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Nabiximols for the Treatment of Cannabis Dependence
A Randomized Clinical Trial

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IMPORTANCE There are no effective medications for treating dependence on cannabis.

OBJECTIVE To examine the safety and efficacy of nabiximols in the treatment of patients with cannabis dependence.

DESIGN, SETTING, AND PARTICIPANTS This parallel double-blind randomized clinical trial comparing nabiximols with placebo in a 12-week, multisite outpatient study recruited participants from February 3, 2016, to June 14, 2017, at 4 outpatient specialist alcohol and drug treatment services in New South Wales, Australia. Participants had cannabis dependence (as defined by the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*) and were seeking treatment, were nonresponsive to prior treatment attempts, were 18 to 64 years of age, had no other substance use disorder, had no severe medical or psychiatric conditions, were not pregnant, were not mandated by a court to undergo treatment, and provided informed consent. Results for primary efficacy measures and all secondary outcomes were obtained using a modified intention-to-treat data set.

INTERVENTIONS Participants received 12-week treatment involving weekly clinical reviews, structured counseling, and flexible medication doses—up to 32 sprays daily (tetrahydrocannabinol, 86.4 mg, and cannabidiol, 80 mg), dispensed weekly.

MAIN OUTCOMES AND MEASURES Primary outcome was self-reported number of days using illicit cannabis during the 12-week period. Other outcomes included alternate cannabis use parameters (periods of abstinence, withdrawal, cravings, and problems), safety parameters (adverse events and aberrant medication use), health status, other substance use, and treatment retention.

RESULTS A total of 128 participants (30 women and 98 men; mean [SD] age, 35.0 [10.9] years) were randomized and received at least 1 dose of study medication. Participants had used a mean (SD) of 2.3 (2.1) g of cannabis on a mean (SD) of 25.7 (4.5) days in the past 28 days. Treatment retention was comparable for the 2 groups (placebo, 30 of 67 participants [44.8%]; nabiximols, 30 of 61 participants [49.2%]), and both groups used similar mean (SD) doses (placebo, 18.5 [9.5] sprays daily; nabiximols, 17.6 [9.5] sprays daily, equivalent to a mean [SD] of 47.5 [25.7] mg of tetrahydrocannabinol and 44.0 [23.8] mg of cannabidiol). For the primary end point, the placebo group reported significantly more days using cannabis during the 12 weeks (mean [SD], 53.1 [33.0] days) than the nabiximols group (mean [SD], 35.0 [32.4] days; estimated difference, 18.6 days; 95% CI, 3.5-33.7 days; $P = .02$). Both groups showed comparable improvements in health status, with no substantial changes in other substance use. Medication was well tolerated with few adverse events.

CONCLUSIONS AND RELEVANCE This study demonstrates that cannabinoid agonist treatment, in this case using nabiximols, in combination with psychosocial interventions is a safe approach for reducing cannabis use among individuals with cannabis dependence who are seeking treatment.

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Supplemental content

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Apart from alcohol and tobacco, cannabis is the most widely used psychoactive substance and accounts for the largest number of people dependent on illicit drugs globally.[1,2] In Australia, 10.4% of adults reported using cannabis in the past 12 months,[3] of whom approximately 10% describe dependent patterns of use.[4] Cannabis dependence is associated with a range of cognitive, psychiatric, and physical health problems[1,4,5] and accounts for the second largest number of drug treatment episodes in Australia.[6]

The effectiveness of existing treatments for cannabis dependence is unsatisfactory. Approximately 80% of patients relapse to regular use within 1 to 6 months of either cannabis withdrawal[7,8] or counseling (eg, cognitive behavioral therapy [CBT]) interventions.[9] As with the treatment of other chronic addiction conditions, there is interest in combining long-term medication with psychosocial interventions,[10] although no efficacious pharmacotherapies for cannabis dependence have been established.[11]

A promising approach is the use of cannabinoid agonist pharmacotherapies, akin to opioid or nicotine replacement treatment.[12] The rationale is to provide a safer route of administration than smoking, reduce unsanctioned drug use by ameliorating withdrawal and cravings,[7] and facilitate greater engagement in psychosocial interventions, leading to improved health and psychosocial functioning. However, cannabinoid agonist treatment may also be associated with adverse events (AEs) and aberrant medication use in people with a history of illicit cannabis use. Although short courses (eg, 5-7 days) of cannabinoid agonists for treating acute cannabis withdrawal successfully suppress withdrawal symptoms,[7,13-15] the high rates of relapse after acute withdrawal indicate that longer-term treatment (eg, ≥12 weeks) may be required to achieve longer-term outcomes.[10,11]

The longer-term use of dronabinol, a synthetic oral tetrahydrocannabinol (THC) product, for cannabis dependence was examined in a 12-week randomized placebo-controlled trial in 122 patients with cannabis dependence.[16] Although dronabinol, 60 mg daily, was well tolerated and reduced withdrawal symptoms, there was no advantage compared with placebo in achieving abstinence or reducing days of cannabis use. More recently, a 12-week, 40-participant, placebo-controlled feasibility randomized clinical trial examining nabiximols for cannabis dependence concluded that "nabiximols in combination with Motivational Enhancement Therapy/CBT was well tolerated and allowed for reduction of cannabis use,"[17(p2)] suggesting that larger trials are warranted.

Our study examined the efficacy and safety of nabiximols in the treatment of patients with cannabis dependence. The primary hypothesis for the study is that a 12-week treatment program with nabiximols will result in significantly less illicit cannabis use—as assessed by self-reported cannabis use days over the 12-week period—compared with placebo. Secondary hypotheses are that nabiximols treatment will result in significant improvements in a range of secondary cannabis treatment outcomes, including periods of abstinence, measures of cannabis withdrawal, cravings, and cannabis-related problems, compared with placebo; will have an acceptable AE and abuse liability profile in a population with cannabis dependence; and will result in significant improvements in general health and psychosocial measures compared with placebo.

