Marijuana's Potential for Chronic Pain

What does science know so far?

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MARIJUANA'S POTENTIAL FOR CHRONIC PAIN

What does science know so far?

By Leesa Klich, MSc, RHN

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About the author

Leesa Klich, MSc, RHN is a science-based holistic nutritionist and creator of Nutrition Interactions. Leesa earned her Master's degree in Biomedical Toxicology and Nutrition and after a short time in food R&D, Leesa enjoyed a 12-year career in drug/supplement safety. While Leesa thoroughly enjoyed her time in pharmacovigilance (fancy word for drug safety), several things in her life started pointing toward some of the benefits of a more holistic approach to health. After moving across Canada and graduating as a Registered Holistic Nutritionist, Leesa is blending her extensive experience in health science with her education in holistic nutrition. Leesa likes to say that she lives "at the intersection of science and holistic health, and it's very interesting here."

Learn more by checking out Leesa's website, or downloading some of her free science-based health resources.

You can also find Leesa on Facebook, Instagram, Pinterest, Twitter, YouTube and Periscope (as @NutritionInteraction).

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Introduction

Hi!

Thank you for your interest in this special report I created for the 2016 Fibromyalgia Summit.

It summarizes many of the recent scientific studies on the medical use of marijuana and cannabinoids for pain. (Sorry, it doesn't dive into the legal or political arenas).

While I know that this plant has been used medicinally for thousands of years, and there are thousands of people who it helps with multiple conditions, the medical research is still ongoing.

This report focuses on marijuana and cannabinoids specifically for pain; however it is also being researched for a lot of other conditions like post traumatic stress disorder, multiple sclerosis and several neurological diseases as well.

Reading this report can give you a snapshot of the medical information published in the past few years about marijuana and cannabinoid use for treatment of chronic pain.

Why medical marijuana for chronic pain?

Even though I am a Registered Holistic Nutritionist with a Master's degree in Toxicology and Nutrition, and over a decade experience in pharmaceutical safety, I started this report knowing very little about fibromyalgia, chronic pain, or medical marijuana.

After a Skype call with the organizer of the Fibromyalgia Summit, I started looking into ways I could use my "science-based, holistic approach" to create a meaningful contribution for the online summit. I came upon this video from "One Minute Medical School" that inspired me to dig into the research on the use of cannabinoids for fibromyalgia and pain (see 0:58):

I also started following a few people who have fibromyalgia resources online, and joined a fibromyalgia support group in Facebook. I did this to understand what it was really like to have fibromyalgia, to see what I could offer, what people were saying about medical marijuana, and what scientific information might help the most.

I learned some very profound things from people who have fibromyalgia and chronic pain, and was inspired to create this video to share my new insights:

- 2:19 Profound thing #1 - How incredibly under-serviced pain is when it comes to modern medicine.
- 4:05 Profound thing #2 - How much trust is needed from your healthcare professionals to get a diagnosis or treatment.
- 6:34 Story of how this all "came together" for me

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My approach to the research

The approach I took in researching what science knows so far about marijuana's uses for chronic pain was hopeful, enthusiastic, and scientific.

I had "heard" many promising uses for marijuana. I knew that strictly regulated use of medical marijuana was available in Canada, and parts of the USA, and Europe. I knew there were a couple of cannabis-based medications approved for use by Health Canada, the FDA and/or the EU. And I certainly knew of the campaigns to have marijuana legalized.

I had also heard that it was a safe and effective plant, and wanted to really understand exactly *how* safe and *how* effective it was.

So, I put on my "scientist" hat and limited my social media exposure to a few key fibromyalgia and marijuana sites, trying to avoid getting overwhelmed by the vast amount information available online. Then, I dug into the medical literature at the university medical school library where I live. I focused specifically on clinical studies of marijuana and cannabinoid use for pain that were published from 2010-2015.

What is in this special report?

While fibromyalgia has many symptoms, and can occur along with other conditions; and while medical marijuana is approved and being researched for many different uses, this report focuses specifically on the science behind use of medical marijuana and cannabinoids for chronic pain.

In a nutshell, the number of *large high-quality* clinical studies published to date is fairly limited. Despite cannabis' long-time use, there really does not seem to be a scientific consensus on its safety or effectiveness.

As you probably know, large high-quality clinical trials are the types of studies needed to get a medication approved by Health Canada or the FDA.

In fact, just about every study I read calls for more research to be done.

Well executed clinical trials are very important when it comes to recommending treatments to large numbers of people. And while many animal or tissue studies can provide great insight, they are not enough to truly understand the safety and effectiveness of a treatment for use in people.

Case reports and people's individual experiences can also provide some excellent information. However, they are also limited when it comes to truly understanding the overall safety and effectiveness of a treatment.

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And most of the clinical studies of medical marijuana are observational, and aren't the "gold standard" large randomized clinical trials I had hoped to find.

Here is a fabulous chart outlining the strength of different types of scientific evidence.

That's why I called this report: "Marijuana's Potential for Chronic Pain – *What does science know so far?",* because research into the pharmacology and medical uses of cannabinoids continues to this day.

Here is a very powerful quote:

> "Our insight into these possibilities is dependent on the contribution of one unique healing plant; for clinical cannabis has become a therapeutic compass to what modern medicine fails to cure."(Russo EB, 2004)

And I can now truly see how modern medicine fails to cure a lot of the physical pain that people experience every single day.

Summary of this report

There were several clinical studies and review articles published since 2010 on the use of medical marijuana and cannabinods for pain; however, they didn't seem to have a consistent and clear message. I think this quote nicely sums it all up:

> "There are more than 60 systematic reviews and meta-analyses discussing the safety, toxicology, potency, and therapeutic potential of exogenous cannabinoids. However, the general consensus of these reports is largely mixed and inconclusive. The uncertainty surrounding safety and efficacy of exogenous cannabinoids is not a product of the lack of research, but rather a product of the extreme variability in study methodology and quality."(Sachs *et al*., 2015)

Thank you

Thanks again for your interest in this special report. I hope that it provides you with a summary of what medical science has published in the last few years about marijuana and cannabinoid efficacy for pain treatment, as well as its safety.

