EDITOR'S CHOICE

A Randomized Controlled Trial of Topical Cannabidiol for the Treatment of Thumb Basal Joint Arthritis

John T. Heineman, MD, MPH,* Grace L. Forster, BS,† Kristen L. Stephens, MD,* Patrick S. Cottler, PhD,* Michael P. Timko, PhD,‡ Brent R. DeGeorge Jr, MD, PhD*§

Purpose Since the passage of the Agricultural Improvement Act of 2018, hand surgeons have increasingly encountered patients seeking counseling on over-the-counter, topical cannabidiol (CBD) for the treatment of pain. To this end, we designed a human clinical trial to investigate the therapeutic potential of CBD for the treatment of pain associated with thumb basal joint arthritis.

Methods Following Food and Drug Administration and institutional approval, a phase 1 skin test was completed with 10 healthy participants monitored for 1 week after twice-daily application of 1 mL of topical CBD (6.2 mg/mL) with shea butter. After no adverse events were identified, we proceeded with a phase 2, double-blinded, randomized controlled trial. Eighteen participants with symptomatic thumb basal joint arthritis were randomized to 2 weeks of twice-daily treatment with CBD (6.2 mg/mL CBD with shea butter) or shea butter alone, followed by a 1-week washout period and then crossover for 2 weeks with the other treatment. Safety data and physical examination measurements were obtained at baseline and after completion of each treatment arm.

Results Cannabidiol treatment resulted in improvements from baseline among patient-reported outcome measures, including Visual Analog Scale pain; Disabilities of the Arm, Shoulder, and Hand; and Single Assessment Numeric Evaluation scores, compared to the control arm during the study period. There were similar physical parameters identified with range of motion, grip, and pinch strength.

Conclusions In this single-center, randomized controlled trial, topical CBD treatment demonstrated significant improvements in thumb basal joint arthritis-related pain and disability without adverse events. *(J Hand Surg Am. 2022;47(7):611–620. Copyright © 2022 by the American Society for Surgery of the Hand. All rights reserved.)*

Type of study/level of evidence Therapeutic II.

Key words Arthritis, cannabidiol, CBD, disability, pain, thumb basal joint.

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*From the *Department of Plastic Surgery, University of Virginia, Charlottesville, VA; †School of Medicine, University of Virginia, Charlottesville, VA; ‡Department of Biology, University of Virginia, Charlottesville, VA; and §Department Orthopaedic Surgery, University of Virginia, Charlottesville, VA.*

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Corresponding author: Brent R. DeGeorge Jr, MD, PhD, Department of Plastic and Orthopaedic Surgery, University of Virginia, Box 800376, 1300 Jefferson Park Ave, Charlottesville, VA 22903; e-mail: brent.degeorge@virginia.edu.

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Given the devastating consequences of the opioid crisis, practitioners caring for patients with chronic pain are searching for more effective and safer alternatives. *Cannabis sativa* is comprised of more than 480 components, with 113 classified as cannabinoids (Table 1), including cannabidiol (CBD).[1] Cannabidiol does not elicit the psychotropic effects associated with delta-9-tetrahydrocannabinol (THC).[2] As a result of the 2018 Agriculture Improvement Act, or Farm Bill, the Drug Enforcement Agency reclassified cannabis with less than 0.3% THC, defined as hemp, from a schedule I to a schedule V substance.[3] Cannabis with greater than 0.3% THC, defined as marijuana, remains a Drug Enforcement Agency schedule I substance but has been legalized by 18 states for recreational use. These rulings resulted in a proliferation of CBD-derived, over-the-counter products in 48 states. The advertised potential benefits of CBD are many, but the primary indication is pain relief.[4–6] To date, the only CBD drug to earn US Food and Drug Administration (FDA) approval is Epidiolex, an oral CBD for the treatment of refractory epilepsy.[7,8] In the endocannabinoid system, CBD has antagonistic effects on cannabinoid receptor 1, cannabinoid receptor 2, and a myriad of G protein–coupled receptors that promote anti-inflammatory pathways and may limit neuropathic pain.[9] Cannabidiol has been also shown to act as a serotonin 5-HT_{1A} receptor agonist and may involve peroxisome proliferator-activated receptor ($PPAR_{\alpha}$ and $PPAR_{\gamma}$) agonism and intracellular calcium release.[10,11] Dunn et al[12] showed that osteoarthritic joint chondrocytes express a number of these CBD receptors.

