

# **CANNABIS THERAPEUTICS**

**A novel approach to pain and other disease state management**

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## CONTENTS

Executive summary – introduction .....	3
Cannabis research - 50 years to date .....	4
The role of endocannabinoids & cannabinoids .....	4
Cannabinoid Receptors .....	4
Endocannabinoids .....	4
Current and novel cannabinoid receptor ligands .....	4
Cannabis derived medicines .....	5
Cannabinoids- where will they lead medicine and the treatment of disease	5
Safety and Efficacy of Cannabis Based Medicines .....	6
Safety .....	6
Efficacy .....	7
Clinical Data and Therapeutic Use .....	8
Drug Access & Pharmaco-economics .....	8
Drug access .....	8
Economics .....	9
Alternative Cannabinoids and modes of administration .....	9
Modes of administration .....	9
Recommendations / Future Issues .....	10
Pharmacovigilance (IMMP) .....	10
Viability of dispensing novel treatments .....	10
Cost of Medicines and Patient Access .....	10
Glossary .....	12

## EXECUTIVE SUMMARY – INTRODUCTION

The joint Symposium held by the Academy of Pharmaceutical Sciences and the Royal Pharmaceutical Society of Great Britain on the topic of 'Cannabinoid Medicines' examined the recent scientific history, the current state of affairs and the practical future of this therapeutic avenue.

A majority of the discussion surrounded 'grass roots' pharmacology and its links to clinical capacity. Presentations were from a significant body of researchers, affiliated with prestigious institutions. Attendance at the symposium was from a mixture of backgrounds, including scientific institutions, pharmaceutical companies, regulatory agencies, and the hospital settings.

There is increasing interest in the viability, nature, action and mode of administration of cannabis based medicines as agonists of the cannabis receptor. However, there are other targets involving the endogenous cannabis system that widens the scope and potential for therapeutics; including the antagonism and selective inhibition (functional capacity) of the cannabis receptor systems- this topic however was not discussed in detail and is somewhat outside the probable scope of cannabis extracts, at least to date.

Cannabis based medicines appear to be a legitimate advance in therapeutic option. The practical application of these as a clinical tool will increase as the knowledge of their action (the capacity of all cannabinoids to influence the receptor systems), the mode of administration is better studied, and their clinical investigation and use is enhanced.

New Zealand is taking a cautious approach to the investigation of these medicines in the general population, as compared to the introduction of other drug classes- for instance barbiturates and benzodiazepines. This is a sensible approach that provides us with the unique opportunity to study their effects at the clinical therapeutic level and these ramifications to society. Furthermore, it would be appropriate to ensure that as novel cannabinoids (cannabis extracts) make it to the market that we are also vigilant in the use/inception of these substances; for the ratios of the cannabinoids seen in nature (as whole plants) are significantly different.

Clinical trails perhaps have not supported significantly the purported outcomes of this medicine. Although in say this, the sheepish approach taken by other countries to the study and inception of a potential therapeutic avenue is not based entirely on what is termed "lack of clinical data"- but because of its history as a recreational drug and complications with INCB/UNODC, its sanctions and the vito power of particular nationals.

Please note the recommendations/future issues section for further comment.

## **CANNABIS RESEARCH - 50 YEARS TO DATE**

The introduction of cannabis, as a crude medicine, to modern European therapeutics was as late as the 1890's. However, American drug policy since the 1930's has regrettably altered the scene for all foreign drug policy; the result has been the removal of cannabis from Pharmacopeias and significant hurdles for research and therapeutic use internationally.

The Royal Pharmaceutical Society established a working party to evaluate the therapeutic potential of cannabinoids, the result of which has been a significant boost to research into this rather novel class of medicines. Basic and clinical pharmacology, in the area of cannabis therapeutics, is growing and has attracted prestigious medical research institutions including the Universities of Aberdeen, Leiden and London.

The description and functionality of the major cannabinoids, the elucidation of the cannabinoid receptors and their influence on tissue and organ systems has separated recreational use from therapeutic, and hence some of the stigma associated to cannabis use.

There remain questions as to the efficacy of this class of medicines; however, the relative safety of cannabis derived medicines has allowed much of the basic and advanced pharmacology to be studied in humans and lead to its use as an adjunct medicine in several disease states.

## **THE ROLE OF ENDOCANNABINOIDS & CANNABINOIDS**

### **Cannabinoid Receptors**

Several distinct regions in the brain, the peripheral nervous system, many organs and tissues contain specific protein receptors that recognise THC, CBD and other cannabinoids. The discovery of specific cannabinoid receptors prompted the search for putative naturally-occurring chemicals that interact with the receptors, the endocannabinoids.

