CBD & Women's Health

A White Paper by Radicle Science & Wholistic Research and Education Foundation

Abstract

The Rae Wellness study on CBD and Women's Health is one of the first and largest randomized, controlled human studies to evaluate the effects of commercially available non-prescription CBD products. To our knowledge, it represents the first CBD study to focus exclusively on women's health and wellness.

In Q4 2020, 1350 females aged 24-44 from across the US were recruited to participate in a 60-day in-home use test (IHUT) comparing the effects of 8 different CBD products by Rae Wellness across well-being, mental health, physical health, digestive health, sleep quality, and sexual satisfaction. Of the 1350 participants, 1218 completed the 60-day IHUT. Radicle Science and Wholistic Research & Education Foundation conducted an IRB-reviewed[1] study consisting of data verification followed by secondary analysis of the Rae Wellness IHUT dataset. The primary objectives of the study were to assess (1) whether women randomized to any CBD product during the 60 day study experienced improvements across a range of health domains compared to the no-treatment control group, and (2) whether there were any differences in performance between the different CBD products.

Per the findings of our Phase I analysis, we observed that consumption of any CBD product led to significant reductions in anxiety over the course of 60 days, when compared to the control group with no consumption. These reductions mainly occurred within the first 30 days of use, and these lower anxiety levels were sustained for at least another 30 days of use. Similar reductions were observed for all products and across different levels of CBD dosage (15-30 mg), THC concentration (0% or up to 0.3%) and mode of delivery (oil or capsule).

In our Phase II analysis, which will be released in Fall of 2021, we will evaluate the impact of CBD consumption on other physical and mental health domains such as well-being, pain, digestive health, sleep quality, and sexual satisfaction. Furthermore, we will assess specific factors that may impact or be predictive of the effects of CBD on various health domains. These factors include any demographic variations, such as ethnicity, as well as behavioral factors, such as variations in time of day the products were consumed.

[1] Reviewed by IRB and certified exempt.

Background

Cannabis sativa[2] has been used for traditional and medicinal purposes for millennia. The plant contains hundreds of chemical substances, including a set of compounds called cannabinoids. More than 100 cannabis-derived cannabinoids have been identified, most abundant of which are cannabidiol (CBD) and tetrahydrocannabinol (THC).

Pre-clinical and clinical research suggests that CBD has considerable therapeutic potential. The compound possesses anti-anxiety, antioxidant, anti-inflammatory, immunomodulatory, and antipsychotic properties, among others, signaling that it could be an effective treatment for a variety of indications.[i] And unlike THC, the main psychoactive ingredient in cannabis, CBD, is non-intoxicating, meaning that it neither causes addiction nor induces serious side effects.[ii]

Following the federal legalization of CBD derived from hemp (i.e. cannabis containing < 0.3% of THC) with the passage of the Agriculture Improvement Act of 2018, consumption of CBD has rapidly expanded within the US. Products containing CBD in various forms, from vapors to edibles, can be purchased online, over the counter, and at cannabis dispensaries across the nation. Approximately one third of Americans state they have tried CBD,[iii] and 14% of Americans say they currently use it.[iv]

Many new CBD users are women seeking relief for anxiety.[v] The prevalence of anxiety disorders among women is nearly twice the rate of men in the US,[vi] and manufacturers of CBD products have claimed that their product can alleviate anxiety, alongside a myriad of other mental and physical concerns. And while anecdotal reports have suggested that certain CBD products can ease anxiety symptoms, virtually no human studies have sought to evaluate these effects.

Of note, most research on the neurological effects of CBD have been conducted among men.[vii] Indeed, women have historically been—and continue to be—underrepresented as subjects in medical research.[viii] As a result, it is unclear how various therapeutic agents, including CBD, may impact women's health and if sex may influence their effects.

