

## Topical CBD for the Management of Acute and Chronic Pain: A Brief Review and Report of an Open-Label Dose-Ranging Clinical Trial

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### Keywords

Cannabis, Types of Pain, Analgesic effects, Phytocannabinoids.

### Introduction

Interest in cannabidiol as an active pharmacologic agent has increased dramatically over the past decade as medical cannabis has become widely available in the United States, Canada and most of the EU. Legal access to cannabis products exists in 33 states and the District of Columbia at the present time. Despite the ready availability of these products, high quality safety and efficacy data are largely lacking.

Widespread concern over the opioid epidemic, which accounted for 72,000 deaths in the U.S. in 2018, has further stimulated interest in cannabinoid therapy as a possible alternative to opioid use. There are, however, significant medical concerns over the safety of cannabinoids and of appropriate delivery systems.

Data from states with easy access to cannabis products has raised concerns about an increased incidence of motor vehicle accidents, work place accidents, adverse psychiatric effects and paranoia, effects on adolescent development and as a possible gateway to substance abuse illnesses [1].

Currently, multiple delivery systems are widely available including smoked and vaped products, oral administration, mucosal absorption, topical delivery systems, and suppositories. Each delivery system poses challenges with pharmacokinetics and pharmacodynamics, both of which are poorly understood. Cannabis products are extracted from the Cannabis Sativa L plant. Over 500 molecules have been extracted from this plant. The two most abundant are delta 9 tetrahydrocannabinol (THC) and cannabidiol (CBD). THC has psychoactive properties and CBD

has no centrally active effects [2,3].

The potential for phytocannabinoids (plant derived cannabinoids) to have a pharmacologic beneficial effect is dependent on the existence of an endocannabinoid system. Endocannabinoid systems exist in all mammalian species and help govern normal homeostasis. Anandamide and 2-AG are the human endocannabinoids. They bind to CB 1 and CB 2 receptors that are widely distributed in human tissues. Anandamide and 2-AG have wide ranging effects on mediating immune responsiveness, pain perception, inflammation, GI motility and mood regulation [4].

Phytocannabinoids are known to have greater affinity for CB 1 and CB 2 receptors than have the endocannabinoids [5]. CBD has greater affinity for CB 2 receptors than does THC. CBD reversibly binds in a steric fashion to these receptors and activates G protein coupled receptors abundant on macrophage and dendritic cells blocking calcium channel activation. These properties make CBD an attractive potential pharmacologic agent, especially since CBD has no direct psychoactive effects [6]. CBD does, however, potentiate 5 HT 4 receptors and can bind with mu and delta opioid receptors, possibly accounting for its anxiolytic and some of its analgesic effects.

Given the above, applying CBD as an agent for pain relief is a rational consideration [7]. Understanding the mechanism of action of CBD also makes the consideration of CBD as a topical attractive. Topical, nonsystemic treatment avoids first pass hepatic metabolism, unknowns about its PD and PK and limits safety concerns to local skin toxicity issues [8].

Consequently, we designed and completed a dose ranging open label study of a novel topical CBD cream in a unique formulation.

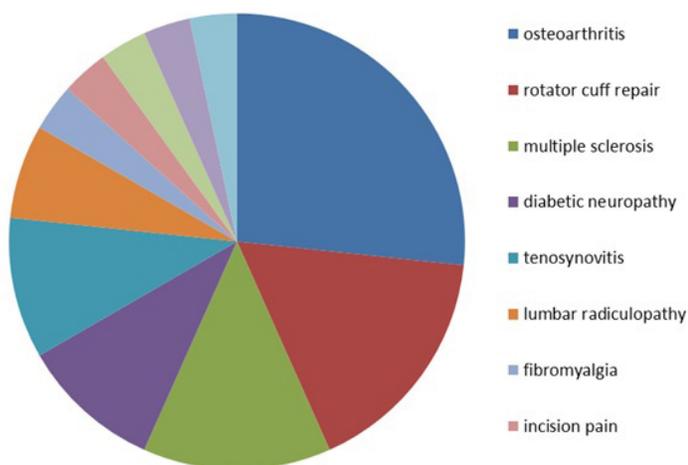
## Methods

After completing stability and uniformity testing for a patented delivery system to deliver multiple concentrations of cannabidiol (CBD), low (2.5%), medium (5%) and high (7.5%) concentrations of the study item was administered to a population of 22 patients with varying etiologies of acute and chronic pain for thirty 14-day treatment periods. Good Pharma initiated the clinical trial in Q1, 2018 as “Topical Application of CBD Suspended in a Proprietary Cream for Use with Various Types of Pain”.