We have subsequently encountered a burgeoning population of patients with thumb basal joint arthritis-related pain seeking counseling on the evidence for over-the-counter CBD use, but there are limited clinical data available to support its safety and efficacy. In a survey we completed of 103 patients with thumb basal joint arthritis, 69% were interested in trialing oral CBD and 80% were interested in trialing topical CBD for treatment of their arthritis-related pain.[13] Twelve of 25 current oral CBD users and 7 of 21 topical CBD users believed that the products were effective in relieving pain, and consequently worth the financial costs.

Numerous studies have shown the safety and efficacy of topical CBD for the treatment of osteoarthritis in dogs and rats.[14,15] Topical administration has been shown to have increased regional bioavailability and attenuation of inflammation and pain without reported side effects. The dose of maximum absorption and efficacy seen in rats was shown to be 6.2 mg/day (approximately 21 mg/kg/day).[15] To date, no studies have been performed to evaluate the safety and efficacy of topical CBD for the treatment of hand arthritis in human subjects. Therefore, we designed a randomized controlled clinical trial to assess the efficacy of topical CBD versus placebo for the treatment of thumb basal joint arthritis-related pain. We selected Visual Analog Scale (VAS) pain scores as our primary study outcome, with patient-reported outcome measures and physical performance metrics as secondary outcomes. Our null hypothesis was that topical CBD would have no effect on our primary outcome.

MATERIALS AND METHODS

The current study was performed with informed consent and reviewed by the US FDA and the University of Virginia Institutional Review Board. Human subjects in the present clinical trial received treatment in accordance with the ethical principles for medical research involving human subjects.

Cannabidiol crystalline powder, 99.07% pure isolate derived from hemp, was obtained from Eco-X, Inc. The product was rated for personal care product formulations and tested by Desert Valley Testing to obtain a Certificate of Analysis. The CBD was mixed to the final desired concentration with pure US Department of Agriculture–certified organic shea butter (Mary Tylor Naturals).

To produce the treatment cream, 3,100 mg of CBD isolate was dissolved in 50 mL of 100% pure US Department of Agriculture organic shea butter that was liquefied by warming to 45°C. The mixture was vortexed intermittently over 15 minutes to ensure complete dissolution of the CBD isolate, and then further diluted with 450 mL of shea butter to yield a final product with a CBD concentration of 6.2 mg/mL. The control was formulated as above with shea butter but without the added CBD isolate. There were no observed differences in color, consistency, or odor of the treatment and control creams. The treatment and control creams were placed in 1 mL syringes with rubber stoppers and stored at room temperature.

Phase 1 skin test

Following FDA Investigational New Drug and institutional approval, a phase 1 skin test was completed with 10 healthy participants (Fig E1, available online on the *Journal*'s website at www.jhandsurg.org). After obtaining informed consent, demographic, medical, and surgical histories and Columbia Suicide Severity Rating Scale (C-SSRS)

TABLE 1. ***Cannabis sativa*** **is Comprised of More Than 480 Components, With 113 Classified as Cannabinoids***

Class	Number of Variants	Biologic Effects
Cannabinoids		
Delta-9 tetrahydrocannabinol (delta-9 THC)	9	Psychoactive, analgesia, antioxidant, bronchodilatory, muscle relaxant, antipruritic, neuroprotective
Delta-8 tetrahydrocannabinol (delta-8 THC)	2	Psychoactive, anticonvulsant
Cannabigerol (CBG)	6	Nonpsychoactive, antitumor, antimicrobial, antidepressant, analgesic, antihyperalgesic
Cannabichromene (CBC)	5	Nonpsychoactive, analgesic, anti-inflammatory, antimicrobial, antidepressant
Cannabidiol (CBD)	7	Nonpsychoactive, analgesia, antioxidant, anti-inflammatory, antianxiety, anticonvulsant, antimicrobial, antitumor
Cannabinol (CBN)	7	Nonpsychoactive, sedative, antipsoriatic
Cannabinodiol (CBND or CBDL)	2	Nonpsychoactive, anticonvulsant
Cannabicyclol (CBL)	3	Nonpsychoactive, anti-inflammatory, antitumor
Cannabielsoin (CBE)	5	Nonpsychoactive, sedative
Cannabitriol (CBT)	9	Nonpsychoactive
Other miscellaneous types of cannabinoids	11	Nonpsychoactive, as per above
Terpenoids	>200	Nonpsychoactive, analgesic, anti-inflammatory, antianxiety, antidepressant, antitumor effects, sedative, anticonvulsant, antimicrobial, antipruritic