Key Points

Question Is cannabinoid agonist treatment, in combination with psychosocial services, a safe and efficacious approach to reducing illicit cannabis use in patients with cannabis dependence who are seeking treatment?

Findings In this randomized clinical trial of 128 participants, a 12-week course of nabiximols, a combination of tetrahydrocannabinol and cannabidiol, resulted in significantly fewer days of illicit cannabis use compared with placebo, and was well tolerated by participants.

Meaning The use of cannabinoid agonist medication appears to be a promising addition to the treatment of patients with cannabis dependence.

Methods

Study Design

This phase 3 multisite outpatient randomized, double-blind, parallel-design study compared a 12-week course of nabiximols with placebo. Medications were dispensed on a weekly basis, and both groups received standardized clinical care.[18] All participants were followed up for confidential research interviews (irrespective of completion of the trial intervention) at weeks 0 (baseline), 4, 8, and 12. Recruitment began February 3, 2016, and ended June 14, 2017. Study procedures are described in greater detail elsewhere.[18] The study was approved by the South East Sydney Local Health District Human Research Ethics Committee. Participants provided written informed consent.

Sites

The study was conducted across 4 specialist outpatient addiction treatment services in New South Wales, Australia: The Langton Centre, St George Hospital, Newcastle Community Health Services, and the Centre for Addiction Medicine (Western Sydney).

Participants

Previous studies of treatment for cannabis dependence have reported on abstinence rates, and this outcome (while not the primary end point in this study) was used to estimate a sample size of 142 participants (71 per group) to detect a doubling of abstinence rates at 12 weeks from 22% (placebo) to 44% (nabiximols) with 80% power (2-tailed) and α = 0.05. Inclusion criteria were age 18 to 65 years, cannabis dependence (as defined by the *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*[19]), inability to stop cannabis use in previous quit attempts, and provision of informed consent and agreement to study procedures, including to not drive and to use reliable contraception. Exclusion

criteria were another substance use disorder other than nicotine or caffeine; severe medical or psychiatric disorder, including history of epilepsy or psychosis; pregnant or lactating women or those planning pregnancy; inability to safely store medication; not available for follow-up; addiction treatment mandated by a court; and treatment for cannabis dependence within past month.

Recruitment

Individuals seeking treatment were screened by telephone for broad eligibility (eg, geographic location and age), with potentially eligible participants invited to attend a medical assessment after providing written informed consent. Eligible participants were referred to the researcher for study enrollment, after which randomization and study treatment were initiated within 3 to 7 days.

Randomization and Blinding

The randomization schedule was developed by an independent researcher, using a permuted 8-block randomization schedule with 1:1 random allocation per site.[18] Participants, clinicians, and researchers were blind to allocation, with only trial pharmacists aware of group allocation.

Clinical Interventions

Study Medications

Each nabiximols spray delivers 0.1 mL, comprising 2.7 mg of THC and 2.5 mg of cannabidiol (CBD); matching placebo used the same carrier and flavoring, but without cannabinoids. Medication canisters were identically labeled and dispensed weekly. Doses were titrated at weekly clinical reviews to optimize clinical effect (reduce cravings, withdrawal, and illicit cannabis use) and safety (minimize AEs). After a 3-day dose induction period, the maximum daily dose (to end week 12) was 32 oromucosal sprays (86.4 mg of THC and 80 mg of CBD) in 4 divided doses.

Clinical Reviews and Counseling Intervention

Weekly clinical sessions enabled monitoring and review of medication use and dose adequacy, experience of withdrawal, cravings, and AEs. Participants were offered 6 structured CBT-based individual counseling sessions, delivered by counselors or nurses who had completed a standardized training program.[20] Participants who did not attend clinical sessions for more than 2 consecutive weeks were discontinued from study treatment. More detail regarding interventions is provided in the trial protocol in Supplement 1.[18]

Outcomes and Measures

The primary end point was self-reported total days of illicit cannabis use during weeks 1 to 12 (maximum, 84 days). Illicit cannabis use was quantified as the self-reported number of days of cannabis use in the preceding 28 days using Time Line Follow Back[21] techniques at 4-week research interviews (weeks 1-4, 5-8, and 9-12). This variable was also used to calculate the proportion of participants achieving abstinence in any of the three 4-week periods, and the number of participants who achieved 50% or greater reduction in cannabis use in the preceding 28 days from baseline (weeks -4 to 0) to week 12 (weeks 9-12) research interviews. Urine drug tests measuring THC and metabolites (11-OH and 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol [THC-COOH]) were performed at research interviews to validate self-reported cannabis use. Urine samples were analyzed as previously reported[22,23]; in brief, cannabinoid analytes were hydrolyzed with β-glucuronidase, extracted via supported liquid extraction, and quantified via liquid chromatography–tandem mass spectrometry. Creatinine was measured colorimetrically via the Jaffe method (eAppendices 11-14, eTables 11-13, and eFigure 3 in Supplement 2).

Adverse events were evaluated during clinical assessments at weeks 2, 4, 8, and 12 by a study medical officer (N.L., A.D., N.P., and M.M.). Potential mental health concerns were monitored using the Brief Psychiatric Rating Scale[24] at 4-week medical reviews. Self-reported aberrant medication behaviors (eg, selling or giving medication to others or repeated unauthorized dose escalation) were assessed at the researcher interviews using the modified Opioid-Related Behaviours In Treatment scale.[25]

Several secondary outcomes were assessed at 4-week research interviews, including the Cannabis Withdrawal Scale,[26] Marijuana Craving Questionnaire,[27] Cannabis Problems Questionnaire,[28] Alcohol Use Disorders Identification Test,[29] Fagerström Test for Nicotine Dependence,[30] general health status and psychosocial function (36-item Short Form Survey[31]), and self-reported participation in crime (Opioid Treatment Index–Crime subscale[32]). Global satisfaction was assessed by asking participants (yes or no) "Would you recommend this medication to a friend seeking treatment?"

