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ORIGINAL ARTICLE

Tetrahydrocannabinol and Cannabidiol in Tourette Syndrome

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Abstract

BACKGROUND Tourette syndrome is characterized by chronic motor and vocal tics. There is preliminary evidence of benefit from cannabis products containing Δ^9-tetrahydrocannabinol (THC) and that coadministration of cannabidiol (CBD) improves the side-effect profile and safety.

METHODS In this double-blind, crossover trial, participants with severe Tourette syndrome were randomly assigned to a 6-week treatment period with escalating doses of an oral oil containing 5 mg/ml of THC and 5 mg/ml of CBD, followed by a 6-week course of placebo, or vice versa, separated by a 4-week washout period. The primary outcome was the total tic score on the Yale Global Tic Severity Scale (YGTSS; range, 0 to 50 [higher scores indicate greater severity of symptoms]). Secondary outcomes included video-based assessment of tics, global impairment, anxiety, depression, and obsessive-compulsive symptoms. Outcomes were correlated with plasma levels of cannabinoid metabolites. A computerized cognitive battery was administered at the beginning and the end of each treatment period.

RESULTS Overall, 22 participants (eight female participants) were enrolled. Reduction in total tic score (at week 6 relative to baseline) as measured by the YGTSS was 8.9 (±7.6) in the active group and 2.5 (±8.5) in the placebo group. In a linear mixed-effects model, there was a significant interaction of treatment (active/placebo) and visit number on tic score (coefficient = −2.28; 95% confidence interval, −3.96 to −0.60; P=0.008), indicating a greater decrease (improvement) in tics under active treatment. There was a correlation between plasma 11-carboxy-tetrahydrocannabinol levels and the primary outcome, which was attenuated after exclusion of an outlier. The most common adverse effect in the placebo period was headache (n=7); in the active treatment period, it was cognitive difficulties, including slowed mentation, memory lapses, and poor concentration (n=8).

CONCLUSIONS In severe Tourette syndrome, treatment with THC and CBD reduced tics and may reduce impairment due to tics, anxiety, and obsessive-compulsive disorder;

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although in some participants this was associated with slowed mentation, memory lapses, and poor concentration. (Funded by the Wesley Medical Research Institute, Brisbane, and the Lambert Initiative for Cannabinoid Therapeutics, a philanthropically-funded research organization at the University of Sydney, Australia; Australian and New Zealand Clinical Trials Registry number, ACTRN12618000545268.)

Introduction

Tourette syndrome is a neurodevelopmental disorder characterized by the presence of chronic motor and vocal tics (sudden, repetitive movements or sounds that are difficult to suppress and can only be delayed with difficulty). Onset is generally in childhood or adolescence with an estimated prevalence of 1%.[1] Tics may persist into adulthood[2]; individuals with persisting tics experience adversity, including discrimination and unemployment,[3] as well as reduced quality of life.[4]

Symptomatic management of tics includes drugs (e.g., α_2-adrenergic agonists or dopamine antagonists) and behavioral therapy. However, a proportion of people with Tourette syndrome continue to have tics due to inadequate response or adverse effects to extant therapies. Effective therapies with acceptable side-effect profiles for tics are therefore needed.

Cannabinoids are a biologically plausible therapy for tics because of their capacity to modulate the "endocannabinoid" system. The predominant endocannabinoid receptor in the central nervous system, the cannabinoid CB_1 receptor (CB_1R), is densely concentrated in the basal ganglia, believed to be the pathobiological nexus of Tourette syndrome.[5] Notably, stimulation of CB_1R can provide retrograde inhibition of excitatory synaptic activity.[6] Uncontrolled observational studies have reported an association with cannabis use and reduction in tic severity,[7,8] although, until recently, only two small, randomized, placebo-controlled trials have been conducted at a single center.[9,10] Both involved ingestion of capsules containing Δ^9-tetrahydrocannabinol (THC), resulting in modest improvements in the frequency and severity of tics. In a recent placebo-controlled study,[11] a single vaporized dose of THC was associated with a nonsignificant trend toward a reduction in a video-based rating of tic severity; this study was underpowered, however, because it included only nine participants.

Cannabidiol (CBD) is a nonintoxicating cannabinoid that can sometimes reduce the unpleasant anxiogenic and psychotomimetic effects of THC when coadministered, thereby improving the safety and side-effect profile of cannabinoid treatment.[12-14] A single case study reported the successful use of nabiximols, an oromucosal spray containing a 1:1 ratio of THC:CBD, in Tourette syndrome at a daily dose of 10 mg of CBD and THC; an 85% reduction in tics over the course of 4 weeks was observed.[15] To date, however, we are aware of no published placebo-controlled clinical trial that has explored the therapeutic utility of repeated dosing with oral THC and CBD, in combination, in Tourette syndrome. Therefore, we conducted an investigator-initiated, 16-week, randomized, double-blind, placebo-controlled crossover trial to examine the effects of a commercially available oral solution containing THC and CBD in a 1:1 ratio on tic severity in persons with Tourette syndrome.

