Intravenous Cannabidiol (CBD) in Cancer: A New Frontier in Motion

Dr. Nathan Goodyear
Medical Director at Brio-Medical

Abstract

As we embark on the future, scientists are tasked with offering improved opportunities for patient health and quality of life through innovation. This paper attempts to review cannabidiol (CBD) history, current uses, and future directions based on innovative technology, specifically intravenous administration of CBD and its relevant potential to improve health and decrease inflammation. Dr. Nathan Goodyear, M.D., MD(H) a renowned cancer specialist, shares his insights as a part of his journey utilizing CBD to support patient care.

CBD is one of the many phytocannabinoids. It is a natural compound dating back 11,700 years, has been used in various forms since its discovery in 1940. Historically, cannabidiol has been primarily administered through oral routes, such as tinctures, capsules, or sublingual lozenges. However, the bioavailability of oral CBD is low, requiring higher and more frequent dosing for therapeutic effect. Intravenous administration of CBD is an optimal delivery method which theoretically offers improved bioavailability and enhances symptom relief for patients. There is limited research available on intravenous administration of CBD. However, preliminary research being conducted by PICO-IV suggests a prolonged metabolic half-life. Historical research suggests that the half-life for intravenous and inhalation delivery being 24+/- 6 hours and 31+/-4 hours, respectively; however, more research is necessary as there is a possibility that the half-life may be significantly longer. Cannabidiol has been known to cause numerous significant effects, including analgesic, anti-nausea, anti-emetic, anxiolytic, anti-insomnia, anti-depressant, anti-psychotic, anti-convulsant, anti-asthmatic, immunomodulatory, antioxidant, anti-inflammatory, anti-bacterial, neuroprotective, improves BBB integrity/permeability, and anti-cancer which suggests significant efficacy in the utilization of CBD via a possible new “gold standard” intravenous administration route.

Introduction:

We are all subject to bias, predetermined ideas, and thought patterns. Medicine and science, as a whole, have moved away from critical thinking, which originates from a curiosity of mind. Group think dominates the education and practice of science in medicine today. The ultimate goal is to control the critical thinking of complex pattern recognition via the oversimplification of the practice of medicine to a mere series of protocols. The recognition and practice of medicine through pattern recognition provide freedom to individualize care.

In contrast, group thinking and protocol medicine shackle the physician's mind. Sadly, the patient suffers. Metacognition frees the mind from the shackles of protocolology to restore science and the practice of medicine to their rightful place of critical thinking and pattern recognition. Cannabidiol (CBD) is the bridge between two worlds—the group think of protocolology and the critical think of pattern recognition.

It is essential to identify what CBD is. CBD, also known as cannabidiol, is one of the many phytocannabinoids. The parent precursor to CBD is CBDA (cannabidiolic acid). Other phytocannabinoids include:

- THC (Delta-9-THC and Delta-8-THC)
- THCA
- THCV
- THCP
- CBDA (Cannabidiolic acid)
- CBDV (Cannabidivarin)
- CBN (Cannabinol)
- CBG (Cannabigerol)
- CBC (Cannabichromen)

Some of these phytocannabinoids will get you high, and some will not. There needs to be more clarity around CBD as a phytocannabinoid simply because the knowledge of the different phytocannabinoids is lost on many. Cannabidiol is one of the several phytocannabinoids that will not get you high. Cannabidiol can be extracted from hemp or marijuana. What separates CBD is the associated percentage of THC. Cannabidiol, by legal definition, contains less than 0.3% THC [i]. At the end of the day, what differentiates marijuana and hemp is the concentration of THC.

Phytocannabinoids are one of the broad classes under the collective umbrella of cannabinoids. Phyto means “plant”, so phytocannabinoids are cannabinoids that are

derived from plants. Other cannabinoids include endocannabinoids and synthetic cannabinoids. Endo means “from within”, so endocannabinoids are cannabinoids that are from within the body—endogenous. Synthetic cannabinoids are artificially constructed in a laboratory.

Cannabinoids, whatever the source, interact with the endogenous endocannabinoid system within the body. The endocannabinoid system is a relatively recent discovery on the landscape. It was first discovered in the 1990s, and it can be defined as:

> “The endocannabinoid system (ECS) is a widespread neuro[immuno]modulatory system that plays important roles in central nervous system (CNS) development, synaptic plasticity, and the response to endogenous and environmental insults. The ECS is comprised of cannabinoid receptors, endogenous cannabinoids (endocannabinoids), and the enzymes responsible for the synthesis and degradation of the endocannabinoid. The most abundant cannabinoid receptor is the CB1 cannabinoid receptors, however CB2 cannabinoid receptors, transient receptor potential (TRP) channels, and peroxisome proliferator activated receptors (PPAR’s) are also engaged by some cannabinoids.” [ii]

According to published evidence, cannabidiol has been shown to have many significant and broad effects [iii]:

- Analgesic (pain relief)
- Anti-nausea
- Anti-emetic (vomiting)
- Anxiolytic
- Anti-insomnia
- Anti-depressant
- Anti-psychotic
- Anti-convulsant
- Anti-asthmatic
- Immunomodulatory
- Antioxidant
- Anti-inflammatory
- Anti-bacterial
- Neuroprotective
- Improves BBB integrity/permeability
- Post-TBI decreased cerebral edema
- Anti-cancer

Inflammation is the foundation of almost any chronic disease of aging. One could even claim that chronic, systemic inflammation is the rate-limiting statement in disease development. Inflammation equals accelerated aging, and disease is merely the end manifestation. Publications have even referred to the process as Inflammaging [iv] [v] [vi]. Chronic diseases of aging include but are not limited to cardiovascular disease, pulmonary disease, neurodegenerative disease, endocrinology disease, neuropsychological disease, autoimmune disease, and cancer. Numerous biomarkers exist to monitor systemic inflammation [vii]:

- hs-CRP
- ESR
- IL-6
- TNF-α

Even vitamin D can be used as an indirect measure of systemic inflammation.

Cannabidiol can be found in the whole plant extract or isolate form. Cannabidiol isolate is CBD in its purest form, isolated from the other constituents common to whole-plant extracts. As a result, CBD isolate should be clear of THC. However, contamination through the production and manufacturing process is possible. In contrast, whole-plant extract is CBD plus all the additional constituents common to the whole plant. These additional whole-plant extracts include terpenes (200+), secondary metabolites, other phytocannabinoids (of which there are 120+), phenols, steroids, polysaccharides, coumarins, glycosides, flavonoids, alcohols, and other plant nutrients. The itemized list of whole-plant extract components does not dictate that they are all present, but the potential is that some combination of the itemized list will be present.
What is the best CBD form to use? Whole plant extract is the form most utilized in traditional, natural, and holistic practices. In contrast, isolates are common in modern-day conventional medicine practice. This isolate philosophy dates back to the “magic bullet theory” first proposed by Paul Ehrlich in the treatment of syphillis with Salvarsan. It is the thought that one chemical can be used to treat one disease—chemicals as therapy. It was the first ‘chemotherapy’. The search for the magic bullet in disease causation and disease treatment, despite disproved of this theory long ago. In contrast, the fledgling paradigm in medicine is the individuality of multiomics: genomics, epigenomics, transcriptomics, proteomics, metabolomics, immunomodulomics, hormonomics, and microbiomics.

A 2011 article, Whole plant extracts versus single compounds for the treatment of malaria: synergy and positive interactions, helps to highlight the benefits of whole-plant extracts compared to isolates [viii]. Of course, the article's authors were looking at treating malaria

with whole-plant extracts, but the principles apply here with CBD across all fronts. The benefits of whole-plant extracts include:

- Pharmacodynamic synergy
- Positive pharmacokinetic interactions
- Complementary constituent mechanisms of action
- Multi-drug resistance inhibitors
- Modulation of adverse effects

Collectively, these individual points can be summarized as the ‘entourage effect ’found in whole-plant extracts. The entourage effect can be defined as the cooperative effects between the various constituents of a plant, whereby the therapeutic effect of the other constituents contributes to the overall therapeutic effects of the main phytocannabinoids. Research points to the benefit of the whole-plant entourage effect in clinical cannabis, which applies here to CBD [ix]. A look at holism can help to explain the entourage effect.

Summary:

CBD, also known as cannabidiol, is one of the many phytocannabinoids, including THC, THCA, THCV, THCP, CBDA, CBDV, CBN, CBG, and CBC. Cannabidiol, extracted from hemp or marijuana, contains less than 0.3% THC. Phytocannabinoids are derived from plants and interact with the endogenous endocannabinoid system within the body. Cannabidiol has numerous significant effects, including analgesic, anti-nausea, anti-emetic, anxiolytic, anti-insomnia, anti-depressant, anti-psychotic, anti-convulsant, anti-asthmatic, immunomodulatory, antioxidant, anti-inflammatory, anti-bacterial, neuroprotective, improves BBB integrity/permeability, and anti-cancer.

Cannabidiol can be found in whole plant extract or isolate form. A cannabidiol isolate is CBD's purest form, isolated from other constituents common to whole-plant extracts. Whole plant extract is CBD plus additional constituents, such as terpenes, secondary metabolites, other phytocannabinoids, phenols, steroids, polysaccharides, coumarins, glycosides, flavonoids, alcohols, and other plant nutrients. The best CBD form to use is whole plant extract, which is most commonly used in traditional, natural, and holistic practices. At the same time, isolates are common in modern-day conventional medicine practice.

History:

How far back in history does CBD go? Paleobotanical studies trace cannabis back 11,700 years ago in Central Asia near the Altai Mountains [x]. China boasts some of the earliest medicinal use and documentation of cannabis. The first documented use of cannabis was in ancient China in the management of pain [xi]. Cannabidiol was first isolated from marijuana in 1940 [xii]. However, because of CBD's lack of euphoric effect, its medicinal and therapeutic potential value was lost on most going into the 1960s until the first isolation of THC in 1964 [xiii]. Just in time for the make Love, not War movement.

Why is this what appears to be a diversion? People, including the government, are confused about CBD and need clarification. This confusion is because of remnant perceptions, born out of the 1960s, devoid of any significant science, that continue to permeate consciousness today. Cannabidiol fits right in the middle of Docēre rāphè because of its broad medicinal effects. It is a natural tool in the art of healing.

The anti-anxiety, or anxiolytic, effect is one of the many broad therapeutic effects listed above. The first article on the anti-anxiety benefits of CBD was published in 1982 [xiv]. This initial article found that CBD blocked anxiety symptoms induced by delta 9-THC in people. In short, CBD had an antagonistic effect to delta 9-THC, similar to an antidote effect. I trust that the FDA is aware that this is the first study. Not a claim, but a 1982 study right out of the gate. A claim supported with evidence is a valid claim.

What is in a claim? According to the exact historical root origin (etymology), claim is from an old French word clamer, meaning to call, name, describe, or proclaim. There is no claim here, just calling out, describing, and proclaiming the research. There is no need to make claims; just follow the research. Let the research make the claim. As scientists, then we follow the research.

Fast forward to today and the 522 articles published since, and we have substantial evidence that proclaims CBD's anti-anxiety benefits. These studies have included in vitro, in vivo, pre-clinical, and clinical studies. Look at a 2019 article, Cannabidiol in Anxiety and Sleep: A Large Case Series, which evaluated 72 adults on CBD for anxiety and sleep [xv]. The results found a reduction in anxiety symptom scores in 79.2% of individuals. Another study published in 2022, Cannabidiol for Treatment-Resistant Anxiety Disorders in Young People: An Open-Label Trial, pushed the bar even higher. This study looked at DSM-5-diagnosed anxiety in 31 young individuals with treatment resistance to standard-of-care conventional anxiety treatment. In this study of properly diagnosed individuals in the treatment of the most challenging cases of anxiety, treatment resistance, with CBD "add-on" therapy yielded a 42.6% reduction, statistically significant, in symptoms according to the Overall Anxiety Severity and Impairment Scale (OASIS) system [xvi].

