Nabiximols as an Agonist Replacement Therapy During Cannabis Withdrawal
A Randomized Clinical Trial

David J. Allsop, PhD; Jan Copeland, PhD; Nicholas Lintzeris, PhD; Adrian J. Dunlop, PhD; Mark Montebello, FACHAM; Craig Sadler, FACHAM; Gonzalo R. Rivas, BNurs; Rohan M. Holland, BNurs; Peter Muhleisen, BPharm, MPSA; Melissa M. Norberg, PhD; Jessica Booth, BSc (Hons); Iain S. McGregor, PhD

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 Δ9-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 ($\chi^2 = 0.79; P = .67$), 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 ($F_{1,48} = 0.29; P = .79$), 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.

TRIAL REGISTRATION anzctr.org.au Identifier: ACTRN12611000398909

Published online January 15, 2014.

Copyright 2014 American Medical Association. All rights reserved.
Cannabis is the most prevalent illicit drug in the world, and its use has been linked to a range of negative health outcomes. Approximately 10% of cannabis users will become dependent, leading to treatment. In the United States, treatment episodes involving cannabis as the primary drug increased from 6% in 1992 to 16% in 2004. 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. Similar increases in cannabis treatment seeking are observed globally. A cannabis withdrawal syndrome was included for the first time in the DSM-5. More than half of cannabis users report withdrawal, with primary symptoms including irritability, insomnia, decreased appetite, depressed mood, anxiety, and restlessness. Withdrawal symptoms are considered to be a major determinant of the high relapse rates observed in individuals receiving treatment.

There are no approved pharmacotherapies for managing cannabis withdrawal. A range of symptomatic medications have been evaluated, including the antidepressants bupropion and nefazodone, the mood stabilizers divalproex and lithium, and the α2-adrenergic agonist lofexidine, with limited benefits. Agonist substitution approaches may be more promising. Oral delivery of synthetic Δ9-tetrahydrocannabinol (THC; dronabinol was the THC formulation used) dose-dependently reduced a subset of cannabis withdrawal symptoms in laboratory and outpatient settings. Nabilone, a synthetic analogue of THC with higher oral bioavailability than dronabinol, was efficacious in a recent laboratory study. 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. The CBD content of nabiximols is of particular interest given that CBD attenuates the paranoia and euphoria associated with THC and may have efficacy in treating anxiety, depression, and psychosis. A recent case study 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, tolerance, or withdrawal. This indicates low abuse potential relative to other cannabinoids, such as dronabinol. 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.
Mandatory psychosocial intervention, was used. This was accompanied by standard de-
toxification 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 (StataCorp) (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-back\(^{49}\); Cannabis Problems Questionnaire\(^{50}\); Brief Treatment Outcome Measure–Social Functioning Scale\(^{51}\); Athens Insomnia Scale\(^{52}\); Severity of Dependence Scale (SDS)\(^{53,54}\); Sheehan Disability Scale\(^{55}\); self-coping and efficacy for Quitting Cannabis Questionnaire\(^{56}\); a subscale from the Depression, Anxiety, and Stress Scale\(^{57}\); Anxiety Sensitivity Index–Revised\(^{58,59}\); Distress Tolerance Scale\(^{60}\); 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.

**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 (\( \chi^2_{270} = 68.67; P = .89 \)). Missing ques-

---

**Figure 1. Study Flow**

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

---

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.\(^{10,45}\)

**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 de-
Statistical Analysis
Power analysis was based on a dronabinol study (30 mg) 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). 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 χ² 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 TMWC scores in a mixed model for repeated measures regression with first-order autoregressive covariance structure. The model was adjusted with covariates known or suspected to influence the experience of cannabis withdrawal (NRT/cigarettes, 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 × treatment; step 2: addition of covariates) explored changes in variance explained using pseudo- R² calculated from log-likelihood ratios (R²L). Akaiki information criteria calculated model fit (smaller values indicate better fit). Separate analyses tested the effect of nabiximols on attenuating DSM-5 cannabis withdrawal symptoms (Supplement [eTable 1]). Effect sizes are reported using the bias-corrected Hedges g (raw difference between 2 means divided by SD adjusted for population size). Parametric statistics were used on Likert data because interval structure can be assumed if scales are presented as symmetrical. 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 χ² 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.

