCP, FACP, FAAN, FAES, MBA, *University of the West Indies/Avicanna Inc.*

Dr. Amza Ali MD, FRCP, trained in neurology and clinical neurophysiology in both the United Kingdom (UK) and in the United States. Dr. Ali is the global Ambassador for Epilepsy by the International League Against Epilepsy (ILAE) and the International Bureau for Epilepsy (IBE)., current president of the Epilepsy society of the Caribbean, and a Fellow of the American Academy of Neurology and American Epilepsy Society. After obtaining his initial medical training from the University of West Indies, Dr. Ali became a certified specialist in neurology by the Royal Colleges of physicians in the UK. He also received a certification in clinical neurophysiology from the Comprehensive Epilepsy Centre at New York Hospital of Columbia. He completed his MBA afterwards at the Rotman School of Management, University of Toronto. Dr. Ali is committed to improving the quality of care and welfare of patients with neurological disorders and towards the theory of convergence and practice in medicine and business including de-stigmatization of diseases and the development of technological innovations that will facilitate sustainable interventions. Dr. Ali's commitment to medicine has been critical in establishing pillars of Avicanna's medical program and clinical research collaborations.

Dr. Hance Clarke, MD, PhD, FRCPC, *University Health Network*

Dr. Hance Clarke is a staff anesthesiologist and Associate Professor at the Department of Anesthesia and Pain Management at the University of Toronto. He is the Director of Pain Services and the Pain Research Unit at the Toronto General Hospital. He is a member of the Royal College Clinician Scientist program and is the knowledge Translation Chair at the University of Toronto Centre for the Study of Pain. Dr. Clark has spent years revitalizing care for patients by developing the world's first translational pain service. This service is aimed at optimizing pain control and preventing the development of post-surgical chronic pain. In addition, he played a leading role in educating the public about pain control, discussing the alternatives to opioid use, and the need for further clinical research for adverse effects of cannabis. With over 100 publications, he is a champion of evidence- based solutions for the opioid crisis and the national pain and addiction strategy. In line with this pursuit of clinical evidence, Dr. Clark will be leading the first medical cannabis real-word evidence trial aimed at creating a national repository of data to evaluate the effectiveness of medical cannabis products.

Neil D'Souza, Senior Manager, Operations, *Shoppers Cannabis Care Centre*

Mr. Neil D'Souza is the Senior Manager of Operations at the Shoppers Cannabis Care Centre. He manages a team of pharmacists and cannabis care advisors who help patients navigate their journey with medical cannabis. Mr. D'Souza is a licensed pharmacist with over 10 years of pharmaceutical and managerial experience in medical cannabis, drug manufacturing, specialty, community, and hospital pharmacy. He has extensive experience working with cross-functional teams, launching new businesses, and managing products while providing tactical and strategical insights. Mr. D'Souza brings a unique perspective to this space with his experience and insight on the patient experience with medical cannabis.

Aras Azadian
CEO, *Avicanna Inc.*

Aras brings extensive senior management experience in the biotechnology and financial sectors including his involvement in several successful start-up companies. In addition to his international experience in corporate development, his diverse roles include his previous position as the president of an investment corporation in the cannabis space and former Chief Operating Officer of an oncology company. Aras holds a Bachelor of Economics degree from York University in Toronto, and an International Masters in Management degree from EADA Business School in Barcelona, Spain.

Pat McCutcheon
CEO and Chairmen, CoFounder *MediPharm Labs.*

Pat is a hands on CEO with a proven track record of over 15 years in the Pharmaceutical industry. As CEO of MediPharm labs, his core focus includes developing high quality business strategies in an evolving industry. Pat also bring together an extremely experienced and professional management team with a strategic range of industry experiences. Our role is to ensure our operations and business activities produce the desired results and are consistent with the overall strategy and mission.

Dr, Kaveh Kahen, PhD
President and CEO at *Sigma Analytics*

Dr. Kahen is a visionary and hands-on executive with 20 years of global experience delivering profitable growth in highly competitive life sciences, analytical testing, and analytical instrumentation markets. He has led major business units with full P&L responsibility and global R&D organizations. Dr. Kahen founded, led, and grew a start-up company to profitability in less than 2 years. He has spearheaded major growth initiatives and led large cross-functional and multidisciplinary teams in multiple projects and locations. He has initiated and managed parallel external collaborations with key opinion leaders in analytical instrumentation. In addition, Dr. Kahen has the innate ability to leverage a strong background in science, technology, finance, and business to drive innovation with a clear goal of revenue generation, customer satisfaction, and growth.

Al Harrington, PhD
Founder of *Viola Inc.*

Viola was founded by Al Harrington, a former NBA player who was a first-round pick in the 1998 NBA draft. Al became personally aware of the medicinal benefits of cannabis after suffering complications from a botched knee surgery towards the end of his NBA career, but the original inspiration for starting the company came from Al's beloved grandmother, Viola, who suffered from glaucoma and diabetes and found immediate relief for her pain after reluctantly trying cannabis. We began operating in Denver, Colorado in 2012 and Viola now operates in Colorado, Oregon, Michigan and California and has grown to become a respected, top-selling national brand in the cannabis industry.

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