A traditional model for study design was used with a primary endpoint of pain relief (efficacy) and a secondary endpoint of safety (AE and SAE). Pain was assessed using a VAS scale from 1-10 with 1 as no pain and 10 as most severe. Safety was measured by considering if any AE or SAEs were reported as well as any skin reactions.

Patients suffering from Osteoarthritis, Rotator Cuff Repair Surgery, Multiple Sclerosis, Diabetic Neuropathy, Tenosynovitis, Lumbar Radiculopathy, Fibromyalgia and Incision Pain were selected after speaking with their physician about alternative pain treatments to opioids. Patients were instructed to liberally apply the topical cream directly to the area of pain.

### Indications



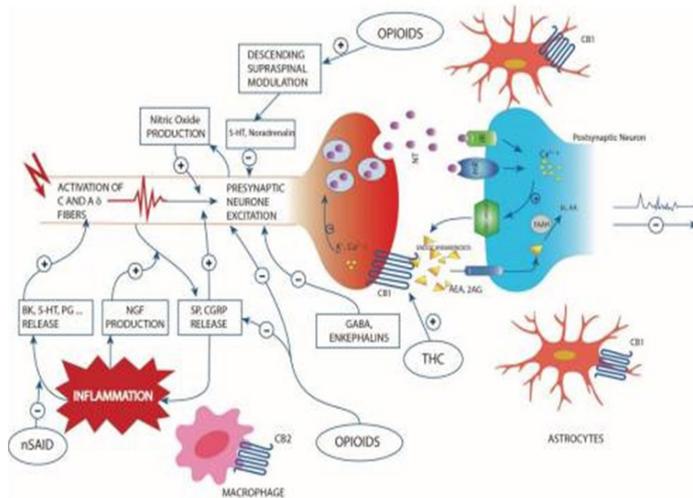
While clinical trials are one way to determine results across various pain symptoms a consideration of the mode of action needs to be understood in scientific terms.

As stated in the Introduction, Phytocannabinoids are known to have greater affinity for CB 1 and CB 2 receptors than have the endocannabinoids. CBD has greater affinity for CB 2 receptors than does THC. CBD reversibly binds in a steric fashion to these receptors and activates G protein coupled receptors abundant on macrophage and dendritic cells blocking calcium channel activation. These properties make CBD an attractive potential pharmacologic agent.

CBD is a serotonin 5 HT-1A receptor agonist and modulates mu and delta receptors. M.O.A. of endogenous cannabinoids and

phytocannabinoids are complex and detailed molecular pathways [4]. CBD does, however, potentiate 5 HT 4 receptors and can bind with mu and delta opioid receptors, possibly accounting for its anxiolytic and some of its analgesic effects [5].

A diagram of a synapse showing the G Protein receptors on the presynaptic neuron, dendrites and macrophage cells presented at the NY Pain Society Conference helps explain the process.

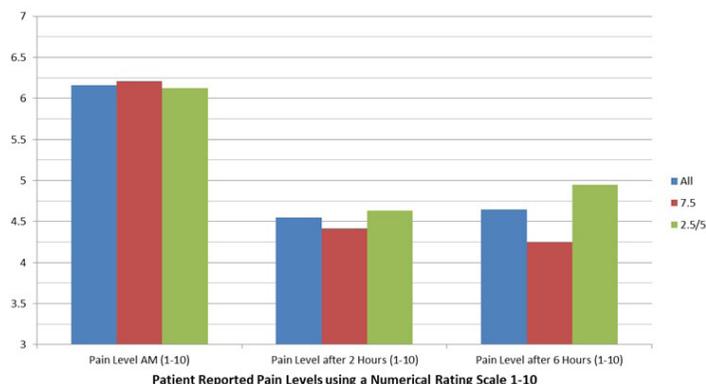


## Results

Following the application of Good Pharmaceuticals topical CBD cream using 2.5% and 5% concentration with 22 subjects over 14 days and using a VAS Pain Scale of 1-10, a consistent and noticeable decrease of 32% reduction of pain was reported.

