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Original Investigation

Nabiximols as an Agonist Replacement Therapy During Cannabis Withdrawal

A Randomized Clinical Trial

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IMPORTANCE There are no medications approved for treating cannabis dependence or withdrawal. The cannabis extract nabiximols (Sativex), developed as a multiple sclerosis treatment, offers a potential agonist medication for cannabis withdrawal.

OBJECTIVE To evaluate the safety and efficacy of nabiximols in treating cannabis withdrawal.

DESIGN, SETTING, AND PARTICIPANTS A 2-site, double-blind randomized clinical inpatient trial with a 28-day follow-up was conducted in New South Wales, Australia. Participants included 51 DSM-IV-TR cannabis-dependent treatment seekers.

INTERVENTIONS A 6-day regimen of nabiximols (maximum daily dose, 86.4 mg of Δ^9 -tetrahydrocannabinol and 80 mg of cannabidiol) or placebo with standardized psychosocial interventions during a 9-day admission.

MAIN OUTCOMES AND MEASURES Severity of cannabis withdrawal and cravings (Cannabis Withdrawal Scale), retention in withdrawal treatment, and adverse events. Secondary outcomes include postwithdrawal cannabis use, health outcomes, and psychosocial outcomes.

RESULTS Nabiximols treatment significantly reduced the overall severity of cannabis withdrawal relative to placebo ($F_{8,377.97} = 2.39$; $P = .01$), including effects on withdrawal-related irritability, depression, and cannabis cravings. Nabiximols had a more limited, but still positive, therapeutic benefit on sleep disturbance, anxiety, appetite loss, physical symptoms, and restlessness. Nabiximols patients remained in treatment longer during medication use (unadjusted hazard ratio, 3.66 [95% CI, 1.18-11.37]; $P = .02$), with 2.84 the number needed to treat to achieve successful retention in treatment. Participants could not reliably differentiate between nabiximols and placebo treatment ($\chi^2_1 = 0.79$; $P = .67$), and those receiving nabiximols did not report greater intoxication ($F_{1,6} = 0.22$; $P = .97$). The number ($F_{1,50} = 0.3$; $P = .59$) and severity ($F_{1,50} = 2.69$; $P = .10$) of adverse events did not differ significantly between groups. Both groups showed reduced cannabis use at follow-up, with no advantage of nabiximols over placebo for self-reported cannabis use ($F_{1,48} = 0.29$; $P = .75$), cannabis-related problems ($F_{1,49} = 2.33$; $P = .14$), or cannabis dependence ($F_{1,50} < 0.01$; $P = .89$).

CONCLUSIONS AND RELEVANCE In a treatment-seeking cohort, nabiximols attenuated cannabis withdrawal symptoms and improved patient retention in treatment. However, placebo was as effective as nabiximols in promoting long-term reductions in cannabis use following medication cessation. The data support further evaluation of nabiximols for management of cannabis dependence and withdrawal in treatment-seeking populations.

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Cannabis is the most prevalent illicit drug in the world,¹ and its use has been linked to a range of negative health outcomes.² Approximately 10% of cannabis users will become dependent, leading to treatment.³ In the United States, treatment episodes involving cannabis as the primary drug increased from 6% in 1992 to 16% in 2007.⁴ Cannabis was mentioned as the primary drug of concern in 287 933 episodes in 2007 and was one of multiple drugs of concern in almost 1 million treatment episodes.⁴ Similar increases in cannabis treatment seeking are observed globally.^{5,6} A cannabis withdrawal syndrome was included for the first time in the *SM-5*.^{7,8} More than half of cannabis users report withdrawal,⁹ with primary symptoms including irritability, insomnia, decreased appetite, depressed mood, anxiety, and restlessness.¹⁰ Withdrawal symptoms are considered to be a major determinant of the high relapse rates observed in individuals receiving treatment.¹¹⁻¹⁸

There are no approved pharmacotherapies for managing cannabis withdrawal.¹⁹⁻²¹ A range of symptomatic medications have been evaluated, including the antidepressants bupropion and nefazodone,^{22,23} the mood stabilizers divalproex^{24,25} and lithium,²⁶ and the α_2 -adrenergic agonist lofexidine,²⁷ with limited benefits. Agonist substitution approaches may be more promising. Oral delivery of synthetic $\Delta 9$ -tetrahydrocannabinol (THC; dronabinol was the THC formulation used) dose-dependently reduced a subset of cannabis withdrawal symptoms in laboratory²⁴ and outpatient settings.^{28,29} Nabilone, a synthetic analogue of THC with higher oral bioavailability than dronabinol, was efficacious in a recent laboratory study.³⁰ These findings suggest that further examination of agonist therapies for cannabis withdrawal are warranted.

Nabiximols (Sativex; GW Pharmaceuticals, UK) is a medication containing THC, cannabidiol (CBD), and various terpenoids derived from *Cannabis sativa* plants. It is delivered as a buccal spray, with absorption through the oral mucosa, leading to a more predictable pharmacokinetic profile than oral THC.³¹ The CBD content of nabiximols is of particular interest given that CBD attenuates the paranoia³² and euphoria³³ associated with THC and may have efficacy in treating anxiety, depression, and psychosis.³⁴⁻³⁸ A recent case study³⁹ reported strong attenuation of symptoms when CBD was used to treat cannabis withdrawal. Nabiximols is approved in many countries to treat muscular spasticity associated with multiple sclerosis. Nabiximols typically produces little intoxication,⁴⁰ tolerance,⁴¹⁻⁴³ or withdrawal.⁴⁴ This indicates low abuse potential relative to other cannabinoids, such as dronabinol.⁴⁵ We hypothesized that nabiximols would reduce the severity of cannabis withdrawal symptoms and increase patient retention during inpatient detoxification, without significant safety concerns or intoxication. Assessment of cannabinoid levels in plasma and urine allowed determination of whether nabiximols provided effective pharmacologic substitution for cannabis. Secondary hypotheses, that use of nabiximols leads to reduced cannabis use and dependence, as well as improved psychosocial outcomes at the 28-day follow-up, were also tested.

