12 September 2014

No. 22

MEDICAL MARIJUANA
(WEED ALL ABOUT IT)

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CONTENTS

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INTRODUCTION

The old Akkadian word qunnabtu, and similarly, qunnabu, used in Neo-Babylonian and Neo-Assyrian eras, were the terms used to refer to the cannabis plant, meaning; “a way to produce smoke.” Although, as most of the spoken language, the word Cannabis actually originates from the Greek word for hemp ‘kannabis,’ which was in-turn derived from the Sanskrit word 'cana.' The second syllable 'bis' comes from the Hebrew 'bosm', meaning 'aromatic'. Literal translation: fragrant cane.[1]

There are three distinctly recognised species of the Cannabis plant.[1] Cannabis Sativa, the most widespread variety, is found in warm, lowland regions, and utilised mostly for its fiber.[1] Cannabis Indica, a bushier and much shorter variety, is better adapted to highland environments and grows more avidly in cooler climates. It is suitable for the manufacture of medicinal preparations, as it has a greater utility as an inebriant.[1] The third, a wild growing type found in Central Asia and Europe, Cannabis Ruderalis, is a shorter, branchless species.[1]

The plant is indigenous to Central and South Asia, and various extracts of it have been used, including its fiber (hemp), its seed and seed oils (hashish). As far back as 2700 BCE, documented evidence of its use, both for medicinal purposes and as a recreational drug have been discovered.[1] The plants’ dried flower buds (marijuana), its resin (hashish) and various extracts collectively known as hashish oil, are the usual products presented when referring to its recreational use.[1] The unique venation pattern and serrated leaflets of the plant, is what makes it so easily distinguishable from other plants,[1] and has become almost a brand on its own, being featured on many a Rastafarian’s crocheted cap.

A variety of types are grown, serving specific purposes:

- When cultivated for seed and fiber production, plants are usually described as non-drug, low-intoxicant, or fiber types[1]
- Plants cultivated for drug production, are described as high-intoxicant or drug types[1]
- Then there is the wild, escaped or hybridised types which may have features of either of the abovementioned types[1]

Cannabis plants produce a group of chemicals collectively called cannabinoids.[1,2] It is on the brachts and floral calyxes of female plants, that glandular trichomes, which secrete the cannabinoids, terpenoids and various other compounds, are found most abundantly.[1] At least 85 different cannabinoids as well as about 483 other identifiable chemical constituents have been isolated from the cannabis plant.[1] The two produced in greatest abundance are Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), of which only THC is psychoactive.[1]

Categorising cannabis plants according to their so-called chemical phenotype (chemotype), has been done since the early 1970's. This distinguishes various plants based on the overall amount of THC it produces and the ratio of THC to CBD.[1] The concentration of THC, known to be the psychoactive substance in cannabis, may range from less than 0.2% in fiber-type hemp (so-called ditch weed) up to 30% in the flower buds of highly hybridized sinsemilla.[2] Interestingly,the THC/CBD ratio produced by a specific plant, is genetically determined and remains fixed throughout the life of a plant.

Environmental factors can however influence the overall amount of cannabinoid production.[1]One can thus appreciate that plants producing high levels of CBD, which is not psychoactive, and low levels of THC would be regarded as a non-drug type, with the reverse applying for drug type plants. With cross-pollination of these two species/types, a plant with an intermediate chemotype will result, which produces similar amounts of THC and CBD.[1] Especially in products labelled as hemp, the limits for THC concentration are strictly regulated by many countries.[1]

It is exactly this ability to produce hybrid species through cross-pollination, and being able to produce a plant with varying concentrations of THC, that have been so ingeniously exploited by recreational users and their suppliers. Cannabis cultivators have managed to increase the average THC content of cannabis plants from 2% in 1980, to 8.55% in 2006, through the crossbreeding and re-crossbreeding of diverse species.[2] Done in order to achieve more intense, longer lasting psychotropic effects.[2] Where exactly does medical marijuana fit in?

Taking a stroll through its history, you realize that it has been used as a medicine all along. Apart from the occasional piece of rope or t-shirt being produced from its fiber, its most frequent use has always been for the treatment of various ailments, some may even argue that its recreational use is a form of self-medication.

Medical marijuana is quite an ambiguous term, as it may refer to either phytocannabinoids found in the plant extracts itself or to the synthetic cannabinoids produced by pharmaceutical companies to mimic the effects of the abovementioned, as both are in current use for the a variety of medicinal indications.[2] Yes, this literally implies that your doctor can (if it's not illegal in your part of the world), give you a prescription to smoke some weed prn and call him in the morning.

A NOT SO BRIEF, BUT INTERESTING LOOK AT THE HISTORY

8,000+ BCE	At an ancient village site, located roughly in the area of modern day Taiwan, the use of hemp cord in pottery has been identified, dating back over 10,000 years. This find puts the cultivation of hemp as one of the oldest and first known human agriculture crops.[3]
2,737 BCE	First recorded use of cannabis as medicine by Emperor Shen Neng of China. [3]
2,000-800BCE	In the sacred Hindu text *Atharvaveda* (Science of Charms), Bhang (dried cannabis stems, leaves and seed) is referred to as "Sacred Grass." Used both in rituals as an offering to Shiva as well as medicinally, it is one of the five sacred plants of India.[3]
700-600 BCE	An ancient Persian religious text, The Zoroastrian Zendavesta, which consists of several hundred volumes, refers to bhang as the "good narcotic."[3]
23-79	Marijuana's analgesic effects are mentioned in Pliny the Elder's; The Natural History.[3]**70** Dioscorides, who served as a physician in Nero's army, includes medical marijuana in his *Pharmacopoeia.*[3]
130-200	Medical marijuana is prescribed by the Greek physician Galen.[3]
200	The East also lists medical marijuana in their first pharmacopoeia. Marijuana is used as an anaesthetic by the Chinese surgeon Hua T'o[3].
300	In Jerusalem a young woman receives medical marijuana during childbirth.[3]
1090-1124	Followers of Hasan ibn al-Sabbah are recruited to commit assasinations in Khorasan, Persia,...their supposed use of hashish leads to the birth of legends. Some of the earliest written tales of the discovery of the inebriating powers of Cannabis were inspired by these legends as well as the use of Hashish as a hypnotic, by a paramilitary organization.[3]
13th Century	*Zahr al-'arish fi tahrim al-hashish*, the oldest monograph on hashish, was written.[3] It has since been lost. The psychoactive nature of Cannabis is described by pharmacist, Ibn al-Baytar.[3] Cannabis is brough to the Mozambique coast of Africa by Arab traders.[3]
1271-1295	The story of Hasan ibn al-Sabbah and his hashish-using "assassins" are reiterated by Marco Polo following his journeys.[3] Cannabis has reached Europe.[3]
1378	One of the first edicts against the eating of hashish was issued by Ottoman Emir Soudoun Scheikhouni.[3]
1578	The antiemetic and antibiotic effects of marijuana are described by China's Li Shih-Chen.[3]
764	The New England Dispensatory adds medical marijuana.[3]

1794 30 years down the line, The Edinburgh New Dispensary adds medical marijuana as well.[3]

1798 After his invasion of Egypt, Napoleon discovers that many of the lower class Egyptian citizens habitually uses hashish, and his returning soldiers bring the tradition with them.[3] He declares a total prohibition of its recreational use.[3]

1840 Medicinal preparations with a Cannabis base are available in America. And in Persian pharmacies Hashish is also made available.[3]

1842 Irish physician O'Shaughnessy publishes cannabis research in English medical journals. The list of indications for which he recommended cannabis—pain, vomiting, convulsions, and spasticity—strikingly resembles the conditions for which modern medical marijuana proponents extol its virtues.[2,3]

1850 The U.S. Pharmacopoeia adds Cannabis.[3]

1850-1915 Throughout the United States, marijuana was widely used as a medicinal drug and could easily be purchased in pharmacies and even general stores.[3]

1890 The chief physician to Queen Victoria, Sir J.R. Reynolds, prescribes medical marijuana to her.[3]

1893-1894 The India Hemp Drugs Commission Report is issued. 70,000 to 80,000 kg per year of hashish is legally imported into India from Central Asia.[3]

1906 The labelling of products containing Alcohol, Opiates, Cocaine and Cannabis, among others, is now being regulated following the implementation of the U.S Pure Food and Drug Act.[3]

1914 The Harrison Act is passed in the U.S. which defined marijuana use, among other drugs as a crime.[3]

1916 United States Department of Agriculture (USDA) chief scientists Jason L. Merrill and Lyster H. Dewey created paper made from hemp pulp, which they concluded was "favorable in comparison with those used with pulp wood" in USDA Bulletin No. 404.

“The USDA Bulletin N. 404 reported that one acre of hemp, in annual rotation over a 20-year period, would produce as much pulp for paper as 4.1 acres (17,000 m2) of trees being cut down over the same 20-year period. This process would use only 1/7 to 1/4 as much polluting sulfur-based acid chemicals to break down the glue-like lignin that binds the fibers of the pulp, or even none at all using soda ash.

The problem of dioxin contamination of rivers is avoided in the hemp paper making process, which does not need to use chlorine bleach (as the wood pulp paper making process requires) but instead safely substitutes hydrogen peroxide in the bleaching process. ...