Summary:

Cannabidiol, a natural compound dating back 11,700 years, has been used in various forms since its discovery in 1940. The first documented use of cannabis was in ancient China for pain management. However, due to its lack of euphoric effect, its medicinal potential was lost until the first isolation of THC in 1964. Cannabidiol's broad medicinal effects, including its anti-anxiety effects, have been widely studied. However, as highlighted above, CBD's benefits are not limited to just anxiety and associated symptoms. The first article on CBD's anti-anxiety benefits was published in 1982, which found that CBD blocked anxiety symptoms induced by delta 9-THC. Since then, 522 articles have published substantial evidence supporting CBD's anti-anxiety benefits, including a 2019 study demonstrating a reduction in anxiety symptom scores in 79.2% of adults and a 2022 study showing a 42.6% reduction in symptoms in treatment-resistant anxiety disorders in young people.

Receptors:

The next logical question should be, but how? How can an herbal extract discovered in 1940 provide broad physiologic effects? There must first be a brief discussion of cannabinoid receptors to answer this question. Think of receptors as the doors and the doorway to cell signaling. Cannabinoids like CBD are the key and the knock on the door to open the door to the inside of the cell. Just as often is the case, this is not a straightforward, sequential signaling process. By far, we are in the infancy of understanding the broad details and effects of CBD receptor signaling.

A 2020 review article, Diversity of molecular targets and signaling pathways for CBD, highlights the simultaneous complexity of CBD signaling. The current knowledge of CBD and receptor interactions can be summarized as follows [xvii]:

Receptors	Effect
CBD_1	Antagonist
CBD_2	Antagonist
GPR55	Antagonist
5-HT1A serotonin	Agonist

Receptors	Effect
TRPV1 channels	Agonist
D2 dopamine	Partial agonist
adenosine A1	Agonist
MOR	Negative allosteric modulator
intracellular PPARγ	Agonist
Sodium channels	Inhibitor
Calcium channels	Inhibitor

It is essential to realize that the CBD interaction with different receptors is not linear or sequential; it is simultaneous across the expressed receptors. Cannabidiol signaling is not one point and one level, but in fact, multi-point and multi-level simultaneously. Sequential and linear thinking need not apply. Here, multi-dimensional thinking is required.

Many receptors are potential doorways for CBD signaling. One article looking at CBD signaling and anti-cancer effects reviewed the evidence basis on the numerous receptors involved [xviii]:

- CBD1/CBD2
- GPR (GPR55, GPR18)
- Heterodimers (CBD + GPR55)
- TRPV1/TRPV2
- TRPM8
- TRPA1
- Nuclear Rc's IProliferator activated Rc gamma (PPAR-gamma)
- Other receptors
    - Opioid receptors
    - Serotonin receptors

That is cancer. What about anxiety? The broad signaling potential, the multiple door effect, also applies here in anxiety. A 2019 study of neuropathic pain and anxiety in rats found anxiolytic effects via the vanilloid type 1 receptor (TRPV1) and serotonin 5-HT1A receptors [xix]. The CBD dose dictates the receptor involvement. The anxiolytic effects were

via the serotonin 5-HT1A receptors at low and intermediate doses [xx] [xxi]. Yet, at high doses, the anxiolytic effects appear to be via the TRPV1 receptor [10] [11].

The story does not end with the vanilloid type 1 receptor (TRPV1) and serotonin 5-HT1A receptors. The CBD1 receptor is also involved in the anxiolytic effects of CBD. Cannabidiol receptors are not equally or ubiquitously expressed: CBD1 receptors are predominantly expressed in the central nervous system, and CBD2 receptors are primarily expressed peripherally on immune cells and tissue [xxii] [xxiii]. Cannabidiol increases CBD1 activation, not by direct effect of binding of CBD to CBD1, but through effecting endocannabinoid metabolism. Here, the CBD inhibits the enzyme fatty acid amide hydrolase (FAAH), which increases the levels of the endocannabinoid anandamide. Anandamide increased CBD1 activation as an endogenous CBD1 agonist [xxiv] [xxv].

Cannabidiol receptor expression is not uniform across CBD1 or CBD2 type, time, or tissue type. I think it is essential to understand that the bias construct of marijuana, since the 1960s, has limited scientific advancement in and around phytocannabinoids. Though not exact to the time, I refer to it as the Cheech and Chong effect. Yet, science shows something different; CBD1 and CBD2 expressions are variable across tissue types and equally variable across tumor types and even tumor grades. For example, a 2022 study looked at cannabidiol receptors in thirty-seven dogs with mast cell tumors and found that there was high CBD1 and CBD2 expression in low-grade mast cell tumors.

In contrast, low CBD1 and CBD2 expression was found in high-grade mast cell tumors [xxvi]. The down-regulation of cannabidiol expression in advancing low-grade to high-grade tumor types is likely an expression associated with dedifferentiation and advancement of tumor growth. This line of logic is supported by tumor growth associated with the depletion of CBD1 receptors [xxvii], and the indirect connection of high endocannabinoid expression in the reduction of the presence of pre-cancer lesions [xxviii]. Further support for this idea of increased CBD expression and suppressed tumor growth is provided by a 2003 and 2008 study on the same topic [xxix] [xxx]. One supports the advancement of high-grade tumors through a decrease in CBD receptor expression, and the other supports the protective effects of CBD receptors in low-grade, early disease. Why tumor immunohistochemistry analysis of receptor status in the oncologic world is limited to estrogen and progesterone receptors in breast cancer only is incredulous and not up to date on the latest science. It is readily apparent that the assessment of CBD receptors must be applied to each tumor type, sub-types, and tumor grade.

Inflammation is at the heart of causation and associated symptoms of any chronic disease of aging. Yet, inflammation is not the enemy. Acute inflammation is part of the body's immune system, which means to protect against all enemies—foreign and domestic.

Here, inflammation is an ally. But, it is the chronic, often low-grade and unrelenting, inflammation that contributes to disease. Here, the literature collectively defines the complex process as inflammasome signaling [xxxi]. Inflammasome signaling is the interconnection and synergy of proteins that direct inflammation signaling locally and systemically.

In light of the collective fields of multiomics, a more up-to-date discussion of CBD and inflammation is through its anti-inflammatory and immunomodulatory effects. Receptors are one of the associated signaling effects involved here. The CBD anti-inflammatory and immunomodulatory effects are through the following receptors:

- CBD1
- CBD2
- TRPV1
- GPR55
- PPAR-γ

Effects also occur by inhibiting endocannabinoid metabolism, primarily inhibiting fatty acid amide hydrolase (FAAH). The ultimate impact of FAAH inhibition is an increase in anandamide and its associated CBD receptor signaling. In addition, CB2/5HT1A heterodimerization is involved [xxxii] [xxxiii] [xxxiv]. Heterodimerization is the concept of joining two different subunits together to form one. This receptor heterodimerization is not unique to CBD receptors but has also been shown with insulin and IGF1 receptors [xxxv].

Cannabidiol also has direct cytokine signaling effects as well. Cytokines are collectively the immune system's means to communicate—the language of the immune system. Much of the pro-inflammatory signaling associated with disease is through cytokines. Cannabidiol has been shown to inhibit the following pro-inflammatory cytokines:

- IL-1α
- IL-1β
- IL-6
- tissue necrosis factor α (TNF-α)

This pro-inflammatory inhibitory activity of CBD has been shown in vivo cancer studies no less [xxxvi]. Even the precursor to CBD, cannabidiolic acid (CBDA), has been shown to be a specific cyclooxygenase II inhibitor (COX2) [xxxvii]. Cyclooxygenase (COX) is an enzyme that increases prostaglandin production and results in inflammation.

Three COX isoforms can be expressed in the body: COX-1, COX-2, and COX-3. Cyclooxygenase type II is not highly expressed in healthy cells. In cancer, increased expression and activity of COX-2 increases inflammatory signaling and promotes oncogenesis. The resultant effects on the hallmarks of cancer include [xxxviii]:

- Inhibition of apoptosis (programmed-cell death)
- Promotion of new angiogenesis
- Invasion
- Promotion of metastasis
- Immunosuppression

Summary:

CBD, an herbal extract discovered in 1940, has broad physiologic effects through its interaction with various receptors. The current knowledge of CBD and receptor interactions is multidimensional and multipoint, with CBD1 and CBD2 expressions variable across tissue types and tumor types. CBD1 and CBD2 expressions are not uniform across tissue types, and the Cheech and Chong effect has limited scientific advancement in phytocannabinoids.

Inflammation, often associated with chronic diseases of aging, is a complex process that CBD interacts with in a unique way. Inflammasome signaling, the interconnection and synergy of proteins that direct inflammation signaling locally and systemically, is a key area of CBD's influence. CBD's anti-inflammatory and immunomodulatory effects through receptors such as CBD1, CBD2, TRPV1, GPR55, and PPAR-γ, coupled with its ability to inhibit endocannabinoid metabolism, primarily inhibiting FAAH, which increases anandamide and its associated CBD receptor signaling, offer a promising avenue for therapeutic interventions.

Cannabidiol also has direct cytokine signaling effects, inhibiting pro-inflammatory cytokines like IL-1α, IL-1β, IL-6, and TNF-α. This pro-inflammatory inhibitory activity of CBD has been shown in vivo cancer studies. The precursor to CBD, cannabidiolic acid (CBDA), is a specific cyclooxygenase II inhibitor (COX2), which increases prostaglandin production and results in inflammation.

In cancer, the increased expression and activity of COX-2 can lead to inflammatory signaling and promote oncogenesis, contributing to the hallmarks of cancer. However, the potential of CBD in this context is promising. The assessment of CBD receptors, a crucial step, must be applied to each tumor type, sub-types, and

tumor grade, offering a new perspective and potential therapeutic approach in oncology.

Pharmacokinetics and Pharmacodynamics of CBD:

The most common CBD delivery technique is the oral route, through tincture, capsules, or sublingual (lozenges). For those with chronic anxiety or stress, regular oral daily use is the best strategy. The bioavailability of oral CBD dosing sits at 6% because of high first-pass liver metabolism [xxxix] . This low oral dosing bioavailability and variable pharmacokinetics will require higher and more frequent dosing for therapeutic effect. The half-life of orally delivered CBD is 18-32 hours [xl], which direct daily or twice daily dosing every 12 hours to maintain therapeutic levels due to the low bioavailability as well as the variable pharmacokinetics. For acute anxiety or stress, aerosolized, smoking, or vaping delivery techniques have been shown to achieve rapid peak plasma concentrations at less than 10 minutes with an increase in bioavailability at 31% [xli]. The differences in bioavailability points to improved rapid delivery of CBD via the pulmonary route versus the oral route. As a physician, smoking would be my least favorite dosing option for obvious reasons. Rapid aerosolization or vaporization would be my preferred delivery option for acute anxiety dosing. For those with chronic or severe anxiety, a combination of approaches may be required. For those with chronic or severe anxiety, a combination of approach may be required. For example, twice daily dosing of CBD daily followed by direct or as needed aerosolized or vaporization dosing, on top of the oral dosing, for acute anxiety or stress. These doses should be directed and adjusted with guidance from practitioners with knowledge and clinical experience.

Oral delivery of CBD, regardless of dose, shows consistent pharmacokinetics. Maximum concentration (Cmax) is achieved 4-5 hours after dose. Equally, the half-life of CBD, 14-17 hours, showed consistent pharmacokinetics following oral CBD. Compared to single dosing, multiple dosing strategies have been shown to increase Cmax and prolong the half-life of CBD [xlii].