Treatment process measures were extracted from clinical records, including treatment retention (days in protocol treatment); medication doses; participation in counseling, medical, and nursing sessions; and reasons for study termination. Study blinding was tested by asking participants to estimate which medication group they were assigned to at research interviews at weeks 4, 8, and 12, with the last available interview used for analysis.

Statistical Analysis

Results for the primary efficacy measures and all secondary outcomes were obtained using a modified intention-to-treat data set, comprising all participants who were allocated to a study group and received at least 1 dose of medication (details of participants who were randomized and did not receive study medication are provided in eTable 1 in Supplement 2, but excluded from further analyses). Site differences for key variables at baseline were tested using simple regression (eAppendix 1 in Supplement 2). All P values were from 2-sided tests and results were deemed statistically significant at $P < .05$.

Primary Analysis

Analysis of the primary outcome, total days of cannabis use across the 12-week trial, was performed using a modified intention-to-treat data set with no imputed data (excluding participants who did not initiate study medication after randomization). To address concerns of missing data, a modified

intention-to-treat data set with multilevel multiple-imputation was also conducted. A per-protocol analysis (comprising only participants who completed the 12 weeks of study treatment) is also reported.

The primary analysis was an analysis of covariance, with total days of illicit cannabis use across the 12-week trial as the outcome, with 4 factors: treatment (2-level factor: placebo vs nabiximols), site (4-level factor: Langton, St. George, Western Sydney, and Newcastle), treatment × site interaction, and number of days cannabis was used in the 4 weeks prior to baseline. In the event of significant omnibus effects for treatment, site, or the treatment × site interaction, estimates of the difference between factor levels were obtained using covariate-adjusted means, with *P* values adjusted for multiple comparisons using the Benjamini-Hochberg procedure.[33]

To assess whether the assumptions of a linear model (analysis of variance) approach were met, residuals were examined (eAppendix 5 and eFigures 1 and 2 in Supplement 2). The departure from normality was small, and as analysis of variance is robust to nonnormality, the primary analysis presented used a linear model. The Wilcoxon Mann-Whitney test was also conducted to examine for similarity in results using a nonparametric analysis.

Urine drug tests were used to validate self-reported cannabis use. However, urinary THC markers cannot be used to detect illicit cannabis use (reliant on detection of THC and its metabolites) in patients who were prescribed a THC-based medicine such as nabiximols; thus, analysis of urinary THC markers for verification of self-report was restricted to the placebo group. Two approaches were used: (1) a multiple regression model with log-transformed, creatinine-adjusted cannabinoid levels as the outcome and self-reported days' use of illicit cannabis, participant age, and sex as predictors, and (2) analysis of concordance between 2 binary variables—self-reported abstinence in the past 28 days and urinalysis estimate of abstinence based on creatinine-adjusted THC-COOH levels[34]—consisting of receiver operating characteristic curve analysis and logistic regression of urinary THC on self-reported abstinence (eAppendices 11-14, eTables 11-13, and eFigure 3 in Supplement 2).

Secondary Analyses

Logistic regression was used to test group differences in the odds of achieving the following binary outcomes: any 4-week periods of abstinence during the 12-week trial; reducing the number of days of cannabis use by 50% or more between baseline (weeks -4 to 0) and week 12 (weeks 9-12); correctly guessing treatment allocation; and intention to recommend treatment to a friend (from the last available research interview). For count variables (number of counseling sessions, AEs, and aberrant medication behaviors) either Poisson or negative binomial regressions were used, dependent on dispersion of scores. Change in 4-week scores for several secondary variables (Cannabis Withdrawal Scale, Marijuana Craving Questionnaire, Cannabis Problems Questionnaire, Fagerström Test for Nicotine Dependence, Alcohol Use Disorders Identification Test, and 36-item Short Form Survey) was tested using factorial mixed models for repeated measures regression (MMRM), with treatment and time (4-level factor: weeks 0 [baseline], 4, 8, and 12) as the fixed effects, and participant identification as the random effect. These MMRMs yielded omnibus main and interaction effects as well as estimates of group differences at each time point, with *P* values adjusted for multiple comparisons using the Benjamini-Hochberg method. Factorial logistic MMRM was used to analyze between-group differences in odds of committing a drug-related crime during the course of the study. Treatment retention was analyzed using a Kaplan-Meier plot and a Cox proportional hazards regression model. Dose of medication was quantified by averaging participants' self-reported number of sprays per day across the maintenance phase of the study in weeks 2 to 12 (week 1 was dose titration), which was then analyzed for group differences using simple regression. All statistical analyses were performed in R, version 3.4.1,[35] using lme4,[36] tidyverse,[37] survival,[38] and mice[39] packages.

Results

Study Recruitment and Retention

The CONSORT diagram is presented in **Figure 1**. A total of 409 individuals registered for screening and 272 (66.5%) were excluded, usually owing to being unable to be contacted, and were deemed lost to follow-up (n = 150) or unable to attend for treatment (n = 42). A total of 137 participants were enrolled, of whom 9 did not initiate treatment after randomization (6 placebo and 3 nabiximols; eAppendix 1 in Supplement 2), resulting in 128 participants for analysis (67 in the placebo group and 61 in the nabiximols group). Of these 128 participants, 77 (60.2%) completed the week 12 research interview (40 [59.7%] in the placebo group and 37 [60.7%] in the nabiximols group).