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), 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: F₈,₃₇₇.₉₇ = 2.39; P = .01) (Figure 2 and Table 2). The effect remained significant after adjusting for covariates (treatment × time: F₈,₃₂₅.₃ = 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: F₈,₃₈₄.₄₁ = 2.03; P = .04) as well as irritability, anger, and aggression (treatment × time: F₈,₃₇₅.₇₉ = 2.49; P = .01). Loss of appetite was also attenuated (main effect: F₁,₇₆.₈₁ = 5.09; P = .03) (Table 2). After adjustment for covariates, nabiximols still reduced cravings (treatment × time: F₈,₃₇₆.₂ = 2.04; P = .03) as well as irritability, anger, and aggression (treatment × time: F₈,₃₆₇.₉₇ = 2.49; P = .004) (Table 3). Adjusting for covariates removed the main effect of nabiximols on appetite loss (F₁,₈₆.₆₉ = 1.88; P = .18) but introduced a significant reduction in depression (treatment × time: F₈,₃₅₂.₅ = 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 (F₁,₅₀ = 4.12; P = .04). Placebo withdrawal peaked on day 3.00 (1.70) of abstinence, whereas nabiximols withdrawal peaked on day 2.30 (1.88) (F₁,₅₀ = 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, temazen- pam, 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 [3.8-5.46]). 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]; \( F_{5,50} = 0.30; P = .59 \)), the proportions reporting specific AEs (Author Table 2), or the severity of AEs (placebo, 0.81 [0.65]; nabiximols, 1.12 [0.68]; \( F_{5,50} = 2.69; P = .09 \)). 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