Surprisingly, CBD has a prolonged metabolic half-life across the different spectrum of delivery methods. The half-life for intravenous and inhalation delivery is 24 +/- 6 hours and 31 +/-4 hours, respectively [xliii]. In contrast, the half-life of oral CBD, via multiple-dose delivery method, is out to 2-5 days [xliv]. The combination of delivery methods will need to take into account the combined multiple pharmacokinetic properties unique to each delivery method.

Should CBD taken with food, fed state, or accompanying fasting? Whatever the oral supplement, herbal extract, or medication, the same question is asked. Cannabidiol is lipophilic. A dietary intake of a higher-fat meal will improve the absorption and bioavailability of oral CBD. When comparing fasting versus food, CBD taken with food, not fasting, will enhance absorption and bioavailability [xlv]. The fed state has been shown to increase CBD absorption and bioavailability by 22-30% [xlvi] [xlvii] over fasting.

The rectal delivery route has proven to be one of the better delivery routes for CBD. The rectal suppository administration of CBD bypasses liver first-past metabolism, increasing bioavailability compared to other common routes of delivery. The most common route of CBD delivery in the U.S. and around the world is the oral route. In contrast to the poor bioavailability of oral CBD, rectally delivered CBD reaches a bioavailability of 13 to 50% [xlviii] [xlix].

To overcome the poor bioavailability of the oral and pulmonary routes, the intravenous route provides 100% bioavailability. A company, PICOIV, is providing Innovation in the CBD and medical cannabis industry that is elevating this potential. The result will empower physicians to broaden disease and treatment strategies and better treat patients. This new intravenous CBD delivery requires new technology to push the highly lipophilic CBD into an aqueous solution. Fortunately, PICOIV (**www.PICOIV.com**) is the pioneering company that is the first to provide sterile picomolar CBD in an aqueous solution for intravenous delivery.

Summary:

Cannabidiol delivery is primarily through oral routes, such as tinctures, capsules, or sublingual lozenges, which is the best strategy for chronic anxiety or stress. However, the bioavailability of oral CBD is low, requiring higher and more frequent dosing for therapeutic effect. For acute anxiety or stress, aerosolized, smoking, or vaping delivery techniques can achieve rapid peak plasma concentrations, increasing bioavailability by 31%. For chronic or severe anxiety, a combination of approaches may be required, such as twice-daily dosing daily followed by direct or as-needed aerosolized or vaporization dosing. CBD has a prolonged metabolic half-life across different delivery methods, with the half-life for intravenous and inhalation delivery being 24+/- 6 hours and 31+/-4 hours, respectively. Cannabidiol should be taken with food, fed state, or accompanying fasting to enhance absorption and bioavailability. Rectal delivery routes have proven to be better for CBD delivery, with rectally delivered CBD reaching 13 to 50% bioavailability. PICOIV, a pioneering company, provides innovative intravenous CBD delivery

technology, empowering physicians to broaden disease and treatment strategies and better treat patients.

The excitement surrounding CBD in the treatment of anxiety, as well as in other diseases and conditions, is very high. However, a dive into the pharmacokinetics and pharmacodynamics of CBD and other phytocannabinoids opens our eyes to how limited and early our understanding of this topic is. Moreover, many of the studies that have looked at the pharmacokinetics and pharmacodynamics of CBD are confounded with the simultaneous use of other phytocannabinoids. Does this co-administration of CBD with other phytocannabinoids affect CBD pharmacokinetics and pharmacodynamics? Time and more research will help to provide such answers. Fortunately, innovative companies, i.e., PICOIV, will help provide more research, present new ideas, and advance medical innovation. Patients demand innovation. Equally, doctors should demand innovation in themselves, their clinical practice, their associated hospitals, and the industry as a whole.

Cannabidiol metabolism:

New discoveries occur through innovation. There is no better example of scientific innovation than that currently coming from the collective fields of multiomics. Metabolomics is one such field of research within the collective umbrella of multiomics. The science is never settled. Saying that the science is settled is, quite honestly, unscientific.

The oral dosing of CBD is the preferred route of delivery. As a result, oral dosing dominates the scientific literature in bioavailability, pharmacokinetics, and pharmacodynamics. Cannabidiol is heavily metabolized through the liver. In oral dosing, extensive first-pass metabolism occurs in the liver. According to published in vitro and animal research, CBD is a potent inhibitor of the cytochrome P450 isoenzyme complexes [i]. These P450 complexes play critical roles in metabolism and detoxification and are highly concentrated in the liver. According to these in vitro and animal studies, CBD primarily affects the CYP2C9, CYP2C19, CYP1A1, CYP1A2, CYP3A4, CYP3A5, and CYP2D6 complexes [ii] [iii].

There are two parts to liver metabolism: phase I and phase II. Many will refer to hepatic phase I and phase II metabolism as phase I and phase II detoxification. The root origin of detoxification goes back to the early 20th century, removing poisonous chemicals. A more modern, updated meaning of detoxification is applied to addiction—the removal of addictive substances from the body [iii]. As the actual meaning of detoxification applies to

removing toxins and toxicants, of which CBD is neither, metabolism, in the context of metabolomics, is a more appropriate word to use here. Metabolomics can be defined as the comprehensive analysis of metabolites, their function, and inter-relationship in a biological organism.

Phase I metabolism involves the cytochrome P450 system. The name comes from these enzymes absorbing light at 450 nm. Phase I metabolism involves three chemical modifications:

- oxidation
- reduction
- hydrolysis

Phase I metabolism makes the parent compound more polar.

Glucuronidation is part of phase II metabolism. Many refer to this collective process as biotransformation. Phase II metabolism further modifies the products provided through Phase I metabolism. Phase II metabolism involves six chemical modifications:

- Glutathione conjugation
- Amino acid conjugation
- Methylation
- Sulfation
- Acetylation
- Glucoronidation

After phase II modification, the body can eliminate the inactivated chemicals, toxins, or toxicants via the bowels and bladder.

Glucuronidation is CBD's predominant phase II metabolism pathway, with sulfation as a secondary phase II pathway [liv]. The result of CBD metabolism is that approximately 82% of what is taken into the body is eliminated through hepatic metabolism [lv].

The hepatic metabolism of CBD results in at least 40 metabolites [lvi] [lvii] [lviii] [lix]. The awareness of metabolites' contribution to overall physiologic function has increased substantially thanks to the fledgling field of metabolomics. Hydroxylation of CBD at the 4, 6, and 7 positions yields the predominate cannabidiol first-pass-metabolites. The most abundant active CBD metabolite is 7-hydroxycannabidiol [lx].

Long has the dogma been that metabolites are inactive compounds destined for destruction and elimination? Research in the metabolomics of hormones has begun to dispel this incorrect dogma. Metabolites are now known to contain some metabolic activity. Some metabolites show more physiologic activity compared to their parent compound of origin. Currently, the collective metabolomic contribution of CBD metabolites is unknown [lxi]. However, just as in hormone metabolites, I fully anticipate that further research and new discoveries will show that CBD metabolites contribute significantly to overall CBD metabolomics.

In the era of soaring liver disease, mainly non-alcoholic fatty liver disease (NAFLD), one must differentiate the hepatic metabolism of CBD between healthy and diseased liver. Diseases of the liver and the resultant associated operative dysfunction are associated with an increase in maximum concentration (Cmax) compared to normal controls. The half-life of CBD is also increased in the diseased liver compared to normal controls. In both Cmax and half-life, the increase in CBD levels and associated metabolites showed a positive correlation from low to mid to high liver dysfunction [lxii]. Contrary to hepatic metabolism, no effects on CBD levels or metabolites have been noted in variable levels of renal function.

Summary:

Metabolomics is a field of research that focuses on analyzing metabolites, their function, and inter-relationships in a biological organism. Oral dosing of CBD is the preferred delivery route, and it is heavily metabolized through the liver. The culturally preferred oral delivery route has significantly impacted the innovation of different CBD delivery methods. As a result, advancements in CBD metabolomics are stunted.

Cannabidiol, a potent cytochrome P450 isoenzyme complexes inhibitor, plays a crucial role in metabolism and detoxification. Its hepatic metabolism results in the production of at least 40 metabolites, with glucuronidation being the predominant phase II metabolism pathway. This underscores the significance of CBD in the metabolic process, making CBD metabolomics research all the more important.

Research in the metabolomics of hormones has begun to dispel the false dogma that metabolites are inactive compounds destined for destruction and elimination. Metabolites are now known to contain some metabolic activity, and some metabolites show more physiologic activity than their parent compound of origin. Currently, the collective metabolomic contribution of CBD metabolites is unknown, but further research and discoveries will show that CBD metabolites contribute

significantly to overall CBD metabolomics. In the era of soaring liver disease, it is essential to differentiate the hepatic metabolism of CBD between liver of healthy and diseased individuals.

Drug to drug interactions:

The availability of data surrounding the potential for CBD to contribute to drug-to-drug interactions is limited at current. Yet, the evolving understanding of CBD CYP liver metabolism provides insight into likely potential interactions that practicing clinicians should be aware of.

The CYP3A4 complex is the predominant metabolism pathway of prescription medications. As a result, there will be an increase in the potential for drug-to-drug interactions with CBD use in conjunction with other prescription medications utilizing the same CYP3A4. As highlighted above, CBD in in vitro and animal studies has been shown to inhibit CYP3A4. This inhibitory effect would be associated with increased prescription systemic drug levels using the same CYP3A4 metabolism pathway. The result would be the potential for an increase in potential side effects. The same concept would apply to other CYP enzymes. The good news is that human studies have not shown CYP450 inhibition by CBD. This knowledge by no means excludes the risk. Increased dosing with increased co-administered prescription medications will likely increase the potential for CYP450-induced side effects. Knowledge and training create the prepared—fortune favors the prepared.

Summary:

Cannabidiol's potential to interact with prescription medications is limited, but understanding its CYP liver metabolism can provide insight. The CYP3A4 complex, the predominant metabolism pathway, is associated with increased drug-to-drug interactions. CBD has been shown to inhibit CYP3A4, but human studies have not demonstrated CYP450 inhibition. Increased dosing with co-administered prescription medications may increase CYP450-induced side effects. Knowledge and training, through innovation, will help create more prepared doctors. Moreover, patients will experience a more healing clinical experience.

Cannabidiol Side effects:

Some of the most common side effects associated with CBD include:

- Sedation

- Poor sleep
- Appetite suppression
- Nausea
- Dry mouth
- Fatigue
- Diarrhea
- Drowsiness

Clinical trials of the synthetic cannabidiol Epidiolex. Increased side effects compared to placebo include [lxiii]:

- Elevated liver Transaminase
- Sedation, somnolence, lethargy, fatigue
- Appetite suppressant
- Diarrhea
- Decrease in weight
- Insomnia, sleep disruption
- Gait disturbance
- Infections

The most common side effects from CBD, whether in healthy individuals or not, are diarrhea, nausea, headache, and somnolence. Many concern themselves with the potential for addiction from acute or chronic CBD use. The FDA's data on Epidiolex shows there is no risk for dependence associated with acute or chronic CBD use [lxiv].

An interesting note regarding CBD side effects, the impact is clearly influenced by dose. Take CBD and sedation for example. Low dose CBD has been associated with increased stimulation and wakefulness [lxv] [lxvi]. Low-dose doses are not clearly defined, but they most likely include CBD doses less than the minimum therapeutic dosage level of 300 mg and higher [lxvii]. In contrast, high dose CBD is associated with sedation, increased sleep time, and decreased nighttime awakenings [lxviii]. High-dose, for optimal sleep aid benefit, was found at 160 mg per day. Dose clearly dictates side effect potential versus actual intended effect. Additionally, the term high-dose is relative as doses at 10 mg/kg or higher are required to elicit the broad, pre-clinical anti-cancer benefits.

