

Dr. Ed

'The Case for CBD'

2019

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Dr. Edward Jones

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Biographies

Steve Caroll

Steve is the Chief Technical Officer of Afar Medical and has over 25 years of experience in design, development, manufacturing, quality, distribution and sales. Having graduated with an MSc from Cambridge University, Steve has also won the prestigious " Queen's Award" twice for designs that led to technological achievements. He has helped design three worldwide best-selling products and developed over 100 products within the technology sector including high-security technology for NATO and the MOD (UK).

His keen interest in physiology led him to help design new methods of wound management specific for the treatment of thermal Burns and his products have won retail awards in Asia.

Steve is a Certified Personal Trainer as well as a Certified Nutritionist and regularly promotes the 'science of nutrition' toward a healthier lifestyle.

He currently serves as a senior advisor to Dr. Ed.

Dr. Edward Jones

Edward is a keen biologist specialising in the field of neuroscience. His scientific training has been carried out in some of the most highly sought-after labs in the neuroscience arena at the University of Manchester. Edward was awarded a first-class degree in Biomedical Sciences in 2013 followed by obtaining a Distinction level Master's degree in Integrative Biology. These two degrees focussed on neuroscience techniques and disease modelling.

Edward then undertook a 4-year Neuroscience PhD in the field of Energy Regulation and Metabolism which involved the development and use of cutting-edge brain manipulation techniques.

He is a co-founder of Dr. Ed.

Alex McMillan

Alex has been in the Marketing industry for the past 10 years working both client and agency side. Most recently he co-founded Manchester based marketing agency Black Bear Digital which works with clients of all sizes from start-ups to public companies on their digital marketing strategies.

Alex looks after internal and client marketing activities along with business development. He has a wealth of knowledge in SEO, Social Media and Web Development. He excels in driving online conversions for clients and data analysis to constantly be developing strategies.

Alex has personal experience with the health effects of CBD and is co-founder of Dr. Ed.

Introduction

Cannabidiol (CBD) was approved by the FDA for medical use pertaining to the prevention or reduction of seizures in June 2018 and this, *inter alia* has created a frenzy of research into cannabis-related pharmacology.

Evidence suggests that CBD might have neuro-active, anti-inflammatory and analgesic (pain-relieving) properties, alongside a potential therapeutic value in the treatment of motivational disorders such as depression, anxiety, and addiction.

So, what is the biological basis for this wide range of potential medical assumptions? The answer (in part) lies in CBD's promiscuous pharmacology—its ability to influence a wide range of receptor systems in the brain and body, to interface with a diverse class of terpenes and its ability to bind not only cannabinoid receptors, but to a host of others too. For a detailed summary of the endocannabinoid system and cannabinoids in human health we suggest reading [‘The Endocannabinoid System and it’s Modulation by Cannabidiol \(CBD\)’](#) which can be found in the ‘Learn About CBD’ section of the Dr. Ed website and Chapter 7 of this report.

This brief report aims to summarize the modality claims for **CBD** and why it might just be the therapy of the future. This report also includes selected results from our latest public survey regarding attitudes to CBD in the UK.

1. A brief history

As far back as 2737 BC a pharmacologist wrote a medical book that cited marijuana and its inherent ability to assist on the voyage to good health.

All these years later and mankind is only just beginning to catch on. In these modern times, with our ever-growing population, toxic abuse of our planet, urbanization and diversity, we need plants more than ever. Plants are the lungs of the Earth; they provide us with essential oxygen, nourishment, and medicine and as we share the same resources (atmosphere), we both synergistically share similar endogenous elements of survival.

Today, we have a greater knowledge of the healing power of plants with their extraordinary range of properties and together with greater analytical tools our ability to harness this healing power will accelerate and grow.

It is on this basis that we (and most of the wider cannabis industry) strongly believe that the *Species of Cannabaceae* will be widely accepted (severe adverse results from Clinical trials and Contra-indications apart), and it will be used with all of its variants for recreation, medicine as well as being deployed widely as a supplement.

The cannabis market is soon (2years) to be +\$20 billion in the USA and growing close to a billion GBP in the UK.

2. Diseases

Let us begin by looking at the broad spectrum of health-benefit claims in regard to CBD.

Any confident, articulate physician skilled in the art of fundraising could make a credible case for CBD and its use in the management of all (some in part) of these ailments. In medical terms CBD is promiscuous by nature as it aims to treat a wide variety of diseases. The list below is non-exhaustive:

Alzheimer's, Anorexia, ***Anxiety**, atherosclerosis, arthritis, cancer, colitis/Crohns, depression, diabetes, ****Epilepsy/seizure**, fibromyalgia, glaucoma, irritable bowel, Multiple sclerosis, ***Stress**, neuro-degeneration, obesity, osteoporosis, ***Pain-relief**, Parkinson's, PTSD, schizophrenia substance dependence/addiction, Inflammation.

