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Guide to Medical Marijuana

Marijuana is the most popular recreational substance in Western societies and has the longest recorded history of human use, over 5,000 years. The popularity of marijuana as a recreational substance is due to its ability to alter sensory perception and induce elation and euphoria. In addition to recreational enjoyment, the components of the marijuana plant (Cannabinoids) have a variety of beneficial medicinal effects unrelated to its psychoactive properties that have been recognized for thousands of years.

As early as the third millennium BC, Chinese texts described its usefulness in the relief of pain and cramps. In ancient India, the anxiety-relieving effect of marijuana was recorded more than 3,000 years ago. The use of cannabis or hashish as a psychoactive substance reached Europe and the Americas through the Arab world in the 19th century. During the same period, marijuana extracts had gained widespread use for medicinal purposes until 1937, when concern about the dangers of abuse led to the banning of marijuana for further medicinal use in the United States. In the past 20 years, there has been a resurgence of interest in its medicinal properties of marijuana.

Despite the significant scientific insights into the mechanisms underlying the therapeutic actions of marijuana, there is still widespread misunderstanding as to how Medical Marijuana works and how to use it effectively. As a Medical Marijuana patient for more than 15 years and founder of CBD Science, LLC (1), I am compelled to present the comprehensive research on Medical Marijuana and outline for health care professionals common sense therapies based on that research.

Legal/Political Background

In 2006, the U.S. Food and Drug Administration (FDA) issued an inter-agency advisory memo opposing the use of Medical Marijuana, claiming there is no evidence of its medical benefits. The memo claimed (2);

"…no sound scientific studies support medical use of marijuana for treatment in the United States, and no animal or human data supported the safety or efficacy of marijuana for general medical use."

In 2011, the Drug Enforcement Administration (DEA) issued a white paper, "The DEA Position on Marijuana," which claimed (3);

"The clear weight of the currently available evidence supports the position that Marijuana has no accepted medicinal treatment in the United States"

The FDA and the DEA position on Medical Marijuana are based neither on a through scientific review nor any cogent line of logical reasoning. The federal government's position just doesn't stand up to scrutiny.

Sound scientific and double blind clinical studies support the medicinal use of Marijuana. The branch of the Federal Government responsible for Medical Science, the National Institute of Health (NIH), is well aware of the medicinal value of Medical Marijuana. In addition to funding many of the studies cited in the footnotes below, the NIH published a paper outlining the value of Medical Marijuana's compounds in the development of Pharmacotherapy in 2006 (4).

The Federal Government maintains conflicting positions on Medical Marijuana. Common sense demands that we examine the conflicting positions and create a coherent policy. The NIH(5), Department of Health and Human Services (HHS)(6), Veterans Administration (VA)(7), Department of Justice (JOD)(8) Patent Office (PTO)(9), and FDA(10) have taken positions in favor of the medical use of Marijuana, while the DEA (11) and Internal Revenue Service (IRS) (12) have taken positions in opposition to the Medical use of Marijuana.

While the Federal Government re-examines the scientific evidence and sorts out its contradictory positions, Medical Marijuana patients can rest assured that scientific research and rigorous double-blind clinical trials conducted between 2003 and 2012(13) have shown that Medical Marijuana Therapy can treat both the disease and the symptoms of disease without the severe side effects associated with other medications.

GW Pharmaceuticals patents have been accepted by the U.S. Patent Office because they have generated over 1,300 patient-years of safety data, and adverse events have been predictable and well tolerated (14). The most common side effects of Medical Marijuana are dizziness (which occurs mainly in the first few weeks of treatment) and fatigue. These reactions are usually mild to moderate and improve within a few days, even if treatment is continued. These side effects are common to many other prescription medications, particularly pain medications.

What follows is a comprehensive reference for Medical Marijuana therapies backed by sound scientific and clinical double blind studies performed in Israel, Brazil, the Netherlands, Japan, the United Kingdom, and the United States over the past 20 years. Many of these studies were funded by research grants originating in the United States under the oversight of the NIH.

The scientific research and the clinical trials have been done. They have shown that Medical Marijuana can be safe and effective treatment for the diseases and symptoms outlined below. But don't take my word for it, read the patent applications specified in footnote #13 and decide for yourself.