Methods

Study Design

The study was a 2-site, randomized, double-blind, inpatient trial with 6 days of nabiximols or placebo treatment, 3 days of washout, and a 28-day follow-up period. Patients were admitted for inpatient detoxification at either Sydney and Sydney Eye Hospital (SSEH) or at Belmont Hospital, New South Wales, Australia, between December 5, 2011, and October 17, 2012, with follow-up completed by November 15, 2012. The trial protocol is available from the authors on request.

This research was approved by the Hunter New England Human Research Ethics Committee. Patients gave written informed consent to take part in the study on day 1 of admission to the unit, which triggered randomization. Participants were compensated with A\$40 for follow-up interviews.

Participants

Inclusion criteria were (1) age 18 to 65 years, (2) met criteria for current *DSM-IV-TR* cannabis dependence with no current alcohol or other drug dependence except for nicotine and/or caffeine, (3) experienced withdrawal during previous quit attempts, and (4) desired to reduce or quit cannabis use. Exclusion criteria were (1) unstable medical or psychiatric conditions, (2) medications initiated or dose changed in the previous month, (3) pregnancy, (4) urine sample negative for cannabinoids (tetrahydrocannabinol [THC]-COOH), (5) positive urine test result for other illicit substances or benzodiazepines, or (6) received formal drug or alcohol treatment in the previous month (excluding treatment for nicotine dependence).

Procedures

Patients were referred from treatment services or responded to media advertisements. Eligibility assessments included urine drug screens, structured medical assessment by addiction medicine specialists, and the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders: Research Version (SCID-RV)⁴⁶ by a psychologist. Withdrawal, as defined by participants' experiencing 3 or more symptoms after cessation of prolonged cannabis use or continuing use to avoid withdrawal symptoms, was assessed during the SCID-RV. Race and ethnicity were documented by self-report (ie, white, Aboriginal, or Torres Strait Islander) for routine documentation. The study flow diagram is presented in **Figure 1**.

Patients were requested to abstain from smoking cannabis for at least 6 hours before admission. After randomization, patients completed a 6-hour orientation with baseline research surveys, including premedication withdrawal measures and detailed timeline follow-back interviews to assess cannabis use, including recent use (up to the night before admission). Study drugs were administered by trained nurses as per protocol.

Nabiximols Dosing

The first dose was administered at 4 PM on day 1 (8 sprays, a total of 21.6 mg THC and 20 mg CBD) and again at 10 PM (8

sprays). A maximal dose (8 sprays 4 times daily provides 86.4 mg of THC and 80 mg of CBD per day) was administered on days 2 and 3. The dose was tapered to 6 sprays 4 times daily on day 4 (64.8 mg of THC and 60 mg of CBD per day), 4 sprays 4 times daily on day 5 (10.8 mg of THC and 10 mg of CBD per day), and 2 sprays 4 times daily (5.4 mg of THC and 5 mg of CBD per day) on day 6. Days 7, 8, and 9 served as the washout period (ie, medication free). The dosing regimen was based on safety data from previous studies (up to 48 sprays per day were tolerated in cannabis-naive individuals),⁴⁷ and observations that cannabis users find 16 sprays to be indistinguishable from a 40-mg dose of dronabinol for intoxication and abuse liability.^{40,45}

Study Medications

Tobacco users were offered nicotine replacement therapy (NRT) using topical patches. Patients were allowed 20 mg of temazepam for sleep difficulties on no more than 2 nights during the 9-day admission. Caffeine-based drinks were not available at 1 site. Other medications taken by individual patients prior to the admission were continued during the treatment episode.

Psychosocial Intervention

A cognitive behavioral therapy-based self-completed workbook,⁴⁸ tailored to an inpatient cannabis withdrawal intervention, was used. This was accompanied by standard detoxification care from trained nurses, which includes guided psychotherapy standardized across groups and study sites.

Blinding/Randomization

An independent statistician generated a randomization list for each site using random block sizes in Stata, version 11.1 (Stata-Corp) (initialization seed 675). Patients, investigators, and outcome assessors were blind to treatment allocation until all research procedures were complete. Blinding was maintained by the use of a matched placebo developed by GW Pharmaceuticals, UK. The success of patient blinding was formally assessed before hospital discharge.

Measures

The primary outcome measure was the Cannabis Withdrawal Scale (CWS).^{10,18} The CWS is a 19-item scale measuring withdrawal symptom severity on an 11-point Likert scale for the previous 24 hours (0, not at all; 5, moderate; and 10, extreme). Researcher-administered baseline and follow-up interviews collected information on demographic details and cannabis, alcohol, and tobacco use with the modified timeline follow-back⁴⁹; Cannabis Problems Questionnaire⁵⁰; Brief Treatment Outcome Measure-Social Functioning Scale⁵¹; Athens Insomnia Scale⁵²; Severity of Dependence Scale (SDS)^{53,54}; Sheehan Disability Scale⁵⁵; self-coping and efficacy for Quitting Cannabis Questionnaire⁵⁶; a subscale from the Depression, Anxiety, and Stress Scale⁵⁷; Anxiety Sensitivity Index-Revised^{58,59}; Distress Tolerance Scale⁶⁰; and the Barratt Impulsiveness Scale.⁶¹ Adverse events (AEs) were quantified daily using a 4-point severity scale (0, none; 1, mild; 2, moderate; and 3 severe). Intoxication was evaluated before and after dosing using an 11-point Likert “stoned” scale. Medication adherence was assessed from medication records. Dose adequacy was assessed by patient interview.