* **Most touted CBD health benefit-claims**

** **Approved to combat seizures by the FDA (Epidiolex)**

3. Mode of functionality

An intricate web of cellular molecules and signalling pathways respond to the prevailing environment around us and in order to protect us will physically express receptors for endogenous and (in some cases) exogenous compounds to help mount an appropriate response. "Fight or flight" is the most commonplace appropriation whereas the release of endogenous adrenaline will make you heart pump faster for example, flooding muscular tissue with oxygen in preparation to 'fight' or 'fly'. Perception- to- chemical- to- physical. While the adrenaline example is quite dramatic, other molecular responses might not be so such as when the compound has a "calming" effect or a "relieving" effect.

- It should be noted that not all cannabinoids have their mode of operation around the ECS receptors; other receptors within the body can be/are used including various G-protein coupled receptors and adenosine receptors.
- Some studies indicate that CBD also facilitates the engenderment of actions towards the serotonin system. Animal studies have demonstrated that CBD directly activates multiple serotonin receptors in the brain of which there are 14 sub-types. These interactions have been implicated in its ability to reduce drug-seeking behaviour. CBD's influence on the serotonin system may also account, in part, for its anti-anxiety properties, which have been robustly demonstrated across animal studies.

Believe it or not, mankind was not meant to suffer from persistent chronic pain, be suicidal within the depths of anxiety or indeed stressed to the point of heart failure, sleeplessness and chronic weight-gain/loss. Mankind slipped the net of evolution in a most devastating fashion. Place the average human in clean, fresh air with a local, organically derived diet where they can be friend/family orientated and take some daily exercise and guess

what - people can thrive and instances of chronic health issues both mental and physical can be reduced. But what about exogenous help?

Enter the endo-cannabinoid system (ECS) and cannabidiol (CBD).

4. Some pertinent facts

- Hemp and marijuana are different forms of cannabis with differing phytocannabinoid profiles.
- Marijuana plants contain around 10 percent THC (tetrahydrocannabinol - a psychoactive cannabinoid) or even greater, compared to the much lower 0.3 percent or below for hemp.
- Full-spectrum hemp extract, broad-spectrum hemp extract, CBD, hempseed oil, and hemp oil are all different things and the industry needs to be very clear to consumers about what they are purchasing. Hempseed oil for example has little to no CBD content.
- A full-spectrum hemp extract or oil contains all the plant compounds found in the cannabis plant.
- A broad-spectrum product, in contrast to full-spectrum, has THC removed but attempts to leave all other phytocannabinoids and terpenes (plant compounds) intact.
- CBD isolates are simply a cannabidiol extract.
- THC — Tetrahydrocannabinol is a lipid that has powerful psychoactive potential.
- CB1 and CB2 are the primary endogenous receptors for certain phytocannabinoids particularly THC and THCV. CBD has negligible affinity for these receptors and is instead theorized to function through other receptors and by influencing how other endo and phytocannabinoids interact with CB1 and CB2.

5. Evidence

Does CBD work?

It is worth noting that *in-vivo* human trials are limited and conclusive medical evidence in regard to the health benefits of CBD are scarce. Given the undertaking of what constitutes a meaningful clinical trial, it is hardly surprising. However, the sheer potential of this market will encourage focus and expect true clinical results to begin emerging from 2020 onwards.

Over previous years, there have been several studies in regard to cannabidiol and their interface with the central nervous system (CNS), peripheral nervous system (PNS) and endocannabinoid system (ECS), which have enabled strong claims from sellers and advocates to stand behind the cause. These, alongside many powerful and abundant anecdotal claims, a need to quell the opioid crisis with an *au naturel* inference, have all played their part in creating what appears to be an unstoppable cascade of products for sale. Not to mention costly, slick advertising campaigns and celebrity endorsements.

Additionally, the three main claims: reduce pain reduce anxiety and reduce stress are typically accentuated ailments truly reflective of our current societal lifestyle, increasing knowledge and to a lesser extent, aging society especially in regard to chronic pain.

So, what is the outcome? It appears that exogenous cannabidiol (CBD) can help, possibly not with the root cause in all cases, but with the symptomatic outcomes of all three. CBD does this by acting directly on the nervous system and our internal means of communication via chemical neurotransmission.

Pain, anxiety and stress all promote hypothalamic responses to situations regularly encountered by modern humans and both pre- and post-synaptic information exchange is mediated in a similar way. Accordingly, cannabinoids appear to interact with numerous systems that function through the hypothalamus (or closely linked brain areas) in some way including serotonin signalling.

