Radicle Aces (Advancing CBD Education & Science): An Open-Label, Multi-Arm, Randomized Controlled Trial To Evaluate The Safety And Real-World Effects Of Different CBD Products

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ABSTRACT

Radicle ACES is the first multi-brand, Institutional Review Board-approved randomized controlled trial to evaluate the effectiveness of commercially available CBD products. We recruited 3000 participants from across the United States who reported symptoms of anxiety, sleep disturbance, or long-term pain, and randomized them to receive a 4-week supply of 1 of 13 different commercially available CBD products, or to receive no product until the end of the study (i.e., waitlist control). Using validated health indices, we then evaluated changes in well-being, anxiety, pain, and sleep quality over the course of 4 weeks. We compared the effects of taking any CBD product relative to waitlist control, as well as the relative effects of CBD dosage and spectrum, across all health outcomes.

ARTICLE

Use of CBD to treat mental and physical health symptoms has increased dramatically in recent decades. Thirty-three percent of Americans report having tried CBD and over 30 million Americans use CBD regularly. CBD users commonly report use to improve pain, anxiety, or sleep. Unfortunately, due in part to nearly a century of illegality, research restrictions, and lack of federal research funding, very few high-quality research trials have investigated the efficacy of CBD for treatment of these symptoms. Radicle ACES (Advancing CBD Education & Science) is the first multi-brand, Institutional Review Board (IRB)-approved randomized controlled trial to evaluate the effectiveness of commercially available CBD. The objective of Radicle ACES is to investigate the real-world effects of different CBD products on well-being, quality of life, anxiety, pain, and sleep, with the hopes of providing data that can empower consumers, healthcare providers, and regulators to make more informed decisions about these products.

In August of 2021, we recruited 3000 individuals from across the United States to participate in a 4-week long trial comparing the perceived health benefits of 13 different commercially available CBD products (for full list see Table 1 below). Participants could be included in the study if they were 21 years old and older, resided in the United States, and experienced symptoms of anxiety, sleep disturbance, or chronic pain. Individuals were excluded if they were pregnant or breastfeeding, currently using CBD, or taking medications with

Arm #	Arm	CBD dosage/serving
1	Waitlist control	N/A
2	Altwell Broad Spectrum Hemp Extract Gummies	25mg CBD/serving
3	Trokie Fast Melt Tablets	15mg CBD/serving
4	Healer Whole Plant Hemp Drops	5 mg CBD per 5 drops/serving size 5-25 drops
5	Puraura Premium Tincture Lemon Flavor	100mg CBD/serving
6	Columbia Care CBD softgels	30mg CBD/serving
7	Lord Jones Full Spectrum Hemp-Derived CBD tincture	20mg CBD/serving
8	MD Farma Clinical CBD softgels	25mg CBD/serving
9	Charlotte's Web Hemp Extract	5mg CBD/serving
10	Prospect Farms Balance tincture	35mg CBD/serving
11	Rae Wellness CBD capsules	20mg CBD/serving
12	Peels CBD Oil tincture	34 mg CBD/serving
13	Versea Broad Spectrum Hemp Enriched Oral Spray	40mg CBD/serving
14	Maven 2500mg Total Hemp Extract Tincture	10 mg hemp extract/serving

Table 1. Radicle ACES study arms

which CBD could interfere. 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.

Participants were randomized at baseline to one of 14 different study arms: 13 represented product conditions, where participants received one of 13 different CBD products at the beginning of the study and were asked to use the product throughout the study period, and 1 represented the waitlist control condition, where individuals received their CBD product after completing the study and were asked to abstain from using CBD products throughout the study period.

Study products took the form of capsules, tablets, tinctures, softgels, gummies, and an oral spray. Suggested usage and dosage of CBD per serving varied by product (see Table 1). To reflect real-world usage, participants were instructed to use the study product based on product label instructions, healthcare provider advice, and personal preference.