*Adapted from Russo et al.[1]

scores were collected. Vital signs (heart rate and blood pressure) were obtained. Participants then underwent baseline testing to include urine pregnancy (if applicable), complete blood count (white blood cell count, hemoglobin, hematocrit, and platelet count), basic metabolic panel (sodium, potassium, bicarbonate, chloride, glucose, calcium, blood urea nitrogen, and creatinine), and liver function (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, and total bilirubin) tests. Data were deidentified and stored on a secure database.

Participants were provided 1-mL syringes of 6.2 mg/mL CBD with shea butter and instructed to apply the cream to their nondominant thumb basal joint 2 times daily. They were provided a symptom diary for recording skin changes and other noticed adverse events or side effects. Participants were seen 1 week after application for skin surveillance. Vital signs, laboratory tests, and C-SSRS information were collected. Symptom diaries were completed by the participants. A 1-week washout was then allowed, followed by a repeat skin check, vital signs, laboratory tests, C-SSRS scores, and symptom diary evaluation.

Phase 2 randomized controlled trial

The study was registered on ClinicalTrials.gov (NCT0461137). Eighteen healthy subjects with symptomatic thumb basal joint arthritis were recruited from an UVA Hand Surgery Clinic. The inclusion criteria included participants over the age of 18 with a history of symptomatic and radiographically documented thumb basal joint arthritis. The exclusion criteria included thumb basal joint corticosteroid injection within 3 months of study initiation; a history of active pregnancy, nursing, or actively planning a pregnancy; non-English speaking status; blindness; severe cardiac, pulmonary, liver, or renal disease; mental illness; incarcerated or imprisoned status; skin disease or conditions; active

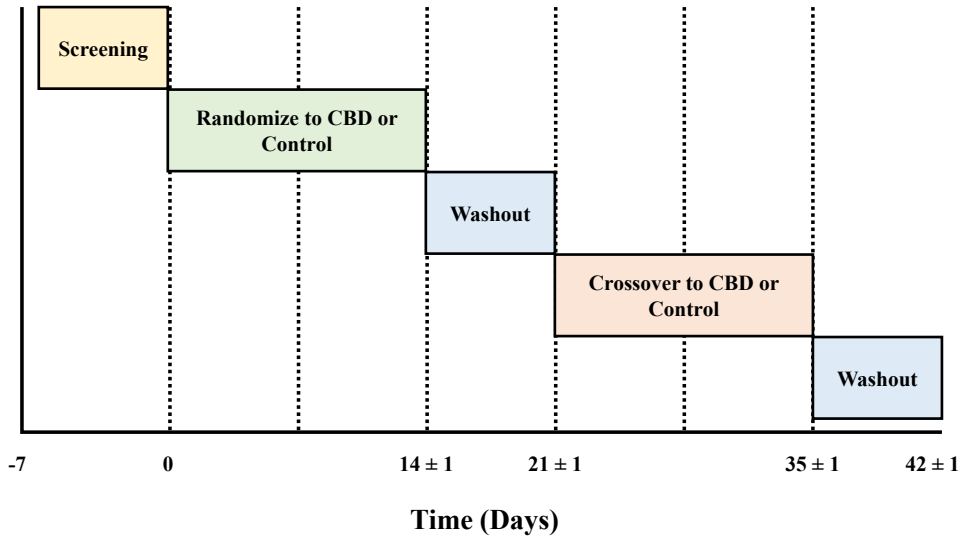

FIGURE 1: Double-blinded randomized controlled trial with crossover schedule.

depression or suicidality; cytochrome P450 substrate medication usage; and/or substance abuse history. Participants were not permitted to receive corticosteroid injections during the study period. Study participants were not permitted to apply topical agents during the study period; however, they were allowed to take acetaminophen or nonsteroidal anti-inflammatory drugs per their usual routine. All participants were evaluated at enrollment by a certified hand therapist and provided with a thumb basal joint orthosis and standardized education on rest, immobilization, edema control, and activity modification for thumb basal joint arthritis.