Methods

STUDY DESIGN

This randomized, double-blind, crossover trial was conducted at a single site, Wesley Medical Research Institute (WMR), in Brisbane, Queensland, Australia. It comprised two 6-week treatment periods (4 weeks of dose escalation followed by 2 weeks of stable dosing) separated by a 4-week washout period. All procedures were conducted in accordance with the trial protocol approved by the Human Research Ethics Committee of Uniting Care Health (provided with the full text of this article at evidence.nejm.org). Written, informed consent was obtained from all participants by the principal investigator (P.E.M.). The trial was prospectively registered with the Australian and New Zealand Clinical Trials Registry (ACTRN12618000545268).

PARTICIPANTS

Participants 18 to 70 years of age were recruited from movement disorder clinics in South East Queensland and nationwide through the Tourette Syndrome Association of Australia. Potential participants were prescreened by using an Internet-based registration page and a telephone interview before being invited to WMR for a full assessment. Participants had a confirmed diagnosis of Tourette syndrome made by a neurologist or psychiatrist, and medical

correspondence was reviewed by the principal investigator. All participants had at least a moderate-to-severe burden of tics with a total tic score of ≥20 of 50 on the Yale Global Tic Severity Scale (YGTSS; range, 0 to 50 [higher scores indicate greater severity of symptoms]). Antidepressant and benzodiazepine medications were continued during the study if prescribed for depression and/or anxiety but participants taking other tic-suppressing medication (e.g., tetrabenazine, antipsychotic agents, clonidine) were excluded. Patients using cannabis-based products outside of the trial were also excluded; this was assessed with a urinary drug screen at the start of each treatment period (any current cannabis users agreed to cease use at least 1 month before trial entry). Other exclusion criteria included a major neurologic or psychiatric comorbidity (confirmed via general practitioner records), a recent history of active suicidality, and pregnancy. Participants agreed not to drive a motor vehicle or operate heavy machinery during the trial, consistent with Australian State and Territory laws.

INVESTIGATIONAL PRODUCT

The investigational product was an oral formulation containing 5 mg/ml of THC and 5 mg/ml of CBD (both plant-derived) in medium-chain triglyceride (MCT) oil. The product was manufactured in a Good Manufacturing Practice facility (Linnea SA, Riazzino, Switzerland) and batch-tested to ensure compliance with the Australian Therapeutic Goods (Standard for Medicinal Cannabis) order TGO 93. An inert hemp seed oil (tested to confirm the absence of cannabinoids) was used as placebo. The products were identical in their visual appearance and smell. As a result of trial delays related to the coronavirus disease 2019 (Covid-19) pandemic, expired active stock was replaced with a dose equivalent 1:1 THC:CBD oral formulation in MCT oil purchased from Little Green Pharma Ltd. (Perth, Western Australia, Australia). Neither manufacturer was involved in the conception and design of the study or the interpretation of the results.

The active oil or placebo was administered in doses starting at 1 ml per day (i.e., 5 mg of THC and 5 mg of CBD) and increased by 1 ml every 7 days up to a maximum of 4 ml daily (i.e., 20 mg of THC and 20 mg of CBD). Participants were instructed to take each milliliter as a separate divided dose (i.e., 4 ml daily equated to four 1-ml doses spread over the day). Participants were permitted to remain on a lower dose if escalation was associated with intolerable adverse effects. This was a decision made by the principal investigator, and the maximum dose reached was recorded. Each participant took the first dose at the study site at the start of each treatment period and was observed for 30 minutes, during which time nursing observations and an electrocardiogram were conducted. Participants were required to return empty bottles to receive a further supply, and medication adherence was assessed at each visit via a medication diary and the recorded weight of returned bottles.

OUTCOMES

The primary outcome was the total tic score on the YGTSS,[16] a clinician-led rating of number, frequency, intensity, complexity, and interference from motor and vocal tics. Secondary outcomes included YGTSS global score (total tic score plus impairment; range, 0 to 100), a video-based assessment of tic severity (Modified Rush Video-Based Rating Scale [MRVRS]; range, 0 to 20),[17] depressive symptoms (Montgomery–Åsberg Depression Rating Scale [MADRS]; range, 0 to 60),[18] anxiety symptoms (Hamilton Anxiety Rating Scale [HAM-A]; range, 0 to 56),[19] and obsessive-compulsive symptoms (Yale–Brown Obsessive-Compulsive Scale [YBOCS]; range, 0 to 40).[20] For all scales, higher scores indicate greater severity of symptoms. These measures were assessed at baseline (Visit 1), week 2 (Visit 2), week 4 (Visit 3), and week 6 (Visit 4, conclusion) of each treatment period. Adverse events were recorded at each study visit by the principal investigator.