Figure 1. Study Flow

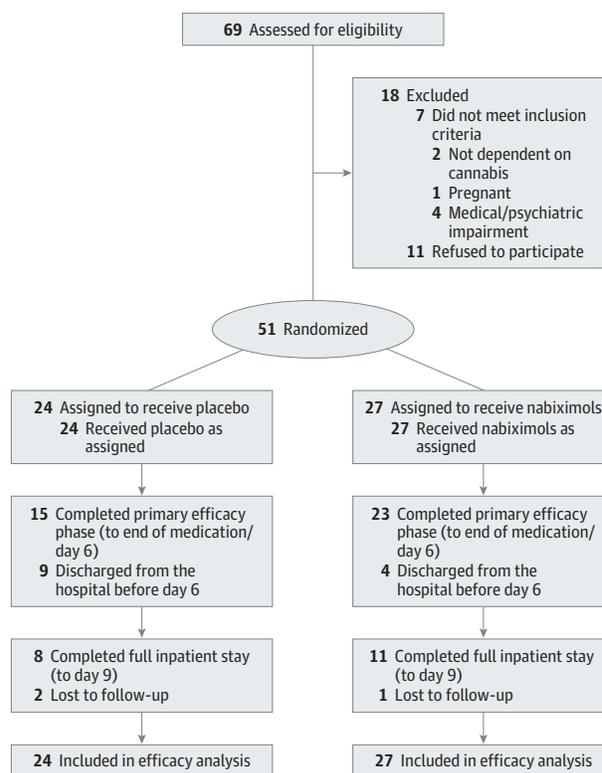


Diagram shows the number of participants at each stage of the study.

Measurement of Plasma and Urinary Cannabinoids

With consent from patients, blood samples were collected on day 1 (baseline, premedication), day 3 (peak dosing), and day 7 (first day after medication completion) to allow determination of cannabinoid levels (THC, CBD, and THC-COOH) relative to withdrawal signs (sample sizes are reported in the Supplement [eFigure 2]). Blood was collected at 12:30 PM (30 minutes after the midday nabiximols dose) and centrifuged at 1500g for 10 minutes, and plasma was stored at -20°C . Urine samples were also collected on days 1, 3, and 7. Assessment of levels of the secondary THC metabolite (THC-COOH) in urine allowed baseline and peak cannabinoid levels to be compared across groups, as well as verification of self-reported abstinence at 28 days. The analytical methods used for cannabinoid determination are reported in the Supplement (eMethods).

Missing Data

Analysis revealed 14.4% missing data from baseline to day 7 (first day with no medication), and 28.6% to day 9. The majority was whole CWS questionnaires missing resulting from early dropout. The Little test was used to assess the data missing completely at random ($\chi^2_{2976} = 68.67$; $P = .89$). Missing questionnaires were imputed using multiple imputation,⁶² generating 5 different plausible data sets allowing for the uncertainty in predictions.⁶³

Table 1. Baseline Characteristics According to Treatment Group^a

| Characteristic | Nabiximols (n = 27) | Placebo (n = 24) | Total (N = 51) | P Value ^b |
|--|------------------------|---------------------|-------------------|----------------------|
| Demographics, No. (%) | | | | |
| Age, mean (SD), y | 34.96 | 35.88 | 35.39 | .72 |
| Male sex | 18 (67) | 21 (88) | 39 (76) | .08 |
| Aboriginal or Torres Strait Islander | 2 (7) | 1 (4) | 3 (6) | .62 |
| Completed school | 15 (56) | 13 (54) | 28 (55) | .99 |
| Unemployed | 15 (56) | 12 (50) | 27 (53) | .67 |
| Married, including de facto | 4 (15) | 9 (38) | 13 (25) | .35 |
| Substance use history, mean (SD) | | | | |
| Cannabis use, g ^c | 23.39 (16.79) | 22.52 (24.54) | 22.98 (20.66) | .88 |
| Carboxy-THC/creatinine ratio, ng/mg | 2392.70 (1441.69) | 3285.56 (5525.82) | 2815.63 (3911.64) | .49 |
| Years of cannabis use | 20.11 (9.83) | 20.79 (8.67) | 20.43 (9.22) | .79 |
| Cannabis SDS | 11.96 (3.03) | 12.13 (2.35) | 12.04 (2.71) | .83 |
| Alcohol SDS | 0.31 (0.87) | 0.63 (1.28) | 0.45 (1.08) | .28 |
| Alcohol use, U/wk ^d | 3.65 (8.42) | 5.86 (8.33) | 4.71 (8.37) | .36 |
| Nicotine dependence, Fagerstrom score | 3.11 (2.76) | 2.75 (2.47) | 2.94 (2.61) | .63 |
| No. (%) nicotine dependent ^e | 19 (70) | 17 (71) | 36 (71) | .97 |
| Cigarettes/wk | 76.68 (69.07) | 65.55 (64.29) | 71.34 (66.38) | .56 |
| No. SCID-RV cannabis dependence items | 6.19 (0.75) | 5.91 (0.97) | 6.06 (0.86) | .26 |
| No. other drug use disorders | 0.65 (1.44) | 1.09 (1.29) | 0.85 (1.38) | .28 |
| Cannabis Withdrawal Scale score | 2.51 (1.57) | 1.68 (0.96) | 2.12 (1.37) | .02 |
| Psychosocial functioning scores, mean (SD) | | | | |
| BTOM Social Functioning | 7.79 (3.45) | 6.91 (3.23) | 7.38 (3.35) | .36 |
| Sheehan Disability Scale, total | 18.11 (7.25) | 11.33 (7.59) | 14.92 (8.09) | .002 |
| Self-efficacy Scale | 2.99 (1.26) | 3.05 (1.26) | 3.03 (1.25) | .88 |
| Anxiety Sensitivity Index-Revised | 51.50 (24.88) | 44.63 (28.26) | 48.20 (26.51) | .37 |
| DASS Depression | 19.15 (10.66) | 14.25 (11.31) | 16.80 (11.14) | .12 |
| DASS Anxiety | 13.58 (8.46) | 10.67 (6.57) | 12.18 (7.68) | .18 |
| DASS Stress | 22.42 (9.09) | 21.29 (9.53) | 21.88 (9.22) | .67 |
| Distress Tolerance Scale | 2.79 (0.78) | 2.81 (0.73) | 2.80 (0.75) | .93 |
| Athens Insomnia Scale | 10.58 (5.19) | 8.33 (3.94) | 9.50 (4.72) | .09 |
| Barratt Impulsiveness Scale | 81.89 (10.72) | 82.08 (11.60) | 81.98 (11.03) | .95 |

Abbreviations: BTOM, Brief Treatment Outcome Measure; DASS, Depression, Anxiety, and Stress Scale; SCID-RV, Structured Clinical Interview for DSM-IV-TR Axis I Disorders: Research Version; SDS, Severity of Dependence Scale; THC, tetrahydrocannabinol.