CBD dosing is well tolerated at wide dosing with very low toxicity potential. No significant side effects or toxicity have been shown at oral doses up to 1500 mg per day or in intravenous dosing up to 30 mg [lxix]. Doses above 1500 mg per day orally or 30 mg intravenously are not contraindicated, but users and providers should be aware that use above these levels will be associated with an increase in side effect potential.

Summary:

Cannabidiol, a popular phytocannabinoid, has been linked to various side effects, including sedation, poor sleep, appetite suppression, nausea, dry mouth, fatigue, diarrhea, and drowsiness. The synthetic cannabidiol drug Epidiolex has also been linked to increased side effects compared to placebo. However, the FDA's data on Epidiolex shows no risk of dependence. Cannabidiol dose also plays a significant role in its side effect potential, with low doses causing increased stimulation and wakefulness. In contrast, high doses cause sedation, increased sleep time, and decreased nighttime awakenings. Cannabidiol dosing is well tolerated at a wide range of doses with very low toxicity potential.

Purpose:

This white paper seeks to centralize the 14,000+ studies from in vitro, in vivo, animal, and human studies published on CBD in the arena of clinical application in cancer. I intend to move beyond the Cheech and Chong bias of phytocannabinoids born out of the 1960s, which has limited the clinical advancement and application of CBD and other phytocannabinoids. Ignorance of the potential for CBD clinical application, whether from commission or omission, is simply no longer acceptable with the advancement of worldwide research and general public use. As highlighted above, the potential focus areas and the disease directive are significantly broad. This initial research on CBD will focus on the treatment of symptoms associated with chronic inflammation and that which results from the lack of homeostasis, trauma, and disease that result from chronic inflammation.

Cannabidiol alone or in combination with THC as medical cannabis has been shown to benefit the following symptoms and quality of life measures [lxx] [lxxi] [lxxii]:

- Analgesic (pain relief)
- Anti-nausea
- Anti-emetic (vomiting)
- Anxiolytic
- Anti-depressant
- Immunomodulatory
- Antioxidant
- Anti-inflammatory
- Insomnia
- Fatigue

Cannabidiol side effects are well known due to the broad public and clinical use. Generally, the use of CBD is well tolerated with low risk. The majority of human studies from which side effects have been followed include epilepsy, anxiety, depression, bipolar, and psychosis studies [lxxiii]. Most of these studies have included acute oral dosing, not chronic oral dosing, due to limited documentation of true chronic CBD dosing. To be exact, most chronic dosing is more aptly described as multiple daily dosing instead of once daily dosing. Moreover, many studies that have evaluated and documented CBD side effects have included combined phytocannabinoid therapy, i.e., THC and CBD. Tetrahydrocannabidiol, whether delta-9 or delta-8, is not cannabidiol and cannabidiol is not tetrahydrocannabidiol. This point may seem obvious. However, the unique effects of the 200+ phytocannabinoids is lost on most because of the limited research and differentiation between the different phytocannabinoids beyond THC and CBD. The current broadly recognized side effects from CBD use includes [lxxiv]:

- Fatigue
- Drowsiness
- Dry mouth
- Appetite suppression
- Vomiting
- Diarrhea
- Weight loss

Reports of serious adverse events from CBD appear to be primarily limited to epilepsy research in children. Serious adverse events associated from CBD use include [lxxv]:

- Pneumonia
- Elevated liver enzymes

It is important to mention a side effect not mentioned in the current published literature around CBD — Jarisch-Herxheimer reaction. The classic definition of the Jarisch-Herxheimer reaction is “a transient clinical phenomenon that occurs in patients infected by spirochetes who undergo antibiotic treatment” [lxxvi]. Spirochetes include the obvious cause of Lyme disease and Borrelia burgdorferi. However, Jarisch-Herxheimer reactions have also been reported in the bacteria Treponema pallidum, a causative agent of syphilis. The speculative cause of the reaction post-treatment is the release of endotoxins [lxxvii] [lxxviii] or, more likely, membrane lipoproteins [lxxix] [lxxx] . Even some speculate that viruses

or yeast, though with little to no evidence, can cause Jarisch-Herxheimer reactions with treatment. However, Jarisch-Herxheimer reactions are typically self-limited when properly managed with prevention, early diagnosis, and early intervention. Interventions to prevent sequelae and adverse events are equally mild and limited.

A Jarisch-Herxheimer like reaction to CBD has been found reported in the non-scientific literature [lxxxi]. Despite the reporting in the non-scientific literature, the scientific literature provides no publications to corroborate this connection. However, experience does point to a reaction similar to a Jarisch-Herxheimer reaction in individuals without immune compromise. The reaction has been found to be short-lived and easily managed with early intervention with intravenous fluid support. No sequelae of any type have been observed. In contrast, no Jarisch-Herxheimer reactions have been seen in patients who are immunocompromised—cancer patients. In some of the sickest of patients, i.e., stage IV, intravenous CBD has proven safe and well tolerated. Beyond a connection to compromised immune function, another possibility exists—the gut microbiome.

The fledgling, yet incredibly exiting, area of research across all aspects of disease is the gut microbiome. The gut microbiome falls under the collective umbrella of the microbiomics. Microbiomics is the study of the microbiome impact on the function of the body to promote wellness, which literally means healing in action, or to contribute to disease.

The human microbiome is the collection of the independent, yet interconnected, microbiome populations throughout the body. The human microbiome can be sub-divided into the skin microbiome, oral microbiome, gut microbiome, and the tumor microbiome for example. Of particular interest is the gut microbiome connection to the immune system and the gut microbiome connection to the tumor microbiome. The microbiome, particularly the gut microbiome, plays an important role in the development, diagnosis, and the treatment of many human tumors. To be specific, the gut microbiome modulates cancer treatment efficacy and susceptibility to treatment toxic side effects [lxxxii].

One may think the gut microbiome contribution to cancer is limited to the gut, particularly in colorectal cancer. This assumption would be a logically one. However, as the environment within the body never ceases to amaze, the gut microbiota can affect both local and distant tumors through the influence of the [lxxxiii]:

- Immune environment
- Inflammation
- Cancer metabolism

The gut microbiome and the tumor microbiome do not exist in isolation. A 2019 article, Tumor Microbiome Diversity and Composition Influence Pancreatic Cancer Outcomes, blew the lid off the possibilities of the gut-tumor microbiome connection. In this study of pancreatic cancer, it was found that the gut microbiome can colonize pancreatic tumors. Let me rephrase this statement to be clear: the gut microbiome can seed the tumor microbiome of pancreatic tumors. Was that a mike drop??Beyond the tumor seeding effect of the gut microbiome, the impact included:

- Alteration of the tumor bacterial composition
- Modulation of immune function

The ultimate impact of any and all treatments for cancer should be patient safety and overall survival. Is the treatment safe for patients? Does the therapy improve survival. In pancreatic cancer, the seeding of the tumor microbiome of pancreatic by the gut microbiome negatively effected the natural course and survival of pancreatic cancer patients. Maybe the medical communities look at cancer, or the look at Jarisch-Herxheimer reactions with CBD treatments, is no a different than a horse on the race track with blinders. We only see what we can see because it is all we want to see. Ultimately, we have blinded ourselves to what we can see.

The goal of any cancer strategy should be prevention. Much of conventional medicine focuses on early detection, which is great. But, how about prevention so that there is no detection at all. A focus on prevention requires a focus on the multiplicity of causation of cancer. I want to highlight a few areas that can be the target and focus for prevention. To focus on prevention, one must direct the attention to lifestyle.

To see the direct effects of lifestyle, look no further than the Prospective and Urban Rural Epidemiology study published in the Lancet in 2019 [lxxxiv]. According to the Prospective Urban and Rural Epidemiology (PURE) study, conducted between January 2005 and December 2016, cancer is the #1 cause of death, ahead of CVD, in high-income Countries [lxxxv]. More, cancer is responsible for twice as many deaths as cardiovascular disease (CVD) in high-income countries. Of course, the U.S. would classify itself as a “high-income” country. And according to the CDC in 2010, cancer was the leading cause of death, ahead of CVD, in twenty-one states. Alaska was the first state to cross that threshold in 1993.

Could the gut microbiome be where cancer all begins? Could the gut's environment, including the gut microbiome, be critical in the development of cancer and essential in the

future of cancer treatment? Could diet influence healing versus dis-ease potential through its effects on the gut? Research is early here, but the sunrise view is looking like yes.

A recent study on the question found that diet does influence the toxicity potential of chemotherapy by up to 100 fold [lxxxvi]. The mechanism is through the alteration of the gut microbiome. It is essential to realize that this was a human gut microbiome model in earthworms, but the implications are enormous. If diet increases chemotherapy toxicity through the gut microbiome, it makes sense that the opposite can be true. Of course, this connection is known to be true [lxxxvii]. Simply stated, diet is the first treatment that dictates treatment toxicity and likely treatment response. Of course, the same would apply to health versus dis-ease potential.

We are at a Galileo threshold moment on cancer. The evidence is leading away from the old paradigm in the causes and treatment of cancer. Whether because of willful or un-willful ignorance, there will be those that are a part of the ignorant resistance. The historical perspective has been to look at the solid tumor as the problem. Maybe that is just a distraction or a diversion. The diet, the gut microbiome, the immune system, the TME, and their interrelated connections discussed are the actual frontier in the fight against cancer and the battle for healing.

But how? Is it just theory yet unproven? Is it an application? Is it evidence-based? A recent study helps to answer these questions. This study highlights the link between the gut, inflammation, and cancer. In this study, the gut microbiome in the presence of a leaky gut was shown to increase LPS endotoxins (gram-negative bacterial toxin) that stimulate increases in TLR4, a pattern recognition receptor, expression in colorectal cancer. The result is an increase in growth signaling through a significant and heavily utilized cancer growth pathway, the Akt/PI3k/mTOR pathway. The result is an increase in liver metastasis [lxxxviii]. Bam! Remember, metastasis is linked to a 90% cause of morbidity and mortality in cancer. This is the same TLR4 receptor mechanism by which chemotherapy [lxxxix] [xc] [xci] [xcii] and surgery [xciii] cause cancer recurrence and metastasis. But there is so much more. Lipopolysaccharide borne out of an altered gut microbiome and associated leaky gut is linked to insulin resistance [xciv] [xcv], diabetes [xcvi] [xcvii], and Alzheimer's disease [xcviii]. This effect shows that it is not just about cancer, but many chronic diseases of aging.

The easiest way to change the gut microbiome is not probiotics but diet. The best probiotic and the best prebiotic is diet. In contrast, the worst probiotic is diet. Diet is a love language with your gut microbiome. Weird, I know. Feed the gut and gut microbiome healthy food, and it will love you back. Feed it junk, don't be surprised when it gives you trash back.

Is there any evidence that links diet directly to cancer? I have heard many patients recount their Oncologists' claim that diet has no connection to cancer. Not only is there a connection, but the mechanism how is described in the published science. This direct connection can be found between diet—> LPS—> TLR4—> cancer. This direct connection occurs in prostate cancer [xcix]. This connection has also been implicated in breast cancer development [c] and colorectal cancer development [ci] and recurrence [cii].

How about more, but with a different perspective? Chemotherapy induces changes in the gut microbiome, particularly a decrease in overall diversity, which increases systemic inflammation via the microbiota-gut-brain axis to increase fear of cancer recurrence (FCR). Why is this relevant? Fear of cancer recurrence is an actual entity and area of research that follows the growing problem of fear in the cancer industry. Fear of cancer recurrence reduces physical, mental, and emotional well-being, reduces the overall quality of life, increases recurrence, and increases mortality. I have written previously on how chemotherapy, radiation, and surgery increase cancer recurrence and metastasis. Here, chemotherapy alters the gut microbiome to increase fear of cancer recurrence, which is beyond the increase in systemic inflammation via LPS in metabolic endotoxemia.