Baseline Characteristics

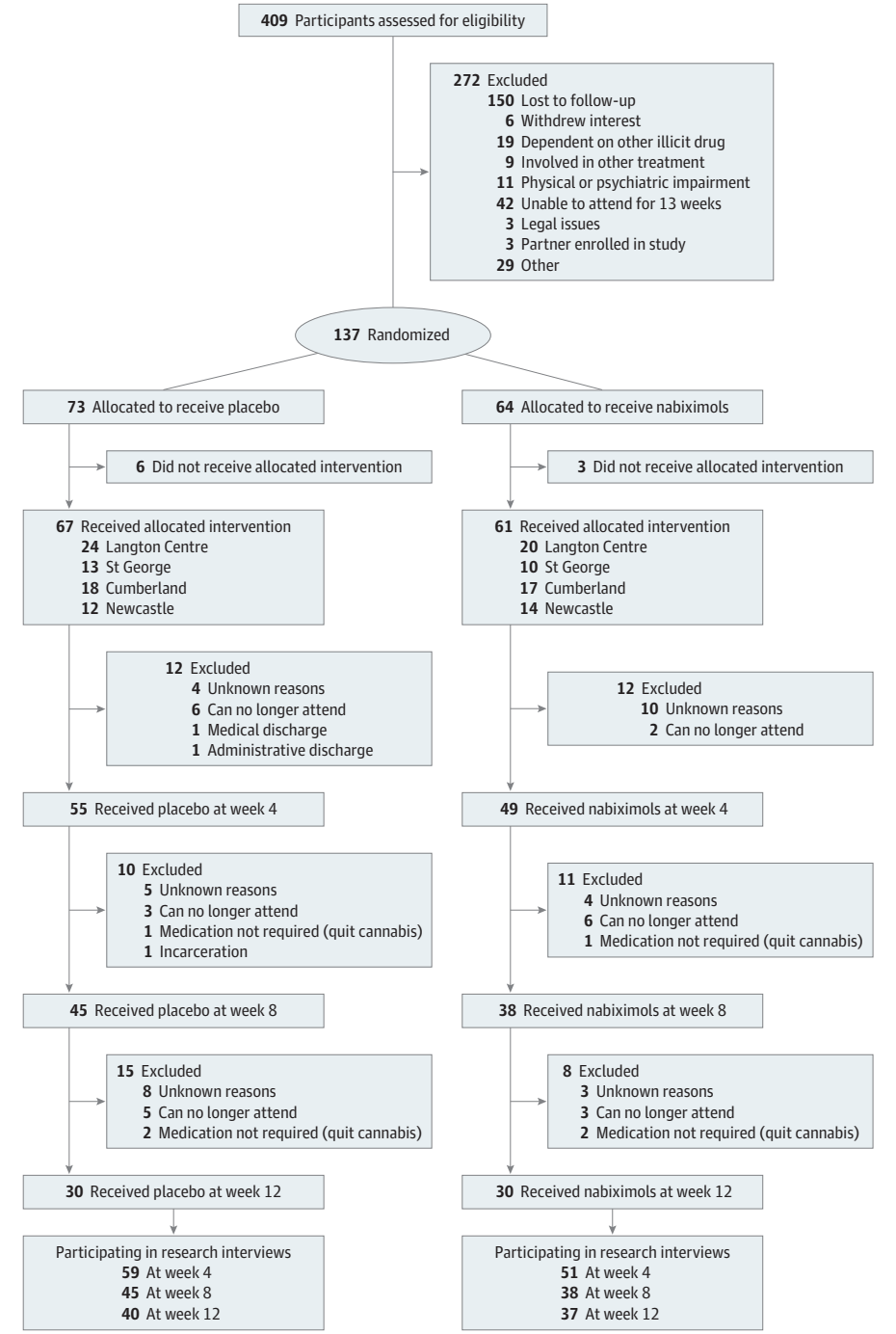
Baseline characteristics were similar between the intervention groups and are shown in **Table 1**. Participants had used a mean (SD) of 2.3 (2.1) g of cannabis per day on a mean (SD) of 25.7 (4.5) days in the past 28 days. All participants reported using cannabis flower and usually smoked using devices known as bongs (94 [73.4%]) or cigarettes known as joints (30 [23.4%]). There were no significant differences across sites at baseline except that 1 site had significantly higher age and duration of regular cannabis use than the other sites (eAppendix 1 in Supplement 2).

Participation in Treatment

Treatment retention is shown in **Figure 2**A. A total of 60 participants (46.9%) completed the 12-week treatment protocol: 30 participants (44.8%) in the placebo group and 30 participants (49.2%) in the nabiximols group. There were no significant between-group differences.

Medication use is shown in Figure 2B. There was no significant between-group difference in the mean (SD) number of sprays per day during weeks 2 to 12 (placebo, 18.5 [9.5] sprays; nabiximols, 17.6 [9.5] sprays, equivalent to a mean [SD] of 47.5 [25.7] mg of THC and 44.0 [23.8] mg of CBD). Similarly, there were no significant between-group differences in

Figure 1. CONSORT Flow Diagram



the mean (SD) number of CBT sessions attended (2.4 [2.2] in the placebo group and 2.6 [2.3] in the nabiximols group).

Cannabis Use

Primary End Point: Frequency of Cannabis Use

Figure 3 shows the means and distribution of days used during the trial for each group. The placebo group used illicit cannabis a mean (SD) of 53.1 [33.0] days (of 84 days) across the 12-week trial, compared with 35.0 [32.4] days in the nabiximols group, a significant difference of 18.6 days after adjusting for baseline cannabis use (95% CI, 3.5-33.7 days; $P = .02$).

The effect of treatment when controlling for site, treatment × site interaction, and baseline use was similar irrespective of statistical approach (eAppendix 4 and eTable 3 in Supplement 2). With multilevel multiple-imputation, the estimated difference was 10.6 days (95% CI, 1.0-20.2 days; $P = .04$) and in the per-protocol analysis, the estimated difference was 20.3 days (95% CI, 3.2-37.4 days; $P = .02$) (eAppendices 2 and 3 and