[2] Cannabis is the official name of the species of plant that has low-THC varieties (i.e. "hemp") and high-THC varieties (i.e. "marijuana"). To avoid confusion as well as the racist past of the term "marijuana", it is common practice to use "hemp" or "CBD" in reference to the low-THC variety legal at the federal level and "cannabis" or "THC" to refer to the high-THC variety legal only in certain states. We abide by this practice in all of our communication.

The primary aims of our analyses were to assess:

1. Whether women who consumed any CBD products over the course of 60 days experienced a greater reduction in their anxiety symptoms relative to those who consumed no CBD product, and
2. Whether certain CBD products performed better than others.

Study Design

Between October 1-7, 2020, 1350 females aged 24-44 from across the US were recruited to participate in a 60-day in-home use test (IHUT) comparing the perceived health benefits of 8 different CBD products by Rae Wellness. The inclusion criteria for the IHUT were: women; between the ages of 24-44; reported symptoms associated with at least 4 out of 6 health issues (stress; anxiety; pain; sleep issues; digestive issues; low libido). Individuals were excluded if they were: pregnant or breastfeeding. Qualified individuals were advised to consult with their healthcare provider before participating if they had a diagnosed medical condition, were on any prescription medication or supplements, or had any upcoming medical procedures planned.[3]

Of the 1350 participants who enrolled, 1218 completed the 60-day IHUT. The vast majority (97%) reported experiencing at least one symptom of anxiety (see Table 1 for more detailed demographic information on the study sample). Radicle Science and Wholistic Research & Education Foundation conducted an IRB-approved study consisting of data verification, followed by secondary analysis of the Rae Wellness IHUT dataset.

The participants were randomized to one of 9 groups in the IHUT: 8 groups received one of 8 different CBD products in the mail, and one group served as the control and did not consume any CBD product.

The CBD products varied by method of delivery (oil or capsule), concentration of THC (up to 0.3% THC or 0% THC), and dosage of CBD (15, 20, 25 and 30 mg; see *Table 2* for a break-down of the formulations for each treatment group).[4]

Participants were asked to use the product once daily every day for 60 consecutive days, and to complete a health questionnaire online on 3 occasions: before initiating the product

[3] The inclusion criteria were: women; between the ages of 24-44; reported symptoms associated with at least 4 out of 6 health issues (stress; anxiety; pain; sleep issues; digestive issues; low libido). Individuals were excluded if they were: pregnant or breastfeeding. Qualified individuals were advised to consult with their healthcare provider before participating if they had a diagnosed medical condition, were on any prescription medication or supplements, or had any upcoming medical procedures planned. 4,489 prospective participants responded to and completed the screening questionnaire. 3,514 of these prospective participants (78.3%) qualified for the study. Of these, 1,350 were randomly selected to participate in the study.

[4] We split CBD treatment dosage into lower dosage (15 mg and 20 mg) and higher dosage (25 mg and 30 mg) for comparison within our figures. We note that this classification should not be interpreted as dose level in comparison to a preferred standard dose, but as dose level relative to other doses in this study.

(baseline), 30 days after initiating the product, and 60 days after initiating the product. Those in the control group were also asked to complete the health questionnaire at each time point but did not receive nor consume any CBD product during the study period.

The health questionnaire included 7 questions which are used to assess anxiety, known as the GAD-7 scale.[ix] Based on their responses to these questions, individuals can receive a score between 0 and 21, with higher scores representing higher levels of anxiety. The health questionnaire also included questions drawn from other validated health indices (including SF-6D General Wellness, PROMIS GPH-4 Physical Health, DSFQ Digestive Health, MOS Sleep Scale, and FSFI Sexual Satisfaction) to explore potential effects of CBD for quality of life, mental health, and physical health.