If the new (1916) hemp pulp paper process were legal today, it would soon replace about 70% of all wood pulp paper, including computer printout paper, corrugated boxes and paper bags." [4] However, mass production of cheap newsprint from hemp had not developed in any country, and hemp was a relatively easy target because factories already had made large investments in equipment to handle cotton, wool, and linen, but there were relatively small investments in hemp production.[3]

1915-1927 In the U.S, prohibition of recreational use of cannabis first begins in California (1915), followed by Texas (1919), Louisiana (1924) and New York (1927).[3]

1928 Britain follows suit and bans the recreational use of Cannabis.[3]

1930 91,471 kg of hashish is legally exported into the Northwest Frontier and Punjab regions of India from the Yarkand region of Chinese Turkestan.[3] Legal taxed imports of hashish continue into India from Central Asia.[3]

1934-1935 The Chinese government moves to end all Cannabis cultivation in Yarkand and its production becomes illegal in Chinese Turkestan.[3]

1936 Reefer Madness, an American propaganda film was made to deter American youth from using Cannabis.[3]

1937 The Marijuana Tax Act is passed in U.S. Congress, criminalizing the drug.[3] In response Dr. William C. Woodward, testifying on behalf of the AMA, told Congress that, "The American Medical Association knows of no evidence that marijuana is a dangerous drug" and warned that a prohibition "loses sight of the fact that future investigation may show that there are substantial medical uses for Cannabis." Congress ignored his comments. A part of the testimony for Congress to pass the 1937 act derived from articles in newspapers owned by William Randolph Hearst, who had significant financial interests in the timber industry, which manufactured his newsprint paper.[3]

1941 Cannabis is subsequently removed from the U.S. Pharmacopoeia and its medicinal use is no longer recognized in America.[3]

1942 Meanwhile, U.S. scientists working at the Office of Strategic Services (OSS), the CIA's wartime predecessor, developed a cannabis concoction codenamed TD, meaning Truth Drug. This chemical substance was injected into tobacco cigarettes and food to help loosen the reserve of interrogation subjects.[3]

1960 The analgesic and antibiotic effects of cannabis are confirmed by Czech researchers.[3]

1971 First evidence suggesting marijuana may help glaucoma patients.[3]

1975 Nabilone, a cannabinoid-based medication appears.[3]

1976 The U.S. federal government created the Investigational New Drug (IND) Compassionate Use research program to allow patients to receive up to nine pounds of cannabis from the government each

year.[3] Today, five surviving patients still receive medical cannabis from the federal government, paid for by federal tax dollars. At the same time the U.S. FDA continues to list marijuana as Schedule I meaning: "A high potential for abuse with no accepted medical value." [3]

1985 Dronabinol, a synthetic THC, is approved by the FDA for management of nausea and vomiting in cancer patients following chemotherapy.[3]

1986 The Anti-Drug Abuse Act is signed by President Ronald Reagan, raising federal penalties for distribution and possession and reinstating mandatory minimums which officially begins the U.S. international "war on drugs."[3]

1992 In reaction to a surge of requests from AIDS patients for medical marijuana, the U.S. government closes the Compassionate Use program. That same year dronabinol is approved for AIDS-wasting syndrome.[3]

1995 Amsterdam coffee shops selling locally produced hashish and all kinds of hashish-making equipment start appearing.[3]

1996 California is the first U.S. State to re-legalize medical marijuana use for people suffering from AIDS, cancer, and other serious illnesses.[3] In the same year, Arizona passed a similar bill with numerous states following suit thereafter, resulting in similar initiatives in Alaska, Colorado, Maine, Montana, Nevada, Oregon, Washington, Washington D.C., Hawaii, Maryland, New Mexico, Rhode Island, and Vermont.[3]

1997-2001 In direct contradiction to the IOM recommendations, President Clinton, continuing the Regan and Bush "war on drugs" era, began a campaign to arrest and prosecute medical cannabis patients and their providers in California and elsewhere.[3]

2001 Britain's Home Secretary, David Blunkett, proposes relaxing the classification of cannabis from a class B to class C. Canada adopts federal laws in support of medical marijuana, and by 2003 Canada becomes the first country in the world to approve medical marijuana nation-wide.[3] To date, 21 US states have legalised medical marijuana, as have Austria, Finland, Germany, Israel, Italy, the Netherlands, Portugal and Spain. Now, the big question. Why the sudden renewed fascination with such an old substance? Especially one that in modern day society is clouded by so much controversy and red tape.

Marijuana is after all, the most commonly used illicit drug on earth.[5] In most countries, the use and distribution of the substance is illegal and deemed a crime. Even in the United States (US), despite the legalisation of medical marijuana in various states, federal law remains unchanged, outlawing all use of cannabis. And eventhough it is now obtainable for use in various medical conditions, the US Food and Drug administration (FDA), has not approved the smoking of cannabis

for any condition or disease, as it deems that there is a lack of evidence concerning the safety and efficacy of cannabis for medical use. In 2006, the FDA issued an advisory against smoked medical cannabis stating: "marijuana has a high potential for abuse, has no currently accepted medical use in treatment in the United States, and has a lack of accepted safety for use under medical supervision." [6] Many reasons come to mind regarding this sudden resurgence of interest. The 3 that I find most conspicious,are:

Firstly, the vast amount of knowledge that has been gained on the endocannabinoid system over the last decade and its role in pain regulation, as shown in multiple preclinical trials. Secondly, the paucity in the development of new analgesic agents. And lastly, the enormous amount of pressure and influence that an ignorant and demanding public are able to generate, strong-arming national governments into making law-changing decisions, lacking any sound evidence base to back it up. (the loudest voices are unsurprisingly those of recreational users)

RECENT ADVANCES IN ANALGESIA

The use of opium for its analgesic effect as early as 3400BC, evidenced by inscriptions found on Sumerian clay tablets, as well as the fact that it remains to this day, the cornerstone for the treatment of moderate to severe pain, emphasises the slow progress that has been made in the field of analgesia. A study published recently, proposed that the reason for this lies in our poor understanding of the sensory information processing occurring at spinal cord level. Especially alluding to the dorsal horn where sensory neurons, relaying pain signals, first enter the central nervous system.[7] True, we know more than our predecessors of 10 years ago, but as on-going research has revealed, even our current interpretation of signal processing seems much too elementary.

Advancements in technology are slowly assisting in clarifying the roles of interneurons, identifying new targets and molecular substances critical in relaying sensory information or inhibiting it, which will hopefully result in novel drug targets for future analgesic agents.[7] In his 2010 review article on the development of new analgesic agents, Igor Kissin[8] highlights that despite an enormous amount of research in the field of pain management, the only new agent developed between 1960 and 2009, sufficiently effective to result in the introduction and development of many similar drugs, which act at the same target, was sumatriptan.[8]

He assessed the development of analgesic agents over a period of 50 years, looking at its success in terms of whether it remained in medical practice, whether its efficacy was sufficient to result in the production of similar agents with the same target, and using Hill's[9] approach, also reviewing whether its molecular target or mechanism of action was novel,[9] either via an incremental improvement on an existing drug mechanism,[9] a novel selective mechanism arising from a

better understanding of the mechanism of an existing analgesic drug[9] or through a completely novel mechanism.[9] Finally, he reviewed the impact that the agent had on publications in biomedical journals.[8] This review identified only 3 drugs, pentazocine, sumatriptan and celecoxib, which were developed on the basis of a modified molecular target arising from existing analgesics,[8] but with an important modification.

Drugs identified with completely novel molecular targets were; ziconotide, dronabinol, ketamine and capsaicin (topical).[8] With the exception of ziconotide, these drugs were known to have analgesic properties for a long period of time, but their unique molecular targets were only discovered relatively recently.[8] The degree to which their introduction represents a therapeutic advance, is not necessarily equitable to the novelty of their discovered molecular targets however.[8]

In terms of new publications on analgesic agents, opioid analgesics, especially morphine, predominated, which some would argue is indicative of the insufficient progress that has been made in the development of new analgesics especially because it persists, even in areas such as the treatment of neuropathic pain, where the effectiveness of opioids is rather low, for example.[8]

Research leading to the development of new analgesics and directed at various molecular targets related to pain mechanisms produced thousands of new publications.[8] The mere diversity of molecular targets suggested indicates that our understanding of clinical pain mechanisms is still limited; and in his opinion, this is probably the main reason for the limited success in the development of new analgesics.[8]

However, he further suggested 3 factors that may be contributing to the apparent drought of novel analgesics:

1) Insufficient mechanism-based approach to clinical pain syndromes[8]
2) inadequate predictive validity of animal models for pain in humans,[8] and
3) the absence of the comparative benefit requirement for the approval of an analgesic agent.[8]

For clarification of the last point, the FDA requires a newly proposed analgesic agent only to show benefit when compared with a placebo. For these studies, smaller patient cohorts are required, making it easy to perform, and therefor large numbers of analgesics may be approved which often rapidly falls out of favour again due to inferior effectiveness against existing agents.[8]

A new novel agent that has been approved by the FDA in 2011 for use in chronic pain since Kissen's review definitely deserves a mention. Tapentadol is a centrally acting analgesic that is both a noradrenaline reuptake inhibitor as well as a μ-opioid receptor agonist.

A small study by Mercadante et al showed its effectiveness in cancer pain[10] and a systematic review by Riemsma et al,[11] reported that tapentadol showed statistically favourable results over oxycodone for pain intensity, 30% and 50% pain relief, patient global impression of change (PGIC), and quality of life.[11] Furthermore, some of the most important adverse effects of chronic opioid treatment were significantly less frequent with tapentadol as compared to oxycodone.