Cognitive functioning was assessed at baseline and at the conclusion of each treatment period by using a computerized assessment tool (Cambridge Neuropsychological Test Automated Battery; key metrics and direction of impairment from each test are available at https://www.cambridgecognition.com/cantab/). The following cognitive tests were selected based on the domains typically affected by THC as well as some relevant to the safe operation of a motor vehicle[21] (attention, working memory, and executive functioning): Reaction Time Task, Spatial Working Memory, and Multitasking Test. To control for practice effects, all participants completed an initial test battery at the screening visit that was then discarded.

PLASMA CANNABINOIDS

Blood was collected via venipuncture into ethylenediaminetetraacetic acid Vacutainer tubes at baseline and week 4 of each treatment group. Blood was centrifuged at 1500 × *g* for 10 minutes at 4°C, and the supernatant plasma was aliquoted and stored in 1.8-ml cryotubes at −80°C until subsequent analysis. Plasma was analyzed via liquid chromatography–tandem mass spectrometry according to previously described validated methods.[22] The primary analytes of interest were THC, CBD, and the terminal metabolites of THC

(11-carboxy-tetrahydrocannabinol [11-COOH-THC]) and CBD (7-carboxy-cannabidiol [7-COOH-CBD]).

POWER CALCULATION

The estimate for the difference between the placebo group and the active treatment group for the change in total tic score between baseline and 6 weeks was informed by data from randomized, placebo-controlled trials of antipsychotic medication for Tourette syndrome[23,24] and a previous trial of THC.[10] The estimate for the standard deviation of the paired difference between placebo and treatment was a conservative choice because an appropriate estimate was not available. Of note, the estimate was purposefully larger than the standard deviation for the change estimate in the aforementioned antipsychotic trials. For a mean difference of 9 between treatments in the change in total tic score from baseline to 6 weeks (effect size of 0.9), assuming the mean difference under the null hypothesis of 0 and within-participant standard deviation of 15, a 5% type 1 error rate (two-sided), and power of 80%, a minimum of 21 participants was estimated. Conservatively estimating a 10% dropout rate, a target of 24 participants was determined.

RANDOMIZATION, BLINDING, AND ALLOCATION CONCEALMENT

The randomization schedule was generated in STATA 15 (StataCorp LLC, College Station, Texas) using permuted block sizes of 4 and 2, prepared by an independent statistician (E.B.) and held at a central location. For the target sample size of 24, a total of 12 participants were randomly assigned to receive active drug followed by placebo and 12 to receive placebo followed by active drug. Identical containers labeled according to the randomization sequence were prepared by the drug distributor before being provided to the trial pharmacy. Trial participants, trial personnel (including the principal investigator, research nurses [T.T. and L.H.], and study pharmacist), and outcome assessors were blinded to the treatment allocation. Video-based ratings were completed by an independent blinded rater (L.G.) who was also blinded to other outcome data. All raters were blinded to order (i.e., active then placebo or vice versa) but not visit number within each treatment period. P.E.M. trained all raters, and initial assessments of study participants were completed in parallel to ensure reliability and fidelity.

STATISTICAL ANALYSIS

Data analysis was performed in the R software (Version 4.0.2) environment and analyzed on an intention-to-treat basis. A linear mixed-effects model assessed the influence of treatment type (active/placebo) on primary and secondary outcomes while controlling for study period and washout (treatment × period) effects. Model fitting was performed for each outcome, assessing which interactions should be retained (as well as the inclusion of random intercept and random slope) based on the Akaike information criterion. The final model included fixed effects for visit (change in outcome per twice-weekly visits), treatment type, visit × treatment interaction, and a nested order × treatment interaction, with a random slope and intercept per participant per study period (due to the potential for an insufficient washout, each participant's active and placebo period was treated independently) with an independent within-group correlation structure. The interaction effect of visit × treatment type was retained throughout model fitting because it was the primary effect of interest. Models were fitted using the nlme package.[25] Restricted maximum likelihood estimates are reported with 95% confidence intervals (CIs). Normality of residuals was assessed, and homoscedasticity was verified.

An additional sensitivity analysis using an independent sample Hills–Armitage t test to adjust for period effects was also used.[26] The relationship between plasma cannabinoids at Visit 3 (week 4) in the active period and change in behavioral measures from baseline was assessed with the Pearson correlation.

ROLE OF THE FUNDING SOURCE

The philanthropic donors funding the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

PARTICIPANTS

From March 2019 to March 2021, a total of 139 potential participants were prescreened (Fig. 1), and 22 (including 8 female participants) gave informed consent and were randomly assigned to treatment (Table 1). As a cohort, participants had a severe burden of tics, moderate levels of obsessive-compulsive disorder and anxiety, and mild levels of depression. The study cohort was representative of the broader population with Tourette syndrome in terms of ethnicity, sex, and comorbidity (Table S1 in the Supplementary Appendix). Only six participants had not previously used cannabis. All participants completed the first