^a The 2 measures that were significantly different at baseline were adjusted for in all efficacy analyses by their inclusion as covariates.

^b Statistical comparisons are from: (1) 1-way analysis of variance for continuous variables, (2) Fisher exact test for categorical variables with any cells in the contingency table with less than 5 variables, and (3) χ^2 test for all other categorical variables.

^c Weekly cannabis use in grams in the month before entering the study, measured by modified timeline follow-back.

^d Weekly alcohol use in units in the month before entering the study, measured by modified timeline follow-back.

^e Participants were classed as dependent on nicotine if they had a Fagerstrom score between 1 and 10.

Statistical Analysis

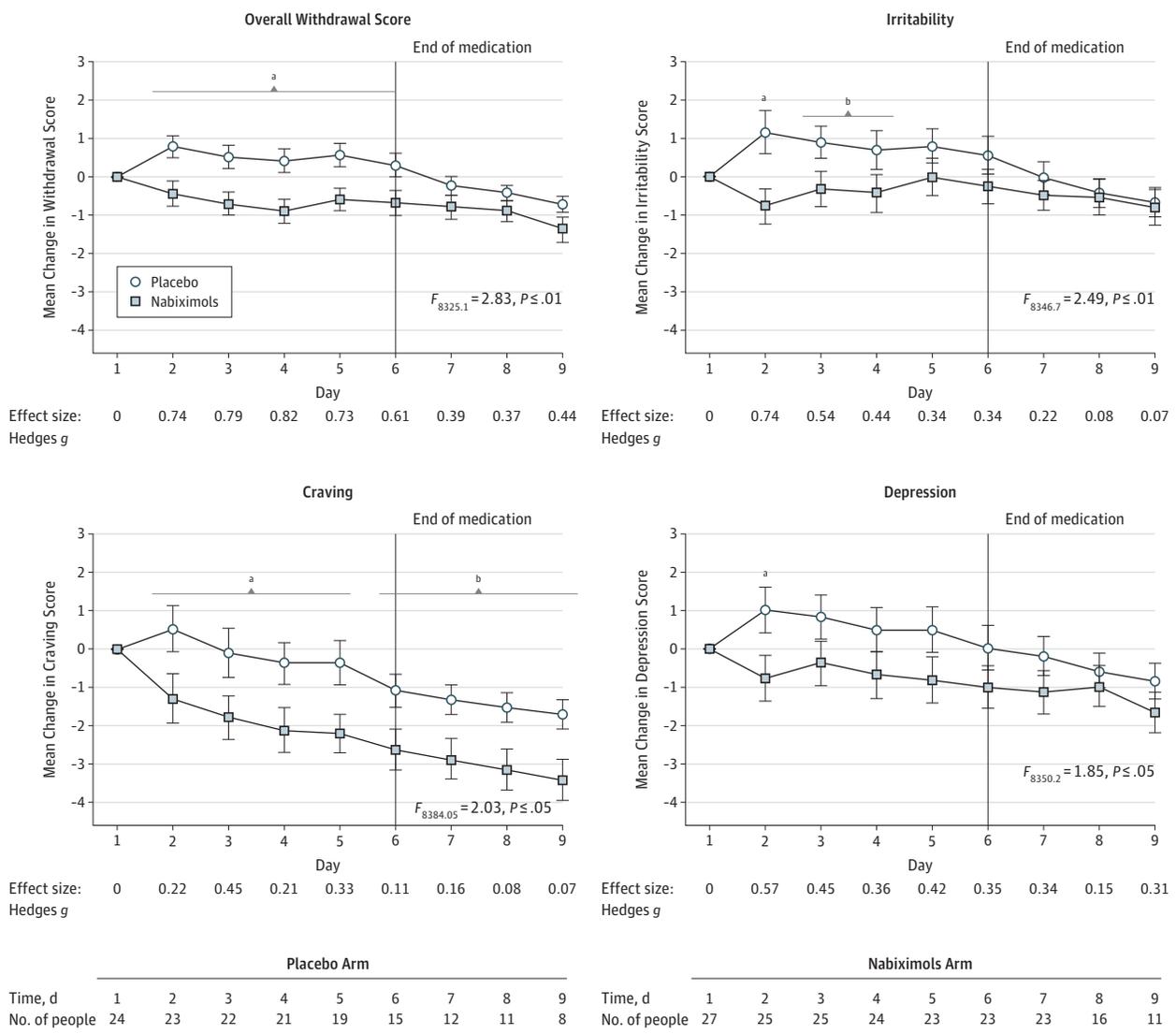
Power analysis was based on a dronabinol study (30 mg)²⁸ using the Total Marijuana Withdrawal Checklist (TMWC) scores (a proxy for the CWS). The analysis suggested that 20 participants per group would provide 99.5% power to detect a 27% suppression of withdrawal with agonist treatment (mean [SD] increase in TMWC score of 6.2 [1.0] from baseline to abstinence while the patient received placebo compared with an increase of 4.5 [2.0] with dronabinol, using repeated-measures analysis).²⁸ Intention-to-treat analysis included all 51 randomized participants. For descriptive statistics, group differences in continuous variables used 2-way analyses of variance, and categorical variables used Pearson χ^2 or Fisher exact test when cells had a count of less than 5. Statistical analyses were performed with SPSS, version 21 (SPSS Corp).

The primary analysis compared main effects and the interaction of treatment and time on mean difference from

baseline CWS scores in a mixed models for repeated measures regression with first-order autoregressive covariance structure.⁶⁴⁻⁶⁶ The model was adjusted with covariates known or suspected to influence the experience of cannabis withdrawal (SDS scores),^{10,18} baseline variables that were significantly different between groups (CWS scores and Sheehan Disability Scale scores), and other possible moderators of withdrawal (use of NRT/cigarettes,⁶⁷ temazepam, and caffeine during abstinence).