5.1 PAIN

To avoid discussing the modality of Pain in 20 pages, here is a brief insight.

There are two types of pain, nociceptive and chronic. Pain is useful for bringing our attention to injury. Different types of pain use different neuronal fibres to communicate with the brain and the brain provides a perception in regard to the extent of that injury. Pain is in the brain!

Each type of pain is accompanied by inflammation, which is our bodily response to abnormalities brought about by pain (cuts etc). The inflammatory response is a cascade of heterogeneous cells whose primary goal is to help repair and disinfect this abnormality. Typically, our endothelium will vasodilate and deliver agents of repair (e.g. white blood cells) to the site of pain. Inflammation also brings pain.

The world's best-known painkiller (aspirin) is an anti-inflammatory commonly quoted as an NSAID (non-steroidal anti-inflammatory drug). Ironically, if Aspirin was put out to market today, it is very unlikely it would be approved and realised to the mass market due to side effects including stomach bleeds. The side effects and implications of long-term opioid use are substantially more serious and beyond the scope of this report. This is one of the simple reasons why the observed pain-killing potential of CBD is so special: **there appear to be very few side effects.**

CBD has been shown, for example, to limit the release of key immune and inflammatory factors such as Tumour Necrosis Factor – Alpha (TNF - α). Put into context, this effect has been further shown to reduce immune cell infiltration and inflammation in the intestines of (Inflammatory Bowel Disease) animal models. It has these powerful modulatory effects, seemingly with no significant side effects.

The limited ‘side effects’ are a big draw for the general public and for the industry too. Nearly every extant pharmacological solution brings about side effects, non-better known than opioids.

5.2 ANXIETY & STRESS

Described briefly, anxiety is a feeling of uneasiness and worry which is usually generalised and not focused, often an overreaction to a situation that is seen as menacing when in fact it isn't. There are a number of causes, but modern science suggests genetic predisposition is the most likely cause and that anxiety is an inherited trait. However, anxiety disorders can also be induced by long term drug abuse and childhood experiences also have a role to play.

Anxiety disorders are characterized by excessive nervousness, fear, apprehension, and worry that is out of proportion to the actual danger faced. OCD, PTSD, panic disorder and phobias are considered forms of anxiety disorders but the most common form ‘generalised anxiety disorder’ is what most of us would consider ‘anxiety’. Symptoms include nervousness, tension, panic, a sense of doom, increased heart rate, sweating, fatigue, and/or trouble concentrating. Almost one in three adults in the US and UK experience an anxiety disorder at some time in their lives, thus it is a common mental health issue.

According to the most recent results of the Psychiatric Morbidity Survey, over 3 million Britons are living with some form of anxiety.

Existing preclinical evidence supports CBD as a treatment for generalized anxiety disorder, panic disorder, social anxiety disorder, obsessive–compulsive disorder, and post-traumatic stress disorder when administered acutely. It is thought that CBD alters the activity in certain limbic and paralimbic brain areas associated with anxious behaviours. Additional rodent research suggests this effect may work, in part, through the serotonin system, specifically CBD interaction with the 5HT-1A serotonin receptor.

‘Current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders.’

Neurotherapeutics 12(4) pp. 825-836

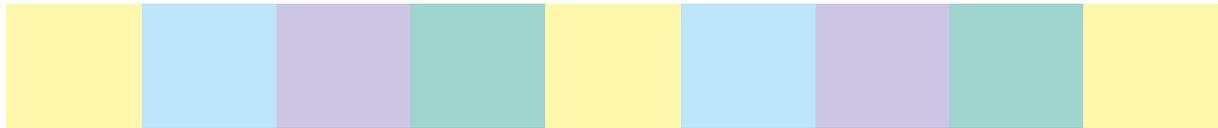
As with pain, the mechanism (s) by which cannabidiol produces anti-anxiolytic effects are not fully understood although research is aiming to address this quickly. It is the general consensus of those in the field that current evidence indicates CBD has considerable potential as a treatment for multiple anxiety disorders, with need for further study of chronic and therapeutic effects in relevant clinical populations.