### **Endocannabinoids**

The endocannabinoids system is critical to the bodies overall homeostasis, and influences all of our main organ and tissues systems. This is a unique biological system, its mechanisms are responsive and capable of adaptation and thus allows for a biological response aligned to system demand or environmental conditions.

### **Current and novel cannabinoid receptor ligands**

The term "cannabinoid" has different meanings. In a more narrow sense, it designates the natural cannabinoids of the cannabis plant. In the broadest sense, it includes all chemicals that bind to the cannabinoid receptors and related compounds.

The clarification of the structure of several potent ligands and the development of high quality, standardised extracts has radically changed the science of cannabis medicine, from a crude drug substance, to providing a more selective approach to the treatment of certain medical conditions.

Certain ratios of cannabinoids have so far emerged to be the basis of the specificity of pharmacological effects; such extract-ratios appear to have better therapeutic profile than single compounds- however in saying this it is clear that pure extracts have market and therapeutic value.

Technology in profiling the extracts has been more fully developed allowing reproducible composition to clinical trials and to produce viable pharmaceuticals for the market (Arno Hazekemp, 2007). This body of research has examined the effective extraction of the medicine from the plant and also considered several modes of administration. The standardisation of cannabis extracts has promoted further clinical studies using the less common cannabinoids to act on other manifestations or diagnosed diseases.

## **CANNABIS DERIVED MEDICINES**

### **Cannabinoids- where will they lead medicine and the treatment of disease**

In 1998 a working party was established, under the umbrella of the Royal Pharmaceutical Society, to evaluate the therapeutic potential of cannabinoids. Over the last 10 years the number of patients exposed to cannabinoids has amplified in line with the variety of conditions showing response to their effects. Indications tested include pain, multiple sclerosis, cachexia from cancer and AIDS, head injury, epilepsy, Gilles de la Tourette syndrome and Huntingtons disease, each of which have shown acceptable response. More interestingly are the new lines of investigation into obesity, diabetes and stroke; disease states that existing therapeutics have had only marginal impact upon- perhaps cannabis will help to better control these burgeoning diseases of modern lifestyle and culture.

The use of cannabinoids in the modern clinical setting is dependant upon their gradual introduction and the safe use of these medicines by clinicians and their patients. It is likely that cannabinoids will continued to be employed for the treatment of co-existing disease as an adjunct to promote the efficacy of other drugs in the patients regimen (e.g. to promote the efficacy of opioid drugs); used along side other drugs to treat a separate ailment/pathology related to the main disease state (cachexia due to AIDS or cancer); used as a single treatment for a pathology responsive to cannabinoids (obesity/diabetes/stroke); or possibly as a panacea for overall maintenance/protection, much like aspirin is used to prevent the occurrence of stroke and heart disease in healthy individuals.

It is important now to clarify that all cannabinoids need not hold psychoactive or sedative properties, such is the case for THC, but that they may be specific to the receptor without such action.

## **SAFETY AND EFFICACY OF CANNABIS BASED MEDICINES**

### **Safety**

The relative safety of naturally occurring cannabinoids, especially those currently employed (THC/CBD), has meant that considerable data has been obtained from studies in humans. However, absolute safety does not exist for any therapeutic intervention.

Adverse reactions, even severe ones, are limited and transient in nature. For instance, the psychotic type reactions (paranoia and hypertension) that are noted in overdose tend to reduce in severity, or cease to exist, after chronic use due to a noted tolerance to their effects.

Further safety concerns still exist when examining the potential for interactions with other drugs in the patients regimen. Patients using cannabinoids are likely to be consuming several drugs to treat co-existing pathologies. Novel cannabioid medicines (other than THC and CBD) have the potential to further escalate such a potential, where in nature the quantity of a single cannabinoids that exists in the whole plant or whole plant extracts is small and relative to the other components of the plant.

The safety of available and novel cannabis based medicines can be concluded based upon the relative safety of marijuana, its historical use and those clinical studies that have been conducted. However, there remains issues relating to ratio of pure extracts and validity to those constructs aligned to marijuana, where marijuana has a variable but specific concentrations of constituents that make up the entire drug substance. It is probable that the pharmacological profile will differ among that of pure extracts, high concentration synthetics or novel cannabinoids. Caution should be taken with the chronic use of cannabinoid and their acute use in pathologies where significant volumes of drugs are taken in the daily regimen- for example in AIDS and cancer, heart disease.

Safety and tolerability of cannabinoids still require to be further examined. For example, cannabinoids, due to their lipophilic nature (fat soluble) means that they are deposited in fatty tissue (adipose tissue), the accumulation of these may have some significant response that has so far not been highlighted in clinical trails or the rather limited chronic clinical use in real world. Unlike endocannabinoids, those extracts of the cannabis plant are not metabolised after action to the same capacity due to the saturation of the endogenous enzyme; therefore the fat soluble substance accumulates.