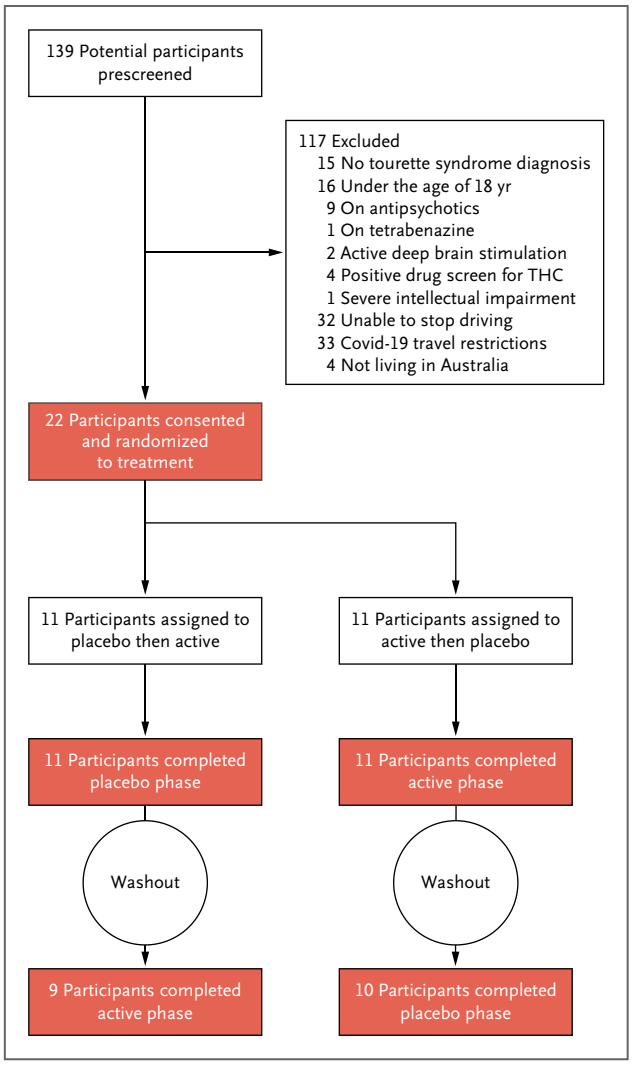

Figure 1. CONSORT Flowchart of Enrollment and Random Assignment of Participants.

CONSORT denotes Consolidated Standards of Reporting Trials; Covid-19, coronavirus disease 2019; and THC, Δ^9-tetrahydrocannabinol.

period of treatment. Three participants withdrew after the first period (two receiving placebo and one receiving active drug). Three participants in the active period were unable to reach the maximum indicated dose because of adverse effects (drowsiness and cognitive slowing). Of these, two participants took 3 ml of the target 4 ml daily dose, and one participant tolerated a 0.25 ml daily dose only. No side-effects limited the dose administered during treatment with placebo. At the final trial visit, most of the cohort (n=17 [77.3%]) correctly guessed their treatment allocation.

Table 1. Demographic and Clinical Characteristics of the Cohort at Baseline (N=22).*

Characteristic	Value
Sex	
Male	14 (63.6)
Female	8 (36.4)
Ethnicity	
White	20 (90.0)
Asian	2 (9.1)
Alcohol use	
Current	13 (59.1)
Former	6 (27.3)
Never	3 (13.6)
Tobacco use	
Current	5 (22.7)
Former	4 (18.2)
Never	13 (59.1)
Cannabis use	
Current†	2 (9.1)
Former	14 (63.6)
Never	6 (27.3)
Education level	
Did not complete high school	4 (18.2)
Completed high school	13 (59.1)
Completed university degree	2 (9.1)
Completed master's degree	3 (13.6)
Age — mean (±SD), median (range), yr	31.0±12.5, 29 (18–70)
YGTSS total tic score — mean (±SD), median (range)	35.7±7.6, 35 (22–50)
YGTSS global score — mean (±SD), median (range)	73.9±13.2, 75 (49–100)
MRVRS — mean (±SD), median (range)	13.4±4.2, 12 (7–20)
YBOCS — mean (±SD), median (range)	15.0±11.4, 17 (0–37)
MADRS — mean (±SD), median (range)	15.0±10.4, 14 (0–36)
HAM-A — mean (±SD), median (range)	17.8±10.4, 17 (2–37)

* Values are presented as no. (%) unless otherwise indicated. For all scales, higher scores indicate greater severity of symptoms. HAM-A denotes Hamilton Anxiety Rating Scale (range, 0 to 56); MADRS, Montgomery–Åsberg Depression Rating Scale (range, 0 to 60); MRVRS, Modified Rush Video-Based Rating Scale (range, 0 to 20); YBOCS, Yale–Brown Obsessive-Compulsive Scale (range, 0 to 40); YGTSS global score, Yale Global Tic Severity Scale, global score (range, 0 to 100); and YGTSS total tic score, Yale Global Tic Severity Scale, total tic score (range, 0 to 50).

† Current cannabis users were required to cease consuming cannabis at least 1 month before trial entry, and this was corroborated with a urine drug screen.