6. Dr. Ed 2019 Survey

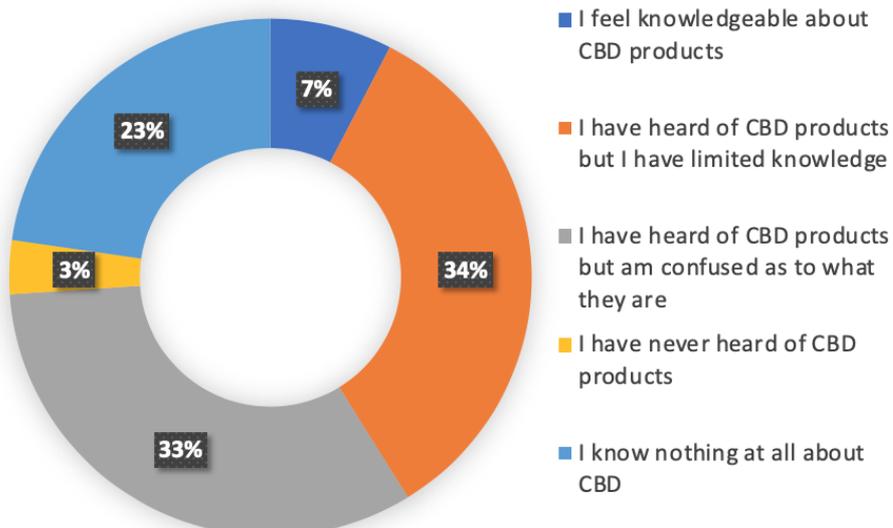
We surveyed 2000 randomly selected United Kingdom residents and asked them a series of questions relating to cannabidiol based around general CBD knowledge and pervading myths around the compound. Responders were from a range of ages, professions, attitudes and a mix of male and female in order to represent the wider UK population.

These data informed this section of the report have been compiled into a series of charts below.

The survey was carried out by OnePoll.



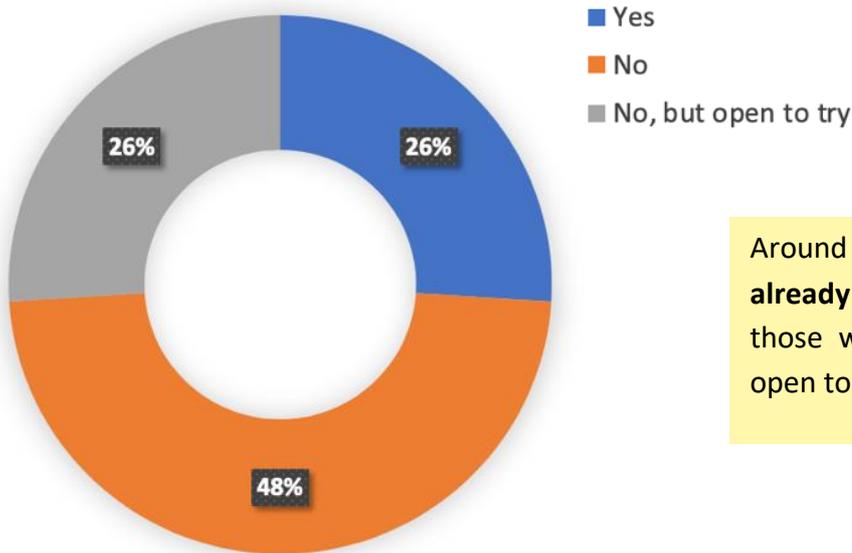
Basic Knowledge of CBD



Knowledge of CBD is increasing in the UK in line with the rapidly growing cannabis industry. **The majority of those surveyed had at least some knowledge or awareness of CBD.**

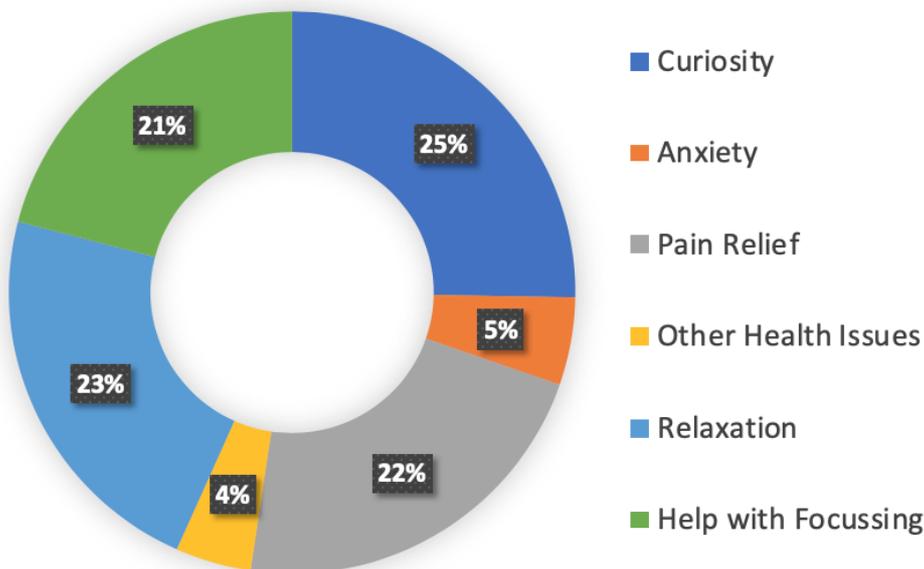
CBD Use in the UK

Have you tried CBD?