TABLE 1: Demographic characteristics of participants (N=1218)	
	N (%)
Gender	
Female	1218
Age (years)	
24-34	539 (44.25)
35-44	679 (55.75)
Ethnicity	
White	839 (68.88)

African American	39 (3.20)
Asian	41 (3.37)
Hispanic-Latino	100 (8.21)
Native-American	7 (0.57)
Hawaiian-pacific-islander	3 (0.25)
Multiracial	54 (4.43)
Other	5 (0.41)
Prefer Not to Answer	130 (10.67)
Geography	
Midwest	301 (24.71)
Northeast	289 (23.73)
South	388 (31.86)
West	240 (19.70)
Symptoms (prior to study)	
Sleep Issues	1161 (95.32)
Digestive Issues	977 (80.21)

Stress	1208 (99.18)
Pain	1085 (89.08)
Anxiety	1181 (96.96)
Low Libido	878 (72.09)
CBD Use	
New to CBD	560 (45.98)
CBD user	658 (54.02)
Supplement Use	
Does not Supplements	636 (52.22)
Uses Supplements	582 (47.78)

Table 2: Characteristics of different groups and products

Group	Sample Size	Designation	Form Factor	Extraction Method	Dilution	Formulation	THC Per Serving (%)	Dosage[a]	CBD per Serving

1	139	R-101	Oil	CO2	MCT	Broad	0	Higher	30
2	139	R-102	Oil	CO2	MCT	Broad	0	Lower	20
3	134	R-103	Oil	CO2	MCT	Full	<0.3	Higher	30
4	141	R-104	Oil	CO2	MCT	Full	<0.3	Lower	20
5	133	R-105	Capsule	CO2	Rice Powder, Piperine	Broad	0	Lower	15
6	130	R-106	Capsule	CO2	Rice Powder, Piperine	Broad	0	Higher	25
7	132	R-107	Capsule	CO2	Rice Powder, Piperine	Full	<0.3	Lower	15
8	132	R-108	Capsule	CO2	Rice Powder, Piperine	Full	<0.3	Higher	25
9	138	CONTROL	N/A	N/A	N/A	N/A	N/A	N/A	N/A

[a] We sorted product groups into lower dosage (15 mg and 20 mg) and higher dosage (25 mg and 30 mg) for comparison within our figures. We note that this classification should not be interpreted as dose level in comparison to a preferred standard dose, but as dose level relative to other doses in this study.

Data Analysis

Radicle Science conducted the data analysis using various statistical and machine learning models:

- We calculated the mean change in each participant's GAD-7 anxiety score from baseline to day 60.
- We ran an ANOVA with Tukey-pairwise comparisons to compare the mean change in anxiety scores from baseline to day 60 between the product groups and between each product group and control.
- We ran bivariate and multivariate linear mixed models using data at each time point (baseline, 30 days and 60 days) to assess if (1) being assigned to any product group led to lower anxiety scores over time relative to control, and (2) any of the product groups performed better than the other product groups over time, even after adjustment for potential confounds or imbalances in the data.[5]
- We used clustering and classification models using machine learning principles to further validate the statistical findings, and to partition the general population of participants into segments to better understand the relationships between different groups.

[5] Adjustment here refers to correcting for confounds or imbalances in the data which may lead to spurious results. For instance, we would expect that people with higher baseline scores for anxiety would experience greater improvement, simply because they had more room to improve. Thus, if certain groups *happen* to have higher baseline anxiety (those in the treatment group R102, for example), then the higher levels of improvement we observe in these groups may have more to do with their baseline anxiety than their specific treatment. To disentangle these effects, we adjusted for baseline anxiety in our multivariate linear mixed model.

Results

The analysis results are organized into four categories: (1) Effects of CBD, (2) Formulation, (3) Dosage, and (4) Mode of Delivery.

Effects of CBD

- In our Phase I analysis, we observed that every product group experienced significant[6] reductions in their mean anxiety scores relative to control throughout the study period (*see Figure 1*).
- We did not, however, find evidence of differences in anxiety score reduction *between* any of the product groups. In other words, all the CBD products performed similarly well and significantly better than control (*see Figure 1*).
- The greatest mean change in anxiety score occurred between baseline and day 30 for ALL product groups, and these lower anxiety levels were sustained with continued CBD use up to day 60 (*see Figure 1*).