After obtaining informed consent, demographic, medical and surgical histories, and C-SSRS scores were collected. Vital signs were obtained. Thumb basal joint disease-specific information was collected, including duration of symptoms, laterality of symptoms, and history of prior intra-articular corticosteroid injection(s). Patient-reported outcome measures were obtained for VAS pain; Disabilities of the Arm, Shoulder, and Hand (DASH); Single Assessment Numeric Evaluation (SANE); and Patient-Reported Outcomes Measurement Information upper extremity. X-rays of the thumb basal joint were obtained and Eaton-Littler scores were provided by the evaluating hand surgeon. Physical exam data were gathered, to include grip strength, appositional strength, oppositional strength, thumb metacarpophalangeal (MP) joint passive flexion, thumb MP joint passive extension, and Kapandji score. Participants then underwent baseline laboratory testing, including urine pregnancy (if applicable), complete blood count, basic metabolic panel, and liver function tests. Data were deidentified and stored on a secure database.

Participants were then randomized to start with the treatment (6.2 mg/mL CBD with shea butter) or control (shea butter alone; Fig 1) cream. The study was centrally randomized and double-blinded with allocation concealment. Participants were instructed to apply 1 mL of the cream to their symptomatic thumb basal joint 2 times daily. They were provided a symptom diary for recording skin changes or other noted adverse events or side effects. They were evaluated 2 weeks later for study endpoints, including skin surveillance, vital signs, physical exam, outcome measures, C-SSRS scores, symptom diary evaluation, and laboratory tests. A 1-week washout was allowed, followed by study endpoint recording. Participants were then provided the other cream for crossover. They were again instructed to apply 1 mL of the cream to their symptomatic thumb basal joint 2 times daily, with study endpoints recorded 2 weeks later. After another 1-week washout, final study endpoints were recorded. The study was then completed.

Statistical analysis

Using VAS pain scores as our primary study endpoint and the ability to detect a 1.5 difference between groups, which exceeds the minimal clinically important difference of VAS pain by 50%, with an alpha level of 0.05 and a power of 80%, the study required 16 patients per group. We included 2 additional patients to accommodate possible losses to follow-up. Secondary endpoints included patient-reported outcome measures; hand functional assessments; changes in recorded laboratory parameters;

TABLE 2. Baseline Demographics and Characteristics of Participants in the Randomized Controlled Trial

Participants	n = 18
Mean age, years	64.2 ± 11.0
Gender	
Male	5
Female	13
Race or ethnicity	
White or Caucasian	15
Black or African-American	2
Hispanic or Latinx	1
Comorbidities	
Myocardial infarction	0
Congestive heart failure	1
Peripheral vascular disease	2
Cerebrovascular accident	0
Dementia	0
Chronic obstructive pulmonary disease	0
Connective tissue disease	0
Peptic ulcer disease	0
Liver disease	1
Diabetes mellitus	2
Hemiplegia	0
Chronic kidney disease	1
Solid tumor	1
Leukemia	0
Lymphoma	0
Acquired immunodeficiency syndrome	0
Social history	
Current smoking	3
Former smoking	5
Never smoking	10
History of alcohol consumption	14
History of previous cannabis use	0
Psychiatric history	
Anxiety	2
Depression	4
Mean body mass index, kg/m^2	27.6 ± 4.7
Mean Charlson Comorbidity Index*	2.3 ± 1.1

*Charlson Comorbidity Index scores ranged from 0 to 31. A lower score predicts increased 10-year survival.