Around a **quarter of respondents had already tried CBD**. Only a quarter of those who hadn't tried CBD would be open to doing so.

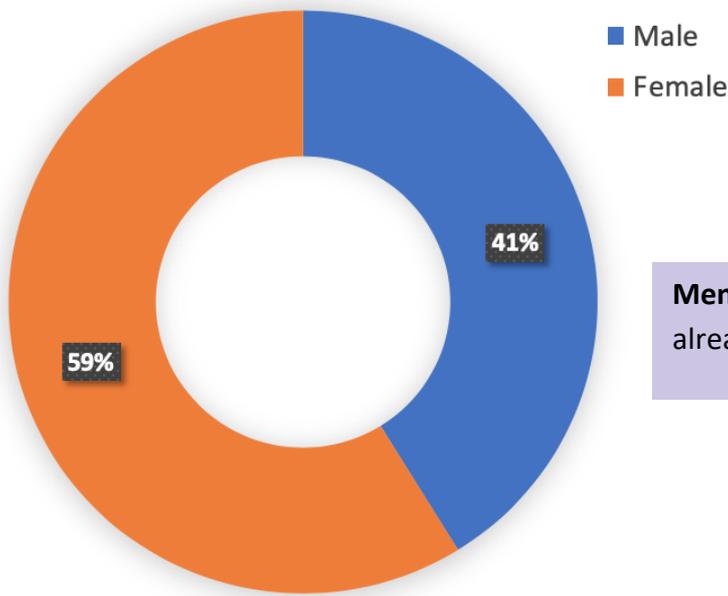
Reason for using CBD



Curiosity is the largest driving force behind CBD purchases followed by **Relaxation** and **Pain Relief**.

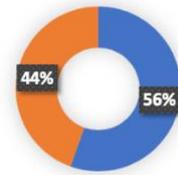
Curiosity is the largest driving force behind CBD purchases followed by **Relaxation** and **Pain Relief**.

CBD Use: Gender

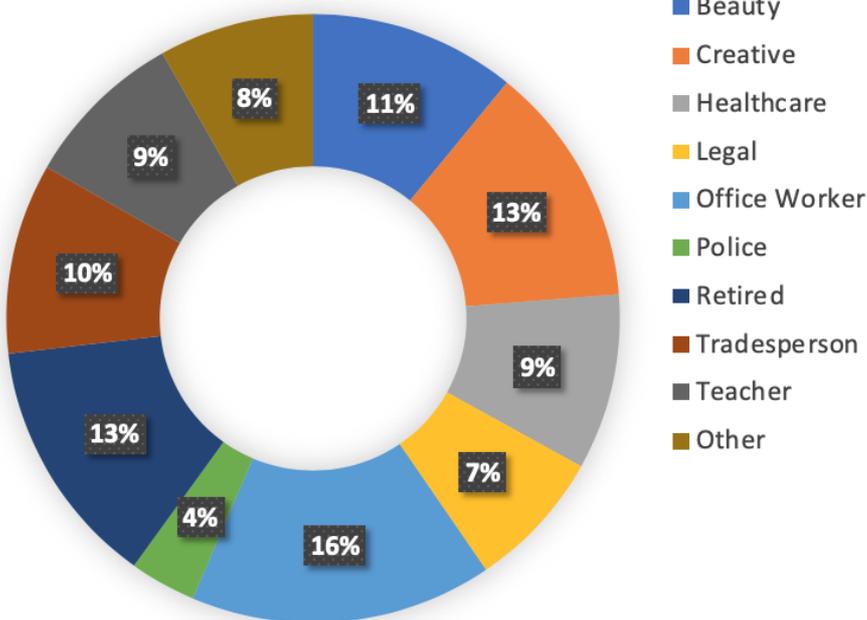


Women are more likely to have tried CBD overall but younger men are more likely than their female counterparts.

Men are more open to trying CBD overall if they haven't already.

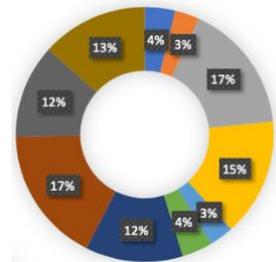


CBD Use: Profession



Office Workers are the most likely professionals to have used CBD based on our survey.