[6] When we refer to significant results, we mean that the likelihood of falsely rejecting the null hypothesis (in this case, that there are no differences between treatment groups and control) is very small (less than 5%). Put another way, we can be fairly confident that our results are not the result of random variation. See here for more information on determining and interpreting statistical significance.

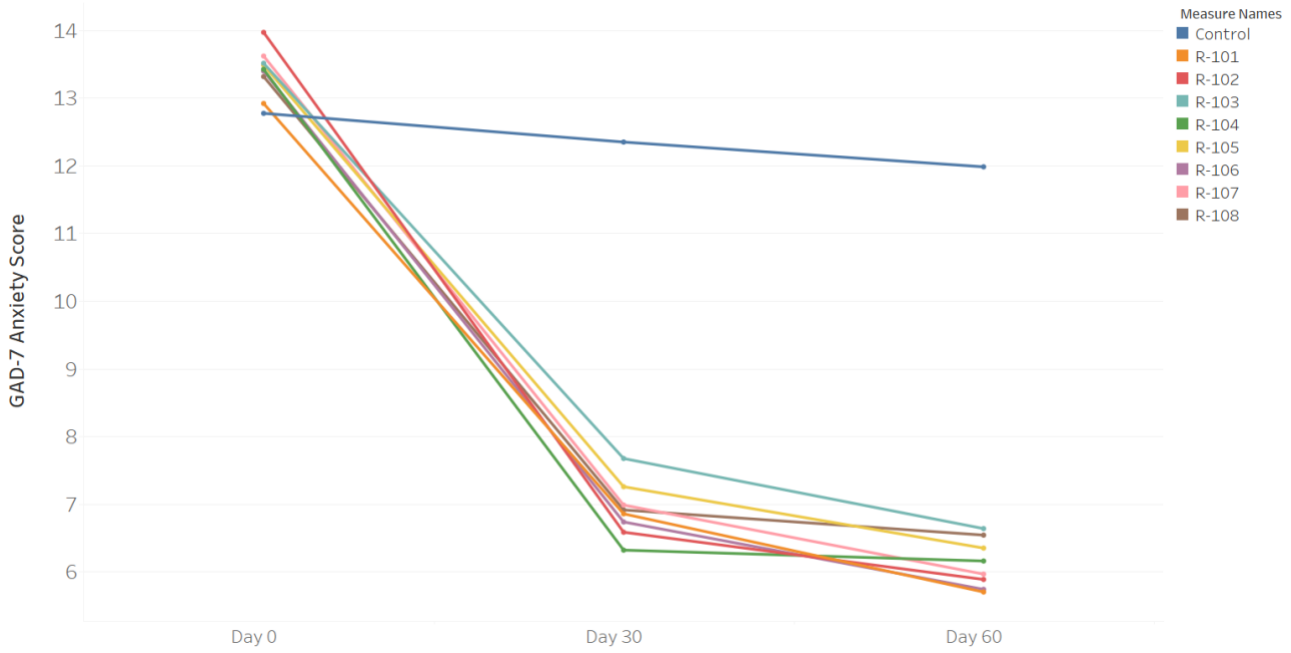

Figure 1: Mean change in anxiety score throughout time by product group

Our results suggest that, for comparable populations using these CBD products, individuals who consume as little as 15 mg of daily CBD could realize substantial reductions in anxiety within 30 days of use and these reductions could be sustained for up to 60 days with continued consumption.

Formulation

- We did not observe significant differences in mean change in anxiety score from baseline to day 60 between similar products containing full-spectrum CBD (up to 0.3% THC) versus broad-spectrum CBD (with 0% THC) (*see Figure 2*).