Post hoc pairwise comparisons compared withdrawal between groups on each day of treatment adjusted for multiple comparisons using the Bonferroni method. Hierarchical model building (step 1: time, treatment, time \times treatment; step 2: addition of covariates) explored changes in variance explained using pseudo- R^2 calculated from log-likelihood ratios (R^2_{LR}).⁶⁸ Akaike information criteria⁶⁹ calculated model fit (smaller values indicate better fit). Separate analyses tested the effect of nabiximols on attenuating

Figure 2. Mean Change From Baseline in Withdrawal Score for Overall Withdrawal Scores and for Symptoms That Were Significantly Suppressed by Nabiximols



The adjusted model graphs show the mean values across all 5 multiply imputed data sets. Effect sizes (Hedges *g*) for change in withdrawal scores each day relative to baseline are reported. Sample sizes in each treatment arm before multiple imputation are also shown. Significance was based on the unadjusted mixed models for repeated measures (MMRM) post hoc pairwise comparisons

between groups on each day, adjusted for multiple comparisons using Bonferroni adjustment. Treatment × time interactions shown: Omnibus type II test of fixed effects from adjusted MMRM. Error bars indicate standard error. ^a*P* ≤ .01. ^b*P* ≤ .05.

DSM-5 cannabis withdrawal symptoms (Supplement [eTable 1]).⁷ Effect sizes are reported using the bias-corrected Hedges *g* (raw difference between 2 means divided by SD adjusted for population size).⁷⁰ Parametric statistics were used on Likert data because interval structure can be assumed if scales are presented as symmetrical.⁷¹ Residuals from the primary withdrawal efficacy analysis were normally distributed.

The effect of nabiximols on retention in withdrawal treatment was assessed with a stepwise Cox proportional hazards regression model, first looking at treatment alone,

then controlling for SDS, Sheehan Disability Scale, and CWS scores and the use of NRT/cigarettes, temazepam, and caffeine. The proportions of people in each treatment group reporting each AE were analyzed using χ^2 or the Fisher exact test. Time to relapse between the end of the inpatient stay and the 28-day follow-up were assessed using a Kaplan-Meier survival analysis. Finally, changes in cannabis-related problems, the severity of cannabis dependence, and cannabis use levels were assessed using the mixed models for repeated measures approach. All tests were 2-sided, with significance set at *P* ≤ .05.

Table 2. Outcome Measures: Unadjusted Model^a

| Outcome Variable | Mean Scores | | Time | Treatment | Time × Treatment | R ² _{LR} ^c | AIC ^d |
|--------------------------|-------------|-------------------------|---|---|---|---|------------------|
| | Baseline | Abstinence ^b | | | | | |
| Overall withdrawal score | | | | | | | |
| Nabiximols | 2.51 (1.57) | 1.88 (1.64) | F _{8,377.97} = 3.94 ^e | F _{1,77.97} = 11.01 ^f | F _{8,377.97} = 2.39 ^f | 0.50 | 1444.12 |
| Placebo | 1.68 (0.96) | 2.22 (1.62) | | | | | |
| Irritability | | | | | | | |
| Nabiximols | 1.80 (2.40) | 1.44 (1.84) | F _{8,367.97} = 1.48 | F _{1,75.06} = 3.09 | F _{8,367.97} = 2.49 ^f | 0.42 | 1775.13 |
| Placebo | 1.31 (1.81) | 2.19 (2.34) | | | | | |
| Depression | | | | | | | |
| Nabiximols | 2.78 (2.59) | 2.04 (2.43) | F _{8,377.62} = 1.39 | F _{1,71.95} = 2.74 | F _{8,377.62} = 1.85 | 0.45 | 1928.86 |
| Placebo | 1.71 (2.26) | 2.32 (2.62) | | | | | |
| Anxiety | | | | | | | |
| Nabiximols | 4.07 (3.29) | 1.26 (2.11) | F _{8,389.19} = 8.96 ^e | F _{1,69.15} = 0.96 | F _{8,389.19} = 1.08 | 0.81 | 1964.28 |
| Placebo | 3.42 (3.02) | 1.64 (2.21) | | | | | |
| Cannabis cravings | | | | | | | |
| Nabiximols | 3.89 (2.81) | 1.87 (2.28) | F _{8,384.05} = 4.38 ^e | F _{1,73.2} = 10.28 ^f | F _{8,384.05} = 2.03 ^g | 0.66 | 1812.78 |
| Placebo | 2.04 (1.88) | 1.81 (2.26) | | | | | |
| Physical symptoms | | | | | | | |
| Nabiximols | 1.27 (1.42) | 1.07 (1.21) | F _{8,374.81} = 2.89 ^f | F _{1,75.46} = 3.66 | F _{8,374.81} = 1.43 | 0.18 | 1261.96 |
| Placebo | 0.84 (0.83) | 1.42 (1.50) | | | | | |
| Sleep difficulty | | | | | | | |
| Nabiximols | 2.95 (2.41) | 2.79 (2.58) | F _{8,343.86} = 3.93 ^e | F _{1,80.65} = 2.79 | F _{8,343.86} = 0.98 | 0.60 | 1984.70 |
| Placebo | 2.29 (1.92) | 3.29 (2.23) | | | | | |
| Restlessness | | | | | | | |
| Nabiximols | 3.44 (3.36) | 2.8 (2.69) | F _{8,359.46} = 1.51 | F _{1,81.38} = 0.64 | F _{8,359.47} = 0.66 | 0.45 | 2237.29 |
| Placebo | 3.21 (2.39) | 3.52 (2.99) | | | | | |
| Decreased appetite | | | | | | | |
| Nabiximols | 3.56 (3.31) | 2.12 (2.88) | F _{8,357.5} = 2.52 ^f | F _{1,76.81} = 5.09 ^g | F _{8,357.5} = 1.13 | 0.61 | 2248.24 |
| Placebo | 1.95 (2.96) | 2.34 (2.62) | | | | | |

Abbreviation: AIC, Akaike information criterion.

^d Measure of model fit; a smaller value indicates a better model fit.

^a Mixed models for repeated measures output using all days (1-9) as predictors in the model.

^e P ≤ .001.

^f P ≤ .01.

^b Abstinence means were calculated during days 2 to 6 (drug administration phase excluding baseline). Detailed description of values on all days of inpatient stay are reported in Author Table 2.

^g P ≤ .05.