Why the lengthy diversion into the gut microbiome and cancer? If the gut microbiome has been shown to be a direct and indirect contributor to cancer, metabolic disorders (type II Diabetes), cardiovascular diseases, neurological disorders, and psychological disorders, such as schizophrenia, why could the gut and the tumor microbiome not be a contributor to the Jarisch-Herxheimer reaction associated with some patients with intravenous CBD? Time and research will answer this question. First, we must unblind our vision.

The answer to the Jarisch-Herxheimer dilemma can be found in the concomitant therapies with which I treat cancer patients. Most patients with chronic inflammatory disease, including cancer patients, that received intravenous CBD also received daily intravenous fluids, intravenous vitamin C, intravenous magnesium, zinc, and aggressive probiotic support. Anecdotally, when these same preventative and treatment strategies were implemented in the non-cancer population, there was a complete elimination of the Jarisch-Herxheimer like reactions. This prevention of the Jarisch-Herxheimer symptoms has been found even in patients who had experienced the reactions previously. In addition, the addition charcoal as another proactive preventative or treatment option.

> "Although Physicians, as a part of their training, are taught that the dosage of a drug that is prescribed for the patient must be very carefully determined and controlled, they seem to have difficulty in remembering that the same principle applies to the vitamins."

—Linus Pauling

What Linus Pauling is describing is that the same attention to detail in pharmacokinetics, pharmacodynamics, bioavailability, frequency, duration, and dose applied to conventional pharmacologic research is not applied and, in fact, is lost on the more natural, holistic, and integrative medical therapies. Yet, the pharmacologic and scientific principles apply to both. This research will apply and document the sound pharmacologic principles of pharmacokinetics, pharmacodynamics, and bioavailability to optimize the frequency, duration, dose, and method of delivery of CBD to treat symptoms and conditions associated with lack of homeostasis, trauma, and disease.

The ultimate goal is to continue to follow the curiosity of mind that has been characteristic of the great discoveries that have provided growth and clinical advancement, which have dominated the history of medicine from times of antiquity to Hippocrates to modern-day conventional medicine. We will ask and answer questions built on the solid collection of research surrounding the potential clinical application of CBD to bring the scientifically sound clinical practice of CBD into the mainstream consciousness of the medical community and the general public.

The rising tide of cancer no longer allows an early diagnosis strategy in the approach to cancer. The best answer to cancer with those diagnosed with cancer is the immune system; beyond the immune system, the best answer to cancer is to never get it. But in prevention and in treatment, the best answer to cancer is the immune system.

Summary:

This white paper aims to centralize over 14,000 studies on CBD in clinical application in cancer, moving beyond the criminalization and historical bias of phytocannabinoids. The research focuses on treating symptoms associated with chronic inflammation and the lack of homeostasis, trauma, and disease. Cannabidiol has been shown to benefit symptoms and quality of life measures, including analgesic, anti-nausea, anti-emetic, anxiolytic, anti-depressant, immunomodulatory, antioxidant, anti-inflammatory, insomnia, and fatigue. However, most studies have included only acute oral dosing, not chronic oral dosing, which limits documentation of proper chronic CBD dosing.

Cannabidiol side effects include fatigue, drowsiness, dry mouth, appetite suppression, vomiting, diarrhea, and weight loss. Serious adverse events from CBD use include pneumonia and elevated liver enzymes. A CBD side effect not mentioned in the current literature is the Jarisch-Herxheimer reaction, which occurs in patients infected by spirochetes who undergo antibiotic treatment. My personal clinical experience now is almost five months with IV CBD. However, this reaction is typically self-limited when adequately managed with prevention, early diagnosis, and early intervention.

The gut microbiome is a pivotal area of research in the field of microbiomics, which studies the impact of the microbiome on the body's function and health. The human microbiome, including the skin, oral, gut, and tumor microbiomes, plays a crucial role in the development, diagnosis, and treatment of many human tumors. The gut microbiome's ability to modulate cancer treatment efficacy and susceptibility to toxic side effects is a significant finding. It can affect both local and distant tumors through the influence of the immune environment, inflammation, and cancer metabolism. In pancreatic cancer, the gut microbiome can colonize tumors, altering the tumor's bacterial composition and modulating immune function. The ultimate goal of any cancer strategy should be prevention, focusing on the multiplicity of causation of cancer. Lifestyle factors can be targeted and focused on for prevention, as evidenced by the Prospective and Urban Rural Epidemiology study published in the Lancet in 2019.

The gut microbiomes' contribution and effects on transcriptomics, proteomics, metabolomics, immunomodulomics, and harmonics are yet to be determined. Equally, the gut microbiome's impact on the pharmacokinetics and pharmacodynamics of CBD is unknown. Currently, some of the most exciting work in cancer is on the relationship between the gut microbiome and cancer. Time and innovation will enable advancements in these areas. This innovation will elevate the practice of medicine and empower better care for patients.

Obesity

It is hard not to list Obesity as the #1 pandemic. Others have called cancer the ‘sickness of the century’ [ciii]. A quote from the journal Current Issues in Molecular Biology published in 2021 provides an appropriate synopsis:

“…one of this era’s leading causes of mortality worldwide, which is becoming more threatening day by day due to the increasing number of cancer cases and the

> ability of this disease to resist the existent therapeutic and pharmacological approaches." [3]

There are many that would try to normalize obesity; however, obesity is stop number one on the cancer prevention strategy. The chronic inflammation and metabolic dysfunction are central to oncogenesis, progression, and metastasis.

Recently published data in the Journal of American Medical Association found that the obesity rates increased from 32.7% to 40.9% in young adults [civ]. The data followed young adults between the years 2009 to 2020. What is amazing about this data is that it essentially ends pre-COVID.

What does the future beyond the COVID pandemic hold? Look to the children to see that glimpse into the future. A September 2023 publication, pre-print, found a five point increase in pediatric obesity during the prime pandemic years [cv]. This study followed kids from January 2021 to August 2022.

"Cancer Is Striking More Young People, and Doctors Are Alarmed and Baffled". This was the title of a recent Wall Street Journal article published on January 11, 2024. Cancer is striking more and more young people. Doctors alarmed? If doctors are just now becoming alarmed, they have have not been paying attention. Myself and others have been repeatedly sounding the alarm over this new pandemic. I use to call it the coming pandemic. Unfortunately, the future cancer pandemic has officially arrived. Baffled? Again, only those not paying attention would be surprised, or 'baffled'. The trend of younger and younger patients with cancer is not anything new; it has been building momentum. The past COVID pandemic has only accelerated this trend.

Is this trend a fait de complis? Of course not. Cancer is the reaction of cells to an inhospitable environment. One that in the short-term, promotes cell survival; yet in the long-term, it promotes this thing called cancer.

What classifies as pediatrics? Who classifies as children. According to the Centers for Disease Control (CDC), children and adolescents are those ages two to nineteen. The CDC reports a 19.7% obesity prevalence amongst children and adolescents age two to nineteen followed between the years 2017 and 2020 [cvi].

The connection between obesity and cancer is a direct one and very important in the discussion of treatment, including the use of intravenous CBD. Obesity increases the risk of several associated cancer types [cvii]:

- Adenocarcinoma of the esophagus.
- Breast (post-menopause)
- Esophageal
- Colorectal
- Uterine
- Ovary
- Pancreas
- Gallbladder
- Stomach
- Kidneys
- Liver

More than a major contributor to carcinogenesis, obesity has been shown to play a role in recurrence as well as mortality and survival [78] [cviii] [cix]. A goal of survival is great, but we need to aim higher—survivors who thrive. How about we strive to have our patients heal as they live?

A rising tides raises all ships. Obesity and chronic inflammation contribute to the rising tide that raises most cancer rates. These ships, unfortunately, are destined for sinking and an inclusion criteria requires patients with cancer undergoing treatment, those individuals in remission, and those seeking prevention.

Summary:

Obesity is considered the #1 pandemic, with cancer being the "sickness of the century." Obesity rates have increased from 32.7% to 40.9% in young adults between 2009 and 2020, marking a significant increase from pre-COVID. A pre-print study found a five-point increase in pediatric obesity during the prime pandemic years. The trend of younger patients with cancer is not new, as it has been building momentum since the past COVID-19 pandemic. The Centers for Disease Control (CDC) reports a 19.7% obesity prevalence among children and adolescents aged two to nineteen between 2017 and 2020. Obesity increases the risk of several associated cancer types, including adenocarcinoma of the esophagus, breast (post-menopause), esophageal, colorectal, urinary, pancreas, gallbladder, stomach, kidneys, and liver. Obesity also plays a role in recurrence,

mortality, and survival. To combat obesity and associated diseases like cancer and to be true to the foundation of what it means to be a physician, translated healer, and a doctor, translated teacher, it is essential to aim for survivors who thrive and strive to heal as they live. Cannabidiol is a natural therapy that can be both a bridge between integrative medicine and conventional medicine and empower patients to thrive, not just survive this thing called life.

Cannabidiol and cancer:

Of all phytocannabinoids currently known, CBD has been shown to have the most significant positive anti-cancer effects. The vast majority of the studies involving CBD and cancer have been pre-clinical studies. Despite the limitation of human observation and interventional studies, pre-clinical studies show CBD to retain strong and consistent evidence of positive anti-cancer impact via the following mechanisms:

- Pro-apoptosis [cx] [cxi]
- Anti-proliferative [cxii]
- Cell cycle arrest [cxiii] [cxiv] [cxv]
- Inhibits chemotaxis [cxvi]
- Inhibits cancer cell migration [cxvii] [cxviii]
- Inhibits adhesion [cxix]
- Anti-angiogenesis [cxx] [cxxi]
- Inhibits invasion potential [80]
- Inhibits metastasis potential [cxxii] [cxxiii] [cxxiv]
- Increases survival [85]
- glutathione depletion [86] [cxxv]
- Increases ROS [cxxvi]
- Increases chemosensitivity [cxxvii] [cxxviii]
- Alters the tumor microenvironment [cxxix] [cxxx]
- Immunomodulation [cxxxi] [cxxxii]
- Promotes autophagy [94] [cxxxiii] [cxxxiv]
- Inhibits extracellular microvescicles [cxxxv] [cxxxvi]

- Radioprotective [86]
- Nephroprotective [cxxxvii]
- Cardiprotective [cxxxviii]
- Inhibits cancer stem cells [cxxxix] [cxl] [cxli]

Beyond these direct anti-cancer mechanisms, CBD is shown to serve well in precision therapy stacking. Precision Therapy Stacking is the principle of adding different therapies together in a specific combination and sequence, i.e., intravenous vitamin C plus whole-body hyperthermia, photodynamic endolaser therapy with indocyanine green (ICG) followed by immune checkpoint inhibitor therapy or the sequence of hyperbaric oxygen therapy (HBOT), low-dose metronomic chemotherapy with insulin potentiation (LDMC-IP), and sonodynamic therapy, to augment and maximize the physiologic impact for the right patient at the right time. The goal is to synergize and maximize the intended effects of treatment in Genomics, Epigenomics, Transcriptomics, Proteomics, Metabolomics, Immunomodulomics, Hormonomics, and Microbimics. These exciting fields of “omic” research are bringing the future of precision medicine to patients today in Integrative Oncology.