The wait is over; pain and suffering for millions can be reduced or eliminated right now without severe side effects.

But first, let me clear up some common misconceptions about Medical Marijuana:

- Myth: marijuana kills brain cells.
- **Truth**: Medical Marijuana does not kill brain cells. The act of smoking – inhaling and holding your breath – can temporarily reduce one's brain cells, but that has nothing to do with Medical Marijuana. It has to do with the way you are taking the medicine, i.e. your "Method of Delivery." Medical Marijuana (regardless of its method of delivery) has Neuro-protective and Antioxidant properties (15).
- Myth: Smoking Marijuana is as bad as or worse for your lungs than smoking cigarettes.
- **Truth**: A study of 5,000 young adults in four cities over two decades recently published (1/10/12) in the Journal of the American Medical Association (JAMA) found that with regular use (a joint a day or up to three joints a week), the lung function of Marijuana smokers actually improved over time (16). The same study saw lung function drop significantly for cigarette smokers.
- Myth: Marijuana causes cancer
- **Truth**: Medical Marijuana does not cause cancer, and there is research to support the hypothesis that it can help cure different kinds of cancer (colon, breast, and skin) (17).
- Myth: Marijuana is a "gateway drug" that leads to heroin, cocaine, or crack (18)
- **Truth**: According to Joycelyn Elders, MD, former US Surgeon General, *"Much of their [US drug-policy leaders] rhetoric about marijuana being a 'gateway drug'* ***is simply wrong****. After decades of looking, scientists still have no evidence that marijuana causes people to use harder drugs"* Dec. 14, 2002 editorial published in The Globe and Mail (18).
- Myth: Marijuana causes memory diseases, such as Alzheimer's, Parkinson's or Huntington's.
- **Truth**: Medical Marijuana does not cause Alzheimer's, Parkinson's or Huntington's diseases, but it can relieve the symptoms of these diseases and sound scientific studies provide evidence that it can be preventative (19).

- Myth: Smoking high THC Marijuana gives you all the medicinal benefits that Medical Marijuana has to offer.
- **Truth**: Smoking high THC doesn't access all the medicinal benefits that Medical Marijuana has to offer. Research shows that patients who just smoke high-THC Medical Marijuana are accessing only a quarter of the medicinal value of Medical Marijuana, and too much THC can imbalance the system so that frequent users of High THC Marijuana are propone to paranoia (20).
- Myth: The Marijuana "experience" is dose dependent and context independent.
- **Truth**: The Medical Marijuana "experience" is a function of three factors (21).
    - Dose (metabolic "state" of the system)
    - Set (internal landscape)
    - Setting (external landscape).

Medical Marijuana is Bi-Phase (22). This means that at high levels, it produces the opposite effects i.e. euphoria can turn into paranoia (23) and anti inflammation can turn into-inflammation (24). Too much of anything, including Medical Marijuana, is a problem. However, if you understand how Medical Marijuana works, you can minimize the negative and enhance the positive. If Medical Marijuana is used effectively, it will help you find your natural balance, and as that balance emerges your use of Medical Marijuana will decrease as your feeling of well-being increases.

How to Get the Medicinal Effects you are looking for

The effects of Medical Marijuana vary greatly. The two explanations for the different effects are the different "strains" or "cannabinoids". The Cannabis Culture (Collectives, Dispensaries, Growers, and Patients) uses the strain explanation – different effects are produced by different strains - Indica or Sativa. The scientific community (Researchers, Laboratories, and Pharmaceutical Companies) use the "cannabinoid" explanation – different effects are achieved by the use of different cannabinoids (Delta 9 Tetrahydo-Cannabinol i.e. THC or Cannabidiol i.e. CBD). Both explanations are useful and patients will benefit from Medical Marijuana therapies (Chart #1 and Chart #2) based on either or both. Below is a summary of each explanation from a medicinal and scientific perspective.

Strains(25).

How do Strains Work?