TABLE 3. Thumb Basal Joint Arthritis Characteristics of Participants in the Randomized Controlled Trial

Characteristic	Participants
Symptomatic disease laterality	
Right	6
Left	4
Bilateral	8
History of thumb basal joint corticosteroid injection	10
History of thumb basal joint surgery	0
Eaton-Littler x-ray classification	
Stage 1 – Subtle carpometacarpal joint space widening	2
Stage 2 – Joint space narrowing, osteophytes, loose bodies < 2 mm	9
Stage 3 – Advanced joint space narrowing, osteophytes, and loose bodies > 2 mm	4
Stage 4 – Stage 3 findings plus arthritis of the scaphotrapeziotrapezoidal joint	3

changes in vital signs; and adverse event monitoring. *P* values were calculated with Dunnett's multiple comparisons to a single control at a significance of.05. A 1-way analysis of variance was performed to determine whether a significant difference was present, followed by a *post hoc* multiple comparisons test.

RESULTS

After no skin changes, side effects, vital sign, C-SSRS scores, or laboratory abnormalities or changes were noted at baseline, 1 week after CBD application, and 1 week after washout in the phase 1 study, the data were returned to the FDA (Figs E1 and E2, available online on the *Journal*'s website at www.jhandsurg.org). We were then permitted to proceed with the phase 2 randomized controlled trial.

Table 2 reports the baseline demographics and characteristics of 18 participants with symptomatic thumb basal joint arthritis. The mean age was 64.2 years. The mean Charlson Comorbidity Index score was 2.3 (range of 0–31, with lower score predicting increased 10-year survival). There were 10 nonsmokers, 5 former smokers, and 3 current smokers. No subjects reported current cannabis use and none were taking acute or chronic opioid medications. Table 3 describes thumb basal joint arthritis characteristics. Ten participants reported a history of thumb basal joint corticosteroid injection(s), although none within 3 months before study enrollment. The Eaton-Littler x-ray classifications of thumb basilar joint arthritis, from most to least common, were stage 2 (9 participants), stage 3 (4 participants), stage 4 (3 participants), and stage 1 (2 participants).

TABLE 4. Safety Data of Participants in the Randomized Controlled Trial

Safety Measure	Participants
Mean heart rate	
Initial visit	69.3 ± 13.4
Crossover visit	72.6 ± 15.0
Final visit	70.4 ± 10.5
Mean systolic blood pressure	
Initial visit	141.3 ± 23.8
Crossover visit	138.7 ± 19.4
Final visit	137.5 ± 11.2
Mean diastolic blood pressure	
Initial visit	74.3 ± 12.6
Crossover visit	74.2 ± 11.0
Final visit	71.1 ± 11.7
Mean C-SSRS score*	
Initial visit	0
Crossover visit	0
Final visit	0
Total number of reported side effects or adverse events	
Crossover visit	0
Final visit	0
Abnormal laboratory values†	
Initial visit	0
Crossover visit	0
Final visit	0

*C-SSRS scores range from 0 to 25. A higher score indicates an increased risk of suicide.
†Laboratory values included a complete blood count, basic metabolic panel, and liver function tests.

Table 4 reports safety data. There were no adverse events with respect to the mean heart rate, blood pressure, C-SSRS scores, laboratory tests, skin changes, or patient-reported side effects.

Table 5 reports mean patient-reported outcome measures and physical exam parameters. Cannabidiol treatment resulted in significant improvements ($P < .05$) in VAS pain, DASH, and SANE scores from baseline compared to the control arm. The mean VAS pain scores (range of 0 to 10, with a lower score indicating less pain) were 5 at baseline, 5 with the control cream (0% reduction), and 2 with the CBD cream (60% reduction; $P < .05$). The mean DASH scores (range of 0 to 100, with a lower score indicating less disability) were 36 at baseline, 31 with the control cream (14% reduction), and 22 with the CBD cream (39% reduction; $P = .05$). The mean SANE scores (range of 0 to 100, with a higher score indicating greater global well-being) were 67.5 at baseline, 67.5 with the control cream (0% increase), and 78.5 with the CBD cream (16% increase; $P = .05$). Cannabidiol treatment resulted in an improvement in Patient-Reported Outcomes Measurement Information upper extremity scores (range of 0 to 100, with a higher score indicating greater function, calculated as standardized T-scores and calibrated in the general population to a mean of 50 and a standard deviation of 10) from 39 at baseline and 38 with the control cream (3% decrease) to 42 with the CBD cream (8% increase), but the difference was not statistically significant. The improvements in VAS pain scores, DASH scores, and SANE scores all exceeded the reported minimal clinically important differences for these parameters.