Table 1. Demographic and Baseline Characteristics of Participants

Characteristic	Participants, No. (%)		
	Placebo (n = 67)	Nabiximols (n = 61)	Total (N = 128)
Age, mean (SD), y	33.8 (10.3)	36.2 (11.5)	35.0 (10.9)
Female sex	14 (20.9)	16 (26.2)	30 (23.4)
Born in Australia	56 (83.6)	51 (83.6)	107 (83.6)
Aboriginal or Torres Strait Islander	6 (9.0)	4 (6.6)	10 (7.8)
Tertiary education	22 (32.8)	27 (44.3)	49 (38.3)
Employment as main source of income	36 (53.7)	35 (57.4)	71 (55.5)
In a relationship	27 (40.3)	18 (29.5)	45 (35.2)
Have ≥1 child	23 (34.3)	21 (34.4)	44 (34.4)
Current legal problems	6 (9.0)	2 (3.3)	8 (6.2)
Baseline cannabis use			
No. of days cannabis used in last 28, mean (SD)	25.6 (4.5)	25.9 (4.6)	25.7 (4.5)
Amount of cannabis used, mean (SD), g/d	2.6 (2.5)	2.0 (1.4)	2.3 (2.1)
Age at first cannabis use, mean (SD), y (range, 5-40 y)	15.0 (4.3)	16.0 (3.4)	15.5 (3.9)
Duration since first regular cannabis use, mean (SD), y	15.2 (9.8)	16.2 (9.9)	15.7 (9.8)
ICD-10 score, mean (SD) (maximum = 8)	7.2 (1.1)	6.9 (1.2)	7.1 (1.2)
Other variables			
Fagerström nicotine dependence score, mean (SD) (maximum = 10)[a]	2.1 (2.4)	3.4 (2.8)	2.7 (2.7)
AUDIT score, mean (SD) (maximum = 50)	4.4 (5.1)	4.7 (4.3)	4.5 (4.7)
BPRS-18 score, mean (SD) (maximum = 128	23.6 (11.5)	24.1 (12.0)	23.8 (11.7)
Sheehan disability scale score, mean (SD) (maximum = 30)	14.1 (8.2)	12.9 (7.4)	13.5 (7.8)
SF-36 score, mean (SD) (maximum = 100)			
Physical functioning	87.2 (18.4)	86.2 (20.7)	86.71 (19.4)
Role limitations owing to physical health	36.6 (42.3)	34.4 (41.4)	35.57 (41.7)
Role limitations owing to emotional problems	48.3 (44.7)	48.1 (45.8)	48.18 (45.0)
Energy or fatigue	43.4 (18.3)	40.8 (19.3)	42.19 (18.8)
Emotional well-being	56.1 (20.2)	54.7 (18.1)	55.06 (19.2)
Social functioning	54.9 (30.6)	59.1 (26.7)	56.60 (28.8)
Pain	69.8 (26.2)	70.5 (25.6)	70.12 (25.8)
General health	49.3 (19.7)	53.9 (21.6)	51.48 (20.6)
OTI crime			
Committed any drug-related crime in last month	24 (35.8)	21 (34.4)	45 (35.2)
Committed any nondrug-related crime in the last month[b]	3 (4.6)	1 (1.6)	4 (3.2)

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; BPRS, Brief Psychiatric Rating Scale; *ICD-10*, *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*; OTI, Opioid Treatment Index; SF-36, 36-item Short Form Survey.

[a] Fagerström nicotine dependence score only for participants who identified as smokers (total, 106 [82.8%]; placebo, 58 [86.6%]; and nabiximols, 48 [78.7%]).

[b] Refers to crimes related to selling cannabis to others. Does not include use or possession for personal use.

eTable 2 in Supplement 2). A nonparametric Wilcoxon-Mann-Whitney rank sum test estimated a 16.0-day difference in the location of the distributions of the treatment groups (U = 722; P = .04). Although there were differences in cannabis use across sites, the omnibus interaction between treatment and site was nonsignificant (eAppendix 4 and eTable 3 in Supplement 2).

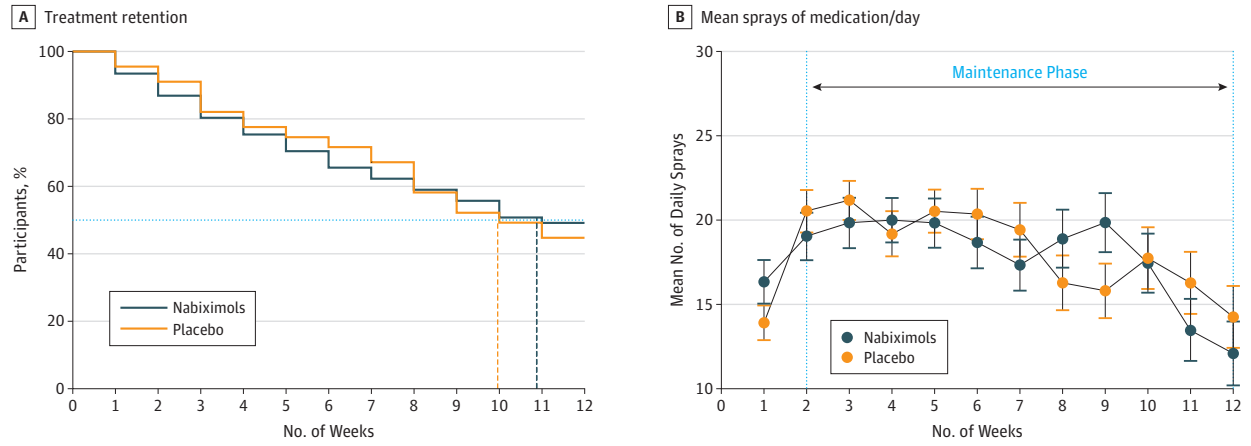
Secondary Outcomes

Of the 104 participants who were still participating in the study at the 12-week research interview, 23 (22.1%) had 1 or more 4-week periods of abstinence during the trial: 10 of 55 (18.2%) in the placebo group and 13 of 49 (26.5%) in the nabiximols group, a nonsignificant difference (odds ratio, 1.63; 95% CI, 0.55-4.90; P = .31). A significantly lower proportion of the placebo group (11 of 38 [28.9%]) reduced their cannabis use by 50% or more from baseline to week 12 than the nabiximols group (20 of 37 [54.1%]) (odds ratio, 0.35; 95% CI, 0.13-0.90; P = .03; number needed to treat, 4; 95% CI, 2-29). Cannabis-related problems (Cannabis Problems Questionnaire), withdrawal (Cannabis Withdrawal Scale), and cravings (Marijuana Craving Questionnaire) improved in both groups over time, but with no significant between-group differences (**Table 2**).