Their conclusion was that the benefit–risk ratio of tapentadol appears to be improved, compared to WHO step 3 opioids, when administered together.[11] In an editorial by Cervero,[12] he echo's Kissin's sentiments with regards to the relevance of laboratory studies in animal models and its translation into human clinical pain. The truth however is that most of our knowledge on pain mechanisms has traditionally been derived in exactly this way, using brief, noxious stimuli and very restricted injuries (for obvious ethical reasons), which clearly cannot be equated to clinically relevant pain, and definitely not to the entity of chronic pain.[12]

Other challenges in pain research that he brings to the fore is that of measuring the effectiveness of any newly developed drugs against very powerful analgesic agents in current use, particularly the opioids.[12] And to also take into account the cognitive and emotional aspects that invariably accompanies chronic pain, which is particularly difficult to assess in lab experiments, but decidedly of great importance.[12]A review article published in 2010, in the Yale Journal of Biology and Medicine,[13] concluded that many patients continue to experience intense pain following surgery, in spite of our efforts to develop new standards of pain management and an increased focus being placed on the introduction of pain management programs.[13]

Their review touches on the discoveries made in terms of molecular mechanisms involved in pain transmission, new pharmacologic products that have become available, novel routes of delivery of analgesic agents, other modes of analgesia and organisational and procedural aspects in pain management.[13] Our better understanding of central sensitisation, the role of NMDA receptors in the so-called wind-up, various molecules, enzymes and receptors discovered that are actively involved in pain transmission such as substance P, neurokinin receptors, COX2, nitric oxide and other superoxides, have lead to a multimodal approach of analgesia, attempting to intercept various pathways that may lead to a patient eventually developing chronic pain.[13]

As well as attempting to decrease the side effects of a previously opioid based regime.[13]The only new products that became available during the time of their review was extended release epidural morphine and iontophoretic transdermal fentanyl, as well as the introduction of intravenous acetaminophen, which was a major step forward.[13] Adjuvants that saw an increased use were capsaicin, ketamine and the antiepileptic medications gabapentin and pregabalin, as well as dexmedetomidine.[13] The COXIB's also experienced a renewed interest.

Newer PCA modes of administration were also introduced such as intranasal, transdermal, regional and pulmonary. In an attempt to prolong the duration of action of local anaesthetics, novel delivery systems have been researched. Enter liposome or polymer encapsulation, but problems with shelf life; toxicity and aggregation, have seen it not achieving the potential it was hoped to.[13] Addressing the psychological aspects of pain, especially in patients with chronic pain has also been studied extensively.

In general, current evidence does indicate a treatment response with the use of cognitive behavioural therapy, although the effect sizes are small.[14] It is possible to effect change in pain, mood and disability.[14] Changes that are not achieved by chance or by exposure to any other treatment.[14] James Wilson et al[15] reviewed the advances in cancer pain management, highlighting drug therapies, neuraxial drug administration techniques, the use of radio and chemotherapy and the use of spinal cord stimulation at various levels through the application of electric currents, in order to achieve a neuromodulatory effect on sensitised sensory neurons.[15]

They also make mention of new preparations of fentanyl available for breakthrough pain, via novel routes such as buccal, sublingual and intranasally, which are widely used in palliative care. In their consideration of agents used in the management of neuropathic pain, they reaffirmed the effectiveness of tricyclic antidepressants and the gapapentinoids when used as adjuncts to opioids.[15] Pregabalin especially has consistently been shown to have a morphine-sparing effect, therefor lowering the incidence of side effects associated with it.

Duloxetine, a serotonin and noradrenaline reuptake inhibitor has been shown to reduce pain in a very small group of patients only, and more studies are required to elucidate its analgesic properties.[15]Topical Lignocaine medicated plasters containing a 5% concentration, has been shown to be a remarkably safe and convenient treatment strategy for post-herpetic neuralgia as well as for localized neuropathic pain.[15] Products are now available which can deliver intrathecal drug therapy.

These devices consist of a battery powered implantable pump with a 20 to 40ml drug reservoir and intrathecal catheter inserted under general anaesthesia, which are fully programmable to deliver a continuous infusion of the chosen drug (drugs that can be used: preservative free morphine, clonidine, hydromorphone, baclofen, bupivacaine and ziconotide) as well as allowing patient administered pre-set boluses via a hand held device.[15]

Its use is however currently reserved for specific indications only, but its effectiveness in pain relief holds great promise. A randomized controlled trial comparing it to comprehensive medical management, have reported significantly less drug-related toxicity, sustained pain control and improved quality of life.[15] Indeed, we have made progress; some may argue that we did quite well.

But you will notice, that not very many new drugs have come about. A lot of new administration techniques for old drugs yes, but does sticking a drug into an arbitrary place make it necessarily more effective? Sometimes yes, sometimes…eh…. let's not publish these results…. One thing the scientific folk have done, and continue to do, is make brilliant new discoveries.

And with the advancement of technology, they don't have to go out and water peas everyday, only to wait for months before their theories are proven true or false. They have discovered a magnitude of cellular receptors, ligands, signaling mechanisms, neurotransmitters, enzymes, metabolites…. (the list is endless), in a phenomenally short period of time. The next step now, is to catch up and try to make sense of it all, try to utilize this newfound knowledge, and hopefully, produce a novel, miracle drug.

BIOLOGY (The endocannabinoid system)

One of the many discoveries made this century! We harbour our own stash! Well, first came the discovery of the receptors and later only their endogenous ligands. Thus far, 2 distinct cannabinoid receptors have been identified and extensively researched, CB_1 and CB_2. (Thanks go out to the rodents) However, there is some pharmacological evidence suggesting the existence of more receptors associated with the endocannabinoid system, with particular interest in the GPR-55 receptor. Further studies are however required to substantiate this preliminary association.[16,17,18,21]

CB_1 receptors are in fact, among the most numerous receptors in the brain, concentrated in the hippocampus (highest levels found in the dentate gyrus), cerebellum, amygdala, internal and external segments of globus pallidus, hypothalamus, basal ganglia, substantia nigra, mesolimbic dopamine pathways implicated in[15,17,20] psychological "reward" system, and in association areas of the cerebral cortex (frontal and anterior cingulate cortex).[16,18,21] What has caught most attention, leading to an abundance of preclinical research to be done, are their presence in the pain pathways, both centrally and peripherally.

There is a relative paucity of receptors in the brainstem, perhaps explaining the lack of serious respiratory or cardiovascular toxicity of the cannabinoids.They are also expressed peripherally, including endothelial cells, heart, lungs, adipocytes, the adrenal glands, liver, prostate, testis, uterus, ovary, tonsils, bone marrow and thymus.[16,18,20] At the cellular level, CB_1 receptors are localized mainly to the nerve terminals and axons and are for the most part, absent from dendrites and the neuronal somas.[18,19] This ultra-structural finding,[19] suggesting a predominantly presynaptic localization of CB_1 receptors, is consistent with the functional finding that activation of CB_1 receptors inhibits calcium channels and activates potassium channels, leading to inhibition of neurotransmitter release.[18,19,21]

The peripheral CB_2 receptor is expressed mainly in cells of the immune system (mast cells, B cells, T4 and T8 cells, microglial cells, macrophages, natural killer cells and, to a lesser extent, monocytes and polymorphonuclear neutrophils) and lymphoid tissue (spleen, tonsils and thymus).[16,18,20] Originally thought to be absent from the CNS,[19] recent studies suggest that they are indeed expressed in microglia, dorsal root ganglia, in the lumbar spinal cord, on sensory neurons and sparsely in several brain regions.[16,18,19,20]

And furthermore, that these receptors can be strongly induced in sensory neurons and the spinal cord in neuropathic and inflammatory pain models, as well as in spinal microglia and macrophages, as shown in human postmortem spinal cord specimens of patients who suffered from multiple sclerosis and amyotrophic lateral sclerosis.[16,18,19,20]Endocannabinoids are the endogenous ligands of cannabinoid receptors. They are eicosanoid mediators, derived from arachidonic acid. The 2 most prevalent and extensively studied, are Anandamide (N-arachidonoylethanolamine or AEA) and 2-arachidonoyl glycerol (2-AG).[19,20]

For completeness, other endogenous ligands shown to have cannabimimetic actions are Noladin ether (2-arachidonoylglyceryl ether), Virodhamine (o-arachidonoylethanolamine) and N-arachidonoyldopamine.[19,20] Endocannabinoids are produced on demand, either by activity-dependent or receptor-stimulated cleavage of membrane phospholipid precursors. After their production, they can immediately be released from the cells, since they are highly lipophilic and poorly suited for storage. This enables them to effectively regulate both excitatory and inhibitory synaptic transmission.[19,20] Regulation of endocannabinoid signaling occurs via its synthesis, release, uptake and degradation.[19]

When membrane depolarization occurs, a subsequent increase in intracellular calcium levels occurs which, together with the receptor stimulation, can activate enzymatic processes leading to the cleavage of membrane phospholipid precursors and subsequent synthesis of endocannabinoids.[19] Once released, they are rapidly inactivated by re-uptake and enzymatic degradation. Interference with this inactivation process, may provide a pharmacological means to modify cannabinoid-mediated functions.[19] Despite their similar chemical structures, AEA and 2-AG have distinct biosynthetic and degradation pathways.[19]