There were no identified differences in physical parameters (range of motion, grip, or pinch strength) during the study period. Mean thumb MP joint passive flexion (range 0° to 55°) was 52° at baseline, 49.5° with the control cream, and 50.5° with the CBD cream ($P = .94$). The mean thumb MP joint passive extension (range 0° to −10°) was −1° at baseline, −3° with the control cream, and −7.5° with the CBD cream ($P = .63$). The mean Kapandji score (measure of thumb opposition with range of 0 to 10) was 9 at baseline, 9 with the control cream, and 9 with the CBD cream ($P = .99$). Grip strength was 23.5 kg at baseline, 23 kg with the control cream, and 24 kg with the CBD cream ($P = .90$). Opposition strength was 4 kg at baseline, 4 kg with the control cream, and 4 kg with the CBD cream ($P = .80$). Apposition strength was 6 kg at baseline, 6.5 kg with the control cream, and 6.5 kg with the CBD cream ($P = .55$).

DISCUSSION

Cannabis has been used anecdotally for the treatment of disease for thousands of years. However, the recent isolation and characterization of the pharmacologic targets of hemp-based, nonpsychoactive cannabinoids, combined with changes in legislation regarding cannabinoid prohibition, has led to heightened physician and public interest in their therapeutic potential. Cannabidiol has subsequently been marketed for the treatment of a myriad of diseases, and the CBD market is projected to exponentially increase to $1.3 billion by 2022.[5] Given that there is no medical-grade topical CBD currently available for prescription or insurance coverage, patients continue to rely on over-the-counter products with concentrations as high as 400 mg/mL, far

TABLE 5. Outcome Measurements of Participants in the Randomized Controlled Trial*

Measurement	Baseline	Control	CBD
Mean patient-reported survey scores			
VAS pain	5 ± 0.5	5 ± 0.4	2 ± 0.3†
DASH	36 ± 4.2	31 ± 3.4	22 ± 3.3†
SANE	67.5 ± 5.7	67.5 ± 5.2	78.5 ± 4.6†
PROMIS upper extremity	39 ± 1.7	38 ± 1.5	42 ± 1.8
Mean physical exam measurements			
Thumb MP joint passive flexion	52° ± 6.6°	49.5° ± 5.7°	50.5° ± 5.2°
Thumb MP joint passive extension	−1° ± 6.0°	−3° ± 4.2°	−7.5° ± 3.9°
Kapandji score	9 ± 0.3	9 ± 0.4	9 ± 0.2
Grip strength, kg	23.5 ± 2.8	23 ± 2.8	24 ± 2.3
Opposition strength, kg	4 ± 0.6	4 ± 0.5	4 ± 0.6
Apposition strength, kg	6 ± 0.7	6.5 ± 0.7	6.5 ± 0.6

*VAS pain scores ranged from 0 to 10, where a lower score indicates less pain. DASH scores ranged from 0 to 100, where a lower score indicates less disability. SANE scores ranged from 0 to 100, where a higher score indicates greater global well-being. PROMIS upper extremity scores ranged from 0 to 100, where a higher score indicates greater function. Thumb MP joint passive flexion ranged from 0° to 55°. Thumb MP joint passive extension ranged from 0° to −10°. Kapandji scores ranged from 0 to 10, where a lower score indicates less motion. *P* values were calculated with Dunnett's multiple comparisons to a single control at a significance of.05. A 1-way analysis of variance was performed to determine whether a significant difference was present, followed by a post hoc multiple comparisons test. PROMIS, Patient-Reported Outcomes Measurement Information System.
†$P < .05$ versus baseline

exceeding our concentration of 6.2 mg/mL, which was based on the maximum effective dose in a rat model and the highest concentration allowed for our study by the FDA. There remain no known clinical safety and efficacy data for over-the-counter, topical CBD products, which are being sold for 5 to 20 cents per 1 mg of CBD.