Validation of Self-reported Cannabis Use

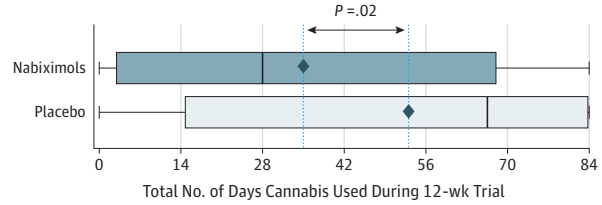
Urinalysis indicated that the self-reported number of days using cannabis was significantly positively associated with urinary THC-COOH levels (eAppendix 11, eTable 11, and eFigure 3 in Supplement 2). The odds of having a negative test result for THC-COOH after self-reported abstinence were 8 times higher than after self-reported use (odds ratio, 7.9; 95% CI, 2.5-26.0; P < .001), confirming the validity of self-reported cannabis use (eAppendices 13 and 14 and eTables 12 and 13 in Supplement 2).

Figure 2. Treatment Retention and Mean Number of Sprays of Medication per Day



A, Treatment retention. The risk set at initiation of the study was 67 participants receiving placebo and 61 participants receiving nabiximols. Vertical broken lines indicate estimated median lifetime: the estimated time when half the original sample had discontinued treatment. B, Daily mean (SD) doses of medication used during the 12-week period. Maintenance phase excludes the first week when dose was being titrated.

Figure 3. Frequency of Cannabis Use During the 12-Week Trial



Dotted vertical lines and diamonds indicate the mean number of days used for each group. The *P* value indicates the significance level of the treatment group coefficient from the regression of 84-day cannabis use on (1) treatment, (2) site, (3) treatment × site, and (4) baseline cannabis use, rounded to 2 decimal places. The solid vertical lines represent the median number of days used.

AEs and Aberrant Medication Use

Study medications were generally well tolerated, with no significant between-group differences in AEs (eAppendix 6 and eTables 4-6 in Supplement 2). A total of 32 participants (25.0%) reported an AE (placebo, 17 of 67 [25.4%]; and nabiximols, 15 of 61 [24.6%]), with 14 participants (10.9%) reporting 2 or more AEs. Headache was the only AE reported by more than 5% of participants (total, 7 of 128 [5.5%]; placebo, 2 of 67 [3.0%]; and nabiximols, 5 of 61 [8.2%]). One serious AE was reported by a participant in the placebo group who was hospitalized for suicidal ideation in the first week in the study and subsequently discontinued treatment. Brief Psychiatric Rating Scale scores were stable across the 2 groups over time, with no significant main effects of treatment or time, nor treatment × time interaction.

A total of 21 of all 70 participants who completed the Opioid-Related Behaviours In Treatment scale at week 14 (30.0%; placebo, 14 of 37 [37.8%]; nabiximols, 7 of 33 [21.2%]) reported any aberrant medication behaviors (eAppendices 7 and 8 and eTables 7 and 8 in Supplement 2), with no significant group differences. The most common behaviors were giving or selling medication to someone else (12 of 70 [17.1%]) and altering the dose in some other way (10 of 70 [14.3%]), referring to unauthorized dose escalation.

General Health and Patient Satisfaction Outcomes

Data on summary general health and psychosocial functional outcomes, other substance use, and crime are shown in Table 2. Omnibus tests revealed that, across both groups, there was general improvement in several outcomes (36-item Short Form Survey and Opioid Treatment Index-Crime subscale), with significant main effects of time, but no between-group differences, nor interactions between treatment and time. There were no significant changes over time in other substance use (Fagerström Test for Nicotine Dependence and Alcohol Use Disorders Identification Test), nor any between-group differences or interactions.

There were high levels of global satisfaction with the medication, with most participants indicating they would recommend the medication to a friend seeking treatment (placebo, 41 of 55 [74.5%]; nabiximols, 42 of 51 [82.4%]).

Testing the Study Blinding

The proportion of participants who correctly guessed their treatment allocation was significantly lower in the placebo group (27 of 55 [49.1%]) than the nabiximols group (42 of 51 [82.4%; odds ratio, 0.21; 95% CI, 0.08-0.50; *P* = .001).

Discussion

Our study demonstrates that cannabinoid agonist treatment, in combination with psychosocial interventions, reduced illicit cannabis use in patients with cannabis dependence who were seeking treatment. Participants who received nabiximols used illicit cannabis on two-thirds as many days (mean, 35 of 84 days [41.7%]) as those allocated to placebo (mean, 53 of 84 days [63.1%]), an estimated mean difference of 18.6 days, representing both a statistically and clinically meaningful

Table 2. Raw Mean (SD) Values, Main and Interaction Effects, and Simple Effects for Secondary Variables Across the 12-Week Trial