Interestingly, they are amongst the least likely to be open to trying CBD for the first time



7. The Endocannabinoid System and its modulation by Cannabidiol (CBD)

Foreword

An interesting review article appeared only a few months ago in a journal called Alternative Therapies (in Health and Medicine). Although the journal title may sound wishy-washy it is a peer reviewed journal with some interesting papers within. This paper in particular '[The Endocannabinoid System and its Modulation by Cannabidiol \(CBD\)](#)' is one of the more thorough looks at the endocannabinoid system we have seen; a review encompassing some well-known research into the system. However, we must remember that despite the often-touted miracle discovery of the endocannabinoid system, this is still a new area of research and much more work needs to be done in the field before we can draw definitive conclusions about how the system works in its entirety and the full role (endo)cannabinoids play in human health. What follows below is a summary of this paper as well as additional research into the endocannabinoid system. The paper is freely available if you would like to delve into the full article and follow the citations.

Overview

The endocannabinoid system (ECS) is a signalling system with multiple parts, many of which are likely unknown as of writing. Based on current evidence, the ECS is present in all animals and is affected by diet, sleep, stress and a host of other factors including exposure to our own natural endocannabinoids and phytocannabinoids like cannabidiol (CBD). Understanding how the ECS works and how we can modify its activity may offer tremendous therapeutic potential in the treatment of a wide range of health disorders ranging from mental health issues to pain, nerve damage, metabolic diseases like diabetes and brain disorders like Parkinson's Disease.

Introduction

Interest in the use of phytocannabinoids derived from cannabis has increased tremendously over the last few years, driven largely by changes to laws regarding the consumption of cannabis in the USA. Heightened research interest surrounding the mechanism of action of tetrahydrocannabinol (THC), the primary psychoactive ingredient of cannabis and other compounds like cannabidiol (CBD) has resulted from increased consumer interest. Phytocannabinoids interact with enzymes, endogenous ligands and receptors that collectively embody the endocannabinoid system (ECS). The ECS is one of the most evolutionarily conserved signalling systems currently known to science and thought to be 600-million years old. The system is present in every studied animal species with the exception of insects. Its primary function is to restore balance (homeostasis) following cellular stress. As such, the system is in a constant flux of up and down regulation. The ECS is incredibly far reaching and interacts with myriad other body systems in some capacity, being involved in pain perception, mood, appetite, memory and reward processing to name just a few.

Following on from ground-break working involving isolation of THC and early research into its mechanism of action, the G-protein coupled receptor to which THC acts as a partial agonist was discovered and dubbed cannabinoid receptor 1 (CB1). Only a few years later in 1992, the endogenous cannabinoid (endocannabinoid) anandamide-N-arachidonylethanolamide (AEA) was identified. A second endocannabinoid 2-arachidonoylglycerol (2-AG) as well as a second cannabinoid receptor (CB2) were discovered in the mid 1990's. These two receptors and two endocannabinoids have seen increased research interest, partly due to the explosion of consumer interest in cannabis derivatives like CBD.

Endocannabinoids

Endocannabinoids are fatty-acid neurotransmitters that act as the signalling molecules of the endocannabinoid system. They produce most of their effects by acting through receptors. While AEA and 2-AG are the most well studied endocannabinoids, other endocannabinoid-like compounds exist that function in similar ways including oleoyl ethanolamine (OEA) and palmitoyl ethanolamine (PEA). Endocannabinoids share some structural similarity with phytocannabinoids (those found in cannabis) but generally have less affinity for the cannabinoid receptors. Like their 'phyto' counterparts they interact with a range of receptors, not just cannabinoid receptors. AEA and 2-AG are regulated by different systems, allowing the two molecules to exert different effects even within the same cell. Pathological and normal physiological conditions can alter the levels of either or both molecules simultaneously.

Anandamide (AEA)

AEA is a high affinity, partial agonist of both CB1 and CB2 receptors. AEA inhibits adenylyl-cyclase activity within cells via both receptors – this appears to be a common effect of cannabinoids.

2-AG

2-AG is very similar in chemical structure to AEA but it is a moderate affinity, full agonist at both CB1 and CB2. It is synthesised by different enzymes to AEA. 2-AG is the most abundant endocannabinoid in the central nervous system (CNS) and plays a major role in CNS development and synaptic plasticity.

Endocannabinoid System Receptors

The cannabinoid receptors (CB1 and CB2) are 7-transmembrane domain GPCRs. These two receptors differ in their protein make-up, distribution, signalling mechanisms as well as other characteristics. Interestingly, despite being dubbed cannabinoid receptors, the only cannabinoids currently known with high affinity for either receptor are THC and THCV (tetrahydrocannabivarin). CBD actually has negligible affinity for both receptors.

CB1

CB1 is the most abundant and densely concentrated receptor in the human CNS. They are particularly prevalent in nociceptive (relating to the perception or sensation of pain) areas of the brain and spinal cord but can also be found on immune system cells, fat tissue, liver, muscle, lungs and the kidneys. Of note, these receptors are entirely absent from areas of the brain stem which control respiration and cardiac activity which is one of the reasons cannabis doesn't suppress breathing or stop the heart even in large

quantities. Conversely, opioids do affect this area of the brain stem and respiratory depression is the key cause of death in cases of opioid overdose.