Despite the wide public consumption of CBD-based products, the evidence of efficacy for pain or inflammation reduction in human clinical trials also remains sparse. We have demonstrated early short-term evidence that twice-daily topical CBD application results in a significant improvement in patient-reported pain and patient-reported outcome measures, including VAS pain, DASH, and SANE scores, without altering patient physical parameters, including grip strength, pinch strength, or thumb range of motion.

Placing these results in context is challenging due to the paucity of available animal or human subject data on cannabinoids for pain relief (Table 6). Oral administration of CBD has been more commonly evaluated for pain relief.[6] Malfait et al[16] studied the effects of oral CBD in a mouse model of arthritis. Cannabidiol treatment showed a dose-dependent reduction of synovial cell tumor necrosis factor α expression suggestive of decreased inflammation. Similarly, Costa et al[17] reported a dose-dependent effect reduction of tissue cyclooxygenase activity and plasma levels of prostaglandin E2, oxygen-derived free radicals, and nitric oxide. Oral CBD treatment for osteoarthritis in dogs is associated with a significant decrease in pain and an increase in activity.[14]

Blake et al[18] documented the safety and efficacy of a mouth spray, composed of a ratio of 2.7-mg THC to 2.5-mg CBD, for rheumatoid arthritis-related pain in the United Kingdom. However, this drug is currently unavailable in the United States. The only human clinical study identified for oral CBD treatment of pain in the United States was a prospective analysis of 131 patients recruited from a pain management center taking daily opioids for chronic pain for over 1 year.[19] Subjects were given 8 weeks of oral CBD that included a mixture of other minor cannabinoids and terpenes. Fifty-three percent of CBD-treated patients self-reported reduced or eliminated opiate use. Cannabidiol-treated patients demonstrated significant improvements in postintervention Pain Disability Index; Pittsburgh Sleep Quality Index; Pain Intensity and Interference; and Patient Health Questionnaire scores, and 94% reported a quality of life improvement.

The topical, or transdermal, route investigated in the present study offers a potential advantage in providing direct delivery of CBD to an arthritic joint or musculoskeletal area. It avoids first-pass metabolism, with a potential improvement in drug bioavailability and steady-state pharmacokinetics.[10]

TABLE 6. CBD Animal Studies and Human Clinical Trials

Citation	Study Type	CBD Dosing	CBD Delivery Method	Title
Animal studies				
Malfait et al[16]	Prospective cohort	25 mg/kg QD	Oral	The nonpsychoactive cannabis constituent cannabidiol is an oral antiarthritic therapeutic in murine collagen-induced arthritis
Costa et al[17]	Prospective cohort	5−40 mg/kg QD	Oral	Oral anti-inflammatory activity of cannabidiol, a nonpsychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw
Gamble et al[14]	RCT	2−8 mg/kg QD	Oral	Pharmacokinetics, safety, and clinical efficacy of cannabidiol treatment in osteoarthritic dogs
Hammell et al[15]	Prospective cohort	0.6−62.3 mg QD	Topical	Transdermal cannabidiol reduces inflammation and pain-related behaviors in a rat model of arthritis
Philpott et al[20]	Prospective cohort	0.1−0.3 mg QD	Topical	Attenuation of early phase inflammation by cannabidiol prevents pain and nerve damage in rat osteoarthritis
Human clinical trials				
Blake et al[18]	Clinical Trial	2.5 mg CBD + 2.7 mg THC QD	Oral Spray	Preliminary assessment of the efficacy, tolerability, and safety of a cannabis-based medicine (Sativex) in the treatment of pain caused by rheumatoid arthritis
Capano et al[19]	Prospective cohort	15 mg QD	Oral	Evaluation of the effects of CBD hemp extract on opioid use and quality of life indicators in patients with chronic pain: a prospective cohort study
Xu et al[22]	RCT	250 mg QID	Topical	The effectiveness of topical cannabidiol oil in symptomatic relief of peripheral lower extremities
Nitecka-Buchta et al[21]	RCT	67 mg BID	Topical	Myorelaxant effect of transdermal cannabidiol application in patients with TMD: a randomized, double-blind trial

BID, 2 times a day; QD, once a day; QID, 4 times a day; RCT, randomized controlled trial; TMD, Temporomandibular disorders.