In AEA biosynthesis for instance, recent studies on knock-out mice have revealed that there is no difference in basal levels of anandamide in those without the NAPE-PLD and GLE-1 enzymes suggesting that the biosynthesis of anandamide may involve multiple enzymatic pathways, and the original belief that N-arachidonoyl-phosphatidylethanolamine (NAPE-PLD) exclusively controls its' biosynthesis has been brought into question.[19,20]However, basal levels were measured, and it is possible that studies examining activity-dependent levels may produce different results. The main enzyme that degrades and inactivates anandamide is fatty acid amide hydrolase, found widely throughout the CNS, predominantly postsynaptically.[19,20]

2-AG is synthesized in a two-step process. First, the enzyme phospholipase C (PLC) cleaves membrane phospholipid precursors to form diacylglycerol (DAG).[20] DAG is then hydrolyzed by a diacylglycerol lipase (DAGL) selective for the sn-1 position, to generate 2-AG.[19,20] 2-AG is then subsequently degraded by monoacylglycerol lipase localised in presynaptic terminals.[19,20] In the CNS, endocannabinoids act as neurotransmitters.[20,21]Upon depolarization of postsynaptic neurons, they are released and travel to presynaptically located CB_1 receptors.[20]This unique retrograde signaling mechanism, puts the endocannabinoid system in a prime position to modulate neuronal excitability, through inhibition of various neurotransmitter release as well as maintaining homeostasis.[20,21]

Both CB_1 and CB_2 receptors are seven-transmembrane G-protein coupled receptors,[19] mainly coupled to Gi/o proteins, and share 44% overall identity[19] (68% identity for the transmembrane domains)[19] With activation, through coupling to the α-subunit of their respective G proteins, both cannabinoid receptor subtypes result in the inhibition of adenylate cyclase activity.[16,18,20,21] Activation of cannabinoid receptors is also positively coupled to mitogen-activated protein kinase (MAPK) and Krox-24, presumably through the activation of G-protein βγ subunits. In addition, CB_1 receptor activation can exert an inhibitory effect on type 5-HT3 ion channels, as well as modulate the production of nitric oxide, result in alteration of sodium channel conductance and activate the Na+/H+ exchanger.[16,18,20,21]

Anandamide has also been shown to have some affinity for the transient receptor potential vanilloid 1 (TRPV1) channels.[16,18,20,21] In contrast to CB_2 receptor activation, CB_1 receptor activation inhibits calcium and activates potassium conductance properties that are linked to the inhibition of neurotransmitter release and suppression of neuronal excitability.[16,18,20,21] What exactly happens when this intricate system is activated? Quite a lot actually, from being analgesic, to having anti-inflammatory and anti-emetic action, even stimulating appetite, to name but a few.

In both the autonomic and central nervous systems, it functions synergistically, side by side with the more familiar dopaminergic, cholinergic and adrenergic systems, therefor enabling it to have an influence on bodily functions as diverse as bone growth and blood pressure.[18] The endogenous cannabinoid, anandamide, seems to have a regulatory role on dopamine release in the mesolimbic reward center, resulting in reinforcement of pleasurable activities.[18] Another significant regulatory role of the cannabinoid system is in the retrograde inhibition of neurotransmitter release upon activation of CB_1 receptors.[18]A significant number of neurotransmitters are subject to this inhibition, including, noradrenaline, dopamine, acetylcholine, GABA, glutamate, glycine, cholecystokinin, daspartate, histamine and serotonin.[18]

Antinociceptive effects:
Electrophysiological as well as c-fos expression studies,[19] supports initial observations that cannabinoids inhibit spinal dorsal neuronal activity to produce analgesia. It has provided evidence confirming the presence and activity of CB_1 immunoreactivity, not only in inhibitory circuits but also in the excitatory circuits.[19] Another significant finding was discovered with regards to the interneurons found in the substantia gelatinosa of the spinal cord, where the CB_1 receptors seem to co-localize with μ-opioid receptors.[17]

The role of the Periaqueductal Gray (PAG) and its subsequent inhibitory effect on pain transmission, first via the rostroventral medulla (RVM) and from there sending inhibitory signals to the dorsal horn, thereby producing analgesia has long since been documented.[19] The effective decreased release of neurotransmitters such as glutamate or GABA, through cannabinoid receptor activation, supports and augments this descending inhibitory pathway.[17,21] In the periphery, the antinociceptive effect of cannabinoids can be mediated by both CB_1 and CB_2 receptors.

Peripherally mediated CB_2 antinociception has been an especially attractive therapeutic target,[19] as compounds that selectively activate CB_2 receptors have the advantage of avoiding CB_1-mediated CNS side effects, such as hypo-motility, catalepsy, hypothermia, and cognitive impairment.[17,19] Nociceptor sensitization occurring as a result of released inflammatory mediators, as seen with a nociceptive insult, may be attenuated through stimulation of peripheral immune cell CB_2 receptors, which suppresses their release.[17] A small trial conducted by Eli Lily on patients with osteoarthritis, using a CB_2 agonist, failed to meet its primary endpoint however.[17]

The alleviation of nausea and vomiting is assumed to be partly due to an antagonistic action on the serotoninergic 5-hydroxytryptamine 3 (5-HT3) receptor of cannabinoids.[18] The presence of CB_1 receptors in the cerebellum and basal ganglia explains both positive and negative influences of cannabinoids on motor tone and coordinated movement, including THC-induced disco-ordination or clumsiness in recreational users on the one hand and amelioration of spasticity in upper motor neuron diseases such as multiple sclerosis on the other.[16]

Activation of CB_1 receptors in the hippocampus results in the modulation of mood, and they exert an influence on many elements of cognition, including concentration, short-term memory processing, attention, and tracking behavior, through their activity in both the prefrontal cortex and hippocampus.[16] Vegetative functions are influenced at the hypothalamic level; “the munchies,” to which recreational marijuana smokers are prone and for which medical marijuana may be prescribed, and is a result of THC stimulation of CB_1 receptors that govern food intake in this area.[16]

The main subjective effect in humans consist of:[22]

- A feeling of relaxation and well-being[22]
- Heightened sensory awareness, where sights and sounds seem more intense.[22]

Central effects seen:[22]

- Short term memory may be substantially impaired, as are simple learning tasks[22]
- Impairment of motor coordination[22]
- Catalepsy[22]
- Analgesia[22]
- Anti-emetic action[22]
- Increased appetite[22]

Main peripheral effects of cannabis are:[22]

- Tachycardia[22]
- Vasodilation, particularly marked on the scleral and conjunctival vessels[22]
- Reduction in intra-ocular pressure[22]
- Bronchodilation[22]

There are three categories of so-called cannabinoids, i.e. Compounds who have an affinity for, bind to and result in the activation of cannabinoid receptors. **Phytocannabinoids** are the constituents isolated from marijuana, which includes THC, its precursor cannabidiol (CBD) and cannabinol, a breakdown product formed spontaneously from THC. A small fraction of THC is converted to 11-hydroxy-THC, which is more active than THC itself, and probably contributes to the pharmacological effect of smoking cannabis.

CBD may activate limbic and paralimbic regions in the central nervous system which can decrease autonomic arousal and feelings of anxiety, in contrast to THC which is anxiogenic.[23] CBD has also been shown to have anti-emetic, anti-inflammatory and anti-psychotic effects. It doesn't seem to affect vital signs such as blood pressure or heart rate, gastro-intestinal transit time or psychological functioning. Proper manipulation of the endocannabinoid system may prove useful in the management of psychiatric disorders such as depresssion, anxiety and anorexia nervosa.[23]

Endocannabinoids, the endogenous ligands as discussed above, and thirdly, the **synthetic cannabinoids**, which are compounds developed for potential medical uses, based on the concept that they would mimic the therapeutic effects of phytocannabinoids, while having no or less psychoactive side effects.[20] Presently there are 4 pharmaceutical cannabinoids available on the market. FDA approved and available since 1985 in the United States, were first Nabilone followed closely by Dronabinol.[2,3] A third product, nabiximols, has been available in Canada since 2005.[2]

Rimonabant has been available in Europe since 2006, but due to concerns over potential aggravation of depression and an increased tendency for suicidal behavior, the FDA have not approved its release in the United States.[2] Its use in reducing appetite in obese individuals and treating nicotine dependence have been shown promising results.[2] The 2 U.S. approved agents are CB_1 receptor agonists, based on cannabis' primary psychoactive component, THC. Dronabinol (Marinol), a Schedule III controlled substance, is in essence synthetic THC, indicated for treating chemotherapy-induced nausea and vomiting and AIDS-related anorexia and wasting.