Variable	Mean (SD) Value[a]								Omnibus Effect[b]	Adjusted *P* Value[c]
	Week 0		Week 4		Week 8		Week 12			
	Placebo	Nabiximols	Placebo	Nabiximols	Placebo	Nabiximols	Placebo	Nabiximols		
Cannabis Withdrawal Scale score	65.1 (37.0)	64.8 (43.5)	47.5 (37.5)	44.7 (27.7)	44.2 (41.0)	42.6 (32.7)	43.6 (37.3)	30.7 (28.9)	Treatment	.56
									Time	<.001
Estimated difference (95% CI)[d]	−0.4 (−13.3 to 12.6)		−6.4 (−20.7 to 8.0)		−2.2 (−18.1 to 13.7)		−14.1 (−31.4 to 3.2)		Treatment × time	.60
Marijuana Craving Questionnaire score	48.2 (16.4)	46.7 (17.9)	36.8 (15.8)	34.3 (13.8)	34.0 (14.0)	27.7 (13.8)	31.2 (15.2)	27.2 (18.9)	Treatment	.29
Estimated difference (95% CI)	−1.5 (−7.0 to 4.1)		−1.4 (−7.6 to 4.9)		−5.7 (−12.6 to 1.1)		−3.4 (−10.3 to 3.5)		Time	<.001
									Treatment × time	.56
Cannabis Problems Questionnaire score	118.1 (44.5)	112.0 (52.8)	81.8 (50.3)	81.3 (48.9)	70.2 (48.5)	61.6 (54.2)	52.0 (43.4)	42.4 (49.8)	Treatment	.56
Estimated difference (95% CI)	−6.0 (−23.2 to 11.1)		1.6 (−16.7 to 19.8)		−6.3 (−26.5 to 14.0)		−4.4 (−24.7 to 15.9)		Time	<.001
									Treatment × time	.91
Fagerström Test for Nicotine Dependence score	1.9 (2.4)	2.8 (2.8)	1.7 (2.4)	2.9 (3.1)	2.0 (2.6)	2.6 (3.0)	1.6 (2.3)	2.8 (3.2)	Treatment	.31
Estimated difference (95% CI)	0.9 (−0.1 to 1.8)		0.0 (−0.6 to 0.6)		−0.3 (−1.0 to 0.3)		−0.1 (−0.7 to 0.6)		Time	.89
									Treatment × time	.85
AUDIT score	4.4 (5.1)	4.7 (4.3)	5.3 (5.3)	3.6 (3.6)	4.6 (4.2)	4.7 (5.8)	5.1 (5.4)	4.1 (5.0)	Treatment	.69
									Time	.91
Estimated difference (95% CI)	0.3 (−1.3 to 2.0)		−1.7 (−3.1 to 0.3)		−0.2 (−1.7 to 1.4)		−1.2 (−2.8 to 0.4)		Treatment × time	.28
SF-36 score										
Physical	87.2 (18.4)	86.2 (20.7)	86.5 (19.4)	89.9 (17.3)	86.6 (19.1)	88.0 (18.6)	90.9 (15.4)	92.4 (13.2)	Treatment	.69
Estimated difference (95% CI)	−1.08 (−7.5 to 5.4)		4.7 (−1.8 to 11.2)		3.11 (−4.1 to 10.3)		2.89 (−4.3 to 10.1)		Time	.28
									Treatment × time	.69
Role limitation-physical	36.6 (42.3)	34.4 (41.4)	35.5 (41.0)	28.1 (39.1)	36.6 (46.1)	20.7 (34.0)	25.0 (40.0)	27.0 (41.8)	Treatment	.56
									Time	.43
Estimated difference (95% CI)	−2.1 (−16.4 to 12.2)		−6.3 (−22.5 to 10.0)		−14.4 (−32.4 to 3.6)		5.2 (−12.8 to 23.3)		Treatment × time	.48
Role limitation-emotional	48.3 (44.7)	48.1 (45.8)	42.4 (43.3)	43.5 (44.2)	43.4 (44.6)	28.6 (38.9)	29.9 (41.0)	36.1 (46.0)	Treatment	.85
Estimated difference (95% CI)	−0.2 (−15.5 to 15.1)		−0.0 (−15.5 to 15.5)		−14.5 (−31.8 to 2.8)		6.2 (−11.3 to 23.7)		Time	.001
									Treatment × time	.43
Energy	43.4 (18.3)	40.8 (19.3)	48.4 (18.0)	47.8 (16.9)	47.8 (19.6)	48.6 (18.9)	54.4 (19.0)	48.8 (23.3)	Treatment	.56
Estimated difference (95% CI)	−2.6 (−9.2 to 3.9)		2.4 (−4.2 to 9.0)		1.3 (−6.0 to 8.6)		−4.7 (−12.0 to 2.7)		Time	<.001
									Treatment × time	.56

(continued)

Table 2. Raw Mean (SD) Values, Main and Interaction Effects, and Simple Effects for Secondary Variables Across the 12-Week Trial (continued)

Variable	Mean (SD) Value[a]								Omnibus Effect[b]	Adjusted *P* Value[c]
	Week 0		Week 4		Week 8		Week 12			
	Placebo	Nabiximols	Placebo	Nabiximols	Placebo	Nabiximols	Placebo	Nabiximols		
Emotional well-being	56.1 (20.2)	54.7 (18.1)	61.8 (20.3)	61.5 (17.6)	62.4 (19.9)	62.6 (19.0)	65.1 (22.7)	64.1 (20.4)	Treatment	.69
Estimated difference (95% CI)	−1.5 (−8.3 to 5.3)		1.4 (−5.6 to 8.3)		−0.6 (−8.3 to 7.2)		−2.1 (−9.9 to 5.6)		Time	<.001
									Treatment × time	.91
Social	54.9 (30.6)	59.1 (26.7)	62.1 (29.5)	63.7 (27.2)	68.0 (28.5)	64.3 (25.4)	71.6 (28.0)	68.0 (29.7)	Treatment	.97
Estimated difference (95% CI)	4.3 (−5.6 to 14.1)		−2.0 (−12.5 to 8.5)		−7.4 (−19.1 to 4.8)		−8.2 (−20.0 to 3.6)		Time	.001
									Treatment × time	.61
Pain	69.8 (26.2)	70.5 (25.6)	73.7 (26.7)	81.5 (22.4)	79.7 (27.8)	76.9 (26.2)	77.8 (24.0)	82.7 (22.4)	Treatment	.61
Estimated difference (95% CI)	0.6 (−8.1 to 9.4)		7.2 (−2.0 to 16.4)		−1.3 (−11.5 to 8.9)		3.3 (−6.9 to 13.5)		Time	<.001
									Treatment × time	.56
General	49.3 (19.7)	53.9 (21.6)	54.7 (19.5)	54.6 (23.6)	52.6 (22.5)	60.0 (24.0)	55.8 (22.2)	58.4 (22.4)	Treatment	.60
Estimated difference (95% CI)	4.5 (−3.0 to 12.0)		−3.7 (−10.5 to 3.1)		1.6 (−6.0 to 9.2)		−4.5 (−12.1 to 3.1)		Time	.45
									Treatment × time	.56
OTI drug-related crime, No. (%)[e,f]	24 (35.8)	21 (34.4)	12 (20.3)	6 (11.8)	13 (28.9)	8 (21.1)	13 (32.5)	4 (10.8)	Treatment	.28
Odds ratio (95% CI)	0.9 (0.1 to 7.2)		0.3 (0.0 to 2.0)		0.4 (0.1 to 3.4)		0.1 (0.0 to 0.6)		Time	.001
									Treatment × time	.40

Abbreviations: AUDIT, Alcohol Use Disorders Identification Test; OTI, Opioid Treatment Index; Pl, Placebo; SF-36, 36-item Short Form Survey.