CB2

CB2 receptors are mainly located in the periphery as opposed to the more central expression of CB1. CB2 can be found primarily on immune tissues, lymphoid tissues as well as the heart and liver. The abundant expression of this receptor in immune tissues highlights the role of the ECS in immune system regulation and modulation of CB2 may be particularly useful in combating inflammatory-based disorders.

GPR55

The discovery of the GPR55 receptor represents a new generation of research that has started to show the ECS is much more complicated than previously thought. Researchers have hypothesised that the GPR55 receptor may be the 'third' cannabinoid receptor due to its affinity for both endo- and phytocannabinoids. GPR55 is expressed widely throughout the brain and periphery and is involved in the regulation of multiple processes including motor activity, nociception, energy expenditure, anxiety modulation and bone metabolism to name only a few.

5HT/Serotonin

Commonly called 'serotonin receptors', these are a class of GPCRs and ligand-gated ion channels found in the central and peripheral nervous system. Serotonin is the predominant endogenous ligand within our bodies and is related to histamine, dopamine and adrenaline. 14 different types of this receptor exist which allows serotonin to exert a wide range of effects in the body. Serotonin is typically associated with the regulation of pain, nausea, anxiety, addiction and appetite. There is emerging evidence that CBD interacts with the serotonin receptor which may influence pain perception and anxiolytic behaviours. As both the ECS and serotonin systems have overlapping control of things like stress and emotional processing, more research effort is being spent to work out how they interact.

Adenosine

Adenosine receptors are a group of GPCRs to which adenosine binds as an endogenous ligand. Caffeine, for example, acts as an exogenous antagonist producing the stimulating effects of coffee. In humans, 4 types are known— A1, A2A, A2B and A3. These different receptor types possess distinct areas of expression, different means of regulation, and different signalling mechanisms. Adenosine receptors provide broad anti-inflammatory effects. Additionally, adenosine modulates synaptic plasticity and neurotransmitter release. CBD can bind A1 receptors but may also, through a yet unidentified mechanism, influence the levels of adenosine circulating in the brain.

Endocannabinoid System Functions

Gastrointestinal

In addition to acting as neurotransmitters (molecules which transmit information along nerves), endocannabinoids also act as autocrine and paracrine regulators. For example, in the presence of inflammatory bowel disease (IBD), endocannabinoids interact with various gut receptors (both cannabinoid and non-cannabinoid) on the cells that produce endocannabinoids (autocrine regulation) as well as nearby immune cells (paracrine regulation) to reduce additional infiltration and inflammation caused by said immune cells.

On top of this role in inflammatory processes, a growing body of work suggests endocannabinoids play a role in normal gut function. AEA for example inhibits gut motility, delays gastric emptying and reduces gastric secretions all indicative of a role in energy balance – these are similar functions to appetite-regulating hormones such as Peptide YY. Additionally, CB1 receptor agonism has been shown across a variety of models to be anti-emetic (anti-vomiting) and can reduce nausea. Conversely, antagonism of the CB1 receptor induces emesis. CBD has been shown to produce anti-nausea effects by indirect agonism of serotonin receptors.

Food Intake and Reward

The control of food intake, energy expenditure and reward involves a delicate interplay between central neurons and peripheral organ systems. An incredibly complex orchestra of processes which we are still unravelling. Hormones and other peptides play a vital role and cannabinoids show similar functional profiles such that they may be putatively included in the category of orexigenic molecules – molecules which stimulate appetite.

Administration of AEA, an endocannabinoid, has been shown to stimulate appetite in various rodent models. Additionally, CB1 receptors are expressed in key hypothalamic brain areas associated with energy regulation. Interestingly, much like the hunger hormone ‘ghrelin’, levels of endocannabinoids gradually increase over time until feeding is commenced, at which point levels drop again.

Cannabinoid-dopamine interactions appear to play an important role in feeding and the dopaminergic system is important in controlling reward processing including the rewarding aspect of food. Leptin, a key energy-balance hormone, has also been shown to regulate hypothalamic levels of endocannabinoids. One of the more common side effects of CBD is changes to feeding behaviour and weight and effects on these feeding systems and hormones are likely culprits.

Pain and Inflammation

Cannabinoid receptors are present on nociceptors and other sensory neurons in pain processing pathways in the brain and spinal cord, often found together with opioid receptors. Activation of CB1 receptors in these areas has been shown to inhibit pain signals to higher brain regions and modulate pain signals in descending pain pathways.