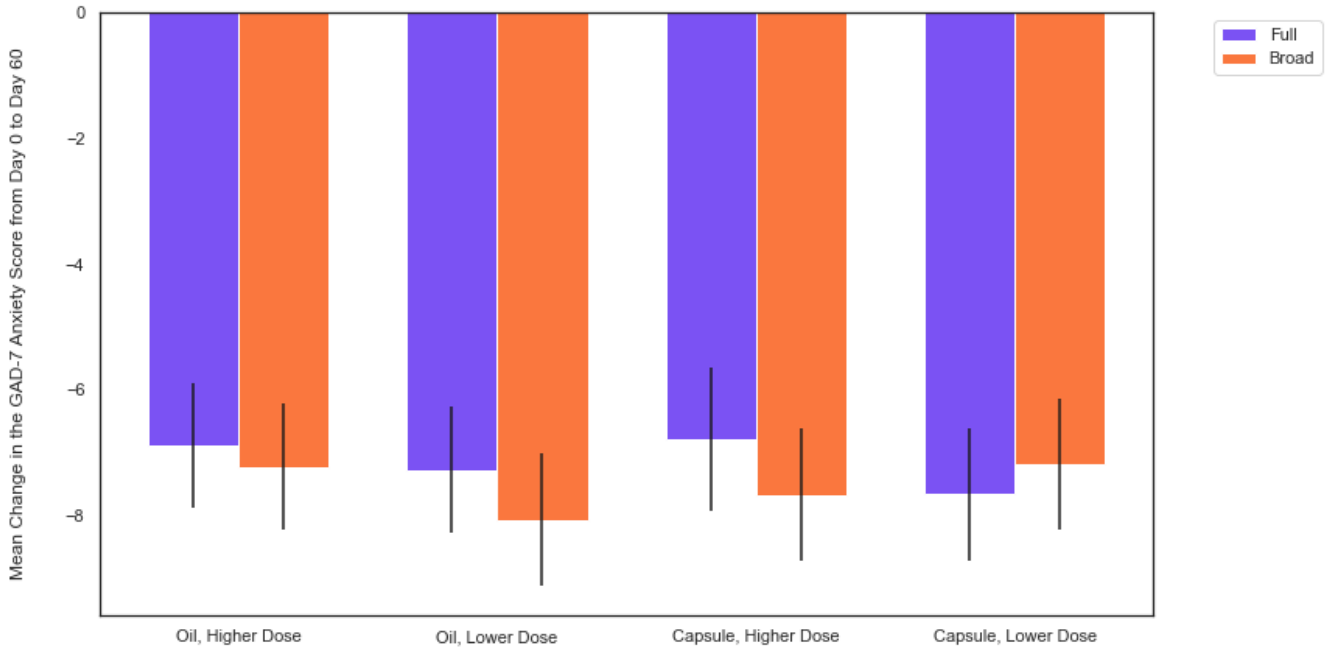

Figure 2: Comparison of mean change in anxiety score by formulation spectrum (full or broad) across products

For the CBD products used by this population, we did not find evidence of the so-called *entourage effect* (i.e., the theory that compounds such as CBD and THC exhibit synergistic effects when taken together), suggesting some full-spectrum (up to 0.3% THC) hemp-derived CBD products may perform similarly to broad-spectrum (0% THC) CBD products for anxiety reduction.

Dosage

- We did not observe significant differences in mean change in anxiety score from baseline to day 60 when comparing similar products with higher versus lower doses of CBD (*see Figure 3*).