Nabilone (Cesamet), which is a synthetic analog of THC, is used and approved for the same indications as dronabinol.[2] Nabiximols (Sativex) contains THC and CBD in a 1:1 ratio and was licensed in 2011 in Europe, for the treatment of moderate to severe refractory spasticity in multiple sclerosis as a sublingual spray.[18] A fifth, Namisol, which is a tablet formulation of THC (>98% THC) is being studied with regards to its effectiveness in ameliorating spasms and pain in adults suffering from acute Multiple Sclerosis, and also in HIV and cancer stricken patients, for the relief of nausea and vomiting.[23]

Specific CB_2 receptor targeting has recently gained attention, resulting in multiple pharmaceutical companies patenting specific CB_2 agonists. This is because they are mainly distributed peripherally;[22] hence adverse CNS effects are not seen, and thus far in preclinical studies, they have demonstrated effectiveness the inhibition of acute nociceptive, neuropathic and inflammatory pain.[22] Human trials still to follow…

Since 2008, so-called designer drugs have surfaced which are synthetic cannabinoids sold over the Internet or in retail outlets.[22] These products are often marketed as incense or herbal products, come in various forms, are undetectable through standard laboratory tests for THC and its metabolites, as it is purely synthetic. They can be very dangerous, containing up to 10 times the strength of natural THC resulting in unpredictable psychotropic effects and often contain a variety of other illicit substances.[22]

PHARMACOKINETICS[24,25]

Absorption: Dependent on the route of administration of course.
Smoking: This is the fastest and most efficient route of drug delivery; from lungs to brain, contributing to its abuse potential. In comparison with the intravenous route, it achieves only slightly lower peak THC concentrations. Bio-availability: 2-56% quite variable (both intra and inter individual) due to differing smoking dynamics ie: how deep and long an individual inhales.

Peak concentrations are generally reached after about 9min. Levels are decreased to ≤5ng/ml after 2hrs.[25] *Oral:* THC has a high octanol/water partition coefficient, and is therefor readily absorbed.[24,25] Absorption is slower compared to smoking, with a delay in reaching peak concentration. Oral THC bioavailability: 4-20%, this may be due to numerous factors including, drug degradation occurring in the stomach, variable absorption rates, significant first-pass metabolism in the liver to its active (11-OH-THC) and inactive metabolites. [24,25]

Following a dose of 15-20mg, peak concentrations reached after 4-6hrs. 2 peaks in THC concentration seen frequently due to enterohepatic re-circulation. [24,25] Compared to the smoked route; Onset of action is delayed, peak concentrations are significantly lower, and duration of pharmacodynamic effects are generally prolonged with a delayed return to baseline. [24,25]

Oromucosal*:* Sativex® contains almost equal amounts of THC and CBD.[25] It is administered sublingually to avoid first-pass metabolism by the liver.[25] Has not been studied sufficiently with regards to pharmacological properties. Trials are ongoing to determine its effectiveness in use for spasticity and as analgesia. *Rectal:* Due to lower first-pass metabolism and a higher absorption rate, the bioavailability of the rectal route may be approximately twice that of the oral route.[25]

Transcutaneous*:* Another route of cannabinoid administration that avoids first-pass metabolism and improves THC bioavailability is topical administration.[25] The skin's aqueous layer however, serves as the rate-limiting step for diffusion and hence absorption of the drug, due to the highly hydrophobic nature of the cannabinoids.[25] No human trials have been done using this mode of delivery, but it may represent a very effective drug delivery system in the near future.[25] *Intravenous:* THC mainly used in this preparation during research.[25] The rapid rate at which peak concentration occurs, and the higher levels achievable, results in a significantly higher rate of adverse psychoactive symptoms.[25]

Distribution[24,25]

As a result of rapid distribution into tissues, as well as metabolism by the liver, once smoking has ceased, the plasma concentrations of THC decreases quite rapidly. [24,25] Like most highly lipophilic substances, the uptake of THC in the initial stages are predominantly by highly perfused tissues such as the heart, lungs,

brain and liver.[25] The volume of distribution (*V*d) of THC is large, around 10 l/kg, despite the fact that it is 95−99% protein-bound in plasma, primarily to lipoproteins.[25] With prolonged drug exposure, THC concentrates in human fat, being retained for extended periods of time. After the initial distribution phase, the rate-limiting step in the metabolism of THC is its redistribution from lipid depots into blood. [24,25] THC rapidly crosses the placenta, transfer to the fetus being greatest in early pregnancy. Its metabolites however do not cross as efficiently. Due to the high lipophilicity of THC, it also concentrates into breast milk from maternal plasma. [24,25]

Metabolism[24,25]

Hepatic: THC is metabolized and undergoes biotransformation predominantly in the liver, by cytochrome P-450 isoenzymes (principally CYP2C9). Following hydroxylation an equipotent metabolite 11-OH-THC is produced.[24] This is the predominant and first product of the oxidative pathway. Significant amounts of 8β-OH-THC and lesser amounts of 8α-OH-THC are also produced. More than 100 metabolites have however been identified.[24,25]

To detect whether a subject has recently used cannabis, the presence of 8*β*,11-di-OH-THC in urine has been reported as being a fairly accurate biomarker. [24,25] 8*β*,11-di-OH-THC is the end product which results following the dihydroxylation of THC.[24]Oxidation of the psychoactive 11-OH-THC produces the inactive metabolite THC-COOH.[25] THC-COOH and its glucuronide conjugate are the major end products of biotransformation and have also been shown to undergo enterohepatic recirculation. [24,25]

Metabolism of CBD is similar to that of THC, through primary and side-chain oxidation.[25]It undergoes significant first pass metabolism, but unlike THC, is excreted unchanged in the feces to a much larger extent. [24,25] However, metabolites of CBD have been identified in urine, (>30 of them), the main metabolic route being initial hydroxylation of the 7-Me group and subsequent oxidation to its corresponding carboxylic acid.[25] When CBD is co-administered, it does not affect the volume of distribution, total clearance or terminal elimination half-lives of THC metabolites substantially. [24,25]

Extra hepatic: Other tissues, including brain, intestine and lung, may contribute to the metabolism of THC. [24,25]

Elimination[24,25]

Being highly lipophilic, THC and its metabolites are sequestered in body fat, and excretion continues for several days to weeks after a single dose. Within 5 days, a total of 80−90% of THC is excreted, mostly as hydroxylated and carboxylated metabolites. [24,25] More than 65% is excreted in the feces, with about 25% being excreted in the urine.

The primary urinary metabolite is the acid-linked THC-COOH glucuronide conjugate, while 11-OH-THC predominates in the feces.[25] Confirmation and quantification of THC-COOH is usually performed after alkaline hydrolysis or *β*-glucuronidase hydrolysis, to free glucuronide-bound THC-COOH for measurement by GC/MS. [24,25]

Lab-testing[23]

Urine tests can detect cannabinoid metabolites for up to 10 days in casual users and up to 14-30 days in chronic users. Although cannabis testing can verify past use, it cannot distinguish between acute intoxication, dependence or abuse. Passive inhalation will not result in a positive urine test for THC. Synthetic cannabinoids cannot be identified through urine testing for THC.[23] Gas chromatography-mass spectrometry done on blood for presence of THC will reveal recent exposure.[23] Saliva and hair testing for cannabis is also possible – used to evaluate chronic exposure to the drug.[23]

LITERATURE REVIEW ON CURRENT WORLDWIDE USES OF MEDICAL MARIJUANA

- Neuropathic pain and relief of spasticity, especially in patients with Multiple Sclerosis
- Chronic pain (neuropathic, cancer etc.)
- Nausea and vomiting as a result of chemotherapy
- Stimulation of appetite and reduction in weight loss in cachectic patients with late stage AIDS and cancer
- Tourette's syndrome (reduce tics)
- Parkinson's disease (to reduce involuntary movements)
- Glaucoma: to reduce pressure in the eye
- Agonist-replacement pharmacotherapy for cannabis dependence.

Professor Gregory T. Carter,[26] a professor of Rehabilitation Medicine at the University of Washington School of Medicine, mentioned an extensive list of indications/uses during a 2009 symposium on chronic pain, for which he feels cannabis and cannabinoids may play a role/be of benefit.

These indications are encompassed in the chronic pain bullet of my list, but for completeness sake I will mention them; Myofascial pain syndrome, Diabetic neuropathy, Neuropathic Pain Syndrome, Phantom limb pain, Osteoarthritis, Fibromyalgia, Central Pain Syndrome, Rheumatoid arthritis, Spinal Cord injury°, Discogenic Back Pain, HIV neuropathy and Malignant Pain.[26]

Although literature does not support this, in fact, no analgesic benefit has been shown in spinal cord injury. A literature review is in order I should think. Evidence-based medicine is the way forward after all. So what research has been done to support the use of medical marijuana I asked?

An Article in Pharmacology,[16] published in 2012 posed the question: “Is there Any Clinically Relevant Cannabinoid-induced analgesia?[16] From the multitude of animal studies conducted, on rodents for the most part, it has been established that Cannabinoids exerts significant analgesic effects comparable to opioids, as well as antihyperalgesic effects, by blocking pain responses in nearly every model of pain tested.[16]

The problem however is that we cannot possibly translate this to humans. Humans have been shown to be less sensitive to the effects of cannabinoids, possibly due to lower concentrations of cannabinoid receptors firstly, secondly, rodents and humans are vastly different from a genetic point of view, and lastly, the pain stimuli introduced to rodents are quite unnatural and therefor the pain signal pathway may not be truly representative of what usually occurs during a nociceptive event.[16]

As far as human trials go, there has been *no* convincing evidence in the reduction of **ACUTE** pain with the use of cannabis and cannabinoids. In contrast to this however, an increasing number of randomised controlled trials studying its use in CHRONIC pain and painful spasticity have shown some efficacy, especially in neuropathic and inflammatory pain. It has also been shown to consistently improve mood, create a sense of well-being and result in decreased anxiety levels, as well as improving sleep quality and the general coping with pain.[16,30]
Both CB_1 and CB_2 receptor subtypes, have been shown to be up-regulated during nociceptive pain.