And mostly, I truly hope that the amount of research into better treatment options and cures for all areas of pain explode in the near future. As I mentioned in my video above, I really see how under-served this area is and wish you much gratitude and gentle hugs.

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1 – Marijuana's Medicinal Past

Marijuana and Cannabis

Cannabis sativa and *cannabis indica* are very versatile plants. They have been used for thousands of years, not only for medicinal, religious or "euphoric" reasons, but also to make fabrics and eat the seeds. The ancient cultures most known for cannabis use are Chinese and Hindu (the plant is indigenous to Central and South Asia); as well as Greek and Middle Eastern. Within the last few hundred years, it reached the rest of Europe, as well as North America.

Use of the cannabis plant has been recommended by physicians and medical texts throughout the ages. A few of the *traditional* medicinal uses have been for chronic pain, seizures, spasticity, constipation, and nausea/vomiting.

Cannabis was listed in the US Dispensatory in 1845. It was removed from the US Pharmacopoeia in 1941 due to concerns about its psychotropic effects and its apparent association with crime.(Jensen *et al.*, 2015)

Cannabinoids (the active compounds) from the cannabis plant were identified in the 1960s, particularly delta-9-tetrahydrocannabinol (THC) which is the rather infamous psychoactive compound in the plant.

In the following years, concerns grew about addiction and other side effects, and cannabis' medicinal value was questioned; which lead to legal issues. However, there were always personal/anecdotal reports of marijuana's ability to help with many health concerns such as glaucoma and nausea/vomiting of chemotherapy.

Note that from a *strictly* scientific perspective, anecdotes are interesting and can be a reason to begin researching something, but are not considered solid scientific evidence. Even a massive number of anecdotes aren't truly scientific evidence. *This does not mean that they are invalid at all*, it means that there is *not enough evidence* to truly understand marijuana's overall safety and efficacy profile.

The demand for marijuana continued, despite the legal challenges. In fact, it's the most popular illicit drug in the world (alcohol and tobacco are more popular, but legal). At least one study shows that marijuana is 75% of the illegal drug trade in the USA.(Greydanus *et al*., 2015)

While smoking cannabis (as a cigarette or in a pipe) is the most popular way to consume it, it can also be vapourized, eaten, steeped and drank as tea, or taken as capsules. It can also be taken as hashish.

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2 – What exactly is a cannabinoid, and how does it work?

Cannabinoids: endo-, phyto- & synthetic

In the 1980-90s endocannabinoid receptors were discovered in the central nervous system. A "receptor" is a type of protein on the outside membrane of a cell. It acts as a "lock" waiting until a very specific compound (that fits like a key) comes by the cell and activates the receptor. When this happens, the cell is signalled to do something.

Technically, a "cannabinoid" is any compound that acts specifically on those cannabinoid receptors.

The endocannabioid system (2-AG, AEA)

The fascinating thing about finding these receptors occurring in our cells is that it tells us that our body naturally makes compounds that interact with those receptors.

"Endocannabinoids" (eCB) are what we call these compounds; "endo" for "within" because they're made within our own bodies.

There are two different types of these receptors: CB1 and CB2. The CB1 receptors are located mostly in our brains (hence the psychotropic/euphoric effects of THC), but also in other tissues such as fat, liver and muscle. Meanwhile the CB2 receptors are located mostly on immune cells as well as in the gastrointestinal tract, and central nervous system, and are thought to have anti-inflammatory and immunosuppressive effects.

These psychotropic, immune, gastrointestinal and inflammatory effects on our bodies is what happens when those cannabinoid receptors are activated by a cannabinoid.

For example, the "reward" feeling, and effects on emotions, memory, and movement.

The roles of the eCB system are said to: "relax, eat, sleep, forget, and protect"; and has been metaphorically referred to as a "microcosm of mind-body medicine".(McPartland *et al.*, 2014)

Endoannabinoids (2-AG, AEA)

The endocannabinoid 2-AG (2-arachidonoyl glycerol) interacts with GABA and other neurotransmitters to help modulate pain, cognition, movement and emotions.

The other main eCB, anandamide (AEA), reacts more with the CB1 receptors, and its actions are similar to THC.

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So, it begs the questions: “if we have these receptors and they play several roles in our physiology, are they absolutely necessary for health?”

What happens if these endocannabinoid receptors on our cells are not triggered?

In other words;

Can we become “deficient” in endocannabinoids?

At least one researcher has proposed a “Clinical Endocannabinoid Deficiency” (CECD) Syndrome that, when this system is not working properly, can manifest as migraine, fibromyalgia, and/or irritable bowel syndrome.(Russo, 2004)

This was re-iterated by other researchers in 2014, in addition is a possible link to autism spectrum disorder as well. However, they do **call for more research, especially clinical trials**.(Smith *et al.*, 2014)

Other researchers have proposed that a “deficiency” in cannabinoids might also be related to depression, schizophrenia, multiple sclerosis, Huntington’s, Parkinson’s, anorexia, and even possibly an infant’s “failure to thrive”.(McPartland *et al.*, 2014)

This CECD syndrome is proposed in just a few published medical journal articles, and does not seem to be a commonly accepted belief in the medical community. Again, more research is needed.

The authors of that 2014 review confirm that most of the studies published have not been randomized clinical trials, but were done in animals (*in vivo*) or in cell cultures (*in vitro*). Results from these studies may not translate to an effect in most people; but we don’t actually know until the studies are done.

So, even if we can become “deficient”, how can that be managed?

Of course, even if more research confirms that there actually is a true CECD deficiency, there is more than one way to treat this. Consuming cannabinoids is just one method.

There are also the possibilities of increasing the body’s own production of the endogenous cannabinoids. Another possibility is slowing down the body’s metabolization of those eCBs so they stay active for a longer time.

McPartland *et al.* (2014) make several important points:

- In animal studies, some NSAIDS help enhance activity and slow degradation of eCBs (note that in rodents acetaminophen had a similar effect, but not when studied in people).

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- Omega-3s may help with the endocannabinoid (eCB) receptors.
- Certain pesticides may negatively impact eCB function.
- Similar to many medications, long-term use of THC can “desensitize” and “downregulate” the eCB receptors, which means that over time they develop a tolerance to the medications and do not function properly. However, one clinical study showed that after four weeks abstaining from smoking marijuana, the number of cannabinoid receptors returned to normal levels.(Hirvonen *et al.*, 2012)
- Some recommended lifestyle approaches that are thought to enhance the eCB system include exercise, maintaining ideal body weight, and stress modification.