The stacking principle is the therapeutic bridge between the future of multi-omics science with the integrative clinical application. Cancer does not occur because of one hit or a magic bullet. The magic bullet theory, attributed to Paul Ehrlich in 1907, has long been disproven. Conventional medicine and cancer care have followed the magic bullet theory paradigm for the last century. The integrative approach to cancer treatment can not fall trap to the same magic bullet theory. The scientific evidence must lead the way, and the science of medicine must be its foundation. The art of medicine must be the innovation that sits atop the scientific foundation. It is not enough to know the what, but one must know the how provided through the collective fields of multi-omics. More than the how, the interconnectivity and inter-relationship of the how must be known. Only then can the clinical application of precision therapy stacking be provided through the multi-omics evidence directed with precision and accuracy.

Stacking is more than just the simple combination and sequence of therapies. Stacking also points to both impact and effect. Though impact and effect appear similar, they have distinct and clinically relevant differences to explore. The word ‘impact ’is more connected to 'influence'. In comparison, the word 'effect' is used more in connection to a 'result'. Precision therapy stacking, whether in combination or sequence, is inconsequential unless the influence results in high treatment efficacy—results. The connection of the dots found in science provides such a consequence of effectiveness through stacking.

The idea of precision therapy stacking effect of CBD in cancer is supported in numerous pre-clinical scientific publications in conventional and integrative treatment strategies [cxlii] [cxliii] [cxliv] [cxlv] [cxlvi] [cxlvii] [cxlviii]. The stacking benefit of cannabidiol has been shown to provide direct augmentation with numerous conventional oncology treatments, including chemotherapy and radiation (highlighted previously). In addition, CBD has shown indirect benefit in the reduction of post-operative immunosuppressive opiates [cxlix] [cl] which is critical in managing post-operative immunosuppressive potential contribution to local recurrence and metastatic risk. Of course, these limited studies highlight only the use of oral CBD. No interventional studies have included any intravenous CBD.

Surprisingly the medical use of CBD in cancer remains a therapy categorized and marginalized to the arenas of alternative medicine. Most of this marginalization is the result of ignorance. The debate of whether this ignorance is willful or not is no longer an acceptable one.

Ignorance is a word that carries a heavy negative connotation. Ignorance can be the result of both active, also known as commission, or inactive, known as omission choices. In many ways, ignorance in the world today with access to more data than ever before, all at the tap of a key, is a deliberate choice. Whether via commission or omission, ignorance is an unacceptable option for physicians in the treatment of cancer. The information is readily available, but pre-existing bias and limited centralization on this topic hinders knowledge growth. This white paper is an attempt to begin the remedy on this matter.

Cancer is not the same cancer we grew up with. Not that the old cancer was good and the new cancer is bad. It is just different. There is a palpable and observable difference. There was cancer pre-pandemic and then there is cancer post-pandemic. They are not one in the same. Cancer is evolving. Unfortunately, the SARS-CoV-2 virus and many of the choices implemented by governments and medical bureaucracies have appeared to accelerate the change.

As cancer evolves, the medical field must also evolve. We must remove ourselves from the childhood playground antics that have long dominated the separation of the conventional, integrative, and natural oncology worlds. We must remove our biases and follow the data. The data is not to preserve a system or style of medicine. Data is a search for the truth. It is a preservation of the curiosity of mind that has historically dominated critical thinking. In contrast, medical bureaucracies appear more to encourage protocol-ology and controlled group think. We must return to our original purpose—the patient. Whether conventional, natural, or integrative, we must follow the science, remove the bias', evolve to work together, all for the benefit of patients. Our origin, our morals, and our ethics demand it. Our profession must demand it because the patients demand it.

I believe being in the science forces one to be more integrative. Interesting word, integrative; the word Integrative comes from the Latin, Integrationem, which means to remake, renew, and restore. Is that not what medicine is all about? It is high time we renew and restore the health of our patients.

Cannabidiol steps into the potential to be a therapy which bridges the gap, in many ways the chasm, that exists between conventional and integrative oncology.

These effects have been shown to occur in many cancer types, including, but not limited to the following cancer types [cli] [clii]:

- Glioblastoma
- Prostate
- Breast
- Lung
- Pancreas
- Colorectal
- Melanoma
- Leukemia
- Lymphoma

Summary:

Cannabidiol, a phytocannabinol, has been shown to have significant positive anti-cancer effects. It's important to note that most studies involving CBD in cancer are pre-clinical, but the available published scientific evidence is extensive and robust. This evidence points to cannabidiol's potential anti-cancer effects, which include a wide range of actions such as pro-apoptosis, anti-proliferative, cell cycle arrest, inhibition of chemotaxis, cancer cell migration, adhesion, anti-angiogenesis, invasion potential, metastasis potential, increased survival, glutathione depletion, increased ROS, increased chemosensitivity, altering the tumor microenvironment, immunomodulation, radioprotective, nephroprotective, cardioprotective, and inhibiting cancer stem cells. This wealth of scientific evidence should instill confidence in the potential of CBD in cancer treatment.

Cannabidiol is not a solo therapy following the past one-size-fits-all paradigm, which has dominated conventional medicine for the last 100+ years. Instead, CBD serves as a beacon of hope in precision therapy stacking, a novel approach that involves adding different therapies together in a specific combination and sequence. This new therapeutic strategy is about treating the right patient with the right combination, sequence, and time—precision medicine. It's an approach that aims to synergize and maximize the intended effects of treatment in Genomics, Epigenomics, Transcriptomics, Proteomics, Metabolomics, Immunomodulomics, Hormonomics, and Microbimics. The stacking principle is the therapeutic bridge between multi-omics science and integrative clinical application, paving the way for a brighter future in cancer treatment.

The idea of CBD's precision therapy stacking effect in cancer is supported in numerous pre-clinical scientific publications in conventional and integrative treatment strategies. CBD has shown direct augmentation with conventional oncology treatments, including chemotherapy and radiation, and indirect benefits in reducing post-operative immunosuppressive opiates. However, the medical use of CBD in cancer remains marginalized due to ignorance and limited centralization.

Cancer is evolving, and the medical field must evolve to work together to benefit patients. Being in the science forces one to be more integrative, as the Latin word "integrative" means to remake, renew, and restore. Cannabidiol has the potential to bridge the gap between conventional and integrative oncology, and its effects have been shown to occur in many cancer types, including glioblastoma, prostate, breast, lung, pancreas, colon, melanoma, leukemia, and lymphoma.

Cannabidiol and Tumor microenvironment (TME):

I want to provide special attention to the TME and the tumor immune microenvironment (TIME). A 2022 article that reviewed the impact of vitamin C in the collective TME described and characterized seven microenvironments within the collective TME [cliii]:

- Metabolic microenvironment
- Immune microenvironment
- Hypoxic microenvironment
- Intratumoral microbiome
- Acidic microenvironment

- Innervated niche
- Mechanical microenvironment

It's crucial to grasp that cancer is not a static entity but a dynamic process. It's a continuous interplay, a constant dialogue, and a perpetual manipulation between the cancer and non-cancer cells within the TME. The TME serves as the primary site of this ongoing interaction, a hub of dynamic cellular communication.

The TME is an environment where a tumor meets the body. A cancerous tumor can no longer be considered a solid ball of cells entirely walled off from the body. The TME is a transition zone between cancer and non-cancer. As much as the TME is vital to cancer growth, the same TME is critical to cancer suppression.

The authors of a 2019 article, Effect of tumor microenvironment on pathogenesis of the head and neck squamous cell carcinoma: a systematic review [cliv], said it well:

> “The outlook on cancer has changed dramatically and the tumor is no longer viewed as a bulk of malignant cancer cells, but rather as a complex tumor microenvironment (TME) that other subpopulations of cells corrupted by cancer cells get recruited into to form a self-sufficient biological structure. The stromal component of the tumor microenvironment is composed of multiple different cell types, such as cancer-associated fibroblasts, neutrophils, macrophages, regulatory T cells, myeloid-derived suppressor cells, natural killer cells, platelets and mast cells”.

The TME can be anywhere and everywhere. It exists around a primary tumor, bone metastasis, liver metastasis, and lung metastasis. It can even be said that a TME exists around circulating tumor cells (CTC) as they interact with the body's cells. Wherever there is an interaction between the cancer cells and the cells of the body, a TME exists.
To better understand the TME, it helps to understand what makes up a TME. According to current published evidence [clv clvi clvii clviii], the TME consists of:

- Cancer cells
- Cancer-associated fibroblasts
- Tumor-associated macrophages
- Natural Killer cells
- T reg regulatory T cells

- Tumor-associated neutrophils
- Myeloid-derived suppressor cells
- Platelets
- Endothelial cells
- Mast cells
- Extracellular matrix

The TME is not a singular process. Wherever circulating tumor cells (CTC) land and prosper, a TME is created. Just as there are millions of cancer cells in a primary tumor, and just as there are millions of circulating tumor cells released from the primary tumor, so are there likely millions of TME. Cancer is a highly heterogeneous process. It is simply an interaction zone between a collection of tumor cells and the body. It is the front line. It is the battleground of acid/base, redox potential, ROS, immune system activity, and altered cellular metabolism that can be used by cancer to survive and thrive or by the body or therapies to target and eliminate cancer. The discovery and understanding of the TME renders the one-size-fits-all approach, which has dominated the last one hundred years obsolete and frankly archaic. A precision therapy approach is the only way to target the heterogeneity that is cancer—the right therapy for the right patient at the right time.

It was declared during the pandemic that the science is settled. Such a statement is itself unscientific. Science constantly evolves as discovery advances via new understanding driven by new questions. Interestingly, science was considered settled about the earth as the center of the universe until Galileo challenged the long-accepted dogma of the Copernicus theory. Galileo was called a heretic at the hands of the Catholic Church inquisition and forbidden from holding or defending his beliefs on the matter because it was contrary to church doctrine. Worse, he faced trial, seclusion, jail, and even execution because he dared to challenge an outdated paradigm.

We are at a Galileo threshold moment in cancer care. The evidence is leading away from the old paradigm in the causes and treatment of cancer. Whether because of willful or un-willful ignorance, there will be those who are a part of the ignorant resistance. The historical perspective has been to look at the solid tumor as the problem. Maybe that is just a distraction or a diversion. The diet, the gut microbiome, the immune system, the TME, and their interrelated connections discussed are the actual frontier in the fight against cancer and the battle for healing.

History is full of repetitive examples of disproved settled science. So repetitive is this error that one could say the constants in life are death, taxes, and disproved settled science.

Unsettled science is not unsettling; it is the actual settling of scientific questions and observations. The evolving understanding of CBD and the tumor microenvironment is the perfect example of the settling of unsettled science.

The endocannabinoid system reviewed above intertwines endogenous and exogenous cannabinoids and the tumor microenvironment. Phytocannabinoids are examples of exogenous cannabinoids. The endocannabinoid system is thought to affect immunomodulation, endothelial function, and the stromal matrix within the tumor microenvironment [clix]. Knowledge of CBD function and the endocannabinoid system within the tumor microenvironment is primitive at best currently. Expect our understanding to advance as new questions and discoveries push new knowledge forward, which is how actual science is supposed to work.

The research regarding intimate details of CBD and the tumor microenvironment is limited. However, a July 2023 article from the Journal of Pharmacological Analysis summarizes the topic's current scientific knowledge. The cell analysis found [clx] :

- CBD reshapes the TME
- CBD is an immunomodulator within the TME
- CBD metabolically reprograms macrophages within the TME
- CBD inhibits pro-growth pathway signaling within the TME
- CBD augments chemotherapy
- CBD augments conventional immune checkpoint inhibiting (PD-1) drugs

This article highlights a new potential impact of CBD in cancer as a means to more reshape and reprogram the TME in addition to or in place of the pre-clinical proposed direct anti-cancer effects. As is always the case, it is a little bit of everything.