PRIMARY OUTCOME

Reduction in total tic score on the YGTSS at week 6 relative to baseline (i.e., the primary study outcome) was 8.9±7.6 in the active group and 2.5±8.5 in the placebo group. The linear mixed-effects model (intention-to-treat) showed a significant interaction of treatment and visit number (P=0.008), indicating a greater decrease (improvement) in tic score over time with active treatment (Fig. 2, Fig. S1,

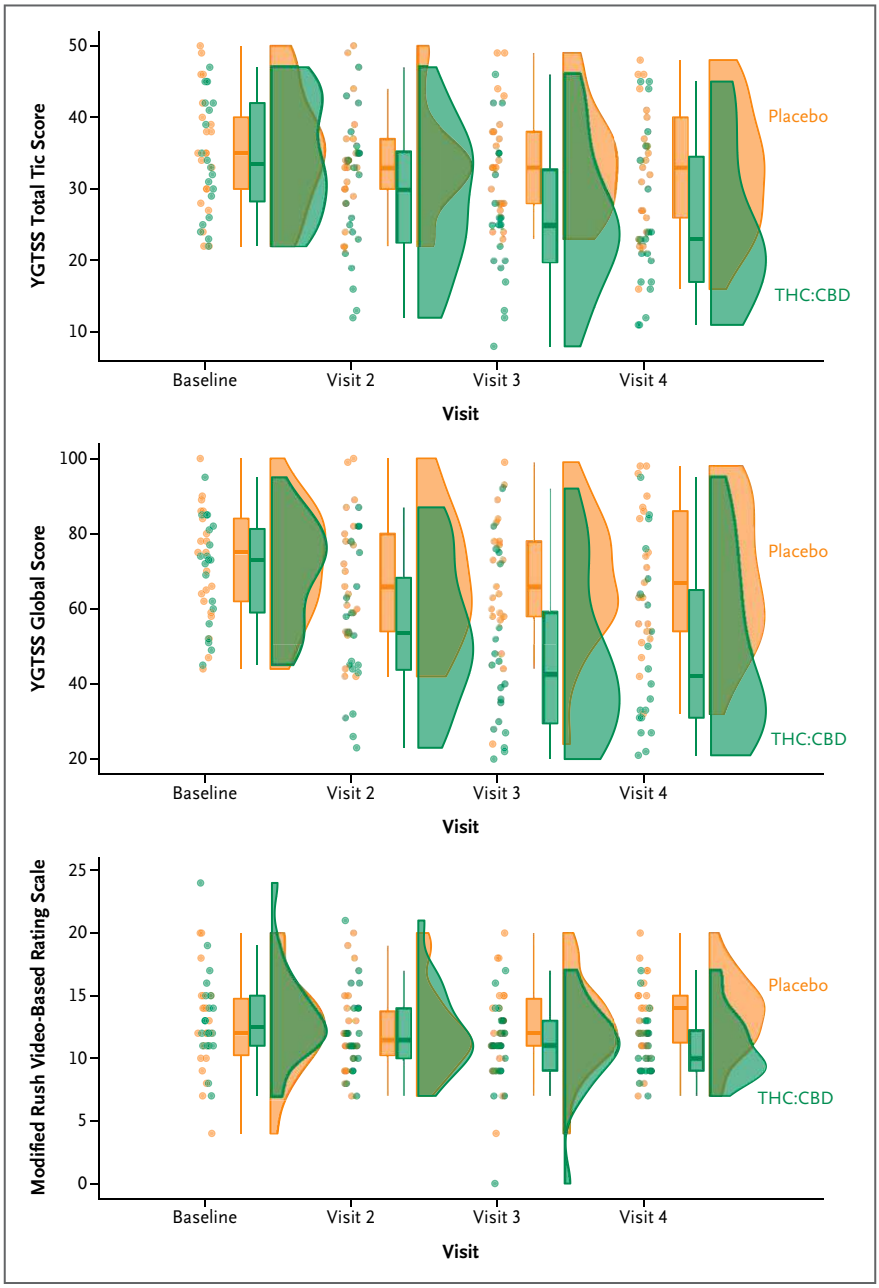

Figure 2. Data for Baseline and Visits 1 through 4.

For each panel (i.e., top, middle, and bottom), individual data points (far left), box and whisker plots (middle), and raincloud plots (far right) showing data for baseline and Visits 2, 3, and 4 for each outcome are plotted. The top panel is the primary outcome as the YGTSS total tic score (range, 0 to 50) over the four visits in each period of the crossover trial. Two secondary outcomes (YGTSS global score [range, 0 to 100] and Modified Rush Video-Based Rating Scale [range, 0 to 20]) are also included. Baseline = week 0; Visit 2 = week 2; Visit 3 = week 4; Visit 4 = week 6. For all scales, higher scores indicate greater severity of symptoms. CBD denotes cannabidiol; THC, Δ^9-tetrahydrocannabinol; and YGTSS, Yale Global Tic Severity Scale.