While, there are several lab, tissue and animal studies published, more clinical trials are needed.

Phytocannabinoids (THC, CBD, etc.)

“Phyto” is a prefix used to specify that the compound comes from a plant.

Marijuana (as with all plants) is a complex living organism, and chemical analysis shows dozens of compounds within it. THC is the only phytocannabinoid believed to have psychoactive properties. Many non-psychoactive compounds are also found in it as well, such as cannabinol (CBN) and cannabidiol (CBD). Over 60 compounds in the cannabis plant are thought to act on the cannabinoid receptors, and are therefore considered cannabinoids. (Jensen *et al.*, 2015)

THC can be extracted from the seeds, stems, leaves, flower or oil. Its psychoactive effect on the CB1 receptors in the brain makes people feel euphoric and relaxed, and can increase appetite. It’s also been known to induce anxiety, depression, and hallucinations, as well as tolerance and withdrawal syndromes. See chapter 6 of this report for a summary on the safety concerns of using cannabis.

The potency of THC in marijuana and cannabis products has increased over the years. Back in the 1960-70s it was about 1-2%, now it can be found at levels of up to 22% potency. (Greydanus *et al.*, 2015)

This is one major difference between using a plant versus using a medication. Plants are complex living organisms with hundreds of phytochemicals. They can also be bred to have differing levels of certain compounds. The levels of those compounds can also be affected by growing conditions (soil, temperature, humidity, sun).

> “Furthermore, the method of administration (e.g., oral, smoked, vaporized) and form of cannabinoid consumed (e.g. stems and buds, hashish, hash oil, extract, synthetic) can impact the bioavailability and consequently the response to use”.(Sachs *et al,* 2015)

All of these factors add complexity to doing high quality clinical trials for the use of medical marijuana.

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Meanwhile pharmaceuticals use very specific levels of very specific isolated compounds. This ensures an expected fairly precise dosage; however, on the downside, it also loses the complexity and interrelationship between other phytochemicals that have effects that we don't even know about yet. Maybe quite positive effects.

THC enters the blood stream very quickly when smoked (3-10 minutes), as opposed to an hour or more when eaten. It is metabolized in the body, and the most active metabolite is 11-OH-THC, which can get to the brain easier than THC itself. THC is stored in the fat tissue and is metabolized by the liver. It is slowly eliminated from the body mostly in the feces, and some is excreted in the urine.(Greydanus *et al.*, 2015)

Cannabidiol (CBD) doesn't interact directly with the cannabinoid receptors, but in a more indirect way. It interacts with the eCB anandamide to help increase its activity on those receptors. Cannabidiol can reduce some of the psychoactive effects of THC, including anxiety. CBD has also been shown to have anti-convulsant, analgesic, anti-inflammatory effects and help reduce vomiting as well.(Greydanus *et al.*, 2015)

Synthetic cannabinoids (approved medications and their approved uses)

Marinol/Dronabinol (synthetic cannabinoid) is sold in sesame oil and is approved for use in the USA. It is approved for nausea and vomiting due to chemotherapy, as well as for HIV-associated anorexia. It acts like THC because it is metabolized to 11-OH-THC, the same active metabolite as that from natural THC itself. This product used to be available in Canada, but was cancelled in 2012.

Cesamet/Nabilone (synthetic cannabinoid) is similar to THC. Nabilone was originally approved by the FDA 25 years ago to help with nausea and vomiting from chemotherapy. It is approved in Canada for the same. Nabilone is more potent than dronabinol, and so is more tightly regulated. Nabilone has been shown to help with MS pain, "medication overuse headaches", and diabetic neuropathy, but is not officially approved for those uses.

Sativex/Nabiximols is a blend of THC & CBD. Sativex is a buccal spray (under the tongue or on the cheek) that was approved for use in Canada in 2005 to help relieve spasticity associated with multiple sclerosis (MS). It also has conditional approval for neuropathic pain for patients with MS, as well as for severe pain in advanced cancer. It is available in some parts of the EU, but is not currently approved in the USA. As mentioned earlier, it is thought that the CBD helps to reduce the psychoactive effects of the THC.

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For a handy table summarizing the approved marijuana-based medications, click here.

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> Approved marijuana-based medications #marijuana #medicalmarijuana #pain #chronicpain… Click To Tweet

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You'll notice that none of these are specifically approved for use in fibromyalgia, and Sativex is the only one approved for pain.

These medications are also sometimes used "off-label" for other indications. Some patients have found benefit from them, and their doctors have agreed to prescribe them for that use. This can be helpful to many patients, and the benefits and risks need to be carefully weighed by the patient and prescribing physician.

Synthetic "designer" cannabinoid drugs (cannabimimetics)

There are also synthetic "designer" cannabinoids (AKA "new psychoactive substances" NPS, or "smart" drugs). These "cannabimimetics" are sometimes sold as air fresheners with the warning "**not for human consumption**" and can have up to 10x the strength of THC. They are designed to have a stronger effect on the CB1 and CB2 receptors. They are sometimes marketed as being "safe" because they are technically tobacco free, and can be cannabis free; however, they have a long list of side effects including anxiety, hallucinations, seizures, paranoia, psychosis, kidney injury, and death.(Greydanus *et al.*, 2015)

Medical Uses for Marijuana and Cannabinoids

While there are many people who have experienced medical benefit with marijuana use, and there are several jurisdictions in the world that allow it, the scientific evidence for the medical use of marijuana is still being researched.