The saying is that the devil is in the details. What a misnomer. This statement directs falsehoods in the details. It is better stated that the truth is in the details. The specific mechanisms are found in the details—truth. The truth in the details include [155] [clxi] [clxii] [clxiii]:

- CBD inhibits PI3K-Akt-mTOR pathway signaling
- CBD reprograms pro-carcinogenic M2 macrophages to anti-tumorigenic M1 macrophages, term called macrophage polarization
- CBD increases anti-carcinogenic M1 macrophages within the TME

- CBD decreases pro-carcinogenic M2 macrophages within the TME
- CBD reduces Ki67 proliferation growth index
- CBD increased expression of Ifnγ, Granzyme B (Gzmb), Perforin, and Fas ligand (FasL)
- CBD increased the number of lymphocytes within the TME
- CBD increased CD8+ cancer cell interaction
- CBD increased Natural killer (NK) cell cancer cell interaction
- CBD increased macrophage tumor cell interactions
- CBD increased CD8+ macrophage interactions
- CBD reprogrammed macrophage metabolism from oxidative phosphorylation to glycolysis
- CBD increased the T cell recognition and cytotoxic activity of cancer cells
- CBD decreased immunosuppressive T regulator cells within the TME
- CBD decreased T regulator: CD8+ T cells within TME
- CBD decreased T regulator: NK cells within TME

An increase in cell-to-cell communication drives CBD's immunomodulatory effect within the tumor microenvironment. As communication is the core of effective or damaged relationships, so too is the disrupted and reprogrammed cell-to-cell communication in cancer. If cancer reprograms its surrounding cells and environment via cell-to-cell communication, why can't improving cell-to-cell communication be used to re-reprogram cancer? Time will tell if CBD can reprogram the tumor immune microenvironment within the tumor microenvironment.

Summary:

Cancer is a dynamic process, with the tumor immune microenvironment (TME) as the primary site of this ongoing interaction. The TME is a transition zone between cancer and non-cancer cells, vital for growth and suppression. The TME can be anywhere and everywhere, including around primary tumors, bone metastasis, liver metastasis, and lung metastasis. The tumor microenvironment comprises cancer cells, cancer-associated fibroblasts, tumor-associated macrophages, natural killer cells, regulatory T cells, myeloid-derived suppressor cells, natural killer cells, platelets, endothelial cells, mast cells, and extracellular matrix. Cancer is a highly heterogeneous process, with millions of TME created where circulating

tumor cells (CTC) land and prosper. The discovery and understanding of the TME render the one-size-fits-all approach obsolete and archaic. A precision therapy approach is the only way to target the heterogeneity of cancer, providing the right therapy for the right patient at the right time.

The pandemic has brought about a shift in our understanding of cancer care, with evidence leading us away from the old paradigm. The diet, gut microbiome, immune system, and tumor microenvironment are now recognized as the true battlegrounds in the fight against cancer. The fact that science is not always settled is unsettling but a testament to the ongoing process of settling scientific questions and observations. The evolving understanding of CBD and its interaction with the tumor microenvironment is a prime example of this process.

The endocannabinoid system, which intertwines endogenous and exogenous cannabinoids and the tumor microenvironment, is thought to affect immunomodulation, endothelial function, and the stromal matrix within the tumor microenvironment. However, a clear understanding of cannabidiol function, let alone in general, and the endocannabinoid system within the tumor microenvironment are primitive at best currently.

Research has illuminated CBD's impact on common cancer proliferation pathways, immunomodulation within the TME, and effects on cell-to-cell communication. This not only underscores a potential new role for CBD in cancer treatment but also suggests its ability to reshape and reprogram the tumor microenvironment. This is a significant finding that could supplement or even replace the pre-clinical proposed direct anti-cancer effects of CBD, warranting further investigation.

Which form of cannabidiol is the best?

Cannabidiol can be found in the whole plant extract or isolate form. Cannabidiol isolate is CBD in its purest form isolated from the other constituents common to whole-plant extracts. As a result, CBD isolate should be clear of THC. However, contamination through the production and manufacturing process is possible. In contrast, whole-plant extract is CBD plus all the additional constituents common to the whole plant. These additional whole-plant extracts include terpenes (200+), secondary metabolites, other phytocannabinoids (of which there are 120+), phenols, steroids, polysaccharides, coumarins, glycosides, flavonoids, alcohols, and other plant nutrients. The itemized list of whole-plant extract components dose not dictate that they are all present, but, the potential is that some combination of the itemize list will absolutely be present.

Back to the question, what CBD form is the best for anxiety and stress relief? Whole-plant extract is the form must utilized in traditional, natural, and holistic practices. In contrast, isolates are common to modern-day conventional medicine practice. This isolate philosophy dates back to the “magic bullet theory” first proposed by Paul Ehrlich in the treatment of syphillis with Salvarsan. It is the thought that one chemical can be used to treat one disease—chemicals as therapy. It was the first ‘chemotherapy’. The search for the magic bullet in disease causation and disease treatment, despite disproved of this theory long ago. In contrast, the fledgling paradigm in medicine is the individuality of multiomics: genomics, epigenomics, transcriptomics, proteomics, metabolomics, immunomodulomics, hormonomics, and microbiomics.

A 2011 article, Whole plant extracts versus single compounds for the treatment of malaria: synergy and positive interactions, helps to highlight the benefits of whole-plant extracts compared to isolates [clxiv]. Of course, the authors of the article were looking at the treatment of malaria with whole-plant extracts, but the principles apply here with CBD. The benefits of whole-plant extracts include:

- Pharmacodynamic synergy
- Positive pharmacokinetic interactions
- Complementary constituent mechanisms of action
- Multi-drug resistance inhibitors
- Modulation of adverse effects

Summary:

Whole plant extract of cannabidiol, per the literature, appears to have the most synergistic clinical impact. Cannabidiol, found in whole plant extract or isolate form, is a natural and holistic remedy for an ever-increasing number of symptoms and disease states. Whole plant extract contains CBD and additional constituents like terpenes, secondary metabolites, phytocannabinoids, phenols, steroids, polysaccharides, coumarins, glycosides, flavonoids, alcohols, and other plant nutrients. The "magic bullet theory" suggests that one chemical can treat one disease, but modern medicine emphasizes the individuality of multiomics. The magic bullet theory has propelled the one-size-fits-all medical paradigm of the last 100+ years. Whole-plant extracts offer benefits such as pharmacodynamic synergy, positive pharmacokinetic interactions, complementary constituent mechanisms of action, multi-drug resistance inhibitors, and modulation of adverse effects, which is more consistent with the natural, holistic, and integrative approaches that power the new paradigm of precision medicine.

Entourage effect:

Collectively, these individuals points can be summarized as the ‘entourage effect’ found in whole-plant extracts. The entourage effect can be defined as the cooperative effects between the various constituents of a plant, whereby the therapeutic effect of the other constituents contribute to the overall therapeutic effects of the main phytocannabinoids. Research points to the benefit of the whole-plant entourage effect in the clinical use of cannabis, which also applies here with CBD [clxv]. A look at holism can help to further explain the entourage effect.

What is holism?

Turn to the modern father of holism—Christian Smuts. Holism is the practice of the holistic theory, as defined by Smuts [clxvi]. Holism or Holistic has no reference to what appears to the be origin word--hole. That, of course, is another rabbit hole that we want to avoid. Christian Smuts defined holism as "the ultimate principle of the universe...the operative factor in the evolution of wholes" [clxvii]. This definition of holism applied to both organic and inorganic as well as biological and non-biological. Holism, according to Smuts, was a counter to the scientific dominance of the time of reduction in research. It was a challenge to how the current scientists evaluated systems. Reduction was a compartmentalization view of how things relate to each other. The idea of reduction compartmentalization was that systems are best studied through their compartments or individual parts-- top-down, almost unrelated perspective in how things in the biological versus non-biological were constructed and related to each other.

In contrast, Christian Smuts discarded the compartmentalization view and pursued the bottom-up approach that the whole transcends the individual parts. The individual parts support and point to the whole. His idea was that systems, whether biological or non-biological, are best served and evaluated through the focus on the parts only to benefit the whole. The whole is more important than the individual parts.

Here in the discussion of whole-plant extract versus isolates for CBD, the whole of the constituents of the plant provide the entourage benefit. In contrast, the isolate is consistent with the reductionist approach isolated from the benefit of the whole provided with the constituents. Holism versus reductionism is found everywhere, even right here in the CBD discussion.

Let there be wine! No, I did not lose track of the topic. Wine is a great place to begin the discussion of specific examples of whole-plant extract versus isolates. A 2019 article, The

influences of red wine in phenotypes of human cancer cells, written in the journal Gene, highlights the distinct differences between wine and diluted ethanol. On its face, the difference is evident. However, a significant volume of research on alcohol uses diluted ethanol. I don't know anybody that drinks diluted ethanol. I do know people that drink wine. The authors concluded:

> "…our studies reveal that the red wines, particularly mature wines (#1 and #3), dramatically decrease the rates of human cancer cell growth and colony formation, while diluted ethanol at same concentration boosts cell growth. The red wines also cause death of the grew up cancer cells and inhibit Pol III gene transcription. It implies that the red wine may contain some bioactive components and function potential to repress cancer development. Thus, identifying the bioactive components in red wine and enhancing their yielding ratio during producing processes will enhance the quality of red wine, which will benefit people with red wine consumption." [clxviii]

The example of the whole-plant extract and its 'bioactive components and function potential' is the red wine and diluted ethanol that of the isolates.

A 2018 review article on cannabinoids in pain management suggests that whole-plant extract outperform isolates in the management in broad classes of pain types [clxix]. However, the positive effects of CBD in pain management is variable in efficacy across the variability of pain types.

Then there is the obvious benefit of whole-plant extract compared to isolates—whole-plant extract CBS is more natural and less process than the isolates. If one is looking for a more natural, non-processed, effective, whole-plant extract CBD is the only way to go. As an physician, and medical director, at a natural, holistic, and integrative cancer clinic, I prefer and primarily like to use whole-plant extract to take advantage of this entourage effect.

Summary:

The entourage effect, a concept originating from Christian Smuts, refers to the cooperative effects between various constituents of a plant. The therapeutic effect of the other constituents contributes to the overall therapeutic effects of the main phytocannabinoids. This effect is particularly beneficial in the clinical use of cannabis and also applies to CBD.

Holism, a holistic theory, posits that the whole transcends the individual parts, supporting and pointing to the whole. In the discussion of whole-plant extract versus isolates for CBD, the whole of the constituents of the plant provide the entourage benefit. In contrast, the isolate is consistent with the reductionist approach isolated from the benefit of the whole provided with the constituents.

When it comes to pain management and a wide range of other symptoms and diseases, whole-plant extract has consistently shown superior performance over isolates. While the effects of CBD in pain management may vary depending on the type of pain, the holistic impact of whole-plant CBD extract, coupled with its natural and less processed nature, makes it a more potent and effective option.

An Integrative Oncology experience with PICOIV:

My experience with intravenous cannabidiol (CBD) has been excellent. I have been using intravenous CBD for over four months now. I am the medical director at an Integrative Oncology Center in Scottsdale, AZ. Over 80% of the patients that I supervise as medical director have stage IV cancer, and a significant majority of those patients are recurrent and deal with substantial treatment resistance. As a result, these patients also typically present with significant comorbidities, i.e., brain metastasis, pleural effusions, pulmonary emboli and deep venous thrombosis, ascites, renal insufficiency, liver insufficiency, significant pain, and cachexia. This is in addition to the often coexisting diseases of hypertension, diabetes, obesity… Even in patients with substantial liver metastasis and liver dysfunction, the high hepatic metabolism of CBD has proven to be well tolerated.