^c Variance in outcome variable explained by model (approximated using -2 log-likelihoods).

Results

Demographics and Clinical Features

A total of 51 patients were randomized to receive placebo (n = 24) or nabiximols (n = 27). Patients reported high levels of cannabis use (mean [SD], 22.98 [20.66] g/wk),⁴⁹ corroborated by day 1 urine (Supplement [eFigure 1]) and plasma (Supplement [eFigure 2]) THC and THC-COOH levels. Patients had smoked cannabis for 20.43 (9.22) years, and their mean score of 12.04 (2.71) on the 15-point SDS scale indicated severe cannabis dependence (Table 1). Groups were well matched apart from differences in baseline CWS and Sheehan Disability Scale scores (Table 1). The Sheehan Disability Scale scores were also significantly different between study sites.

Effects of Cannabis Withdrawal

Nabiximols significantly reduced CWS scores (mean 66% decrease from baseline levels) relative to placebo (mean 52% increase) for the duration of treatment (treatment × time: F_{8,377.97} = 2.39; P = .01) (Figure 2 and Table 2). The effect remained significant after adjusting for covariates (treatment × time: F_{8,325.1} = 2.83; P = .003) (Table 3). Across DSM-5 withdrawal symptoms (Figure 2 and Table 2, and Author Table 1 [available from the author; <http://www.davidallsop.net/>]) the nabiximols group showed significantly lower levels of cannabis cravings (treatment × time: F_{8,384.05} = 2.03; P = .04) as well as irritability, anger, and aggression (treatment × time: F_{8,367.97} = 2.49; P = .01). Loss of appetite was also attenuated (main effect: F_{1,76.81} = 5.09; P = 0.03) (Table 2). After adjustment for covariates, nabiximols still reduced cravings (treatment × time: F_{8,376.2} = 2.04; P = .03) as well as irritability, anger,

Table 3. Outcome Measures: Adjusted Model^a

| Outcome Variable | Mean Scores | | Time | Treatment | Time × Treatment | R ² _{LR} ^c | AIC ^d |
|--------------------------|-------------|-------------------------|-------------------------|------------------------|------------------------|---|------------------|
| | Baseline | Abstinence ^b | | | | | |
| Overall withdrawal score | | | | | | | |
| Nabiximols | 2.51 (1.57) | 1.88 (1.64) | $F_{8,305.53} = 4.16^e$ | $F_{1,81.67} = 4.19^f$ | $F_{8,325.1} = 2.83^g$ | 0.96 | 1310.11 |
| Placebo | 1.68 (0.96) | 2.22 (1.62) | | | | | |
| Irritability | | | | | | | |
| Nabiximols | 1.80 (2.40) | 1.44 (1.84) | $F_{8,328.28} = 1.51$ | $F_{1,77.25} = 0.36$ | $F_{8,346.7} = 2.49$ | 0.43 | 17 774.37 |
| Placebo | 1.31 (1.81) | 2.19 (2.34) | | | | | |
| Depression | | | | | | | |
| Nabiximols | 2.78 (2.59) | 2.04 (2.43) | $F_{8,332.53} = 1.34$ | $F_{1,70.72} = 1.06$ | $F_{8,350.2} = 1.93^f$ | 0.45 | 1922.73 |
| Placebo | 1.71 (2.26) | 2.32 (2.62) | | | | | |
| Anxiety | | | | | | | |
| Nabiximols | 4.07 (3.29) | 1.26 (2.11) | $F_{8,361.84} = 8.88^e$ | $F_{1,68.4} = 0.004$ | $F_{8,373.88} = 1.11$ | 0.83 | 1961.42 |
| Placebo | 3.42 (3.02) | 1.64 (2.21) | | | | | |
| Cannabis cravings | | | | | | | |
| Nabiximols | 3.89 (2.81) | 1.87 (2.28) | $F_{8,363.66} = 4.34^e$ | $F_{1,74.46} = 4.34^f$ | $F_{8,376.2} = 2.04^f$ | 0.59 | 1821.49 |
| Placebo | 2.04 (1.88) | 1.81 (2.26) | | | | | |
| Physical symptoms | | | | | | | |
| Nabiximols | 1.27 (1.42) | 1.07 (1.21) | $F_{8,336.7} = 2.79^g$ | $F_{1,75.54} = 1.04$ | $F_{8,354.08} = 1.45$ | 0.12 | 1265.98 |
| Placebo | 0.84 (0.83) | 1.42 (1.50) | | | | | |
| Sleep difficulty | | | | | | | |
| Nabiximols | 2.95 (2.41) | 2.79 (2.58) | $F_{8,293.45} = 3.73^e$ | $F_{1,90.97} = 0.12$ | $F_{8,311.53} = 1.12$ | 0.76 | 1958.70 |
| Placebo | 2.29 (1.92) | 3.29 (2.23) | | | | | |
| Restlessness | | | | | | | |
| Nabiximols | 3.44 (3.36) | 2.8 (2.69) | $F_{8,327.26} = 1.38$ | $F_{1,83.67} = 0.27$ | $F_{8,345.71} = 0.64$ | 0.45 | 2237.27 |
| Placebo | 3.21 (2.39) | 3.52 (2.99) | | | | | |
| Decreased appetite | | | | | | | |
| Nabiximols | 3.56 (3.31) | 2.12 (2.88) | $F_{8,325.18} = 3.48^e$ | $F_{1,80.68} = 1.88$ | $F_{8,343.87} = 1.15$ | 0.65 | 2242.58 |
| Placebo | 1.95 (2.96) | 2.34 (2.62) | | | | | |

Abbreviation: AIC, Akaike information criterion.

^a Mixed models for repeated measures output using all days (1-9) as predictors in the model. Adjusted model added covariates: baseline scores of outcome variables, baseline Severity of Dependence Scale scores, baseline Sheehan Disability Scale scores, nicotine replacement therapy/cigarette use during abstinence, temazepam use during abstinence, caffeine use during abstinence.

^b Abstinence means were calculated during days 2 to 6 (drug administration phase excluding baseline). Detailed description of values on all days of

inpatient stay is reported in Author Table 2.

^c Variance in outcome variable explained by model (approximated using $-2 \log$ -likelihoods).