Those in the product conditions were asked to complete CBD usage logs several times a week. All participants (in the product arms and the waitlist control arm) were asked to complete weekly health assessments. These health assessments contained questions from validated health indices to assess quality of life, well-being, sleep quality, anxiety, and pain (see list of health conditions and their indices in Table 2 below). Questions evaluating sleep disturbance, anxiety, and pain were asked only among those experiencing these conditions.

Condition	Index
Well-being	World Health Organization (WHO)-5 Well Being Index [2]
Sleep quality	Patient Reported Outcomes Measurement Information System (PROMIS)™ Sleep Short Form (SF)-8B [3]
Anxiety	Generalized Anxiety Disorder (GAD)-7; PROMIS™ Anxiety 4A [4]
Pain	Pain, Enjoyment, and General Activity (PEG) Scale [5]

Table 2. Health assessment indices

Figure 2.

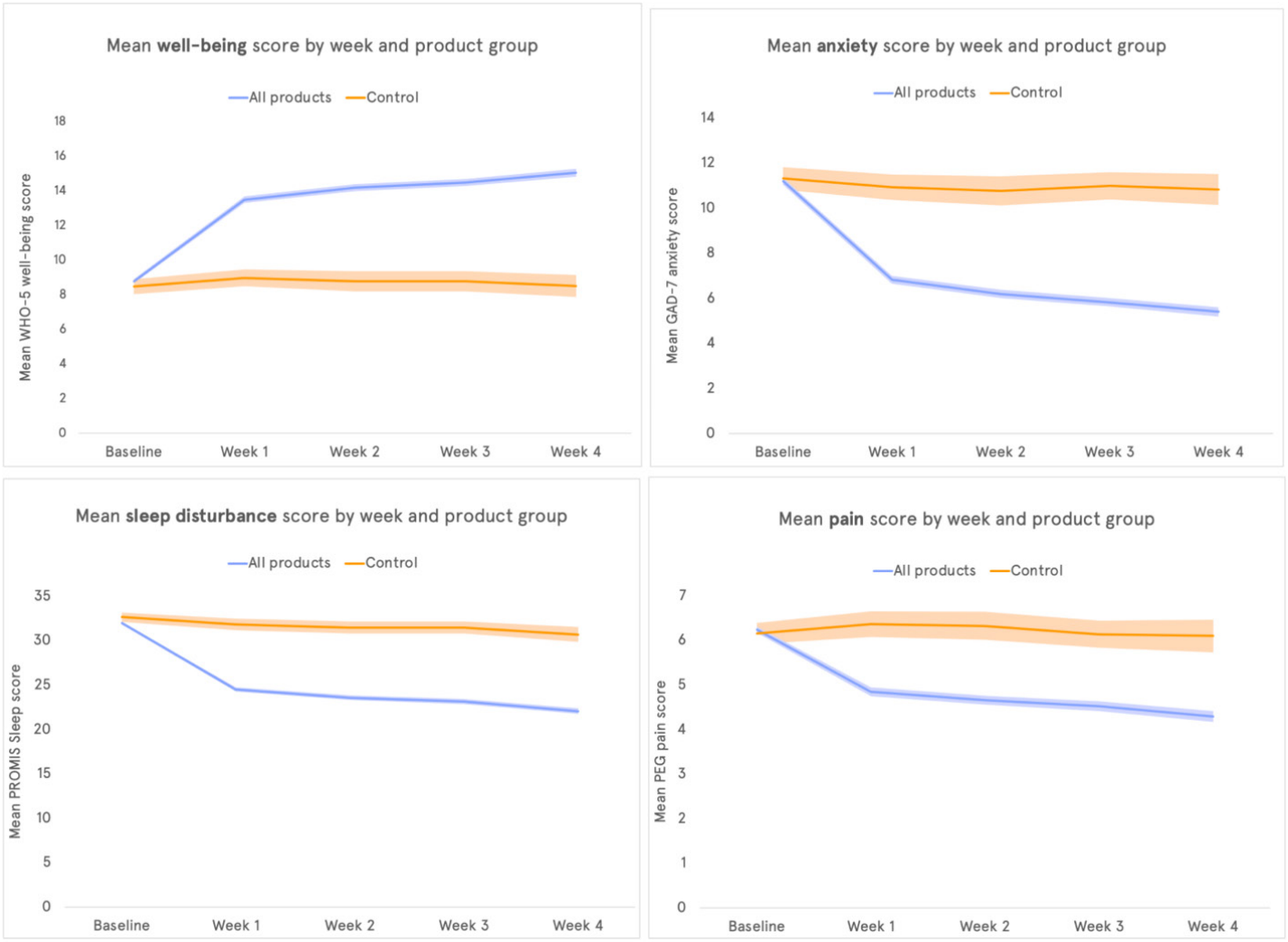

Figure 1. Average health outcome scores through time; all CBD products vs. control

RESULTS

Those taking a product experienced significant improvement across all health outcomes (well-being, quality of life, anxiety, sleep quality, pain), relative to those taking no product (Figure 1).

Across all health outcomes, the largest improvements among participants were observed within the first week of using their product.

Participants often reported that they noticed an effect within one hour (30%) or between 1 and 4 hours (31%) of taking their product.

Participants experienced a 71% improvement in their well-being score, on average, when taking their product throughout the study period.

The majority (63%) of participants with anxiety experienced a clinically meaningful improvement in their anxiety, meaning that they realized a distinct and palpable improvement in the quality of life through improved anxiety symptoms.

The majority (61%) of participants with sleep difficulties experienced a clinically meaningful improvement in their sleep quality, meaning that they realized a distinct and palpable improvement in the quality of life through improved sleep.

About half (47%) of participants with pain experienced a clinically meaningful improvement in

their pain, meaning that they realized a distinct and palpable improvement in the quality of life through improved pain symptoms.