> The use of marijuana and cannabinoids for medical purposes is still being researched. … Click To Tweet

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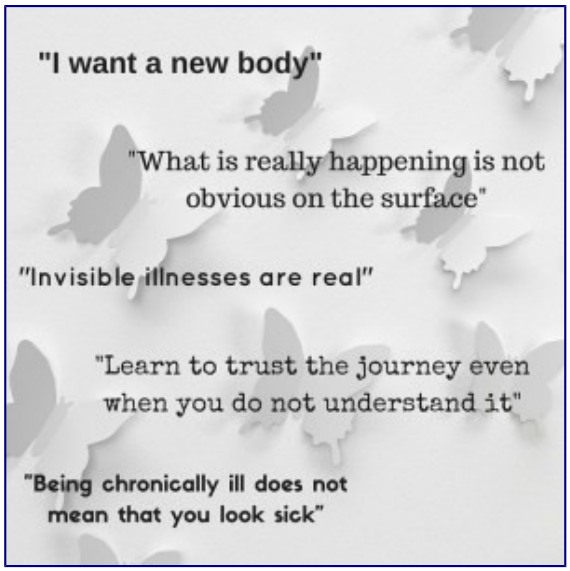
3 – A bit about fibromyalgia and chronic pain

Here are a bunch of quotes I've seen used to represent what it's like to have Fibromyalgia and Chronic Pain:



Fibromyalgia

According to the National Institute of Health Library of Medicine:

> **"Fibromyalgia** is a common syndrome in which a person has long-term pain, spread throughout the body. The pain is most often linked to fatigue, sleep problems, headaches, depression, and anxiety.
>
> "People with fibromyalgia may also have tenderness in the joints, muscles, tendons, and other soft tissues."

Fibromyalgia Syndrome (FMS) is also described as:

> Chronic widespread musculoskeletal pain, stiffness, and tenderness to palpation at specific TPs.(Jay *et al.*, 2015)

There are 18 specific "tender points" (TPs) common to many people who have fibromyalgia. Those tender points, along with 3 months of widespread pain, sleep issues, fatigue, as well as thinking/memory problems ("fibro fog") are commonly used for diagnosis.

Fibromyalgia is often experienced along with depression, anxiety, headache/migraine, irritable bowel syndrome, chronic fatigue syndrome, systemic lupus erythematosis, and/or rheumatoid arthritis.

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Fibromyalgia is a neurological condition, specifically in the central nervous system, thought of as a "central nervous system hypersensitivity". Fibromyalgia includes an increased sensitivity to pain known as allodynia. So, things that would normally hurt a little bit, or not at all, tend to hurt A LOT.

FMS can affect anyone, however, it's most commonly diagnosed in women between the ages 40 – 60. In Canada, it is thought to affect 1.1% of the population, with 6 women affected for every man.(Jay *et al.*, 2015)

Fibromyalgia is also associated with significant disability, as the pain can lead to lowered ability to do many common daily activities.

It's unknown what causes fibromyalgia, but there seems to be a higher risk associated with genetics, early childhood trauma, and learned behaviour.

Pain – What is it?

> "Pain is not just a message from injured tissues to be accepted at face value, but a complex experience that is *thoroughly tuned* by your brain. …the science is clear: every painful sensation is 100% Brain Made®, and there is *no pain without brain*."(Ingraham, 2016)

We used to think that pain was a signal from an injured tissue sent up to the brain. We thought that that pain signal was proportional to the severity of the injury.

We were wrong!

Pain is a two-way conversation between nerves and the brain. And it is *the brain that decides how much pain to perceive*.

> "Paradoxically, even though pain is strongly regulated by your CNS, it is certainly not 'all in your head.' The idea has always been been disrespectful to pain patients, but now it is also scientifically obsolete and can be thrown out with yesterday's trash."(Ingraham, 2016)

But what is the use of pain? Why should we experience it?

> "Pain is a motivator. It exists to get us to act. We hurt when our brains reckon we should do something differently, for safety…but safety is not always possible. The nature of the danger isn't always clear, or avoidable."(Ingraham, 2016)

This is shown in examples of people with "phantom limb pain", where pain is felt in a limb that has been amputated. This is also shown when people with serious injuries don't feel nearly as much pain as you think they should.

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But we can't really "think" ourselves out of experiencing pain

Most people only have a limited ability to "think" themselves out of pain.

> "And the brain can't be manipulated simply by wishing, force of will, or a carefully cultivated good attitude. The brain powerfully and imperfectly controls how we experience potentially threatening stimuli, but I'm sorry to report that *you do not control your brain*. Consciousness and "mind" are *by-products* of brain function and physiological state. (Deep, eh?) It's not *your* opinion of sensory signals that counts, it's what your *brain* makes of them that counts — which happens quite independently of consciousness and self-awareness. This is why many wise, calm, confident optimists still have chronic pain."(Ingraham, 2016)

> "So it often is with pain: *if the brain believes there's a threat, you're going to hurt,* no matter how pointless it is or how intensely you focus on trying to have more reasonable and rational sensations. It's mostly just not up to you."(Ingraham, 2016)

So, how much influence can your mind have on your experience of pain?

> "Most people with chronic pain aren't just a little stressed, they are *a lot stressed*, and often by major life challenges and social problems that they literally cannot solve. Even when their problems are theoretically more manageable, most people find it extremely difficult to troubleshoot their own mental health. So while it's correct to tell patients to 'learn to reduce stress' and 'consider how your thoughts and emotions are affecting your nervous system,' that advice is impractical without more and better information."(Ingraham, 2016)

Impacts of pain

Recognizing and treating pain is one of the most common situations in medicine. Pain has a large impact on several aspects of the quality of life of a person, including biological, psychological, sociological and economic.

Pain medicine is evolving and managing pain "requires a multidisciplinary approach to recognition, diagnosis, treatment and education. A thorough and holistic approach is encouraged in order to explore the multiple factors affecting patients experiencing pain, whether this be acute, chronic, or in many situations, both."(Schug *et al.*, 2014)

> "...The past ten years have witnessed a far greater focus upon the management of acute, cancer and chronic pain; these efforts have culminated an international pain summit leading to the declaration of Montreal that *access to pain management is a fundamental human right*."(Int'l pain summit, 2011)

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Fibromyalgia and Chronic Pain

> "While acute pain is a normal sensation triggered in the nervous system to alert you to possible injury and the need to take care of yourself, chronic pain is different. *Chronic pain persists.* Pain signals keep firing in the nervous system for weeks, months, even years."(Chronic Pain Information Page)

Chronic pain is experienced in fibromyalgia; as well as endometriosis, chronic fatigue syndrome, interstitial cystitis, irritable bowel syndrome, temporal-mandibular joint dysfunction, and more.