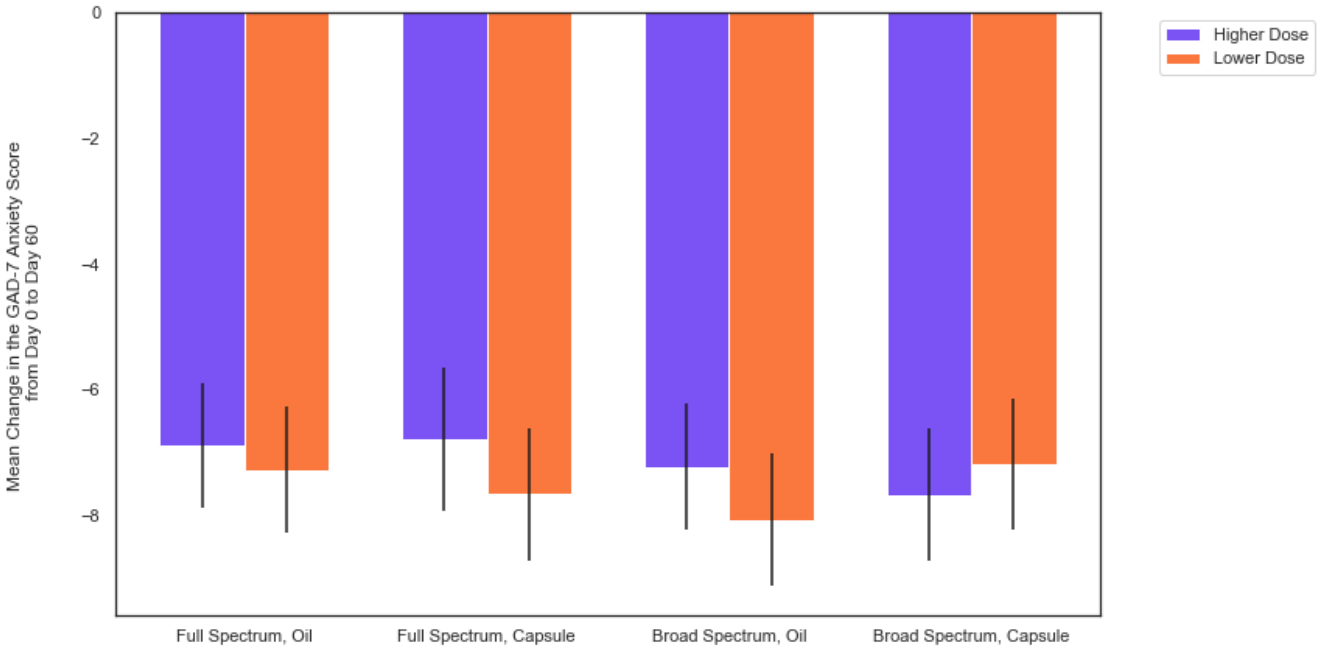

Figure 3: Comparison of mean change in anxiety score by CBD dosage (higher or lower) across products

Our results suggest that, for comparable populations who consume these CBD products, 15-20 mg of CBD may perform similarly to 25-30 mg of CBD for anxiety reduction.

Mode of Delivery

- We did not observe significant differences in mean change in anxiety score from baseline to day 60 between similar formulations and doses that had an oil versus capsule mode of delivery (*see Figure 4*).