For reference the side-effects from the use of Sativex® and marijuana as the crude dose from, include:

Gastrointestinal- nausea and vomiting with acute high doses; constipation and diarrhoea caused by reduced motility and cessation, respectively; dry mouth, local mucosa irritations, plaques and ulcerations and burns as a result of continued use and site specific irritation due to formulation.

Nervous system- dizziness, fatigue and weakness; somnolence and apathy which is common to cannabis use; headache; psychotropic symptoms that result from over-dose, but are transient in nature and reduce with tolerance to the drug effect; and intoxication.

Cardiovascular- tachycardia and hypertension, these reduce with tolerance to the drug.

## **Efficacy**

Acceptable clinical data has been collected to establish efficacy in Multiple Sclerosis, pain management, cancer and AIDS related anorexia.

It is, however, difficult to establish the number of patients that will respond favourably to treatment, as with any drug substance inter-patient variability is common. The efficacy or response of cannabinoids, as with any drug, is also dependant upon capacity of the receptor (action) at these sites, the viability of the target tissue as a result of the co-existing disease or as a result of other drugs taken within the patients overall regimen, and the concentration within the target tissue or organ system.

Side benefits- Possible reduction in the total level of narcotic type drugs administered:

Narcotic type drugs in general are more hazardous to a patient's health; have great number of potentially serious/fatal side-effects and drug interactions; and also are more likely to be diverted or misappropriated for illegal purposes (diversion to street level use). The attractiveness of cannabis based medicines is that the number of narcotic type drug substance taken by an individual patient will be maintained at the current level or decreased; it is feasible that some narcotics will be phased out of a patients daily regimen and substituted with these new class of medicines, especially in therapeutic areas where cannabinoids show greater efficacy.

Further examination of efficacy:

Neuropathic pain scales, for example, currently examine efficacy on a very subjective and limited scale. The scales do not reference the efficacy of the narcotic drug based on a valid reference or comparison with other drug types. It would be useful to examine the effectiveness of all narcotic type drugs (for instance, those drugs used in pain management and sedation) to establish the potency vs overdose vs dependency potential and each cannabinoids ability to provide analgesia or other desired effect.

Comparison of cannabinoids with other narcotic type drugs for efficacy, mode of action, ramifications of short and long-term use, safety of use, overdose and diversion or inappropriate use should be constructed. Thus allowing for a

more objective approach to the prescribing and management of certain disease states.

Additionally it would be prudent to examine further the interaction of other drugs in the patient's regimen, with the isolated cannabinoids delivered in conjunction.

### **Clinical Data and Therapeutic Use**

Rather than discuss separate clinical trails and there merits with regard to specified disease states, it is more useful to consider cannabinoids pharmacology and relative efficacy compared to other drug substances and alternative drug substances. Currently there is a lack of suitable information in this area.

GW Pharma are conducting further trails regarding several pathologies, I intend to examine these along side previously submitted trail data and relevant data relevant alternative on drug products.

## **DRUG ACCESS & PHARMACO-ECONOMICS**

### **Drug access**

One of the main barriers to the effectiveness of cannabis based medicines is ensuring that patients use pharmaceutically derived sources, whether as a cannabis extract or as a whole plant. Cannabis is unlike other controlled drugs in that it is widely available throughout New Zealand and the world, and the harm from habitual taking this drug is far less than other classified drugs, likely even alcohol. Hence the legitimate and safe use of this drug (under a physicians care) and its access may be marred by the ability of cannabis to be used as a recreational drug substance and its ease of access.

In the case of Sativex®, the current choice of cannabis based medicine for 'clinical trail' in New Zealand, we should not want to marginalise access to treatment based upon the dollar value of this medicine. Sativex® is likely to be an efficacious medicine in several major disease states, accounting for a potential population that due to disease state, social circumstance and income will far exceed their ability to pay for this medicine.

Such a scenario will account for a major proportion of the patients that respond well to treatment accessing marijuana illegally, either due to cost associated to the pharmaceutical product, or because they do not fit the criteria for use. The ramifications of the use of illegal cannabis exceed legal junctions and include health consequences to those patients already marginalised by serious disease.

Clinical legitimacy, that is, those disease states that do not have reliable data from clinical trials, will prove difficult where some patients have clinical pathology that does not fit the prescribed criteria but consider cannabis to be efficacious in the treatment of that pathology. Currently to access Sativex®

the physician and patient are required to fit certain criteria, and hence off-label prescribing is not justified or possible. It is therefore most likely that a sub-set of patients will access illegal cannabis to fulfil that treatment. This is where the balance between clinically accepted and diagnosed disease states and those that are not will fall out of line; and also where the line between the use and access of a controlled drug clinically and access to illegal but likely comparable sources of cannabis will be crossed.