According to the Cannabis Culture (CC), "strains" are the key to medicinal benefits. Each strain is a unique combination of compounds in the cannabis plant. The unique compounds that belong to the Marijuana plant are called "cannabinoids," and the most dominant are Tetrahydrocannabinol (THC) and Cannabidiol (CBD), although there are certainly others. Scientific research has revealed how THC and CBD work (the "Mechanism of Action") which is outlined below. The CC believes that the terpenes and the other compounds contained in the natural plant (26) have an important influence. At present we do not know how the cannabinoids,

the terpenes and the other compounds work together in the particular strains but research is currently being performed in this area (27).

There is a common belief in the CC that Indicas have a higher level of cannabinoids than sativas and that they contain more CBD than Sativas. I have not been able to verify these beliefs. In fact, in my survey (Chart #3) of strain cannabinoid content there was no statistical difference between Indica and Sativa in terms of Cannabinoid content, though Sativa strains had more CBD than Indica strains.

Indica strains (28)**,** according to the CC, are sedatives/relaxants and are effective for treating the symptoms of medical conditions such as anxiety, chronic pain, insomnia, muscle spasms and tremors. Common strains include:

- B-Dawg (23% THC/1% CBD)
- Granddaddy Purple (21% THC/1% CBD)
- Black Domina (21% THC/1% CBD)
- Purple Kush (19% THC/1% CBD)
- Purple OG Kush (14% THC/1% CBD)

Sativa strains (29) according to the CC, are a stimulant, and are effective in appetite stimulation, relieving depression, migraines, chronic pain and nausea. Common strains include:

- Green Dragon (22% THC/1% CBD)
- Sour Flower (20% THC/1% CBD)
- Pineapple (18% THC/1% CBD)
- Maui Wowie(16% THC/1% CBD)
- Super Sliver Haze (15% THC/1% CBD)

The CC believes that sativa strains cause feelings of alertness and optimism, and they recommend that patients medicate with this type of Medical Marijuana during the day.

Hybrid strains (30) are cross-breeds of Indica and Sativa strains that produce varieties that carry some characteristics of each parent. For example, the CC believes that adding Sativa to Indica strains adds mental clarity and decreases sedation effects. And, adding Indica to Sativa strains can decrease or even eliminate the Sativa tendency to stimulate anxiety (31). Common hybrid strains include:

- Sour Diesel(24% THC/2% CBD)
- Lavender (22% THC/1% CBD)
- Space Queen(19% THC/1% CBD)
- OG Kush (19% THC/1% CBD)
- Blueberry Diesel (15% THC/1% CBD)

Hybrids are often referenced based upon the dominant sub-species inherited from their lineage, e.g. Pure Indica, Mostly Indica, Mostly Sativa, or Pure Sativa. Instead of using pure Indica or pure Sativa, many patients can benefit from the use of hybrid strains. There are a vast number of strains available for patients, and while the ratios of THC to CBD are similar across Indica and

Sativa strains, the different effects lies with different cannabinoid profile (CBC, CBG, THCV etc) and the affects of terpenes.

Cannabinoids

Scientific research has discovered over 108 cannabinoids as of 2014. THC and CBD are the two dominant cannabinoids across all Marijuana Strains. Over 95% of the research has focused on THC and CBD. The medicinal effects unique to THC and CBD outlined below are based on the general principals uncovered by scientific analysis over the past 50 years. That research was made available to a layman through the pioneering work of Martin Lee, Fred Gardner and Ethan Russo (32) and publications such as O'Shaughnessy's and web sites such as ProjectCBD (www.projectcbd.org). What follows is my understanding of the research presented in the publications mentioned above, the patents submitted by GW Pharmaceutical between 2003 and 2012, and my personal experience since 1996 under my doctor's approval and oversight (33).

How do Cannabinoids Work?

Cannabinoids work by influencing the Endo-Cannabinoid System (34). The Endo-Cannabinoid system (ECS) refers to a group of endogenous lipid signaling molecules and their receptors. The term "endocannabinoid" is derived from the word "endogenous" (meaning "originating from within an organism") and "cannabinoid" (referring to the molecular compounds unique to Marijuana). The ECS regulates the activity both within and between the central nervous system (CNS) (35) and the peripheral nervous system (PNS) (36).

Cannabinoid receptors are a class of cell membrane receptors in your ECS. There are currently two known subtypes, termed CB_1 and CB_2 (37).