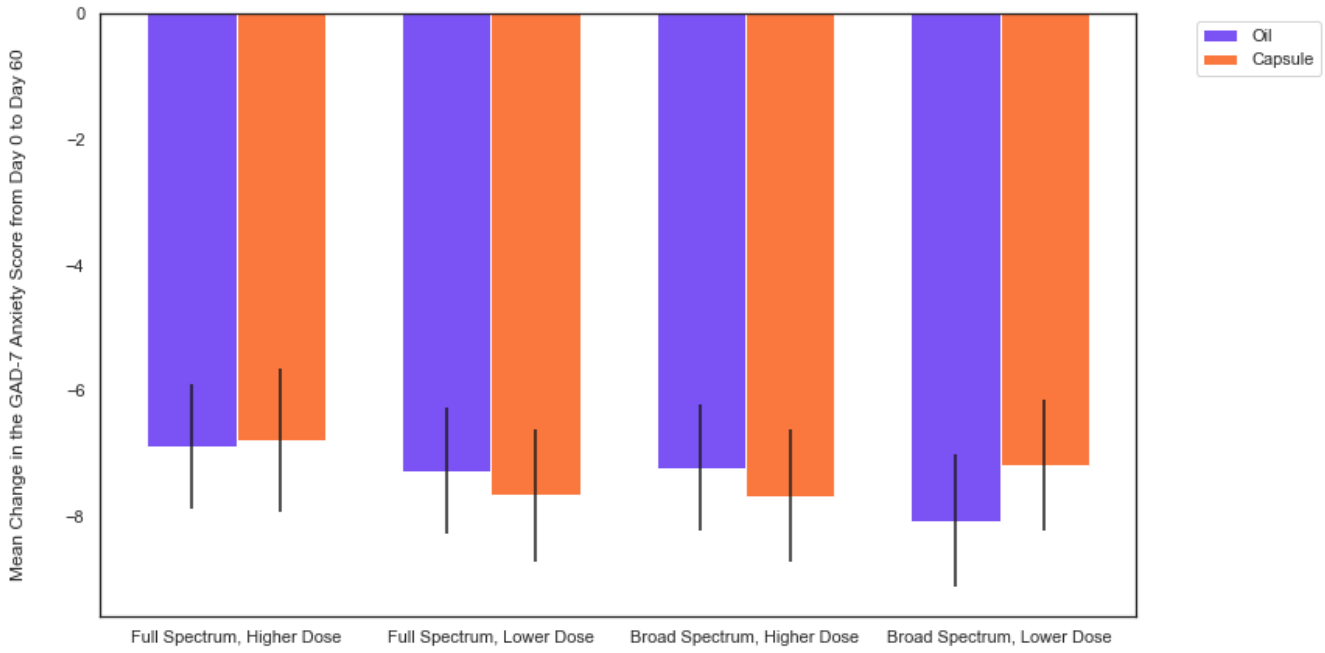

Figure 4: Comparison of mean change in anxiety score by mode of delivery (oil or capsule) across products

Our results suggest that, for comparable populations who consume these CBD products, similar reductions in anxiety could be realized regardless of whether the mode of delivery was oil or capsule.

Main Take-Aways

In this nationwide sample of women, our Phase I analysis indicates that consumption of CBD products led to significant reductions in anxiety over the course of 60 days, when compared to no consumption, with benefits starting at as low as 15 mg of daily CBD consumption. These reductions mainly occurred within the first 30 days of use, and these lower anxiety levels were sustained for at least another 30 days of use. Similar reductions were observed for all products and across different levels of CBD dosage (15-30 mg), THC concentration (0% or up to 0.3%) and mode of delivery (oil or capsule).

The strengths of this dataset include large sample size, randomization, use of validated survey instruments, knowledge of the specific contents of all 8 products, and a control group.

The limitation of this dataset is lack of blinded placebo control. Participants in all 8 product groups knew they were taking CBD. And the control group knew they did not consume any CBD. Without a blinded placebo control group, we cannot say for certain how much of the beneficial effects experienced by the participants in the 8 product groups were due to the placebo effect.

In our Phase II analysis, which will be released in Fall of 2021, we will evaluate the impact of CBD consumption on additional domains of physical and mental health, such as quality of life, pain, digestive health, sleep quality, and sexual satisfaction. Furthermore we will assess specific factors that may impact or be predictive of the effects of CBD on various health domains. These factors include any demographic variations, such as ethnicity, as well as behavioral factors, such as variations in time of day the products were consumed.

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About Radicle Science

Radicle Science is a transformative healthtech B-corp operating at the intersection of big data, digital health, and natural health products to validate natural medicines for the first time in history. Our current focus is helping CBD brands differentiate in a crowded market and gain consumer trust.

Radicle Science disrupts the traditional clinical trial model by combining the reach of a market research company, the medical rigor of a research university, and the agility of a tech company. Our Radicle Vision is a future where affordable natural medicines are trusted by patients, recommended by physicians, reimbursed by insurance, and used widely as pharmaceutical drugs.