> "While between 14% and 26% of the American adult population suffer from chronic pain or arthritis, about 11% complain of chronic *widespread* pain."(Jay *et al*., 2015)

Fibromyalgia's symptoms are very similar to myofascial pain syndrome (MPS), in fact about 70% of fibromyalgia patients also have MPS. One difference is that heat can help myofascial pain syndrome, while it can aggravate fibromyalgia.(Ingraham *et al.*, 2016)

There seem to be several abnormal pain mechanisms associated with fibromyalgia and they lead to a problem with "volume control". People with fibromyalgia seem to be more sensitive to not only pain, but also heat, noise, and even strong odours. There seems to be a "sensory amplification" known as allodynia.

> "This makes FMS a *neurosensory disorder* associated with difficulties with pain processing by the central nervous system (CNS)."(Jay *et al*., 2015)

There is a lot of research and a lot of theories as to how the spinal cord and brain process stimuli differently in people with fibromyalgia. This is where all of the different medications come into play.
It is a fascinating area with exciting research being done at this time, however is not covered in this report.

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4 – Non-marijuana/cannabinoid treatments for pain

Treatments for Fibromyalgia and Chronic Pain

The main goal of treatment is to reduce the pain, but not all patients experience it the same way. Also, some people are very sensitive to certain medications, so the "low and slow" method is recommended. And, the use of non-drug treatments should always be considered. (Jay *et al.*, 2015)

Recommendations for managing fibromyalgia

The "optimal intervention" and the "most successful medical treatment" of FMS includes several approaches:

> "A meta-analysis of FMS treatment interventions found that the optimal intervention for FMS involved *both medication management and nonpharmacological treatments* (especially exercise and cognitive behavioral therapy) to help sleep and reduce pain symptoms."(Jay *et al.*, 2015)
>
> "The most successful medical treatment of FMS is an interdisciplinary approach that coordinates care from a physician, a nurse, a physical therapist, a psychotherapist, a relaxation therapist (biofeedback), and as needed, an occupational therapist."(Jay *et al.*, 2015)

Medications

There are no "gold standard" medications for fibromyalgia. Many medications are prescribed for pain control, but very few are actually approved specifically for fibromyalgia.

Here are the medications with official approvals in Canada and/or the US to help with fibromyalgia (note none are cannabinoids):

- Cymbalta/Duloxetine (analgesic/antidepressant/antianxiety)
- Lyrica/Pregabalin (analgesic)
- Milnacepran (antidepressant) is approved in the US, but not in Canada

Medications used for pain are often analgesics such as acetaminophen and NSAIDs (Nonsteroidal Anti-Inflammatory Drugs).

Also, some anti-depressants can help with pain, as well as sleep and fatigue because of their effect on serotonin and norepinephrine (i.e. SNRIs – Serotonin Norepinephrine Reuptake Inhibitors).

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> **"***Serotonin* is involved in moderating pain, sleep, depression, and hypothalamic hormone release. The majority of the various types of antidepressant medications deal, at least partially, with serotonin reuptake."(Jay *et al.*, 2015)
>
> "When 26 studies evaluated antidepressants in FM by meta-analysis, 13 for amitriptyline, 12 for SSRIs (5 paroxetine, 4 fluoxetine, 2 citalopram, 1 sertraline), and 3 for SNRIs (2 duloxetine, 1 milnacipran), *all agents with the exception of citalopram, showed a positive effect on pain, fatigue, depression, sleep and quality of life."*(2012 Canadian Guidelines)

And, there is some evidence that the CB receptors have a large effect on neurotransmitter release such as serotonin and dopamine among others.(Fiz *et al*., 2011)

Some anticonvulsants (e.g. gabapentin & pregabalin) have also been shown to help with pain. Opioids such as Tramadol are sometimes used, and if so, should be used with caution and regular monitoring.

There are others as well. Definitely speak with your doctor and maybe consider referring them to reference Disease-a-Month – Fibromyalgia and/or 2012 Canadian Guidelines for the Diagnosis and Management of Fibromyalgia Syndrome.

Sometimes the medications work better when strategically combined with each other, as opposed to taking just one.

And don't forget that, in addition to the medications, there is evidence that education, exercise and/or psychological interventions (such as cognitive behavioural therapy) can help as well. (2012 Canadian Guidelines)

Complementary and Alternative Medicine

Other treatments, including complementary and alternative medicine, have had inconsistent results when studied.

There is some evidence that tai chi and qi gong have been shown to help. So have two types of massage therapy "manual lymph drainage" and "connective tissue massage".(Fibromyalgia: In Depth)

People use other approaches as well.

> "A study from the Mayo clinic found, via a survey of 289 patients, that the 10 most common complementary and alternative medical therapies included:
>
> - exercise,
> - spiritual healing (prayers),
> - massage therapy,

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- chiropractic therapy,
- vitamin C,
- vitamin E,
- magnesium,
- vitamin B complex,
- green tea, and
- weight-loss programs."(Jay *et al.*, 2015)

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Special Note from Leesa (Nutrition Interactions) –

If you are taking medications, please know if they interact with alcohol or certain supplements. Make sure your prescribing doctor and/or the pharmacist know any complementary and alternative approaches you are using.

Many medications interact with foods and supplements - Be Aware #medication #drugs #food… Click To Tweet

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The main problem with pain treatment – it's just not very good

"Currently available agents (e.g. antidepressant and anticonvulsant analgesics, opioids and nonsteroidal anti-inflammatory drugs) are inadequate to control all pain or are associated with limiting side effects (e.g. most problematic being sedation with the antidepressant and anticonvulsant group, constipation with the opioids and gastrointestinal and cardiovascular effects with the NSAIDs). *There is a critical need for new treatments.*

"In this context, many people with chronic pain are turning to other therapies including cannabinoids. Due to patient demand, several nations (or states within countries) have developed programs to allow people with serious health conditions to access cannabis (marijuana) for medicinal purposes. Most of these programs (e.g., Canada, Israel, Netherlands, several US States) require physician or nurse practitioner support for the individual patient to be approved for access. Medical professionals have called for more research regarding both potential therapeutic and adverse effects of cannabinoids."(Lynch et al., 2015)

And more research is needed – especially good quality research including large randomized controlled clinical trials.