- CB_1 receptors are expressed mainly in the brain and spinal column but also in the lungs, liver and kidneys. CB_1 receptors mediate the activity generated by the central nervous system.
- CB_2 receptors are expressed in the immune system and in hematopoietic cells. CB_2 receptors mediate the activity in the peripheral nervous system.

The first pass of the metabolic process hydrolyzes (adds hydrogen) the cannabinoids to create active compounds that effect (stimulate or inhibit) ECS receptors. CBD and the first pass metabolites of CBD also bind to (stimulate) receptors outside the ECS system such as:

- TRPV-1 : pain perception, inflammation and body temperature (38)
- A2A : anti-inflammation and anti anxiety by mediating dopamine and glutamate indirectly (39)
- 5-HTP: anxiety, addiction, appetite, sleep, pain perception, nausea, vomiting (40)
- GPR55: modulates blood pressure and bone density (41)

The second pass of the metabolic process oxidizes (adds oxygen) to create compounds that inhibit inflammatory enzymes (42).

Effects Unique to THC

To understand the medicinal benefits of the primary cannabinoids (THC and CBD) it is useful to divide its effects into two categories; those effects that are unique to THC and CBD (and their metabolites) and those effects that are delivered by both THC and CBD. THC and its first metabolite (11-OH-THC) stimulate (i.e. agonist) the CB_1 receptor which mediates the activity (mental activity) in the central nervous system. They also stimulate $CB_{(2)}$ but not as strong as the effect on $CB_{(1)}$ (43). The second metabolite of THC (THC-COOH) provides anti-inflammation effects by inhibiting COX-1 and COX-2. (44)(45).

Psychoactive (46) (47)
Appetite Stimulate (48)
Night Vision (49)
Tachycardia (50)

Effects Unique to CBD

CBD and its first metabolite 7-OH-CBD reduces (it is an antagonist) the activity of the CB_1 receptors thereby reducing mental activity. They also increase the levels of endo-cannabinoids in the system that stimulates the ECS brain receptors (CB_1 and CB_2) by inhibiting the enzymes that destroy them (51).

Anti-Psychotic (52) (53)
Appetite Suppressant (54)
Anti-depressant (55)
Bradycardia (56)

Effects of both THC and CBD

Combining THC and CBD delivers the effects of THC and CBD (and their metabolites). Research has shown that there is a synergistic (1+1=5) effect when you combine THC and CBD. When THC and CBD are combined the negative effects of each (paranoia/ memory extinction) are reduced and positive medicinal benefits outlined below are increased.

Anti-Inflammatory (57)
Anticonvulsant (Spasticity) (58)
Muscle Relaxant (59)
Neuroprotective Antioxidant (60)
Antiemetic (61)
Antinociceptive (62)
Anti-Glaucoma (64)

How should I use Cannabinoids?

While the general effects have been articulated, each individual is a special case (i.e. variation) of the general principal. For example, for most people CBD generates an increase in alertness, but there are some who take CBD and fall asleep almost immediately. And for most people THC is sedative, but there are some who cannot sleep after taking THC. This is because the metabolism of each human is unique (like fingerprints) and the only way to know for sure what the effects will be for you is to test the general principal on your unique metabolism.

Given that each individual is a special case of the general effects how does one determine what is the best for their unique metabolism? The only way to find out is to test what works via self-titration (personal trial and error).

The easiest way to understand how THC and CBD work together is to look at THC as the Agonist (i.e. stimulant mental activity) and CBD as the Antagonist (suppresses mental activity). THC is psychoactive, while CBD is anti-psychotic.

THC = Agonist	**CBD = Antagonist**
Increase Mental Activity	Decrease Mental Activity
Psychoactive	Anti-psychotic
CNS stimulate	Anti-Depressant
Appetite Stimulate	Appetite Suppressant
Tachycardia	Bradycardia

According to Traditional Chinese Medicine (65) when the active (Agonist) and deactivating (Antagonist) forces are balanced, the living system exhibits physical health; when they are unbalanced, a diseased state results. Either imbalance results in physical illness. If one goes too far one direction i.e. too much stimulation (Agonist) with THC and paranoia emerges (too much thinking), or too much Suppression (Antagonist) with CBD and memory extinction emerges (no thinking), then they can simply balance with the opposite. In addition to the medicinal benefits (refer to Chart #2) outlined above, there are five unique ways of combining THC and CBD to balance your CNS and PNS:

- THC alone
- CBD alone
- THC and CBD at the same time
- THC followed (wait 15 minutes) with CBD
- CBD followed (wait 15 minutes) with THC

What is the best? Only you can answer that question via the process of self-titration. I suggest that you start with the cannabinoid (THC or CBD) or a combination of THC/CBD that the research indicated has the highest medicinal effects you seek.