---

**Table 1. Baseline Characteristics According to Treatment Group**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Nabiximols (( n = 27 ))</th>
<th>Placebo (( n = 24 ))</th>
<th>Total (( N = 51 ))</th>
<th>( P ) Value&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics, No. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>34.96 (9.70)</td>
<td>35.88 (8.05)</td>
<td>35.39 (8.89)</td>
<td>.72</td>
</tr>
<tr>
<td>Male sex</td>
<td>18 (67)</td>
<td>21 (88)</td>
<td>39 (76)</td>
<td>.08</td>
</tr>
<tr>
<td>Aboriginal or Torres Strait Islander</td>
<td>2 (7)</td>
<td>1 (4)</td>
<td>3 (6)</td>
<td>.62</td>
</tr>
<tr>
<td>Completed school</td>
<td>15 (56)</td>
<td>13 (54)</td>
<td>28 (55)</td>
<td>.99</td>
</tr>
<tr>
<td>Unemployed</td>
<td>15 (56)</td>
<td>12 (50)</td>
<td>27 (53)</td>
<td>.67</td>
</tr>
<tr>
<td>Married, including de facto</td>
<td>4 (15)</td>
<td>9 (38)</td>
<td>13 (25)</td>
<td>.35</td>
</tr>
<tr>
<td>Substance use history, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis use, g&lt;sup&gt;c&lt;/sup&gt;</td>
<td>23.39 (16.79)</td>
<td>22.52 (24.54)</td>
<td>22.98 (20.66)</td>
<td>.88</td>
</tr>
<tr>
<td>Carboxy-THC/creatinine ratio, ng/mg</td>
<td>2392.70 (1441.69)</td>
<td>3285.56 (5525.82)</td>
<td>2815.63 (3911.64)</td>
<td>.49</td>
</tr>
<tr>
<td>Years of cannabis use</td>
<td>20.11 (9.83)</td>
<td>20.79 (8.67)</td>
<td>20.43 (9.22)</td>
<td>.79</td>
</tr>
<tr>
<td>Cannabis SDS</td>
<td>11.96 (3.03)</td>
<td>12.13 (2.35)</td>
<td>12.04 (2.71)</td>
<td>.83</td>
</tr>
<tr>
<td>Alcohol SDS</td>
<td>0.31 (0.87)</td>
<td>0.63 (1.28)</td>
<td>0.45 (1.08)</td>
<td>.28</td>
</tr>
<tr>
<td>Alcohol use, U/wk&lt;sup&gt;d&lt;/sup&gt;</td>
<td>3.65 (8.42)</td>
<td>5.86 (8.33)</td>
<td>4.71 (8.37)</td>
<td>.36</td>
</tr>
<tr>
<td>Nicotine dependence, Fagerstrom score</td>
<td>3.11 (2.76)</td>
<td>2.75 (2.47)</td>
<td>2.94 (2.61)</td>
<td>.63</td>
</tr>
<tr>
<td>No. (%) nicotine dependent&lt;sup&gt;e&lt;/sup&gt;</td>
<td>19 (70)</td>
<td>17 (71)</td>
<td>36 (71)</td>
<td>.97</td>
</tr>
<tr>
<td>Cigarettes/wk</td>
<td>76.68 (69.07)</td>
<td>65.55 (64.29)</td>
<td>71.34 (66.38)</td>
<td>.56</td>
</tr>
<tr>
<td>No. SCID-RV cannabis dependence items</td>
<td>6.19 (0.75)</td>
<td>5.91 (0.97)</td>
<td>6.06 (0.86)</td>
<td>.26</td>
</tr>
<tr>
<td>No. other drug use disorders</td>
<td>0.65 (1.44)</td>
<td>1.09 (1.29)</td>
<td>0.85 (1.38)</td>
<td>.28</td>
</tr>
<tr>
<td>Cannabis Withdrawal Scale score</td>
<td>2.51 (1.57)</td>
<td>1.68 (0.96)</td>
<td>2.12 (1.37)</td>
<td>.02</td>
</tr>
<tr>
<td>Psychosocial functioning scores, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTOM Social Functioning</td>
<td>7.79 (3.45)</td>
<td>6.91 (3.23)</td>
<td>7.38 (3.35)</td>
<td>.36</td>
</tr>
<tr>
<td>Sheehan Disability Scale, total</td>
<td>18.11 (7.25)</td>
<td>11.33 (7.59)</td>
<td>14.92 (8.09)</td>
<td>.002</td>
</tr>
<tr>
<td>Self-efficacy Scale</td>
<td>2.99 (1.26)</td>
<td>3.05 (1.26)</td>
<td>3.03 (1.25)</td>
<td>.88</td>
</tr>
<tr>
<td>Anxiety Sensitivity Index-Revised</td>
<td>51.50 (24.88)</td>
<td>44.63 (28.26)</td>
<td>48.20 (26.51)</td>
<td>.37</td>
</tr>
<tr>
<td>DASS Depression</td>
<td>19.15 (10.66)</td>
<td>14.25 (11.31)</td>
<td>16.80 (11.14)</td>
<td>.12</td>
</tr>
<tr>
<td>DASS Anxiety</td>
<td>13.58 (8.46)</td>
<td>10.67 (6.57)</td>
<td>12.18 (7.68)</td>
<td>.18</td>
</tr>
<tr>
<td>DASS Stress</td>
<td>22.42 (9.09)</td>
<td>21.29 (9.53)</td>
<td>21.88 (9.22)</td>
<td>.67</td>
</tr>
<tr>
<td>Distress Tolerance Scale</td>
<td>2.79 (0.78)</td>
<td>2.81 (0.73)</td>
<td>2.80 (0.75)</td>
<td>.93</td>
</tr>
<tr>
<td>Athens Insomnia Scale</td>
<td>10.58 (5.19)</td>
<td>8.33 (3.94)</td>
<td>9.50 (4.72)</td>
<td>.09</td>
</tr>
<tr>
<td>Barratt Impulsiveness Scale</td>
<td>81.89 (10.72)</td>
<td>82.08 (11.60)</td>
<td>81.98 (11.03)</td>
<td>.95</td>
</tr>
</tbody>
</table>

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.