Several studies published in the past year have reviewed the research to date, and have noted an unfortunate lack of good quality clinical studies.

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5 - Medical marijuana and cannabinoids for pain – What does the current science say?

A small observational study by Fiz *et al.* published in 2011 specifically looked at 56 women with fibromyalgia; 28 used marijuana and 28 did not. The ones who used it either smoked, ate or did both when they consumed marijuana, and most of them used it daily. Patients used cannabis not only to alleviate pain but for almost all the symptoms associated with FM, and no one reported worsening of symptoms following cannabis use.

You can see figure 1 for the chart of patients who reported relief from use of marijuana; and figure 2 for the charts of results. Two hours after using the marijuana, there were reductions in pain and stiffness, and increases in relaxation, drowsiness, and well-being, compared with their evaluations before using the drug.

No differences were found between the marijuana users and non-users related to sleep, mental health, or the fibromyalgia impact questionnaire.(Fiz *et al.*, 2011)

Another 2014 review article on the Recent advances in the pharmacological management of acute and chronic pain (Schug et al., 2014) says this about cannabinoids:

- There is some efficacy shown for cannabinoids for some neurological disorders including spasticity and neuropathic pain.
- There is limited data, although there are some trials currently underway with cannabinoid receptor medications.

Marijuana and cannabinoids for pain

Here's a summary of several scientific reviews published in 2015, and what they've found regarding the safety and effectiveness of marijuana or cannabinoids for pain:

- This review describes cannabinoids as "safe, modestly effective analgesics". That they "demonstrate a modest analgesic effect and provide a reasonable treatment option for treatment chronic non-cancer pain."(Lynch *et al.*, 2015)
- Another one says that "Gold standard clinical trials are limited; however, some studies have thus far shown evidence to support the use of cannabinoids for some cancer, neuropathic, spasticity, acute pain, and chronic pain conditions". It concludes that "the strongest evidence in support of cannabinoids for pain appears to be for cancer-related pain … Effects on neuropathic pain such as in HIV, MS, and post trauma have also shown positive results. Our literature review showed no improvement to mild improvement in acute pain and spasticity. However, chronic pain results were more promising with some studies showing statistically significant reductions in pain and quality of sleep."(Jensen *et al.*, 2015)
- This next article looked at cannabis for use in headache and found that it "may have a therapeutic role for a multitude of diseases, particularly chronic pain disorders including headache. … Despite the limited evidence and research suggesting a role for

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cannabis and cannabinoids in some headache disorders, randomized clinical trials are lacking and necessary for confirmation and further evaluation."(Baron, 2015)

- Another 2015 review found "moderate-quality evidence to suggest that cannabinoids may be beneficial for the treatment of chronic neuropathic or cancer pain (smoked THC and nabiximols) and spasticity due to MS (nabiximols, nabilone, THC/CBD capsules, and dronabinol)."(Whiting *et al.*, 2015)
- Finally, this article created a table of "Clinical Effectiveness of Cannabinoids". Specifically in terms of pain, it says that cannabinoids are effective for several types of chronic pain (central chronic pain/painful spasms refractive to opiods, chronic pain associated with cancer and rheumatoid arthritis, and neuropathic pain; but it's not been shown to be effective for acute pain). See Table 1 for a summary of its effectiveness for pain and other issues as well.(Keehbauch *et al.*, 2015)

Of course, there are many patients who've benefited from marijuana, and that could be you, but other than the limited published research and the few approved medicines on the market, there is still not enough strong scientific evidence that cannabis works very well, with minimal side effects, for different kinds of pain in very many people.

Clinical trials of cannabinoids for pain

Here is a great overview of where science seems to be from the perspective of truly understanding the safety and effectiveness of use of cannabinoids:

> "There are more than 60 systematic reviews and meta-analyses discussing the safety, toxicology, potency, and therapeutic potential of exogenous cannabinoids. However, the general consensus of these reports is largely mixed and inconclusive. The uncertainty surrounding safety and efficacy of exogenous cannabinoids is not a product of the lack of research, but rather a product of the extreme variability in study methodology and quality."(Sachs *et al.*, 2015)

Here is a simple chart outlining the clinical studies published in the past few years that tested cannabinoids for different types of pain, including cancer pain and neuropathic pain. For more details on these studies, you can see the referenced document (links are in references, starting page 30).

Cannabinoid	Result	Reference
Pain		
Nabilone	Did not have an effect on pain, mood or quality of life, but did improve sleep better than amitriptyline.	Ware MA *et al.*, 2010.
Oral Cannabis Extract	Achieved effective pain relief, especially in people with a high pain score. Also helped with MS muscle spasticity.	Zajicek JP, *et al.*, 2012.

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Smoked Cannabis	Better than placebo for both pain reduction and MS muscle spasticity.	Corey-Bloom J *et al.*, 2012.
Cancer Pain		
Nabiximols (THC:CBD extract)	Helped relieve pain in patients with advanced cancer pain not fully relieved by strong opioids.	Johnson JR *et al.*, 2010.
Nabiximols	Safe and effective medication for opioid-treated cancer patients with poorly controlled pain.	Portenoy RK *et al.*, 2012.
Neuropathic Pain		
Nabilone	Effective in relieving diabetic neuropathic pain symptoms, improving disturbed sleep, quality of life, and overall patient status.	Toth C *et al.*, 2012.
Nabilone with gabapentin	Nabilone was effective and well-tolerated along with gabapentin for MS-induced neuropathic pain	Turcotte D *et al.*, 2014.
Oral mucosal cannabis spray	Was effective, but not much more than placebo for central neuropathic pain in MS.	Langford RM *et al*., 2013.
Oral mucosal cannabis spray	Chemotherapy-induced neuropathic pain was reduced by at least 2 points in a few patients. This was a very small “pilot” study, that now recommends a larger clinical trial.	Lynch ME *et al.*, 2014.
Oral mucosal cannabis spray	There were clinically important improvements in pain, sleep quality and patients’ perception of how severe their conditions were for people with peripheral neuropathy.	Serpell M *et al.*, 2014.
Vaporized via Syqe inhaler	After 20 minutes the pain scores decreased by 45%, and the effects wore off within 90 minutes.	Eisenberg E *et al.*, 2014.
Vaporized cannabis	Provided significant reductions in pain intensity compared to placebo. Low doses may be an effective option for patients with treatment-resistant neuropathic pain.	Wilsey B *et al.*, 2013.
Inhaled THC	25 mg of 9.4% tetrahydrocannabinol herbal cannabis three times daily for five days reduced the intensity of pain, improved sleep and was well tolerated.	Ware MA *et al.*, 2010.
Headache		
Nabilone	Benefits on headache, analgesic consumption and the quality of life in patients with intractable medication overuse headaches.	Pini LA *et al.*, 2012.