[a] Negative estimates indicate nabiximols scoring lower than placebo.

[b] Treatment = main effect of treatment group averaged across time points; time = main effect of time averaged across treatment groups; treatment × time = interaction between treatment group and time.

[c] For omnibus main and interaction effects adjusted for multiple comparisons using the Benjamini-Hochberg procedure for controlling the false discovery rate.

[d] Estimated difference between nabiximols and placebo groups at the time point in question. 95% CIs within each regression model are uncorrected.

[e] Number who committed 1 or more drug-related crimes in the previous 4 weeks.

[f] Omnibus statistics obtained from type 3 Wald χ^2 tests.

reduction. This treatment effect was consistent across study sites, suggesting that the benefits of nabiximols are generalized across different treatment settings. The reductions in illicit cannabis use, and a safer route of administration (compared with smoked cannabis using bongs or joints that are associated with chronic respiratory problems[4,5]) suggest the harm reduction benefits of cannabinoid agonist treatment.

Limitations

Our findings also highlight some limitations of this treatment: only half of the participants were retained in treatment during the 12-week period, illicit cannabis was still used on 41.7% of possible days, and abstinence from illicit cannabis was achieved by only a minority of patients. Although our treatment retention of 46.9% at 12 weeks is comparable with prior randomized clinical trials of cannabinoid agonist treatment (55% at 11 weeks[16] and 67% at 12 weeks[17]), the limited treatment retention across these studies highlights the fact that cannabinoid agonist treatment is not effective for or acceptable to all patients. Further research is required to better understand the reasons for treatment dropout from trials[40]—for example, some participants in both groups thought they were receiving placebo, which may undermine treatment retention—and/or whether improvements in the model of care (eg, treatment duration, cannabinoid preparation, dose, psychosocial interventions, or better targeting of patients) can enhance future treatment outcomes. For example, our findings of reduced cannabis use with nabiximols is in contrast with findings from a trial of fixed-dose dronabinol that suggested no benefit vs placebo.[16] It remains unclear whether our flexible dose schedule, the pharmacokinetic profile of nabiximols (higher bioavailability and more rapid onset of action), and/or the combination of THC with CBD (anticraving[41,42] and neuroprotective[43,44] properties in cannabis users), conveys advantages vs dronabinol.

In our study, as in previous studies, high doses of THC-based medications were well tolerated in this patient group, reflecting their pharmacologic tolerance to THC. Patients with severe mental health problems, such as psychosis or bipolar affective disorder, were excluded from the study, and caution should remain regarding the use of THC-based medicines in such patients.

Despite the nabiximols group reporting significantly less illicit cannabis use than the control group, participants in both groups improved to a comparable degree on a range of secondary cannabis-related (withdrawal and cravings) and general health and psychosocial outcomes (eg, cannabis-related problems and the 36-item Short Form Survey). The interpretation of withdrawal and cannabis scores is difficult in the context of an outpatient study in which most participants in the control group used cannabis on most days throughout the study.

There are several possible explanations for the comparable improvements in general health outcomes: (1) the treatment elements consistent to both groups (counseling, case management, medical and nursing reviews, and therapeutic rapport) were associated with improved general health; (2) the reductions in illicit cannabis use in the control group, while not as great as in the nabiximols group, were nevertheless sufficient to lead to improvements in general health; and (3) participants experienced a possible therapeutic placebo effect related to expectancy issues (particularly as half of the participants in the placebo group thought they were receiving nabiximols). Just as important, nabiximols—even at high doses—does not appear to prevent improvements in areas such as mental health, addressing potential concerns that a THC-based medication may contribute to persistent mental health problems.

Other limitations are worth noting, particularly the low (60.2%) follow-up of participants completing week 12 research interviews. Although statistical analysis (multilevel multiple-imputation) that imputed for missing data resulted in similar findings to nonimputed and per-protocol analyses, the 60.2% research follow-up rate suggests that some caution is warranted in interpreting our findings.

Another limitation is our reliance on self-reported measures of illicit cannabis use, as we are unable to differentiate prescribed from unsanctioned THC use in urine test results at this time. Although the urine drug screening results in the placebo arm indicate adequate validity of self-report in this study, further research is required to develop objective markers of illicit use, for both clinical and research purposes. Finally, our study examined a 12-week medication period, and open-label follow-up studies of longer duration (eg, 6 or 12 months) are needed to establish the safety and effectiveness under real-world conditions.

Conclusions

Cannabinoid agonist treatment is unlikely to be an approach relevant to all cannabis users seeking treatment, as evidenced by the large numbers of individuals who did not complete the study screening process, and the modest 12-week treatment retention rates. Whereas nicotine-agonist and opioid-agonist treatments are considered front-line therapies, our findings suggest a more cautious approach for cannabinoid agonist treatment at this time. The control group demonstrated some benefits from treatment, confirming previous research that psychosocial interventions (CBT and case management) without medication can be effective for some patients. Although further research is required to replicate our findings and to refine how cannabinoid agonist treatment is delivered, our study suggests cannabinoid agonist treatment to be a promising approach for treating patients with cannabis dependence, particularly for those who cannot sustain reductions in illicit cannabis use with counseling-only interventions, in a stepped care approach.

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