Pain levels were measured pre and post application with post application measurements at +1 hour and + 6 hours showing a reduction from a Median score of 7 at time of application to 5 post application. Measurements were also taken following a second and third application in the afternoon and evening with Median scores dropping from 7 to 5. Patients applied the cream up to 4 times per day.

Standard deviation also changed from 2.0 to 2.7 indicating positive results with patients experiencing mild to moderate pain. Changes in pain levels with subjects experiencing severe pain were less noticeable however the introduction of a 7.5% concentration demonstrated a decrease in severe pain of 35%.



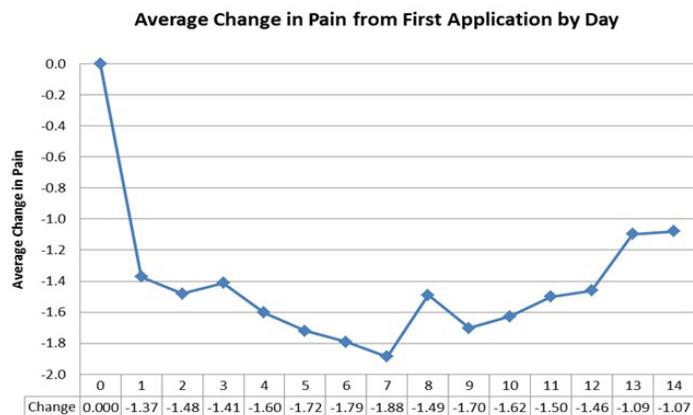
During the entire study there were no AE or SAEs reported.

## Conclusion

Given these results, Good Pharma focused all future efforts into determining the highest concentration (7.5%) of CBD deliverable while considering safety, efficacy and the cost/value proposition. Patient feedback has confirmed that the higher the concentration the more efficacious the results.

This is the first open label dose ranging trial of the efficacy and safety of a topical CBD product to be reported. Previous reports of efficacy and safety have been purely anecdotal. CBD is recognized as having GRAS status and is widely available commercially around the world. CBD products are the source of enormous interest in the medical and lay communities.

These data demonstrate the efficacy and safety of topical CBD for the treatment of acute and chronic pain of various etiologies, with particular efficacy of the 7.5% (2200 mg/oz) in terms of duration of pain relief, fast acting and non-systemic when applied as a topical [9].



These data also have particular significance in the context of the massive public health crisis by the opioid epidemic in the US.

Randomized controlled trials are necessary to further elucidate the role of topical CBD in the treatment of acute and chronic pain. The sponsor of this trial is planning to perform such a study (“A Parallel, Double Blind, Multicenter, Randomized, Placebo Controlled, Single Attack Study to Evaluate the Efficacy and Safety of Cannabidiol Cream in the Acute Treatment of Pain”)

with a primary objective of demonstrating the efficacy and safety of this 7.5% CBD preparation for the relief of acute and chronic pain and their ancillary associated symptoms versus placebo and its safety.

## Disclosures

The authors of this paper have a financial interest in the sponsor (Good Pharmaceutical Development Company, LLC, Lynbrook, NY). Data collection and statistical analysis was performed by TAB Clinical (Cary, NC). Mr Ferguson is the CEO of TAB Clinical. The propriety study item is marketed as PainTx by Good Pharmaceutical Development Co, LLC. Dr Good is the CEO of Good Pharmaceutical Development Co. LLC and Senior Research Fellow at Thomas Jefferson University in Philadelphia, PA.

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