There were not significant differences in effect across study volunteers by sex, age, or prior CBD use.

Product effects generally did not increase with higher doses of CBD per serving. Indeed, products with lower doses of CBD per serving (1 to 15 mg) often outperformed products with higher dosage groups for the improvement of well-being, anxiety, and pain.

About 10% of participants reported any side effects. Nearly all side effects were mild.

METHODS

We examined the effect of any CBD use, relative to waitlist control, on GAD-7, PEG, PROMIS Sleep, and WHO-5 scores using longitudinal mixed effects regression models. The longitudinal models included an unstructured covariance model for the within-subject repeated measures, fixed effects for any CBD use, categorical indicators for time post-baseline (week 1, week 2, week 3, and week 4), and the interaction between any CBD use and time. We further assessed whether sex at birth (female vs. male), age group (21–29, 30–44, 45–59, and 60 and older), and prior CBD use (experienced users, inexperienced users, and familiar users) separately modify the relationship between any CBD use and the outcome of interest using the interaction between any CBD use, time and sex at birth, age group, or prior CBD use.

We used additional mixed effects models with similar longitudinal structure to examine the effects of each product and each product characteristic including CBD form (capsule, oral spray, soft gel, tablet, and tincture), spectrum (broad, full, and isolate) and CBD dose (1 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 34 mg, 35 mg, 40 mg, 50 mg, and 100 mg) on the outcomes of interest, and then performed post-hoc analyses (unadjusted and Bonferroni-adjusted p-values) comparing the effects of each product and each product characteristic to one another.

AUTHOR CONTRIBUTIONS

The authors confirm contribution to the paper as follows: study conception and design: Chen, Pauli, Laird; data collection: Chen, Pauli, Laird; analysis and interpretation of results: Laird; draft manuscript preparation: Saleska, Laird. All authors reviewed the results and approved the final version of the manuscript.

COMPETING INTEREST DECLARATION

The authors declare that they have no known competing financial interests or personal relationships that could have influenced the work reported in this paper.