The use of both opioid and cannabinoid agonists may have synergistic effects, as cannabinoid receptor agonists have been demonstrated to compliment the action of μ-opioid receptor agonists.[15] Therefor, its use as an adjuvant analgesic agent, especially in the opioid-refractory patient population, seems quite appropriate.[29]
A study in 2003, comparing THC, Morphine and placebo, given to healthy volunteers prior to administration of a thermal and electrical pain stimulus, in order to establish whether any alteration in pain thresholds occur, surprisingly revealed lower pain thresholds in the group receiving THC.[16]

Another study applied capsaicin-evoked pain, and volunteers were randomised to smoke one of 3 different dosages of cannabis or placebo. An interesting finding here was that only the median dose showed any significant analgesic effect, whereas higher doses resulted in increased negative side effects and the lowest dose having no appreciable effect.[29] In order to study the efficacy of cannabinoids in acute post-operative pain relief, a trial was performed where patients were randomised to receive 5mg THC per os. This had no effect. Increasing the dose however did show dose-dependent pain relief with higher doses but with substantially more side effects.

Given the current evidence at hand, there seems to be an authorative consensus that it has no role in the management of acute pain.[16] A review of the literature on its use in chronic pain, overwhelmingly involved trials performed in patients suffering from Multiple Sclerosis. Most of these studies consistently report symptomatic improvement in up to 30% of participants receiving cannabinoids, particularly with regards to spasticity and muscle stiffness, neuropathic pain, bladder and sleep disturbances.[27,29]

This relief seems to be sustained when followed up was done at 1 year. Of note is that observer assessment of reduction in spasticity often did not correlate with the perceived improvement of the affected patient.[27,29]A study involving patients with severe cancer-related pain, participants were randomised to receive either a Cannabinoid or Placebo as add on medication. In those receiving cannabinoids, there was a 43% reduction in pain, with subjective relief of between 30 and 50%.[16]

A significant finding of particular interest for us in South Africa is the pain relief achieved in patients with HIV-associated neuropathy. One trial enrolled patients with HIV-associated mixed neuropathic pain due to peripheral or central dysfunction of the nervous system. Patients were allowed to continue their usual regimen of analgesics, and given cigarettes containing from 1% to 8% THC(4 to 32mg). Average daily dose ranged from 4mg to 128mg.[16,29]

Results consistently indicated that cannabis significantly reduced pain intensity, with patients reporting a 34%-40% decrease on cannabis compared to the 17-20% achieved on placebo. More-over, a significantly greater proportion of individuals reported at least a 30% reduction in pain on cannabis (46%-52%) compared to placebo (18%-24%), which is relevant since 30% decrease in pain intensity is generally associated with reports of improved quality of life.

The number needed-to-treat to achieve a 30% reduction in pain intensity was 3.5-4.5, a range achieved by standard non-opioid analgesics (i.e., noradrenergic antidepressants and anticonvulsants)[18,29] Since 1987, Cannabinoids have been approved as an anti-emetic agent in patients receiving chemotherapy as well as for HIV-related cachexia. Nabilone and Dronabinol have been approved by the FDA for the control of acute and delayed nausea and vomiting secondary to cancer chemotherapy.[18,29]

A meta-analysis on available data showed Cannabinoids to be equivalent to or more effective than metoclopramide and neuroleptics for this indication, but their side effect profile is unfortunately less favourable in terms of hypotension, sedation, dysphoria, dizziness and anxiety.[18,29] There are currently no head to head comparisons between cannabinoids and 5HT3 receptor antagonists or substance P/NK1 receptor antagonists in the literature.[18,29] With regard to its use in anorexia, early satiety, weight loss and cachexia[29] seen in late stage cancer patients and advance HIV disease; Trials providing 5mg Dronabinol daily vs placebo, showed a short-term improvement in appetite (38% vs 8% at 6 weeks),

with effects persisting for up to 12 months. Despite the increased appetite, no clinically significant weight gain followed however, which may be due to disease-associated energy wasting. The psycho-active side effects and the unpredictable and varied absorptive pattern seen with oral cannabinoids further limits its use for this indication.[29]What about its application in movement disorders such as Tourette's syndrome or Parkinson's disease? Currently there is not enough evidence in the literature to support its use.

A small observational study of 22 patients with Parkinsons disease, showed a decrease in the mean total score on the Motor Unified Parkinsons Disease Rating scale, when compared to the baseline score, after smoking cannabis. This suggests a possible utility for the drug in this population but lacks the backing of numbers and sound research methodology. Further studies in this regard are therefor recommended.[27]Another controversial proposed use is in glaucoma patients, aiming to reduce the intra-ocular pressure.

A report in the European Journal of Neuroscience in 2000 revealed that there are high levels of CB_1 receptor mRNA and protein expressed in the human eye, supporting a possible role for its use in glaucoma. It acts by reducing aqueous humour production, unfortunately the pressure-lowering effect is not sustained, as tolerance develops rapidly and its side-effect profile further limits its clinical usefulness. It may in fact do more harm than good and is not regarded as an appropriate agent for this indication.[28]

The authors of an aptly named article, "Medical Marijuana: Clearing Away the Smoke," published in The open Neurology Journal, 2012[29], presented a possible algorithm, following a literature review on the subject, which they hoped would be useful in determining whether cannabis might be recommended as a treatment strategy for individual patients. (If its use has been legalised in your country or state of practice of course!!!) I'll give a description of their proposed algorithm, as I would not want to infringe on any copyrights.

Their first logical step is to confirm the diagnosis of neuropathic pain and ensure that there is no other possible underlying cause for the patients' symptoms. Then establish whether the patient has received standard medical therapy, if not, patient will need to be given standard therapy according to current guidelines or protocols available to you.[29] Review whether the standard therapy has been effective.

Only consider marijuana if it has not been, and following counselling of the patient with regards to their openness to the proposed use of marijuana. If the patient is agreeable, full psychological evaluation must be performed to determine whether he/she is at risk of abuse, or mood disorders etc, and exclude any other contra-indications. If risk high and not likely manageable through careful support and monitoring with coordinated care, cannabis is not an appropriate option.

[29]If however the patient is willing, and is not deemed to be high risk, the next step is to determine route of administration preferred by patient, and institution of treatment, with frequent follow-up and evaluation for benefit, efficacy, side effects and diversion.[29]

Contra-indications:[18]
Abn sensitivity to individual components of the preparation
Severe personality disorders and psychosis[18] Strict precautions:[18]
Pregnant and breastfeeding due to possible developmental disorders in the child
Children and Adolescents before puberty
Elderly,as they are more vulnerable to CNS and CVS side effects
Severe CVS disease
Hepatitis C Addictive disorders[18]
Some preclinical data on its anti-tumour effects have suggested that cannabis may have a protective effect against the development of certain tumour types for eg. Hepatic adenoma and hepatocellular carcinoma, and has also shown a decrease in the incidence of various benign tumours.[30] It's antitumour effects are attributed to a multitude of mechanisms, includine the induction of cell death, inhibition of cell growth, inhibition of tumour angiogenesis invasion and metastasis. Another effect shown which may prove useful in risk reduction and treatment of colorectal cancer is the decrease in colonic inflammation. To date, there have been no human studies addressing this issue.[30]

CONCERNS

A good start would be to leave the reader with a truthful thought. There are very few drugs out there without any side effects. Those that are deemed safe are probably just waiting for some poor genetically vulnerable patient to come along to unmask its true adverse potential. Cannabis, as a drug, would for the majority of individuals, bring to mind its recreational use. Images of flowers and peace signs might even accompany the smoky picture.

Compared to other drugs in this realm, it is seen as a gateway drug, with its side effects shrugged off as trivial. Even supposedly educated, high profile personalities seem oblivious to the potential dangers of cannabis.A quote from good 'ole Arnold Schwarzenegger cements this statement: "Marijuana is not a drug, it's a leaf."So does that make pot dealers Florists Arnie?

With a lifetime dependence risk of 9% in marijuana users vs. 32% for nicotine, 23% for heroin, 17% for cocaine, and 15% for alcohol, the addiction risk with marijuana is significantly lower than that of other drugs of abuse. Unlike cocaine dependence, which develops explosively after first use, marijuana dependence comes on insidiously.[2] Tolerance to cannabis and physical dependence occur to only a minor degree, and this mainly in heavy users.[22]

Marijuana, in accordance with most drugs showing addiction potential, exerts its influence through the midbrain reward center, triggering dopamine release in the prefrontal cortex.[2,22] Although its existence was questioned until recently, a withdrawal syndrome is increasingly appreciated, characterized by irritability, anxiety, anorexia and weight loss, restlessness, disturbed sleep and craving, but these symptoms are usually mild and do not result in a compulsive urge to acquire and use the drug.[2,22]

But this all relates to studies done on recreational users, smoking cannabis containing much higher and variable amounts of THC. With peak plasma THC concentrations nearly 20 times lower than that of smoked cannabis, nabiximols for instance, flattens the steep-slope pharmacokinetic profile found in botanical cannabis, with corresponding reductions in adverse psychotropic effects.[2] This pharmacokinetic divergence from botanical cannabis greatly reduces the likelihood of nabiximols inducing dependence.