The patients receiving intravenous cannabidiol from PICOIV have tolerated the intravenous cannabidiol with relative ease and little sequelae. The only significant side effects I have encountered in my patient population have included two patients with an undiagnosed port infection at the time of the intravenous CBD infusion. The patients in question experienced Jarisch-Herxheimer reactions due to CBD's anti-bacterial (bactericidal) activity against gram-positive and some gram-negative bacteria [clxx] [clxxi]. These Jarisch-Herxheimer reactions were easily resolved with intravenous fluids and cessation of the intravenous CBD. Following the reactions, blood cultures from both the port and periphery confirmed bacteremia in one (port and periphery) and port infection in the other (port only). The patients fully recovered; no further medical interventions were required for those who experienced the Jarisch-Herxheimer reactions. Both patients tested negative following antibiotic therapy. Interestingly, the patient with the port infection developed a secondary port infection that was unmasked by intravenous vitamin C in a similar Jarisch-Herxheimer reaction as that with the intravenous CBD.

Beyond these two patients, the use of CBD stacking before low-dose metronomic chemotherapy (LDMC) proved to precipitate milder but similar Jarisch-Herxheimer reactions. These symptoms were mild enough that LDMC therapy following intravenous CBD was able to proceed in all cases except with the patient with two patients previously highlighted. The separation of intravenous CBD and LDMC on distinct, separate days has eliminated these reactions among our patients. The scientific literature provides very little guidance on the possible mechanisms here. The membrane lipoprotein contribution to the Jarisch-Herxhemier reaction provides a likely evidence-based connection to the cytotoxic impact of LDMC. Pathogen-associated molecular patterns (PAMPs) and damaged-associated molecular patterns (DAMPs) and their interaction with pattern recognition receptors (PRRs) provide the most likely potential hypothesis.

Summary:

I have accumulated significant experience as a medical director at an Integrative Oncology Center using intravenous cannabidiol (CBD) for over five months. Over 80% of the patients treated with intravenous CBD have stage IV cancer, often with recurrent and significant treatment resistance. These patients frequently have comorbidities like brain metastasis, pleural effusions, pulmonary emboli, deep venous thrombosis, ascites, renal insufficiency, liver insufficiency, significant pain, and cachexia. Cannabidiol's high hepatic metabolism has proven well tolerated, even in patients with substantial liver metastasis and liver dysfunction. The only significant side effects encountered were two patients with undiagnosed port infections, which were resolved with intravenous fluids and cessation of the CBD therapy. However, intravenous CBD unmasked the unidentified infections, which begs additional questions about CBD's antibacterial, antiviral, anti-fungal, and anti-parasitic effects. Cannabidiol stacking before low-dose metronomic chemotherapy (LDMC) also precipitated milder but similar suspected Jarisch-Herxheimer reactions.

Toxin burden:

A Jarisch-Herxheimer reaction is a response typical of an immune reaction to a toxic burden, whether acute or chronic. Toxins and toxicants are words often used interchangeably to account for such a toxic burden discussion. Toxins and toxicants in the context of a toxic burden, however, not the same. Toxins are something the body produces. The body is constantly bombarded to Toxicants. Toxins are from within (endogenous), and toxicants are from outside (exogenous). According to Merriam-Webster, Toxins are “a poisonous substance that is a specific product of the metabolic

activities of a living organism and is usually very unstable, notably toxic...". Hormone metabolites can be the perfect example of an endogenous toxin. The estrone metabolite, 4-OH estrone, damages DNA, has a high affinity and binds tightly to estrogen receptors, and increases cancer risk; yet, the body can produce these estrogen metabolites. A simple look at estrogen receptor status or estradiol (most biologically active estrogen) levels constitutes tunnel vision and will miss other endogenous toxins, such as estrogen metabolites.

Other Endotoxins, such as Lipopolysaccharide (LPS), are produced from bacteria in the gut and is also another example of an endogenous toxin that can contribute to the carcinogenic process, increase cancer recurrence, and metastatic risk. Lipopolysaccharide is an endotoxin produced from gram-negative bacteria. An increase in systemic LPS is often the result of an imbalanced gut microbiome, commonly referred to as dysbiosis [clxxii] [clxxiii]. Dysbiosis and systemic LPS production does not confine its effects locally to the gut, but can effect metabolism systemically. This process is called metabolic endotoxemia.

What is metabolic endotoxemia?

According to a 2016 article published in the journal Biochimie, metabolic endotoxemia is "low-grade elevation in plasma LPS…that is associated with a heightened pro-inflammatory and oxidant environment often observed in obesity" [clxxiv]. In short, metabolic endotoxemia is the disruption of normal systemic metabolic function through low-grade systemic inflammation from systemic endogenous toxins (endotoxins) produced primarily from the gut.

The primary endotoxin in question here in metabolic endotoxemia is lipopolysaccharide (LPS). In metabolic endotoxemia, the primary LPS source are gram negative bacteria from the gastrointestinal tract—the gut. These are not exogenous toxins, but endogenously produced toxins. But from where? How? It is our lifestyle primarily, which drives the production and dissemination of these endogenous LPS toxins.

You may have heard of the concept of "leaky gut". Though leaky gut is not a ICD10 recognized diagnosis, it is a real process. A leaky gut allows the movement of the endotoxin, LPS, from the gastrointestinal tract, through the gut lining (called tight junctions), into systemic circulation to elicit systemic inflammatory signaling through Toll-like 4 receptors (TLR4). The TLR4 is a transmembrane protein that is member of the broader toll-like receptor family, which belongs to the pattern recognition receptor (PRR) family. Pattern Recognition Receptors induce the innate immune response through recognition of Pathological Antimicrobial Peptides, or PAMPs and lead to the activation

of downstream signaling pathways and the expression of diverse arrays of pro-inflammatory marker gene products that are required for host defense against invading pathogens. The end result of the LPS—TLR4 interaction is chronic, systemic, low-grade inflammation through NF-κB transcription signaling.

Research points to a direct link between LPS and the up-regulation of Toll-Like Receptor 4 (TLR-4) on cancer cells [clxxv]. To expand on the implications here, it is an increase in TLR-4 receptors that is one of the mechanisms by which full-dose chemotherapy contributes chemoresistance and metastasis [clxxvi]. You did read that right. Chemotherapy, just like radiation and surgery, can cause metastasis of the very cancer it is intended to treat.

A Jarisch-Herxheimer reaction is often a catch-basin collection for unexplained immune reactions to intravenous therapies. A Jarisch-Herxheimer reaction is a similar acute reaction which can be found in the more chronic inflammatory reactions, such as in metabolic endotoxemia via the LPS-TLR4-NF-κB inflammatory signaling. This catch-basin is often a means to explain off the need to understand or evaluate the underlying mechanisms. It need not be explained off or away; it merely needs to be understood.

In contrast to the chronic, lower grade inflammation associated with metabolic endotoxemia, a more acute version can be found in what is called a cytokine storm.

What is a cytokine storm and why is it relevant here in the discussion of intravenous CBD and cancer?

According to the National Cancer Institute, cytokine storm is “A severe immune reaction in which the body releases too many cytokines into the blood too quickly.” A better working definition is a triggered immune system response that has gone wrong that promotes overwhelming inflammation and creates cataclysmic, collateral damage to affect different organs in the body. In the case of COVID19–the lungs.

Over the short life-span of this topic, many different titles have come to identify the same process. These different names include:

- Cytokine storm
- Cytokine burst
- Inflammatory burst
- Inflammatory storm
- Immune storm
- Cytokine releasing syndrome (CRS)

- Hypercytokinesis

Many different names for the same underlying process. Names, titles, and categorization are one of the things that conventional medicine does very well. But, does name-calling, titles, and groupings every help provide a solution? Or worse, does it help one critically think?

Why is the cytokine Storm important?

The most often used term for this inflammatory burst is cytokine storm. I believe cytokine storm is the most consistent description of the underlying process and should be the term applied to this inflammatory process. It is a massive surge of inflammatory signaling—a storm of inflammatory cytokines. This acute response is more characteristic of that found in a confined Jarisch-Herxheimer reaction.

The immune system communication dysfunction found in a cytokine storm involves both cytokines and chemokines. Think of cytokines as the communication signals of the immune system. Think of them as a language for communication. Just as communication can be positive and negative, cytokines can produce both a pro-inflammatory signal and an anti-inflammatory signal. Cytokines are meant to be more a local communication and not that of systemic communication. In many ways, cytokines are very similar to hormones in their signaling, but more on a local, what is called the paracrine, effect. Some of the pro-inflammatory cytokines [clxxvii] [clxxviii] [clxxix] [clxxx] implicated in a cytokine storm include:

- increased TNF-alpha
- increased IL-1alpha
- increased IL-1beta
- increased IL-6
- increased IL-8
- increased IFN-alpha
- Increased IFN-beta
- Increased IFN-gamma

Chemokines are also involved in a cytokine storm. Chemokines are a type of cytokine signals mobilization and activation of the different parts of the immune system. Chemokines are like the traffic cop directing traffic at an intersection. Some of the pro-inflammatory chemokines [clxxxi] [clxxxii] [clxxxiii] implicated in a cytokine storm include:

- increased CXCL8

- increased CCL2
- increased CCL11
- increased MCP1

In essence, with the increase in the pro-inflammatory signaling of cytokines and chemokines, the immune system is yelling at the top of its voice without any counter signals to quiet down. If anybody has a house full of kids as I do, the chaos of that experience is understandable. However, the immune system does have the capacity to turn down this excessive, pro-inflammatory signaling with the likes of the suppressing cytokines IL-10, TGF-beta, Th2, and what are called T regulator cells. In a cytokine storm, these signals prove too little and too late to contain the massive immune dysfunction to provide any benefit against the storm.

The typical dosing of the intravenous CBD in my Integrative Oncology center has included 12.5 mg up to 75 mg one to two times weekly. These doses and dosing frequency have proven to be well tolerated. In addition, adjunctive therapies with melatonin, high-dose intravenous vitamin C, and mistletoe on the same day have proven to be well tolerated. Numerous other intravenous Integrative Oncology therapies have proven to provide no combination sequelae.

The intravenous CBD has shown benefit in the coexisting symptoms and conditions of anxiety, depression, seizures, and pain. Of separate distinction, intravenous CBD has proven to lower blood pressure and blood glucose. Several patients have required either the lowering of hypertension medication or the outright elimination of medication. No hypotensive or hypoglycemic episodes have occurred. However, blood pressure and capillary glucose are evaluated before initiating intravenous CBD to consider the exclusion of those with pre-procedure hypotension or hypoglycemia. In my four-month experience with intravenous CBD in cancer patients, only one patient required a scheduled intravenous CBD appointment cancelation for dehydration-related hypotension. Of the many therapies that we use in a complicated patient population over the course of 6-10 weeks, intravenous CBD is one of the more well-tolerated treatments.

Summary:

Intravenous CBD is associated with limited adverse effects in a patient population with significant medical sequelae. A Jarisch-Herxheimer reaction is an immune response to toxic burdens, such as hormone metabolites and endotoxins like lipopolysaccharide (LPS), which can increase cancer risk and recurrence. Metabolic endotoxemia, a low-grade elevation in plasma LPS, is associated with

a heightened pro-inflammatory environment and can lead to chemoresistance and metastasis in chemotherapy. Cytokine storms are severe immune reactions where the body releases too many cytokines, promoting inflammation and collateral damage. The immune system can turn down excessive pro-inflammatory signaling by suppressing cytokines. Still, these signals are insufficient to contain the massive immune dysfunction in metabolic endotoxemia, cytokine storm, and cancer. Intravenous CBD-induced changes in cytokines and chemokines can help manage inflammation and aid in immunomodulation to help with cancer treatment.

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