Table 2. Linear Mixed-Effects Model Parameter Estimates for Primary and Secondary Models.*

Outcome	Fixed Effects — *b* (95% CI), P Value						Random Effects — SD (95% CI)	
	Intercept	Visit	Active Treatment	Active Treatment × Visit	Active Treatment × Second Phase	Placebo Treatment × Second Phase	Intercept	Slope
YGTSS total tic score	38.75 (33.97 to 43.54)	−0.71 (−1.89 to 0.47) P=0.23	−4.10 (−11.04 to 2.84) P=0.24	−2.28 (−3.96 to −0.60) P=0.008	3.54 (−3.34 to 10.43) P=0.30	−6.18 (−12.87 to 0.51) P=0.069	6.99 (4.98 to 9.81)	2.11 (1.44 to 3.10)
YGTSS global score	77.70 (69.32 to 86.07)	−0.97 (−3.28 to 1.34)	−6.19 (−18.32 to 5.94)	−6.05 (−9.36 to −2.74)	2.76 (−9.70 to 15.22)	−12.81 (−24.93 to −0.70)	8.55 (4.25 to 17.20)	3.30 (1.75 to 6.23)
MRVRS	12.74 (10.54 to 14.95)	0.29 (−0.12 to 0.70)	1.29 (−1.93 to 4.51)	−1.15 (−1.74 to −0.56)	−0.07 (−2.82 to 2.67)	−1.58 (−4.19 to 1.03)	3.66 (2.70 to 4.97)	0.54 (0.25 to 1.18)
YBOCS	15.71 (9.54 to 21.89)	0.02 (−0.80 to 0.85)	−2.26 (−11.21 to 6.69)	−1.43 (−2.62 to −0.25)	2.77 (−6.10 to 11.64)	−2.90 (−11.52 to 5.73)	10.04 (7.70 to 13.09)	1.17 (0.62 to 2.22)
MADRS	14.00 (7.83 to 20.17)	0.37 (−0.74 to 1.48)	−1.53 (−10.47 to 7.41)	−1.13 (−2.72 to 0.46)	0.02 (−9.03 to 9.07)	−2.39 (−11.19 to 6.41)	8.62 (5.85 to 12.70)	1.15 (0.19 to 6.98)
HAM-A	14.73 (8.81 to 20.64)	0.27 (−0.81 to 1.35)	1.31 (−7.27 to 9.89)	−2.51 (−4.05 to −0.96)	1.76 (−6.51 to 10.03)	−3.37 (−11.41 to 4.67)	8.56 (6.12 to 11.99)	1.00 (0.34 to 2.92)

* The widths of the CIs have not been adjusted for multiplicity; thus, the CIs should not be used to reject or not reject effects. For all scales, higher scores indicate greater severity of symptoms. CI denotes confidence interval; HAM-A, Hamilton Anxiety Rating Scale (range, 0 to 56); MADRS, Montgomery–Åsberg Depression Rating Scale (range, 0 to 60); MRVRS, Modified Rush Video-Based Rating Scale (range, 0 to 20); YBOCS, Yale–Brown Obsessive-Compulsive Scale (range, 0 to 40); YGTSS global score, Yale Global Tic Severity Scale, global score (range, 0 to 100); and YGTSS total tic score, Yale Global Tic Severity Scale, total tic score (range, 0 to 50).

and Table 2). Participants who received placebo in the second period displayed a nonsignificant trend toward lower tic scores than participants who received placebo in the first period (*b*: −6.19; 95% CI, −12.87 to 0.51), suggesting a possible carryover effect from active treatment. Changes in outcome variables across active and placebo periods are summarized in Table S2.

SECONDARY OUTCOMES

There was also an interaction of treatment and visit for YGTSS global score (*b*: −6.05; 95% CI, −9.36 to −2.74), MRVRS (*b*: −1.15; 95% CI, −1.74 to −0.56), YBOCS (*b*: −1.43; 95% CI, −2.62 to −0.25), and HAM-A (*b*: −2.51; 95% CI, −4.05 to −0.96) (Table 2, Fig. 2, and Fig. S2). A carryover effect was seen for YGTSS global score (*b*: −12.81; 95% CI, −24.93 to −0.70), again indicating that participants who received placebo in the second treatment period had a lower score than those who received placebo first. Active treatment did not result in a decrease in MADRS score. These results were replicated in a sensitivity analysis. There were no changes between active treatment and placebo on computerized cognitive assessments of attention, working memory, and executive functioning, administered at the beginning and end of each treatment period.

PLASMA CANNABINOIDS

As anticipated, plasma THC, CBD, and their metabolites were undetectable or at very low levels in the placebo period and at the baseline commencement visit of the active period, and much higher values were recorded at active Visit 3 (week 4) (Table S4).