Most of the medically prescribed products, including the smoked or inhaled group, contain precise and carefully calculated doses of THC and CBD, in order to prevent unwanted side effects. A 2008 systematic review of studies examining the safety of medical cannabinoids, by Tongtong Wang et al,[31] critically analysed 31 studies. Out of 4779 reported adverse events, most were not serious, dizziness being the most commonly reported. None of the events were unexpected. They found the rate of non-serious adverse events to be 1.86 times higher in medical cannabinoid users than amongst controls, but there was no evidence of a higher incidence of serious adverse events between the groups.[31]

Their findings were unfortunately limited by lack of adequate reporting in the included studies, especially with regard to frequency of adverse events occurring per patient, short follow up periods of the patients, therefor making long-term analysis impossible and the observational studies not having control groups or making adjustments for confounding factors.[31] They too emphasise caution against comparing adverse effects seen with recreational cannabis use, to that of medical cannabinoids. The 2 population groups being compared are vastly different, as are the amounts used, the methods of drug delivery and the existence of comorbidities and the methods of drug delivery,[31] and should therefore be evaluated separately.[31]

A more recent systematic review[27] evaluating the efficacy and safety of medical marijuana in selected neurological disorders (Multiple Sclerosis, Epilepsy and movement disorders), revealed a 1% risk of serious adverse psychopathologic effects. A wide variety of formulations are in use, containing differing amounts of THC and CBD, as well as being administered via various delivery systems eg. Pills, mucosal sprays, vaporised or smoked, hence differing rates of onset, absorption, peak concentration and effect is to be expected. In the studies analysed, 6.9% of the 1619 patients receiving medical cannabinoids, stopped treatment due to adverse effects.

Of the 1118 patients receiving placebo, 2.2% terminated the treatment due to adverse effects. Unfortunately data on exact reasons for discontinuation were incomplete.[27] The most frequently reported adverse effects were;Nausea, behavioural or mood changes, feelings of intoxication, hallucinations, increased weakness, fatigue suicidal ideation, dizziness or vasovagal symptoms.With higher concentrations of THC (not usually an issue in medical formulations) Psychosis, dysphoria and anxiety were increasingly more prevalent.

[27] A real concern that needs emphasis is the administration of a drug invoking suicidal ideation, to a vulnerable population group such as patients suffering from Multiple Sclerosis, who are already at a higher risk for suicide.A longitudinal study spanning over 30 years, found that frequent cannabis use (at least several times a week) predicted later suicidal ideation in susceptible males but not females.[33]Multiple earlier studies (once again on recreational users) have reported a causal relationship between cannabis use and completed suicide,[33] however, when the data is adjusted for other confounders such as presence of established mood or psychiatric disorders, as well as the use of or evidence of use of other drugs and alcohol, no direct relationship could be shown.

Although a definitive link between the use of marijuana per se and suicide has not been shown, there is some evidence to support its contributory role in patients with underlying psychological, behavioural or mood disorders.[32]In this era, with the internet putting potential consumers right at the doorstep of distributors, where a transaction can remain untraceable and anonymous, and where a vulnerable, at risk, teenage population have found a safe haven, the marijuana industry is sure to expand at an alarming and uncontrollable rate. The worry is not so much about the medical products, but that the legalisation of cannabis as a whole will increase the availability of its recreational form, for which we have convincing evidence of potential harm.

Despite an ever increasing body of evidence linking the use of cannabis to induction or aggravation of psychoses and the development of addiction to the substance, advocates for its legalization frivolously contend that smoked marijuana is a harmless natural substance that improves quality of life. Schizophrenia has been posited as a hypercannabinoid condition because schizophrenic patients have significantly elevated cerebrospinal fluid levels of anandamide, the most important endogenous cannabinoid.

Cannabis use has been implicated as a potential cause, aggravator, or masker of major psychiatric symptoms, including psychotic, depressive, and anxiety disorders, particularly in young people. During puberty, a period characterized by significant cerebral reorganization, particularly of the frontal lobes implicated in behavior, the brain is especially vulnerable to adverse effects from exogenous cannabinoids. Adolescent cannabis use is also associated with depressive and anxiety disorders that emerge later in life.

The paradox of marijuana both inducing and relieving anxiety is reconciled by understanding that effects on anxiety levels are dose dependent.[2,31]Cannabis use has been shown to impair cognitive functions on a number of levels; from basic motor coordination to more complex executive function tasks, such as the ability to plan, organize, solve problems, make decisions, retain information, and control emotions and behavior.[34] When an individual is exposed to an unfamiliar situation, where circumstances call for rapid assimilation of data in order to make a decision, our executive functions (higher-level cognitive functions), are of critically importance.

[34] A review on the effects of cannabis on executive functioning in recreational and chronic users, had the following results to show;[34]They divided the evidence from their literature review into three time categories; firstly, they reviewed the acute effects of smoking cannabis for up to 6 hours following intoxication, then they assessed the residual effects, following a period of 7 hours up to 21 days of abstinence, and lastly, reviewed any long term effects following a period of longer than 3 weeks of abstinence. When comparing infrequent or less experienced users of cannabis, with those showing drug tolerance consequent to regular use, the impairment observed following acute intoxication were substantially more evident in the first group.[34]

Attention and concentration, including information processing in the latter group (regular users), were found to be deranged more by acute abstinence,[34] which normalized after acute intoxication, most likely explained by a neuro-adaptive response to chronic, heavy cannabis use.[34] Impairments in aspects of working memory following acute intoxication are well established.[34] In terms of the residual effects up to 21 days of abstinence, only a single study by Whitlow et al. (2004)[35] suggests that decision-making capabilities are impaired and that risk-taking behavior may be enhanced.[35] Unsurprisingly, where executive functioning was shown to be most significantly affected, the population studied were heavy cannabis users, who had been smoking large amounts over prolonged periods.[34]

It is highly likely that a link exists between residual impairments and the duration and quantity of cannabis used.[34] While basic attention and working memory abilities are largely restored following prolonged periods of abstinence, important cognitive functions such as concept formation, planning and decision making seem to endure.[34] If history is to repeat itself, we may be in for a similar scenario to that caused by the explosion of the Tobacco industry. Making a potentially harmful drug more easily available, reducing sentencing of individuals distributing such drugs and relaxing persecutory efforts, previously put in place to protect the public, will undoubtedly have ramifications that may not be evident immediately, but are sure to echo very loudly into generations to follow.

The tobacco industry has basically provided a detailed road map for marijuana:[36]

- Deny addiction potential
- Downplay any adverse effects
- Create as large a market as possible, in as short a time as possible
- Protect that market through lobbying, campaign contributions and other advocacy efforts.

The Marijuana industry has already formed its own advocacy organisation in the USA – The National Cannabis Industry Association.[36] The negative answer to the question: "Has anyone ever died from marijuana?" seems to be evidence enough for most to disregard any other warnings which may be posed. But what if I add, not as a DIRECT result. Most associated deaths could not conclusively show marijuana as the sole cause.

There have been multiple case reports in the literature of relatively young, healthy individuals developing acute coronary vasospasm, angina and acute myocardial infarctions following the use of cannabis. The activation of CB_1 and CB_2 receptors has been shown to modulate the functions of various cellular elements of the vessel wall and therefor may contribute to the pathogenesis of atherosclerosis.[37] CB_1 receptors as mentioned previously are predominantly found in the CNS, but they are expressed in various peripheral tissues as well, including cardiac muscle, vascular endothelium and vascular smooth muscle cells.[37] CB_2 receptors have also been identified on endothelial cells, and pro inflammatory cytokines seem to upregulate their expression.

[37] Activation of these receptors have opposite effects, where CB_1 agonism leads to atherosclerotic plaque enhancement through increased LDL uptake and enhanced expression of macrophages and platelet activation, CB_2 activation results in decrease in T-helper cell activation with reduction in the inflammatory response. Caution and possible complete avoidance of its use in patients with established coronary artery disease, stroke or peripheral vascular disease has been advised.[37]Other complex actions on cardiovascular physiology has been shown with the smoking of Marijuana: mainly a dose-dependent increase in heart rate, decrease in stroke volume, increase in cardiac output and minimal effects on systemic blood pressure.[37]

Similar effects have not been shown when cannabinoids are given systemically. An explanation for this could be that smoking exposes the individual to other particulate and gaseous material arising from plant combustion. A decrease in the maximum exercise capacity in normal healthy individuals following smoking of marijuana, may possibly lead to lowering of the angina threshold.[37] An undeniable association between mortality and marijuana use, is its psychoactive effects, influencing the users' judgement, as well as having a significant effect on coordination and motor impairment, which can lead to fatal motor vehicle accidents (MVA) in drivers who are intoxicated.

Cannabis is the most prevalent illicit drug identified in impaired drivers.[38] Epidemiologic data show that the risk of involvement in an MVA increases two fold after cannabis smoking. Acute intoxication produces dose-related impairment in cognitive and psychomotor functioning and it can produce risk-taking behaviour that further impair driving skills. Other effects include alterations in reaction time, poor performance in divided attention tasks, an increased occurrence of lane crossing and impairment of distance judgement. Higher blood levels of THC and driving within an hour of smoking, were most strongly associated with increased crash and culpability risks.[38]

Smoking marijuana can most definitely lead to respiratory symptoms as a result of the injurious effects of the smoke on larger airways, such as rhinitis, bronchitis and pharyngitis. But smoking marijuana by itself has not been shown to lead to the development of Chronic Obstructive Airways Disease (COPD). In conjunction with tobacco, yes, it does.[39]With regards to its potential cancer risk, epidemiological evidence of a link between marijuana use and cancer have been mostly inconclusive, as various studies have yielded conflicting evidence.