^d Measure of model fit; a smaller value indicates a better model fit.

^e $P \leq .001$.

^f $P \leq .05$.

^g $P \leq .01$.

and aggression (treatment × time: $F_{8,346.7} = 2.49$; $P = .004$) (Table 3). Adjusting for covariates removed the main effect of nabiximols on appetite loss ($F_{1,80.68} = 1.88$; $P = .18$) but introduced a significant reduction in depression (treatment × time: $F_{8,350.2} = 1.93$; $P = .05$) (Table 3). The time course of cannabis withdrawal was shorter in the nabiximols group, taking 3.10 (3.00) days for CWS scores to fall below baseline compared with 4.90 (3.16) days in the placebo group ($F_{1,50} = 41.42$; $P = .04$). Placebo withdrawal peaked on day 3.00 (1.70) of abstinence, whereas nabiximols withdrawal peaked on day 2.30 (1.88) ($F_{1,50} = 1.53$; $P = .19$). There was minimal rebound or increase in withdrawal severity after cessation of nabiximols on day 6 (Figure 2 and Author Figure 1). All other withdrawal symptoms were of lower, although not significantly, severity in the nabiximols group (Author Figure 1).

Retention in Treatment

By day 6 (the first day without medication), 85% of participants receiving nabiximols ($n = 23$) remained in treatment compared with 50% of the placebo group ($n = 12$) (number needed to treat, 2.84 [95% CI, 1.79-10.47]) (Figure 3). Unadjusted Cox regression revealed that patients receiving nabiximols were 3.7 times more likely to remain in treatment until the end of the medication phase (unadjusted hazard ratio [HR], 3.66 [95% CI, 1.18-11.37]; $P = .02$). However, this treatment effect was only of borderline significance after controlling for SDS, Sheehan Disability Scale, and CWS scores, and NRT/cigarettes, temazepam, and caffeine use during abstinence (adjusted HR, 4.09 [95% CI, 0.99-16.75]; $P = .05$). By day 9, following 3 drug-free days, retention differences were no longer significant (nabiximols: 11 [41%];

placebo: 8 [33%]; adjusted HR, 1.48 [95% CI, 0.62-3.8]; $P = .35$; number needed to treat, 13.50 [3.18-5.46]). No medication-related AEs or covariates significantly predicted dropout; the most common reason cited was dissatisfaction with the inpatient environment.

Intoxication and AEs

As shown in Author Figure 2, there were no significant differences in subjective intoxication ratings (change in stoned score from before to after dosing) between the placebo group (0.58 [1.04]; range, 1.00-3.75) and the nabiximols group (0.89 [1.29]; range, 3.00-6.01; $F_{5,188,95} = 0.34$; $P = .89$). There were also no significant differences in the number of AEs between groups (placebo, 5.54 [6.71]; nabiximols, 6.96 [11.02]; $F_{1,50} = 0.30$; $P = .59$), the proportions reporting specific AEs (Author Table 2), or the severity of AEs (placebo, 0.81 [0.65]; nabiximols, 1.12 [0.68]; $F_{1,50} = 2.69$; $P = .09$). One serious AE was reported (threat

of suicide in the placebo group) (Author Table 2). Participants could not differentiate between nabiximols and placebo when blinded, and both groups rated the dose as adequate (Author Table 3).

Medication/Other Drug Use

Most patients ($n = 47$) received at least 1 concomitant medication in the hospital, with no significant between-group differences (Author Table 4). All 36 nicotine-dependent participants used NRT or cigarettes during admission; use of caffeine and other medications carried over from before the study are itemized in Author Table 4.

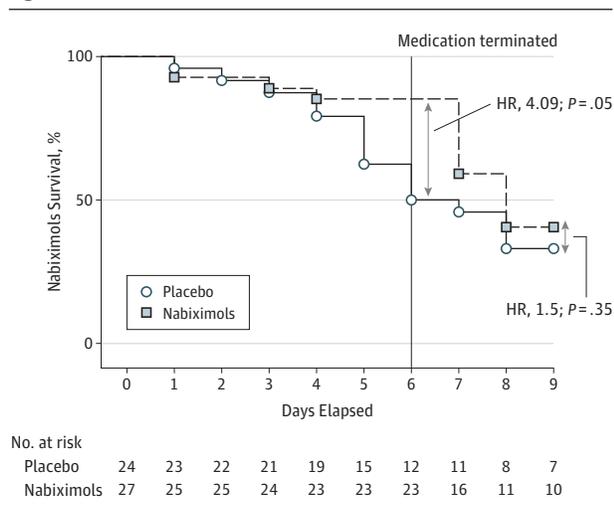
Plasma and Urinary Cannabinoids

Patients did not differ significantly in plasma THC, plasma THC-COOH, or urinary THC-COOH levels at treatment entry (Supplement [eFigures 1 and 2]). The CBD levels were negligible at baseline, consistent with the very low levels of CBD recently reported in New South Wales, Australia, street cannabis.⁷² During peak dosing on day 3, THC and THC-COOH levels were higher in the nabiximols group. As predicted, plasma CBD became detectable in the nabiximols group but remained undetected in the placebo group (Supplement [eFigure 2]). Plasma, but not urinary, THC-COOH levels were higher in the nabiximols group on day 3 relative to their baseline levels on day 1 and rapidly declined in plasma on day 7 once treatment had ceased (Supplement [eFigure 2]). The nabiximols and placebo groups showed similar relatively low levels of THC-COOH at follow-up (Supplement [eFigure 1]).

Outcomes at Follow-up

Weekly cannabis use across all patients decreased by a mean of 19.02 (21.35) g (82%) from baseline levels to the 28-day follow-up, with no significant between-group differences ($P = .29$) (Table 4). The time between hospital discharge and relapse to cannabis use was also not significantly different between the groups (median [95% CI] days: nabiximols, 15 [3.55-26.45]; placebo, 6 [0-27.12]; $\chi^2_1 = 0.06$; $P = .81$) (Supplement [eFigure 3]). The number of cannabis-related problems and the severity of cannabis dependence decreased by 65% from baseline levels across all participants, with no significant between-group differences (Table 4).