For instance, patients with a migraine seeking relief to tension in their CNS need to activate their CB_1 receptor and would start with THC. Two signs will appear that are a warnings signals that the intake of THC should be reduced:

- Issues (analysis paralysis, spacey etc.) caused by thinking too much
- Paranoia
- Insomnia

To reduce the paranoia induced by THC, add CBD and the paranoia will disappear within 10 minutes. Another example is someone who is depressed and is seeking relief, they should start with high CBD and add high THC if the effects of CBD need to be reduced. For example, two signs appear with frequent use of CBD:

- Issues (forgetfulness, anxious) caused by not thinking enough
- Memory Extinction
- Insomnia

If short term memory extinction occurs and it does not suit your needs, the active mind can be stimulated by taking THC.

Another example concerns Multiple Sclerosis, Alzheimer's, and Parkinson's diseases. Someone who is seeking relief from spasticity wants to maximize the anti-convulsant effects of cannabinoids should start with 50% THC and 50% CBD. As outlined above, when you combine THC and CBD you maximize the anti-consulvant effects and minimize the negative of THC or CBD alone. If they find that they need to be active we suggest that they add CBD, on the other hand if they need to be passive (rest) we would suggest that they add THC.

If you go too far one direction i.e. too much agonist with THC and paranoia emerges, or too much antagonist with CBD and memory extinction emerges, simply balance with the opposite.

Chart #1: Medical Marijuana Therapy
Indica and Sativa Treatments

Vertical: Target Symptoms
Horizontal: Strains

	Indica	Sativa
Anxiety	X	
Appetite Stimulation		X
Chronic Pain	X	X
Depression		X
Insomnia	X	
Migraines		X
Muscle Spasms	X	
Nausea		X
Sedative	X	
Stimulant		X
Tremors	X	

Chart #2: Medical Marijuana Therapy
THC and CBD Treatments

Vertical: Target Diseases
Horizontal: Chemo Type: Classes based on THC/CBD ratios

	High THC Agonist	50/50	High CBD Antagonist
ADD (66)			X
ADHD (67)	X	X	
AIDS (68)	X	X	X
Alzheimer's (69)		X	X
Arthritis (70)	X		
Cancer			
Pain / Chemo (71)	X		
Colon (72)		X	X
Breast (73)		X	X
Skin (74)		X	X
Depression (75)	X		X
Diabetes (76)		X	X
Epilepsy (77)		X	
Fibromyalgia (78)	X		X
Glaucoma (79)	X	X	X
Huntington (80)		X	
Irritable Bowel Diseases			
Crohn's disease (81)		X	X
Ulcerative Colitis (82)		X	X
Migraines (83)	X		
Motor neuron diseases (ALS) (84)		X	
Multiple Sclerosis (85)		X	
Nausea (86)	X		
Osteoarthritis (87)		X	
Parkinson's (88)		X	
Psoriasis (89)		X	
PTSD (90)			X
Withdrawal symptoms reduction (91)	X	X	X

Chart #3: Medical Marijuana Survey Winter 2012

Vertical: Cannabis Strain (Indica/Hybrid/Sativa)
Horizontal: Chemo Type: Classes based on THC/CBD ratios

	High THC Agonist	50/50 Agonist/Antagonist	High CBD Antagonist
Indica	B-Dawg 23/1 Granddaddy Purple 21/1 Black Domina 21/1 Purple Kush 19/1 Purple OG Kush 14/1		
Hybrid	Sour Diesel 24/2 Lavender 22/1 Space Queen 19/1 OG Kush 19/1 Blueberry Diesel 15/1	Trident 6/12	Cannatonic 1/16
Sativa	Green Dragon 22/1 Sour Flower 18/1 Pineapple 18/1 Maui Wowie 16/1 Super Sliver Haze 15/1	Harlequin 6.5/8.5	Harlequin 6/11