We challenge the status quo by democratizing clinical trials and unleashing new knowledge. Our virtual, direct-to-consumer, crowdsourced clinical trials (run on our proprietary data analytics platform) offer the first-ever path to natural medicine validation at scale. We generate some of history's first objective health outcome data on various natural medicines across diverse populations and conditions at a fraction of the time and cost of current methods. This will ultimately provide new business and health insights for stakeholders ranging from consumers and physicians to retailers and brands to insurers and regulators.

Our founding community partners include Wholistic Research and Education Foundation, Clean Label Project, Opennest Labs, and Trailblazers. Our studies are designed in collaboration with faculty from UCLA, UC Irvine, Scripps Research, Scripps Health, University of Washington, and Johns Hopkins University.

Our company and team—from our founders and executive team to our advisors and researchers—includes some of the foremost experts and trailblazers on clinical trials, cannabis and cannabinoids, big data and analytics, public health, pharma, FDA, insurance, media, and entertainment, and computational drug discovery. We came together to uncover the objective health outcome data behind natural medicines to unlock broad access to safe and effective treatments for all.

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About Wholistic Research and Education Foundation

Wholistic Research and Education Foundation, is a public non-profit (501c3) dedicated to cannabis & CBD research, education and advocacy. Promoting a multi-disciplinary approach, Wholistic research initiatives explore underlying mechanisms of action that may explain how various cannabinoids deliver their diverse health benefits and their personalized effects. We are involved in numerous groundbreaking CBD and cannabis human clinical trials, real-world data (RWD) collection surveys and educational programs in partnership with several notable institutions, including UC San Diego, University of Utah, UC Irvine, the Autism Society and the Trailblazers community.

- The UC San Diego research project, "Investigating Cannabinoids in Autism Spectrum Disorders", explores whether CBD therapies can reduce behavioral abnormalities in children with Autism, and if so, how. It is truly a first of its kind, multi-disciplinary study that spans clinical, scientific, advanced mathematical, and genetic techniques, across the same cohort of patients, offering the first comprehensive and systematic exploration on CBD efficacy for Autism. The $4.7 million grant for this study represents the largest known private gift to date for medicinal cannabis research in the United States.
- The University of Utah investigation, "Brain Effects of Cannabinoids", uses advanced imaging to visualize personalized effects of CBD and THC on individuals at functional and molecular levels. The objective of the groundbreaking effort is to analyze how the different cannabinoids may result in changes across entire brain networks and neuropsychological functioning, specifically related to attention, memory, processing of novelty and change, as well as stress and pain. The findings of this $740,000 study have the potential to shape the developing field of cannabinoid therapy by understanding the personalized effects of cannabinoids.
- The UC Irvine & UC Institute of Prediction Technology study, "CBD and Cannabis Efficacy for Anxiety and Insomnia", is a first-of-its-kind exploratory survey to assess the potential role of cannabinoids in reducing anxiety insomnia and depression, especially aggravated due to COVID-19. The 7,500 CBD and Cannabis users nationwide who participated in the IRB-approved study make this the largest such study ever conducted. The highly diverse demographics of the study is expected to yield unique Real-World Evidence on the differences in CBD and cannabis use patterns in relation to anxiety levels, prescription medication and supplement usage to assess how each of these factors may impact perceived benefits. Essentially, the experiences of thousands of actual users who participated in this study have the potential to provide much-needed insights on type of formulations, dose, frequency, timing of use, and delivery methods most associated with therapeutic benefit for both CBD and Cannabis, and do so with close attention to any variations for different population groups.

Our Medical Advisory Committee includes world-renowned doctors, scientists, researchers, and policy experts who have been instrumental in our efforts to date. Our collective endeavors are intended not only to fill in the gaps in current research but also to help educate health care professionals and the general public about when and how to recommend CBD. The research-driven data will also enable us to advocate for evidence-based drug policy at the federal level as well as gain support for the establishment of standardized testing and regulation of all cannabis products for public safety.

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