Figure 3. Retention in Withdrawal Treatment



The 2 hazard ratios (HRs) determined from the Cox regression marked on the graph show retention estimates at 2 time points: The day 6 HR (4.09) was computed with all remaining patients censored at day 6 to assess the effect of treatment allocation on retention during the medication administration phase. The day 9 HR (1.5) was computed with all remaining patients censored at day 9 to assess the overall effect of treatment allocation on retention, including the 3-day postmedication washout period.

Table 4. 28-Day Follow-up Measures

| Outcome Variable | Mean Scores | | Time | Treatment | Time × Treatment |
|-----------------------------|---------------|--------------|-----------------------|--------------------|---------------------|
| | Baseline | Follow-up | | | |
| Weekly mean cannabis use, g | | | | | |
| Nabiximols | 23.39 (16.79) | 2.81 (5.94) | $F_{1,48} = 38.79^a$ | $F_{1,48} = 0.52$ | $F_{1,48} = 0.29$ |
| Placebo | 22.52 (24.54) | 5.21 (10.74) | | | |
| SDS score | | | | | |
| Nabiximols | 11.85 (2.19) | 4.11 (5.29) | $F_{1,49} = 103.19^a$ | $F_{1,49} = 0.006$ | $F_{1,49} = 0.0001$ |
| Placebo | 11.79 (2.60) | 4.04 (5.21) | | | |
| CPQ score | | | | | |
| Nabiximols | 13.59 (5.03) | 4.29 (5.56) | $F_{1,49} = 96.17^a$ | $F_{1,49} = 0.79$ | $F_{1,49} = 2.33$ |
| Placebo | 11.33 (4.08) | 4.54 (5.02) | | | |

Abbreviations: CPQ, Cannabis Problems Questionnaire; SDS, Severity of Dependence Scale.
^a $P \leq .001$.

Discussion

To our knowledge, the present study is the first clinical trial to examine the effects of a whole cannabis extract (nabiximols) in the treatment of cannabis withdrawal and only the second controlled clinical trial of agonist substitution medication for cannabis dependence in treatment seekers.⁷³ Our findings provide support for the efficacy of nabiximols in treating cannabis withdrawal, consistent with earlier laboratory studies with synthetic oral THC.^{24,28,29,73} Nabiximols reduced the severity and time course of cannabis withdrawal compared with placebo (Figure 2) and improved retention rates during inpatient treatment. In addition, nabiximols significantly reduced cravings, irritability, and depression. Anxiety and cravings fell below pretreatment baseline levels in both groups during treatment, possibly resulting from high baseline anxiety associated with imminent inpatient detoxification and a lack of cannabis-related cues in the inpatient environment. There was no increase in withdrawal severity on termination of nabiximols, suggesting minimal discontinuation or rebound effects with 6-day use of this medication. Both groups had markedly reduced cannabis use at follow-up, as verified by urinalysis (Table 4 and Supplement [eFigure 1]). This is consistent with an outpatient dronabinol randomized clinical trial in which placebo and active medication groups showed reduced cannabis use at follow-up.⁷³ It appears that inpatient care in treatment-seeking populations may serve as a stimulus to promote reduced drug use regardless of medication given during withdrawal.⁷⁴ Further research exploring the efficacy of nabiximols is clearly warranted, perhaps with an emphasis on integrating withdrawal with postwithdrawal psychosocial interventions.

During peak dosing on day 3, THC and THC-COOH plasma levels were higher in the nabiximols group than in the placebo group (Supplement [eFigure 1]), demonstrating successful medication effects at the time often associated with peak cannabis withdrawal severity (Figure 2). The large spike in plasma CBD levels in the nabiximols group at peak dosing (day 3) (Supplement [eFigure 2]) contrasts markedly with nonexistent CBD levels in the placebo group. Plasma, but not urinary, THC-COOH levels appeared higher in the nabiximols group on day 3 relative to their baseline levels on day 1 and rapidly declined in plasma on day 7 once treatment had ceased (Supplement [eFigure 2]). Despite the higher plasma THC levels on day 3 in the nabiximols group, AEs, including subjective ratings of intoxication, were similar to those of the placebo group (Author Figure 2). Interestingly, participants could

not correctly identify the treatment they had been given, which is consistent with the low abuse potential of nabiximols evident in previous studies.^{40,45} This is clinically relevant because doses used in the present study were higher than doses used with cannabis-naïve or -nondependent patients.^{40,43}

The trial has several limitations. The specialized inpatient setting has limited translation to outpatient settings, where most treatment is delivered for cannabis-related problems. However, it was reasoned that the safety and efficacy of nabiximols were best assessed initially in an inpatient setting without confounders of concurrent illicit cannabis or other drug use. The focus on heavy users reporting past cannabis withdrawal effects limits the generalizability of findings to populations of lighter users. Randomization did not distribute patients equally with respect to baseline withdrawal or Sheehan Disability Scale scores, although both were included as covariates in analyses to minimize the bias arising from these discrepancies. Axis II comorbidity was not assessed. Despite statistical correction for the use of temazepam, administration of sleep medications will have disrupted the magnitude of withdrawal-related sleep difficulties. Use of other psychotropic medications (eg, antidepressants) may also influence withdrawal symptoms, although the use of such medications was balanced by randomization (Author Table 4).

Conclusions

This study supports the use of nabiximols as an agonist therapy for reducing the severity and time course of cannabis withdrawal and for retaining participants in withdrawal treatment. Nabiximols significantly suppressed withdrawal-related irritability (among the most severe and clinically significant symptoms in the outpatient setting),¹⁰ cravings, and depression. However, nabiximols was no more effective than placebo in encouraging long-term reductions in cannabis use. The follow-up outcomes may not be surprising given that the design used was akin to an unassisted relapse prevention model, and there is little precedence for medication-assisted withdrawal to affect long-term abstinence without ongoing support. These findings, however, identify a promising approach for cannabis withdrawal management and strengthen the case for agonist substitution medication for cannabis withdrawal. A direct comparison of nabiximols with other cannabinoid agonists (dronabinol or nabilone) may be of interest in the future to test whether the THC-CBD combination has additional therapeutic benefits over THC alone.

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