Note:

1. ***All cannabinoid medicine has a therapeutic widow, there is a minimum below which it is not effective (usually 5 mg/ml) and a maximum (usually 60 mg/ml) above which the medicine generates the opposite effects that the patient is looking for (Bi- Phasal).***
2. ***How Cannabinoid Therapy affects children under the age of puberty is very different than children over the age of puberty. The reason for this is in order to experience CNS effects your brain receptors have to be developed and they are not developed until puberty (92). This means that children under the age of puberty can't get "high" because their neurotransmitters are not yet fully developed..***

Footnotes:

1. **CBD Science, LLC**; www.cbdscience.com is a consulting firm that advises Non-Profit Collectives (legal under state law and federally endorsed by the Odgen Memo of October 2009) on the development and production of safe and effective Cannabis Based Medicinal Extracts (CBME's).
2. **The FDA position on Medical Marijuana**; FDA interagency Advisory 4-20-2006; http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2006/ucm108643.htm
3. **The DEA position on Marijuana**; **http://www.justice.gov/dea/marijuana_position.pdf**; Both the DEA and the FDA are taking positions in opposition to smoked Medical Marijuana, while at the same time, it appears as though they are leaving the "door" open for medicinal value of the "compounds" contained in Marijuana . This radical shift from, Medical Marijuana has no medicinal value, to the components of Medical Marijuana have medicinal value, is welcome but their position on smoked Medical Marijuana is weakened by recent study by the *Journal of the American Medical Association*, published on Jan. 11, 2012, which states; "**experts have worried that the kinds of lung damage caused by cigarettes could also be brought on by pot smoking. Indeed, cigarette smokers in the study saw their lung function drop significantly over 20 years. But that didn't happen to people who only smoked marijuana. In fact, the study found that the lung function of most marijuana smokers actually improved slightly over time."**
4. **"The Endocannabinoid System as an Emerging Target of Pharmacotherapy**": Pancher NIH 2006 http://pharmrev.aspetjournals.org/content/58/3/389.full.pdf
5. Refer to Footnote #4 and additional research resources below funded by NIH.
6. Department of Health and Human Services holds US patent 6,630,507, entitled "Cannabinoids as antioxidants and neuro-protectants" and is considering granting an exclusive patent license to Kannalife Sciences, Inc of New York to develop Cannabinoid therapeutics.
7. The Gunn Response, March 5th 2010; http://www.veteransformedicalmarijuana.org/files/Gunn-Response.pdf
8. "The Ogden Memo"; Deputy Attorney General David Ogden October 2009 http://blogs.usdoj.gov/blog/archives/192
9. Refer to footnote #15; The United States Patent Office has granted over 10 patents and accepted over 30 applications for patents for GW Pharmaceuticals CBME's between 2003 and 2012.
10. The FDA is conducting multisite phase IIb, clinical trials for the treatment of opioid-refractory cancer pain in the US on GW Pharmaceutical's (www.GWpharm.com) Cannabis Based Medicinal Extract (CBME) called "Sativex" (www.gwpharm.com/Sativex.aspx). GW Pharmaceutical expects to be granted FDA approval for Sativex in 2013.
11. Footnote #1
12. Footnote #2
13. Google US patent search http://www.google.com/patents

Cannabis Related Patents 2003 to 2012:

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5. 7344736 March 18, 2008: GW Pharmaceuticals
6. 7622140 November 24, 2009: GW Pharmaceuticals
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10. 7968594 June 28, 2010: GW Pharmaceuticals
11. 8034843 October 11, 2011 : GW Pharmaceuticals

Cannabis Related Patent Applications 2003 to 2012

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17. Dr. Sean McAllister http://www.cpmc.org/professionals/research/programs/science/sean.html **Dr. Sean McAllister on THC and CBD and Cancer: http://www.youtube.com/watch?v=drW12wqbqwU** Skin Cancer: Antidotal evidence http://www.youtube.com/watch?v=0tghUh4ubbg
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