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As you can see, there are a variety of different medical marijuana products tested for different types of pain. Many of the studies also looked at effects on other factors like sleep and muscle spasticity.

If we look at neuropathic pain, where I found the most studies, it seems that the marijuana-based treatments were effective at reducing the pain.

It is interesting to note that the most common adverse effect for the cannabinoid treatments was the experience of dizziness. See chapter 6 for the review of the safety of cannabinoids.

It is also interesting to read this quote that compares marijuana to other medications for pain relief:

> "Although marijuana has been proven effective for the treatment of chronic pain in most placebo-controlled studies, five randomized, controlled, head-to-head studies did not show that it is superior to diphenhydramine (Benadryl), codeine, or amitriptyline for pain relief."(Keehbauch *et al*., 2015)

Why is there not more research on the use of marijuana and cannabinoids?

> "The classification of cannabis as a Schedule I drug limits the type and quality of research, forcing assessments of safety and efficacy to rely on observational studies."(Sachs *et al*., 2015)

The legal status of cannabis inhibits its research in more ways than one.

It makes many people who use it and benefit from it not openly share this information. Many people do not want to admit that they take it, and may therefore hesitate before participating in studies.

Marijuana's legal status also makes it difficult for researchers to get study proposals easily approved and funded. Plus, obtaining samples of the marijuana for studies can also be difficult.

In addition to the legal issues, there are many other factors that make it difficult to do high quality clinical trials on medical marijuana. These include the number of compounds in the plant, the way it was grown (soil, temperature, humidity, sun), the part of the plant used (stems, buds, hashish, extract, etc.) and how it was consumed (smoked, vaporized, ingested). Also, when it comes to smoking, things like depth of inhalation, puff duration and breath-hold time all affect the dosing.

These factors can make it difficult to get a fairly uniform dosage between the different study participants, which is used to try to more precisely measure its safety and effectiveness.

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Of course, these are not just issues for medical marijuana, but for the use of any product that can have varying amounts of multiple different active ingredients when the effects of each compound is not yet known.

And one last factor I found as to why there isn't more research on the use of medical marijuana. One article called: "Challenges encountered while recruiting frequent marijuana smokers for an outpatient laboratory study" were trying to recruit marijuana smokers who were in good health. They found it difficult to find enough healthy people who admitted to frequent marijuana smoking; and that more than half of the people who were healthy and scheduled a meeting did not show up for it, nor could they be contacted. They recommend establishing several means of contact as well as scheduling several visits.(Votaw *et al.*, 2015)

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6 – What are the safety concerns of medical marijuana and cannabinoids?

Common side effects *associated with* use of marijuana and cannabinoids

Here are some of the side effects *associated with* cannabinoid use. Association means that more people who use cannabinoids tend to experience these effects. It does not mean that cannabis use clearly causes these effects, but it may make an underlying condition worse. It's also possible that people who have these conditions are more likely to use marijuana.

- Common effects such as drowsiness, dizziness, dry mouth, and poor attention
- Addiction
- Motor vehicle accidents
- Effects on maternal and child health
- Cognition and other neurological effects
- Psychiatric conditions (depression, anxiety, amotivational state)
- Sleep
- Cardiovascular effects
- Respiratory effects
- Cancers(Sachs *et al.*, 2015)

Most adverse effects tend to be mild to moderate, and they don't tend to cause permanent damage.

Yes, cannabis can be addictive

A theory of how addictive behaviours develop is that, the experiences required for survival (eating, procreation, etc.) create a sense of pleasure by stimulating the brain's "reward center". However, it is possible that other things not required for survival (such as drugs) can also cause pleasure in that same reward center and therefore keep us going back for more.

Some researchers estimate that 9-10% of people who use cannabis will become addicted. That number increases to 16–17% for people who start using cannabis as teens, and up to 25–50% for daily users. The risk for addiction seems to reduce with age, so that someone who doesn't start using cannabis until age 25 rarely becomes addicted. It has also been found that earlier use of cannabinoids increases vulnerability of use of other drugs, adding support for the "gateway hypothesis".(Sachs *et al.*, 2015)

Also, heavy users tend to have lower income, greater need for socioeconomic assistance, unemployment, and lower life satisfaction.(Sachs *et al.*, 2015)

Again, these are associations, and not proof of causation, but I think they are important to note.

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Public safety and motor vehicle accidents

Just as with alcohol, the higher the level of impairment with cannabis, the higher the risk of motor vehicle accidents. In fact, people under the influence of cannabis are 2 to 7 times more likely to be involved in both fatal and non fatal motor vehicle collisions.(Sachs *et al.*, 2015)

Effects on maternal and child health

> "Cannabis use during pregnancy is associated with poor physical outcomes, including birth defects, low birth weight, and an increased risk of childhood cancer, as well as poor neurodevelopmental outcomes, including aggressive behavior and attention problems in girls. For example, children who were exposed to marijuana prenatally are more likely to demonstrate decreased problem-solving skills, as well as poor memory and attention. Similarly, babies exposed to marijuana prenatally show traits indicative of neurological development problems."(Sachs *et al.*, 2015)

Neurological and mental health effects of marijuana and cannabinoids

Cannabis is known to reduce many aspects of memory, impair IQ and attention, and to reduce inhibitions.

