

## **The case for delta-9-tetrahydrocannabinol (THC)**

### **Background**

Cannabis is the oldest herbal health remedy known to man. It has been used as a medicine for over 5,000 years and was one of the original medicines described in the first pharmacopoeia produced by Emperor Shen Neng in China. Since that early origin it has been used in most ancient civilisations from China to Egypt and India and in the last thousand years throughout Europe and into the Americas. It was a perfectly acceptable medicine until the early 20<sup>th</sup> century. The demonization of cannabis began in the 1920s at the Second Opium Conference in Geneva and further labelled as dangerous and of no medicinal value by the anti-marijuana campaign of Harry Anslinger, the first Commissioner of the Federal Bureau of Narcotics. It was deemed a drug “particularly liable to abuse and to produce ill-effects” by the UN Single Convention of Drugs in 1961. This resulted in the signatories to the UN Convention having to introduce Misuse of Drugs Regulations in the ensuing decade. It is worth noting that the UN and WHO have now admitted there is no scientific basis for the this categorisation of cannabis.

Thus in the history of cannabis it is only in the last 60-70 years or so of its 5,000+ year history that it has been labelled as a drug of abuse and a drug of harm.

Fortunately, in the last few years this overwhelmingly negative attitude to cannabis as a medicine has begun to reverse and it is now legal, in various guises, for medicinal use in 50 countries and over half of the United States. Some countries, notably Canada, Uruguay and some of the US states have now made cannabis for adult consumption legal.

The scientific basis of cannabis as a medicine only started to be unravelled in the 1990s with the discovery of the endocannabinoid system. We now know that all animals, except insects, have a natural “cannabis” system. It consists of cannabinoid receptors in the brain and throughout the body and natural ligands for this cannabis receptors are now known to exist – anandamide and 2AG. The endocannabinoid system has widespread functions including a key role in memory, appetite, inflammation, analgesia, sleep, motor control, bladder and gastrointestinal function and reproductive health as well as a regulatory role in homeostasis, stress and regulation of anxiety behaviour. All the phytocannabinoids – the cannabinoids found in the plant - are doing is interacting with our own inbuilt endocannabinoid system and thus it is little wonder that cannabis has a huge variety of different potential benefits – and a few potential harms.

### **Cannabis Isolates**

The early modern history of cannabis as a medicine has been focussed on isolates. This means medicine produced as single cannabinoid – THC or CBD- without the more so-called minor cannabinoids and terpenes found in the whole full plant. Synthetic THC has also been produced as a medicine and is still available worldwide in the form of Nabilone and Dronabinol. The first licenced cannabis-derived modern medicine was Sativex produced by GW Pharma in the 1990s which is a 50:50 combination of CBD and THC isolates. The recently registered medicine, Epidiolex, is a 99.9% pure CBD isolate. These isolates are being produced in order for cannabis to fit into the pharmaceutical regulatory medicine system. The modern pharmaceutical industry usually produces single molecule chemicals which lend themselves to being introduced into the market through the standard double-blind

placebo-controlled trial system. In my view this pharmaceutical approach to cannabis medicine is fundamentally mistaken.

### **The Whole Plant**

There is no doubt the individual phytocannabinoid isolates have medicinal properties. CBD, for example, is a potent anticonvulsant and has anti-anxiety properties as well as being anti-emetic, neuroprotective and cytotoxic for some cancers. THC, in isolation, other than being euphoriant, has analgesic properties and is also neuroprotective, antioxidant, muscle relaxant, anti-emetic and is a very potent anti-inflammatory agent. However, the natural cannabis plant has around 140 similar cannabinoids, albeit usually in much smaller proportions. All those cannabinoids so far studied also have medicinal properties. CBG (cannabigerol), for example, is known to have anti-cancer effects, is anti-inflammatory, antibacterial and an appetite stimulator. CBC (cannabichromene), also has anti-cancer effects and anti-inflammatory as well as being antidepressant and has an effect on skin disorders. THCV (tetrahydrocannabivarin) is a potent appetite suppressant. The terpenes, which give cannabis its smell, are also present in the natural plant. There are over a hundred terpenes and again all those studied have medicinal properties. Two brief examples include myrcene, which is analgesic and anti-inflammatory as well as a useful sedative, and linalool is anti-anxiety, sedative, has local anaesthetic properties and is a potent anticonvulsant. There is now emerging evidence, particularly in the field of epilepsy, that the whole plant has more beneficial effects than the individual components. This is the so-called entourage effect. In the studies, for example, on childhood epilepsy the full plant extracts have a better anticonvulsant effect than pure CBD isolate (Epidiolex) and have less side effects, require lower dosage and

there are less problems with tolerance developing. This is probably also the case with many other medicinal uses, such as pain. There is now a rapidly developing evidence base that shows the efficacy of full cannabis for a large variety of conditions and in a review for the All Party Parliamentary Group on Drug Policy Reform (see [www.drugpolicyreform.net](http://www.drugpolicyreform.net)) good evidence was found of the efficacy for full extract cannabis for pain, nausea and vomiting in the context of chemotherapy, muscle spasm (spasticity) and, using more recent evidence, epilepsy. There was also moderate evidence, albeit with further studies needed, for the use of the whole plant in appetite stimulation, fibromyalgia, sleep disorders and post-traumatic stress disorder. There was some evidence for the use in some aspects of dementia, bladder problems, Tourette's syndrome and some aspects of Parkinson's disease. These findings have been mirrored in other studies particularly the National Academies for Sciences, Engineering and Medicine's report in 2017 which found there was "conclusive or substantial" evidence for chronic pain in adults, antiemetic treatment in chemotherapy and spasticity symptoms in multiple sclerosis. Whilst more evidence is clearly required in order to understand the medicinal properties of the plant in more detail, there is now a considerable evidence base for the efficacy of the full plant in a whole variety of conditions.