Levels of the parent molecules THC and CBD were too low to be accurately quantified in some participants, and analysis, therefore, focused on the metabolites. Here, despite compliance with study procedures (including a dosing diary and the return of used bottles for weighing), there was a wide variation in the measured level of cannabinoid metabolites during the active period (Table S3). For example, the participant who could only tolerate 0.25 ml of active drug still had higher plasma concentrations of 11-COOH-THC than three other participants who ingested the full 4-ml dose daily. Another participant had more than twice the measured levels of 11-COOH-THC and 7-COOH-CBD compared with the next-highest participant and was treated as an outlier in secondary correlations of clinical response with plasma concentrations.

There was a correlation between plasma 11-COOH-THC concentrations at Visit 3 (week 4) and reduction in YGTSS total tic score from baseline during the active period

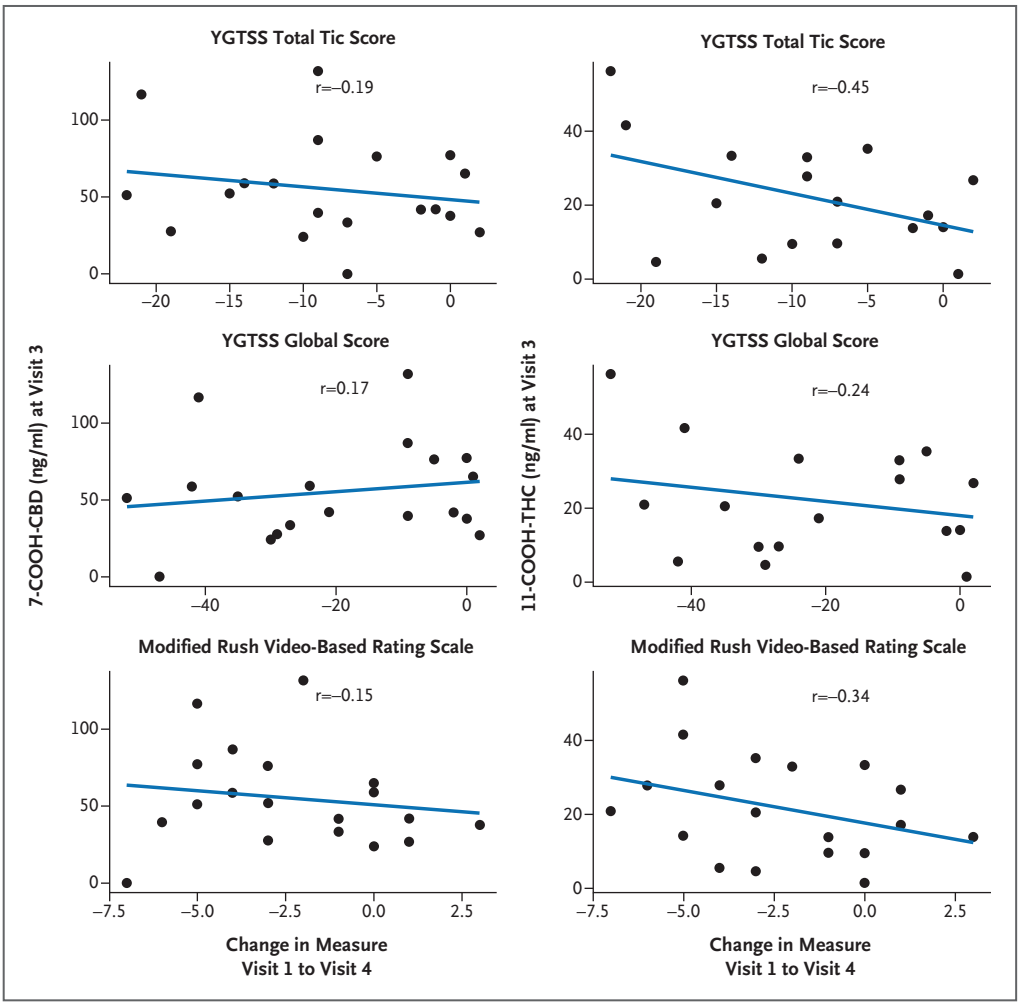

Figure 3. Concentrations of Primary Cannabinoid Metabolites.

Concentrations of 7-COOH-CBD (left column) and 11-COOH-THC (right column) in plasma correlated with change in the primary outcome (YGTSS total tic score [range, 0 to 50]) during the active period. Two secondary outcomes (YGTSS global score [range, 0 to 100] and Modified Rush Video-Based Rating Scale [range, 0 to 20]) are also included. This figure excludes an outlier with high levels of metabolites during the active period. Visit 1 = baseline/week 0; Visit 4 = week 6. For all scales, higher scores indicate greater severity of symptoms. 7-COOH-CBD denotes 7-carboxy-cannabidiol; 11-COOH-THC, 11-carboxy-tetrahydrocannabinol; CBD, cannabidiol; THC, Δ^9-tetrahydrocannabinol; and YGTSS, Yale Global Tic Severity Scale.