Examples from the WHO analgesic ladder should be more fully discussed and how cannabis should be appropriately integrated into these guidelines.

## **Economics**

PHARMAC currently is unlikely to fund such a medicine, due to it being on the 'fringe' of therapeutic products and (perhaps) considered a luxury item, at least initially, by this funding body. Sativex® will likely cost around \$500 dollars per month. It is questionable as to whether this is a feasible option for cannabis based therapeutics, and the provision of these to the New Zealand population. In saying this, it is still the most relevant and possibly effective choice.

The spectrum of disease-states in which cannabinoids show efficacy is expanding. Therefore, the number of patients that hold relevant pathologies and respond to cannabis based therapeutics, will likely reduce the overall cost of these medicines due to scale of economies.

## **ALTERNATIVE CANNABINOIDS AND MODES OF ADMINISTRATION**

### **Modes of administration**

The manner in which cannabis derived medicines are administered differentiates medicinal use from that of recreational. Use, access and mode of administration will change over time as further basic pharmacological research comes to light, understanding or common perception to its use changes, and the approach by which clinicians and patients tackle current and modern disease states.

As novel cannabinoids appear on the market they will provide greater therapeutic options for the clinician and for the patients that may respond better to these alternative cannabinoids, differential ratios of cannabinoids, or modes of administration- it is likely that certain clinical applications will require these.

There are several forms of cannabis derived medicine available to the market, currently these include tinctures, sprays, pure extracts or synthetic concentrates, tablets and due soon sublingual tablets. It is clear that administration will not be limited to a spray, oral and sublingual tablets, tinctures and teas. Several such cannabis drug substances exist, including THC/CBD as oil extracts or as synthetic concentrates. Cannabis raw product (whole plant matter) or 'marijuana' could also be accessed as a pharmaceutical product, these selectively grown inflorescences contain high

concentrations of cannabinoids and may be vaporised to safely extract the cannabinoids (Cannabis: Extracting the medicine; A Hazekamp. 2007).

The INCB/UNODC has provisions for New Zealand that currently exceed our use of cannabis. Our ability to access other sources of cannabinoids, including Sativex®, is therefore limited only to clinical need and Medsafe's recommendation.

## **RECOMMENDATIONS / FUTURE ISSUES**

### **Pharmacovigilance (IMMP)**

New Zealand is in the unique position to provide reliable safety and efficacy data on the use of cannabinoids in medicine. Sativex® and cannabinoid medicines use could well be included into the Intensive Medicines Monitoring Programme (IMMP), a project conducted under authority of Medsafe. Reliable patient data will become available for each disease state, allowing New Zealand to provide greater detail on cannabis therapeutics safety and efficacy to international forum. These real world examples will provide benefit to patient's future care and for international data sets on safety and efficacy.

### **Viability of dispensing novel treatments**

The future will likely lead to the development and integration of high quality, standardised extracts that are preferably low in psychoactive constituents. As such differential MODA classifications (Misuse of Drugs Act 1975) of current and novel cannabinoid medicines should be considered.

There is validity to the idea of pharmacy practice and dispensing of low to high level extracts. Dispensing by pharmacists and use by physicians should be based upon that individual substance and its dose form using a MODA classification that is based upon a rational safety/dependency/diversion scale.

It is important to establish the potential for diversion, safety of use and dependency of each alternative cannabis drug product. While cannabinoids are typically safe medicines there still is the potential for significant adverse clinical effects when high-doses are taken or where pure extracts are administered. Access should be restricted to pure extracts if they are to be made available in the future.

### **Cost of Medicines and Patient Access**

As indicated previously, the cost of pharmaceutically derived cannabis medicines and their limited access will establish a body a patient's likely accessing illegal cannabis for use medicinally. Therefore, a rational approach to this development would be to develop a physician's resource on medicinal and recreational use of cannabis:

A concise physicians 'cannabinoid therapeutics' reference should be produced. Such a resource would include: the safe use of cannabinoid therapeutics by patients for medicinal purposes; quality assessment of cannabinoid therapeutics; safe storage and administration; issues relating to drug-drug interactions; issues relating to chronic use and overdose; relevant reading for the patient and support.

## **GLOSSARY**

### **Endogenous**

Produced by the body, not delivered from external sources. The endogenous cannabinoids are called endocannabinoids.

### **Ligand**

A ligand binds to a specific receptor. The ligands of the cannabinoid receptor are called cannabinoids. The endogenous ligands of the cannabinoid receptor are called endocannabinoids.

### **Therapeutic Option**

The idea that expanding the number of viable medicines and treatments specific for a ailment, pathology or disease state will provide the clinician with options to investigate/find the most appropriate regimen for that patient under their care. With the view of reducing the number, frequency or severity of side-effects and also the total number of drugs taken by the patient in their daily regimen.