### **The Downside**

Cannabidiol, the main non-intoxicating cannabinoid, is remarkably safe and in the great majority of users has no side effects at all. The commonest psychoactive component, delta-9-THC, does have some drawbacks. In the short term after inhalation or oral use it can cause some disorientation, dizziness, dry mouth, anxiety and there is a small, but definite, risk of other problems, such as hallucinations and

psychosis in the short term. However, these side effects are related to the dose of THC and whether it is taken concomitantly with CBD or other non-psychoactive components. A percentage of THC (probably above 15% as guide) without any significant CBD component can have undesirable issues in some vulnerable individuals. In my opinion, for example, it should not be used in those with active schizophrenia or psychosis or indeed a family history of such disorders. Caution should be used when prescribing it for individuals with some cardiac problems, such as cardiac rhythm disorders or recent heart attack. However, in terms of the media these negative problems have, in my opinion, been somewhat overinflated. Whilst there is good evidence that high THC can cause psychosis in vulnerable individuals, the chances of doing so are actually very slim. A recent paper, for example, showed that even in heavy cannabis use the chances of a psychotic episode was about 1 in 2,800 in younger people and 1 in 4,700 in the 35-39 year old age group. For lighter adult cannabis users at least 10,000 men and 29,000 women would need to stop cannabis in order to prevent one case of schizophrenia. For medical use it is common to have CBD in the medicine as well as THC, and CBD counteracts the THC effects and so the chances of inducing a psychotic episode in those using the plant is very small indeed. There is some, albeit controversial, evidence of longer term cognitive damage with adolescents who use high THC cannabis without the concomitant use of CBD. However, whilst there are some studies that show the long term cognitive damage there are others that refute that claim. Cannabis is not addictive but there is a small chance of dependency. The risk is about 9% in adult (mainly high THC) users. This compares to a risk of dependency in alcohol users of about 15% and in tobacco smokers of 32%.

Thus, cannabis in my view is remarkably safe if used sensibly and the risk : benefit ratio is clearly in favour of cannabis usage except for a very small circumscribed group of vulnerable individuals.

### **Prescribing Patterns**

There is now considerable experience, particularly in the United States and Canada, about the use of cannabis as a medicine. It is standard practice to start a prescription for cannabis for all conditions with a high CBD product. CBD can have very useful medical properties and in some people can suffice as the definitive medicine. As an example, around 25% of people with chronic pain respond to a high CBD product either vaped as a flower or as an oil, and need no further treatment. However, many people do need the addition of a small amount of THC to have a better analgesic effect. Thus the second line cannabis treatment would involve a more balanced proportion of THC and CBD. Such an addition will aid about a further 25% of those with chronic pain. That leaves a further proportion of people with pain who can get an even better effect with a higher dose THC product. Overall somewhere around 75-80% of people with chronic pain can be helped by a cannabis product either CBD, a balanced CBD/THC product or a higher THC product. Only around 20/25% of people are not helped at all, or only a little, by cannabis medicine. The same general principle applies to most other conditions, such as fibromyalgia, muscle spasticity and nausea and vomiting. There are a few specific conditions that do require a high CBD product, particularly anxiety and post-traumatic stress disorder. CBD also has antipsychotic properties and for use in those conditions a high THC is unlikely to help.

Cannabis is a very personalised medicine and the individual often has to go through a trial and error process to determine which particularly proportion of THC / CBD is beneficial for their particular condition and indeed many experienced users refine the strain used even further to obtain the best combination of cannabinoids and terpenes. Many will use different strains for different times of the day, perhaps using a more “uplifting” and non-sedating strain in the daytime whilst using a more sedating strain for night-time use. Some need further refinements on method of administration such as a background oil for general painkilling but with a vape for breakthrough pain. Overall there are endless combinations both of strains and methods of administration to help the specific individual for their specific problem. It is, frankly, more of an art than a science. It certainly does not lend itself to the standard pharmaceutical model of double-blind placebo-controlled studies. It is a family of medicines rather than a single molecule pharmaceutical product. The example I have illustrated above with pain makes that point. Around 20-25% of people respond to a CBD product but this is broadly the same range as a placebo responses thus a CBD against placebo trial is likely to be negative. The same would apply with a balanced CBD/THC product against placebo and the same again with a high THC product against placebo. Each one of those strains would be likely to be non-significant against a placebo. However if the totality of cannabis treatment is taken and compared to placebo then around 75% of people will respond to one of the cannabis preparations which would likely be highly significant against the 20-25% placebo response rate. Trials can certainly be designed to reflect this trial and error approach but the standard single molecule, single drug against placebo model simply will not work. The scientific and pharmaceutical industry really need to understand the subtlety of cannabis medicine and assess evidence accordingly.

## **Summary**

In summary, cannabis has a long, distinguished history and it is only in the last 50 or 60 years of many thousands of years of usage that a socio-political negative view has been taken. Cannabis undoubtedly has significant benefits for a large variety of conditions given that it acts through the ubiquitous endocannabinoid system. There are thousands of strains of cannabis with varying proportions of THC and CBD and other minor cannabinoids and terpenes. Each one will have a subtle difference for a given individual and their health and well-being. It is a health remedy that is different from other medicines in that it is simply part of a family and does not fit into a pharmaceutical model and should not be forced down a pharmaceutical route. There are drawbacks for the use of cannabis in some people like any other activity, but overall the risk : benefit ratio is in my opinion strongly in favour of cannabis being more widely used to the benefit of many millions of people across the world.

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