(r=–0.49; 95% CI, –0.76 to –0.05). However, when removing the outlier, this correlation was attenuated (r=–0.45; 95% CI, –0.75 to 0.003) (Fig. 3). Correlations between plasma cannabinoid metabolites and all outcome measures are presented in Table S4.

SAFETY

There were no deaths or serious adverse events. Adverse effects were generally mild (Fig. S3 and Table S5) and only limited dose escalation in three participants (described earlier). The most common adverse effect in the placebo period was headache (n=7); in the active treatment period, it was cognitive difficulties, including slowed mentation, memory lapses, and poor concentration (n=8). One participant reported brief auditory hallucinations (hearing his name called) on 1 day during the upward titration of active drug.

Discussion

In this randomized, double-blind, placebo-controlled crossover study, we found that an oral 1:1 THC:CBD

formulation titrated upward over 6 weeks up to a daily dose of 20 mg of THC and 20 mg of CBD led to a significant reduction in tics as measured by the total tic score on the YGTSS, as well as a reduction in obsessive-compulsive symptoms and anxiety, without major adverse effects. A strength of the study is that tic reduction was observed in both interviewer-led and video-based assessments of tic severity conducted by separate raters blinded not only to treatment allocation but also to other outcome ratings. Depressive symptoms were not affected by THC:CBD, although low depressive symptoms at baseline may have limited the power to detect an effect.

Although many potential participants were screened for this trial, only a small number were recruited. This was primarily due to the driving restrictions mandated by the trial and restrictions on travel within Australia during the Covid-19 pandemic. Nevertheless, the trial almost met its recruitment target of 24 participants.

Despite careful attention to allocation concealment and matching of the placebo to the active agent (color and smell), most participants were able to correctly guess their treatment order. This may have been attributable to symptomatic relief conferred by the active agent but also to its adverse-effect profile, with a greater burden of dyscognitive symptoms reported in the active group. Interestingly, however, there was no difference in objective cognitive functioning between active and placebo groups on a computerized cognitive battery assessing reaction time, executive functioning, and working memory. This may have relevance to legislation pertaining to the operation of a motor vehicle while using medicinal cannabis, although this is a complex matter requiring sophisticated and ecologically valid measures of driving impairment.[27,28] A further consideration is that cognitive testing occurred at the end of the 6-week treatment period, possibly enabling the development of tolerance to any dyscognitive effects. Furthermore, if testing was performed several hours after the last dosing of active drug, the participant may have then been outside the "window of impairment."[21]

A crossover trial is efficient when carryover effects are absent, but carryover effects can lead to interpretation problems when they are present. We attempted to mitigate this issue by inserting a washout period and by modeling treatment condition × phase interactions. Although plasma cannabinoids and their metabolites were present at negligible levels in the placebo period regardless of treatment order (placebo first or second), there nonetheless seemed to be a carryover effect for those who received placebo second, with a trend toward lower tic scores in this group. This may have reduced the observed effect of the active drug treatment (i.e., underestimated the true effect). In crossover trials, there is also a potential confounding effect of a natural fluctuation in tic severity between treatment periods, which can be observed as a natural feature of the condition.

Wide variability in the plasma levels of cannabinoid metabolites was observed during active treatment, as is typical for cannabinoids delivered orally. This route of drug delivery produces highly variable levels of absorption in the gastrointestinal tract.[29] However, one of the benefits of oral drug delivery (as opposed to vaporized) is that it facilitates a slower and more sustained pharmacokinetic profile over time,[30] which may be helpful in a chronic movement disorder such as Tourette syndrome, in which tics are present for most of the waking day. Methods of delivery with improved bioavailability (e.g., sublingual wafer products or oral products with specialized excipients) may lead to a stronger association between dose and metabolite levels.

In conclusion, we present the results of a placebo-controlled, double-blind, crossover study that investigated the effects of repeated dosing of an oral oil containing 5 mg/ml of THC and 5 mg/ml of CBD. This study adds to a small body of literature suggesting that oral 1:1 THC:CBD is an effective treatment for tics and psychiatric comorbidity associated with severe Tourette syndrome. Although the adverse-effect profile was mild in this relatively short study, further work is necessary to identify the longer-term effects of cannabis use in Tourette syndrome, such as the possible development of tolerance to the anti-tic effect. The magnitude of the tic reduction observed was moderate, on average, and comparable to the effect observed with existing treatments such as antipsychotic agents. Furthermore, the adverse-effect profile, including both sedation and increased appetite (among some participants), is similar in nature to adverse effects commonly reported with antipsychotic agents. Given the strong anxiolytic effect of the active drug, it is also not possible from this study paradigm to exclude an indirect effect of tic reduction driven by a reduction in anxiety. Like many studies of psychoactive compounds, blinding among participants was a problem. Larger and longer trials taking the adverse-effect profile of these agents into consideration are warranted.

Disclosures

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Author disclosures and other supplementary materials are available at evidence.nejm.org.

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