A retrospective cohort in 1997, of 64855 men, aged 15-49 years, found that cannabis use was not associated with tobacco-related cancers. An increased risk was shown for lung cancer among cannabis smokers who also predominantly smoked tobacco. Among nonsmokers of cannabis, those participants who had ever used cannabis, there was however a higher associated risk of prostate cancer found.[40] A study reporting an elevated risk of testicular germ cell tumours lacks strength in numbers to validate this observed association.

However, a recent population-based cohort study, published in 2013, examining men (n = 49,321) aged 18-20 years old have been able to show a definite link. Participants were assessed for cannabis use and other relevant variables during military conscription in Sweden in 1969-1970. They were tracked until 2009 for incident lung cancer outcomes in nationwide linked medical registries.[41]At the baseline conscription assessment, 10.5 % (n = 5,156) reported lifetime use of marijuana and 1.7 % (n = 831) indicated lifetime use of more than 50 times, designated as "heavy" use.[41]

They found that even after statistical adjustment for baseline tobacco use, alcohol use, respiratory conditions, and socioeconomic status,[41] those designated as “heavy” users, had a more than a twofold risk (hazard ratio 2.12, 95 % CI 1.08-4.14) of developing lung cancer.[41] Their study provides important data for informing the risk-benefit calculus of marijuana smoking in medical, public health, and drug-policy settings.[41]Unfortunately, it seems that concerned health professionals are losing a battle against the masses. Our warnings are shrugged off, and we don’t have much in terms of ammunition to throw back at them, especially in terms of the medical use of marijuana, as most studies haven’t reported any long-term effects, and the side effects that have been reported are hardly cause for deterrence.

Preliminary studies looking at the effect that legalisation of medical marijuana has had on the incidence of recreational use thereof, have not been able to show a significant increase thusfar, however, it must be noted that, one study was done very shortly after the introduction of this law, and another performed in a single state alone. It's still early days, it could go either way. But sofar, the public still has the upper hand.Of great concern however, is a recent study from Colorado, which showed an exponential increase in the incidence of fatal motor vehicle accidents by intoxicated drivers, following the legalisation of marijuana in this state, when compared to previous years.[42]

To my mind, this means the answer is YES! People have died from Cannabis, and being pedantic about it being a direct or indirect cause is just a form of denial.Anaesthetic considerations; Substances routinely used in anaesthetics such as barbiturates, benzodiazepines, opiates and phenothiazines, which depress the CNS, may be potentiated by Cannabis, resulting in exaggerated hypnotic and sedative effects.[43]

As mentioned above, cannabis interferes significantly with respiratory function, and may result in difficulty with oxygenating and/or ventilating under general anaesthesia, therefor if possible, local anesthesia may be preferable. Smoking cannabis can cause oropharyngitis and uvular edema, which may potentially lead to airway obstruction under general anesthesia.[43] In cases of acute intoxication, avoiding any medication likely to increase the heart rate is recommended.

Consider postponement until patient more clear-minded if possible. After acute consumption, more anaesthetic may be required due to greater catecholamine release, and less in cases of chronic use because of catecholamine depletion. Moreover, one should expect the possibility of psychiatric side effects or withdrawal symptoms in patients during both induction and emergence. It is therefore essential to question patients about cannabis use and maintain a high index of suspicion.[43]

SOUTH AFRICAN STANCE ON MARIJUANA

In February this year, Mario Oriani-Ambrosini, a member of parliament representing the Inkatha Freedom Party (IFP), who has late-stage lung cancer, made a passionate plea in Parliament to legalise the medicinal use of cannabis, by presenting a private members bill. The main aim of Ambrosini's Medical Innovation Bill (see government website to download) is to make provision for innovations in medical treatments, by legalising the use of cannabis for medical, economic and industrial purposes.[44] Other objectives are to establish or identify, one or more research hospitals able to treat at least a 100 patients, where medical innovation can take place, within 3 months of commencement of the act.

These hospitals will be authorised to allow medical practitioners greater professional discretion to administer alternative and innovative medical treatments, following informed consent given by the patients.[44,46] The bill will also codify existing best medical practices, in order for medical practitioners to innovate when management of disease conditions are deemed inappropriate or suboptimal due to a lack of sufficient evidence or research in the field. Section 7 in Ambrosini's Bill suggests that "no one shall be liable or guilty of any offence for growing, processing, distributing, using, prescribing, advertising or otherwise dealing with or promoting cannabinoids for the purposes of treatment and commercial or industrial uses identified by the minister of trade and industry"[46]

During his speech he admitted to using cannabis oil suppositories for pain relief and expressed his belief that this has enabled him to survive his cancer thus far. Ambrosini's speech was met with a standing ovation from Parliament, an indication that the government is open to change. The bill is likely to be presented in the National Assembly early in 2015 according to Ambrosini's legal council.[44]
As things stand, it is presently illegal to possess cannabis or trade in it, in SA. We also currently have no medications approved by the Medicines Control Council that contain THC, other cannabinoids or even synthetic cannabinoids.

Although the government seems open, as well as some pro-marijuana dealers in areas such as the Northern Cape, there are strong voices against the legalization of this drug.[44] Charles Parry, acting vice-president of the Medical Research Council in South Africa is one of these concerned voices. In an article published in the South African Medical Journal this year, he emphatically gives his opinion about the proposed bill. He draws attention to the fact that even though multiple US states have legalized the use of medical cannabis, it has yet to get approved by the US FDA, largely as a result of three shortcomings:[45]

1) The lack of human clinical trials to show that the benefits outweigh the risks;
2) Inconsistencies in the main chemical compound, particularly when smoked;
3) The negative health effects sometimes associated with cannabis use, particularly when smoked.[45]

"Any decisions on legalising the medical use of cannabis must take into consideration the risk of possible harms that have been demonstrated among some people who regularly use cannabis, the possible effects that legalising medical use of cannabis may have on the non-medical use of the drug, possible impact on communities and broader society, and the quality of the evidence supporting the medical use of cannabis."[45] He is however in full agreement that potential great benefit may be obtained from governmental backing to conduct studies in this field, including that of synthetic cannabinoids, and that funding should be made available to support this research, especially where it could lead to medical innovation.

In his opinion: [45]"This research should include:

i. An investigation of factors that led to the policy shifts in countries that have legalised the medical use of cannabis, and what their experiences have been of this policy shift;
ii. Maintaining a watching brief on the literature in this area, as advances in scientific knowledge are taking place rapidly;
iii. Establishing surveillance systems to assess the possible influences of medical cannabis use on non-medical cannabis use; and
iv. Conducting both preclinical and human studies to study the effects of cannabinoids on symptom alleviation and disease status."

Parry is not the only one who is concerned, the Cancer Association of South Africa's head of research, Carl Albrecht, points out that the bill intends to decriminalise the use of dagga across the board. "It seems that anybody would be able to grow dagga, process it and advertise it if it's for treatment. How do you police whether it's for treatment or not? And treatment of what?"[45]Sadly, Mr Ambrosini lost his battle with cancer on the 16th of August this year, and will not be witness to the outcome of his proposed bill. Members of the IFP have pledged to take up his charge and follow through on his vision.[46]

CONCLUSION

So here's the highlights for you in a nutshell:
Marijuana, like opium, has been around and in use for centuries, both as a treatment modality in the field of medicine and as a recreational drug in the field of dreams. The fairly recent discovery of the endocannabinoid system, has finally given us new targets to aim our research at and hopefully bring us closer to understanding its role in analgesic pathways, and how it can be manipulated to enhance its analgesic potency whilst limiting its adverse effects.

Preclinical research has thusfar shown promising results for its use and effectiveness in a variety of pathological conditions. This has however not been translated into human studies, and much more research is required in order to elucidate its beneficial properties and convince the scientific realm (and some governmental organisations) of its potential usefulness.

Synthetic cannabinoids for specific indications are available, but their use is still clouded by much controversy. Which brings me to my next point, although restrictions on potentially dangerous substances in order to protect the public is sensible, when a substance has the potential to improve wellbeing and alleviate suffering, some leeway is necessary. Due to harsh laws and the threat of prosecution, research on cannabis has been severely thwarted. Studying the drug is the only way we will be able to answer very real and important questions, based on sound evidence.Pharmaceutical companies are unlikely to buy in, as cannabis is a plant and therefor in the public domain. This means that in its natural form, it cannot be patented, hence, no profits to be made.

Yes, the synthetic agents may boost their interest, but thusfar, these agents have not made any clinically significant impacts when compared to existing agents, and are no better than smoking a well-rolled joint. The potential harmful effects of relaxing marijuana laws as a whole must not be overlooked. Eventhough preliminary evidence doesn't seem to show an increase in recreational use, the reliability of these studies are brought into serious question when reports of increased fatal motor vehicle accidents in drivers acutely intoxicated with the drug have also been published.

If Marijuana is to become increasingly more available, some serious thought has to be put into road and traffic laws. A zero tolerance rule to some may seem harsh, especially as more people may be using it legitimately as a medically prescribed agent, but surely you can get a pal to cart you around? There is no doubt that there is a potential place for Medical Marijuana, although caution is in order, and we here in South Africa, may very soon have to face it in all it's glory if Ambrosini's Bill is passed.

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