The risk of long-term neurological effects increases the more someone uses cannabinoids and the younger they are when they start. However, many of the impacts from short-term cannabis use are reduced after discontinuing use.(Sachs *et al.*, 2015)

Interestingly, recent neuroimaging studies have shown some structural abnormalities in areas of the brain high in CB1 receptors in people who use cannabis regularly. In fact, there was more significant abnormalities in people who used more cannabis.(Sachs *et al.*, 2015)

There is also evidence of an association between cannabis use and mental illness, including depression, anxiety, psychosis, bipolar disorder, schizophrenia, and an amotivational state. These links are complicated and (again) they are associations, not causation. In fact, it is thought that cannabis use doesn't necessarily cause, but might rather *exacerbate pre-existing* mental health issues like bipolar disorder and schizophrenia.

The associations between cannabis and anxiety are complicated because it is thought that low levels of THC reduces anxiety, while higher levels can increase it. This is also affected by the level of CBD which can mitigate with these THC effects.

Sleep is another common side effect of people who take cannabinoids. This can be beneficial for some. Studies have shown, however, that while cannabinoids can increase the amount of sleep someone gets, the quality of that sleep is often lower.(Sachs *et al.*, 2015)

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Non-neurological side effects of marijuana and cannabinoids

Long-term cardiovascular and respiratory consequences of cannabis use are fairly well evidenced.

It is recommended that people with cardiovascular issues avoid marijuana because of its effects on the heart, such as angina, heart attacks and death.

While cannabis is not tobacco nor does it contain nicotine, it does contain several harmful toxins when burned and inhaled. Some known respiratory adverse effects of smoking marijuana include inflammation, bronchitis and emphysema. Smoking is therefore not a recommended way to consume cannabis.

Cannabis' contribution to lung cancer risk is unclear. Some studies have shown no increased risk, others showed increased risk. Some analyses of the smoke showed that it was similar to tobacco smoke, others show it has higher levels of cyanide and aromatic amines.

In terms of other (non-smoking related) cancers, at least one study has shown an increased risk for prostate and cervical cancers, as well as glioma.(Sachs *et al.*, 2015)

Because there are CB2 receptors on immune cells, effects of cannabinoids have been studied there as well. Again, there have been controversial results with some studies showing immune suppression, and others showing anti-inflammatory and neuroprotective effects of CBD. Interestingly some studies have found that the body's naturally occurring endocannabinoids can have an immune-enhancing response, while consumed cannabinoids can suppress the immune system.

Things to consider before using cannabinoids

A significant amount of research still needs to be done regarding cannabis and pain to further understand the risks and benefits. This would include more research in the different doses of the compounds, as well as the different ways to consume it.

> "However, when recommending medical cannabis, physicians and patients would benefit from discussions of the risks, benefits, and uncertainties associated with cannabis use. Furthermore, medical cannabis should be avoided in vulnerable populations, including individuals under the age of 25 years, individuals with current or past substance use disorders, individuals with a personal or family history of mental illness, those that have compromised cardiovascular, respiratory, or immune systems, and those who are pregnant."(Sachs *et al.*, 2015)

When it comes to pain we must also remember the side effects and medical issues regarding opioids and overdoses!

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> "...A careful consideration of the risks and benefits of cannabis for pain along with further research into its efficacy is necessary to ensure that one controlled substance problem is not simply replaced with another."(Jensen *et al*., 2015)

After all of this, clearly when someone is in pain, the benefits of medical marijuana and/or cannabis-based medications needs to be weighed, not only with the risks of not treating the pain, but also with the other medications available for pain. Their effectiveness and side effects, including addiction and development of tolerance and risk of overdose, needs to be considered very carefully as well so the best treatment decision can be made to help alleviate the pain.

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Final Thoughts

I wanted to leave with a few thoughts about what I found from the research.

First, there are some areas (not necessarily pain) that we have enough evidence for official approvals of certain cannabinoid-based medications (here is a table summarizing these). Because these approvals are based on clinical research, there should have been enough evidence in high quality clinical studies that they're safe enough and effective enough to start prescribing to people. So, for Cesamet/Nabilone (synthetic THC) for nausea & vomiting due to cancer chemotherapy. Marinol/Dronabinol (synthetic THC) for nausea & vomiting due to chemotherapy, and HIV-associated anorexia. And for Sativex/Nabiximols (THC & CBD) for spasticity associated with multiple sclerosis. Sativex also has "conditional" approvals in Canada for neuropathic pain for patients with multiple sclerosis, as well as severe pain in advanced cancer.

Secondly, regardless of individual people's personal experiences with marijuana and cannabinoids for pain, the evidence seems to be building support that it can help some people, particularly neuropathic pain. It also seems that the side effects from using it at effective doses for neuropathic pain are not terribly serious.

And thirdly, what I found over, and over (and over) again in the medical literature was a call for more research. There seems to be an undertone to try to reduce the barriers that hold back high quality studies. Be those legal, financial, accessibility-based or otherwise, researchers believe that medical marijuana has shown enough promise so far, that they want to learn more and further investigate its potential.

Thanks again for your interest in this special report. I hope that I have been able to provide you with a summary of what medical science has published in the last few years about marijuana and cannabinoid use for treatment of chronic pain.

And mostly, I truly hope that the amount of research into better treatment options, and cures for all areas of pain explode in the near future. And not just overcoming the many obstacles for improving our understanding of medical marijuana's potential larger role, but in all areas of pain research.

I wish you much gratitude and gentle hugs.

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Hi, I'm Leesa Klich and I am a science-based holistic nutritionist.

Do you know the amazing number of roles each nutrient plays in your body?

The balance and resilience your body has when it comes to absorbing, distributing, metabolizing and excreting thousands of nutrients from foods and supplements never ceases to amaze me. And scientists are finding out more every day.

I am always creating new "freebies" for my community. Perhaps you're interested in information on turmeric/curcumin, x-ray safety, or the approved cannabis-based medications? If so, you can sign up here.

My goal is to help **Maximize NUTRITION and Minimize INTERACTIONS** by:

- Helping people who are taking medications avoid drug-food and drug-supplement interactions, and to strategically replace nutrients depleted by their medications;
- Helping holistic practitioners who want to learn more about science and research, who want more evidence-based approaches in their practices, and
- Freelancing on health research/writing projects for other health professionals and blogs/websites. Topics that light me up are functional foods, supplements, and safety of medications and procedures.

You can work with me here.

Thanks a bunch!

Leesa :)

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