Hammell et al[15] tested topical CBD in a rat arthritic knee model and observed a significant decrease in arthritic pain. Anti-inflammatory effects were shown by reduced mouse monoclonal CD11b antibody (OX42) and tumor necrosis factor α expression on histochemical analysis of the spinal cord, as well as reduced synovial membrane thickness. Philpott et al[20] reported a dose-dependent reduction in mouse joint inflammation and joint neuropathic pain with topical CBD treatment.

In human clinical trials, Nitecka-Buchta et al[21] performed a double-blind, randomized controlled trial of topical CBD for 60 patients with myofascial pain. Topical application of 67 mg of CBD—including other minor cannabinoids—was applied to masseter muscles twice-daily for 14 days. The VAS pain scores were reduced from 5.6 to 1.7 (70.2% reduction) in the treatment group, versus 5.1 to 4.6 (9.8% reduction) in the control group. Xu et al[22] performed a randomized controlled trial with cross-over for topical CBD treatment of 29 patients with symptomatic lower extremity neuropathy. Topical application of 250 mg of pure CBD was applied up to 4 times daily for 4 weeks. They reported reductions in

Neuropathic Pain Scale scores for intense (5.11 to 4.02, respectively) and sharp (4.01 to 3.09, respectively) pain between treatment and control arms.

In the present study, although topical CBD treatment demonstrated improvements in patient-reported outcome measures, improvements in physical performance parameters were not identified. Most of these range of motion and pinch strength values were essentially identical, so even if the sample were large enough to show that these small differences were statistically significant, it likely would not be meaningful given that the values may remain within the measurement error themselves. It is unclear whether physical functioning would improve with either a longer duration of treatment, higher doses of treatment, or alternative delivery routes. We also do not know whether topical CBD is more or less efficacious than topical diclofenac cream or gel, and a comparison study is warranted in the future.

In addition to the paucity of clinical trials evaluating the efficacy and health outcomes of medical cannabis use, the majority of the available literature has focused on CBD and THC in combination with other cannabinoids. However, few studies have tested pure isolates of CBD or other minor cannabinoids, including cannabichomene, cannabigerol, and cannabinol, as well as other plant-derived phytochemicals (eg, terpenoid and flavonoid compounds), as it is unknown which compound has the greatest analgesic and anti-inflammatory properties.[1] In addition, the synergy of these compounds, or "entourage effect," has been hypothesized to carry greater potential than the pure isolates themselves.[19]

A synergistic effect may also be true of combining topical CBD treatment with evaluation by a certified hand therapist; use of a thumb basal joint orthosis; standardized education on rest, immobilization, edema control, and activity modification orthosis fabrication; and oral nonsteroidal anti-inflammatory drugs and/or acetaminophen as needed, as these cointerventions for all participants in our study are potential confounding variables given that all these individual interventions have been shown to be effective treatments for the condition of basilar thumb arthritis-related pain. However, these nonoperative treatments for symptomatic thumb basal joint arthritis are considered the standard of care, and they were not withheld from our patients.

Further limitations of the present study include the small sample size and the short duration of treatment. The dose utilized in the present study was the maximum dose permitted for investigation by the FDA; however, it remains possible that higher doses may result in more substantial effects. The effect of tolerance with topical CBD is also unclear in the literature and is not addressed in the short duration of treatment in our study. An additional limitation of the study is a relatively homogenous patient sample recruited from an academic teaching hospital hand clinic. The patients who chose to enroll may have a bias to expect a positive effect with CBD and/or may have previously self-medicated with over-the-counter, topical CBD. It is unclear whether the same results would be seen in a more diverse patient population with or without higher Charleston Comorbidity Index scores. Additionally, some patients in our study may have had a history of thumb basal joint corticosteroid injection that could skew baseline scores; however, no injections were given within 3 months of study enrollment.

In this single-center, randomized controlled trial, twice-daily topical CBD application resulted in improvements in thumb basal joint arthritis-related pain and disability without adverse events. Larger, multicenter clinical trials are warranted to further investigate the safety, therapeutic potential, and dose-response of CBD for musculoskeletal pain.

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