Numerous preclinical studies have demonstrated the beneficial effects of cannabinoids, including CBD, in animal models of acute pain, chronic pain, and neuropathic pain, some demonstrating opioid-sparing effects. Human studies investigating CBD-induced analgesia in humans, however, are few.

Although reductions in pain have been reported in numerous animal models, the mechanism(s) for this analgesic effect are still being investigated and are currently not well understood. Their effects on pain may be linked to their anti-inflammatory effects as shown in other rodent models or may be due to interaction with the serotonin

system. Ultimately, CBD-induced analgesia, as well as the compounds effects on inflammation, are likely down to a complex interplay of mechanisms.

Reproduction

Endocannabinoids are involved in local and central regulation of reproduction and are present in most reproductive fluids and tissues. A properly functioning ECS helps orchestrate nearly all reproductive events from gamete production and fertilization to successful pregnancy, birth, and lactation.

Reiterating the importance, pharmacological antagonism of CB1 blocks ECS signalling and leads to failure of pregnancy. High levels of maternal anandamide appear detrimental to placental and foetal development. The enzymatic degradation of anandamide appears to be an early marker of spontaneous abortion and may even be useful as a diagnostic tool for monitoring of early pregnancy.

Hypothalamic-Pituitary-Adrenal (HPA) Axis

Studies of the endocannabinoid system support its importance in modulation of the hypothalamic-pituitary-adrenal (HPA) axis, including regulation of mood and anxiety and extinction of fear learning. Cannabinoid action on neuroendocrine functioning, including ACTH levels, is mediated by CB1 signalling in the hypothalamus. Alternately, pre-treatment with the CB1 antagonist Rimonabant, prior to a stressor, has been shown to blunt HPA function in a mouse model.

The Entourage Effect

In the CBD and wider cannabis industry the term 'entourage effect' has been coined to describe the so-called synergistic effects of consuming multiple (phyto) cannabinoids simultaneously. This idea is not exclusive to cannabis nor to cannabinoids as synergism exists in multiple biological examples. The term actually originated to describe how endocannabinoid-like mediators could increase the biological activity of the endocannabinoid 2-AG at the CB1 receptor. Although there is emerging evidence that terpenes, cannabinoids and phytocannabinoids interact and change the activity of each other at receptors, there is no **clinical evidence** that the entourage effect exists with regards to cannabis consumption. Research hopes to address this directly in the future.

CBD Safety

Based on current studies, CBD is a very well tolerated substance with few significant side effects even when consumed at high doses of 1,500 mg per day on consecutive days. This is not to say that CBD is side-effect free. The most commonly reported side effects include fatigue, dry mouth and changes to appetite and weight. Having said this, when CBD is used to treat medical conditions, the low side-effect profile can improve the likelihood of patients continuing treatment in comparison to FDA pharmaceutical drugs.

It should be noted that the route of administration as well as if cannabinoids are given as extracts or in isolate can all affect physiological outcomes - when given as a broad-spectrum extract, a linear dose-response curve is observed but when CBD is given as an isolate, a bell-shaped-dose-response curve is seen. Not only does the dose-response profile change but so can the side-effect profile. This may point towards the 'entourage effect' being a real response with cannabis extracts but further studies are required to prove this definitively.

8. Conclusions

The public wants CBD. They want alternative and new painkillers; they want safe ways to relieve stress, safe ways to reduce anxiety and to put an end to the opioid empire alongside its awful side effects. The treatment and management of the cannabis genus has been like war and private health, both are sad reflections upon our society and measures of a civilization, which obviously still has some way to go.

All governments should embrace the opportunities presented by new extraction techniques alongside groundbreaking tools for analysis and investigation.

We need to explore all the avenues of potential and learn to align the molecules of this plant to our specific needs. If there is any chance that we can relieve some of the side effects brought about by opioids, then it must be done. And if during this journey we find a way to lighten the mood, relieve the pain, relax, focus, sleep better, and move more freely, then what are we waiting for?

CBD has the potential. Given time, new clinical evidence will emerge hopefully giving credence to the wealth of anecdotal and pre-clinical evidence we already have regarding the benefits of cannabinoids and human health.

Modulating the activity of the endocannabinoid system may offer tremendous therapeutic promise for a diverse scope of diseases, ranging from mental health disorders, neurological and movement disorders, pain, autoimmune disease, spinal cord injury, cancer, cardiometabolic disease, stroke, TBI, osteoporosis, and others. CBD and other cannabis derivatives are not miracle cures or cure-all remedies. Instead they are interesting compounds with diverse therapeutic values.

While clinical evidence in humans remains lacking, the next decade will see markedly more publications potentially unlocking the full power of cannabidiol in the context of human health.