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

<sup>b</sup> 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) \( \chi^2 \) test for all other categorical variables.

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

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

<sup>e</sup> Participants were classed as dependent on nicotine if they had a Fagerstrom score between 1 and 10.
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. During peak dosing on day 3, THC and THC-COOH levels were higher in the nabilaximols group. As predicted, plasma CBD became detectable in the nabilaximols group but remained undetected in the placebo group (Supplement [eFigure 2]). Plasma, but not urinary, THC-COOH levels were higher in the nabilaximols 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 nabilaximols 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).
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]; $\chi^2 = 0.06; P = .81$) (Supplement[eFigure3]).

Thenumber 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).

### 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[eFigure1]). This is consistent with an outpatient dronabinol randomized clini-

---

### Table 2. Outcome Measures: Unadjusted Modela

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Mean Scores</th>
<th>Time Treatment</th>
<th>Time × Treatment</th>
<th>$R^2$</th>
<th>AICd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall withdrawal score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabiximols</td>
<td>2.51 (1.57)</td>
<td>1.88 (1.64)</td>
<td>$F_{8,377.97} = 3.94^<em>$ $F_{1,77.97} = 11.01^</em>$ $F_{8,377.97} = 2.39^f$</td>
<td>0.50</td>
<td>1444.12</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.68 (0.96)</td>
<td>2.22 (1.62)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Irritability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabiximols</td>
<td>1.80 (2.40)</td>
<td>1.44 (1.84)</td>
<td>$F_{8,377.97} = 1.48$ $F_{1,71.05} = 3.09$ $F_{8,377.97} = 2.49^f$</td>
<td>0.42</td>
<td>1775.13</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.31 (1.81)</td>
<td>2.19 (2.34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabiximols</td>
<td>2.78 (2.59)</td>
<td>2.04 (2.43)</td>
<td>$F_{8,377.62} = 1.39$ $F_{1,71.05} = 2.74$ $F_{8,377.62} = 1.85$</td>
<td>0.45</td>
<td>1928.86</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.71 (2.26)</td>
<td>2.32 (2.62)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabiximols</td>
<td>4.07 (3.29)</td>
<td>1.26 (2.11)</td>
<td>$F_{8,389.19} = 8.96^*$ $F_{1,69.15} = 0.96$ $F_{8,389.19} = 1.08$</td>
<td>0.81</td>
<td>1964.28</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.42 (3.02)</td>
<td>1.64 (2.21)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cannabis cravings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabiximols</td>
<td>3.89 (2.81)</td>
<td>1.87 (2.28)</td>
<td>$F_{8,384.05} = 4.38^*$ $F_{1,73.2} = 10.28^f$ $F_{8,384.05} = 2.03^g$</td>
<td>0.66</td>
<td>1812.78</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.04 (1.88)</td>
<td>1.81 (2.26)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabiximols</td>
<td>1.27 (1.42)</td>
<td>1.07 (1.21)</td>
<td>$F_{8,374.81} = 2.89^f$ $F_{1,75.46} = 3.66$ $F_{8,374.81} = 1.43$</td>
<td>0.18</td>
<td>1261.96</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.84 (0.83)</td>
<td>1.42 (1.50)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep difficulty</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabiximols</td>
<td>2.95 (2.41)</td>
<td>2.79 (2.58)</td>
<td>$F_{8,374.86} = 3.93^*$ $F_{1,80.65} = 2.79$ $F_{8,374.86} = 0.98$</td>
<td>0.60</td>
<td>1984.70</td>
</tr>
<tr>
<td>Placebo</td>
<td>2.29 (1.92)</td>
<td>3.29 (2.23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabiximols</td>
<td>3.44 (3.36)</td>
<td>2.8 (2.69)</td>
<td>$F_{8,359.46} = 1.51$ $F_{1,81.38} = 0.64$ $F_{8,359.47} = 0.66$</td>
<td>0.45</td>
<td>2237.29</td>
</tr>
<tr>
<td>Placebo</td>
<td>3.21 (2.39)</td>
<td>3.52 (2.99)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased appetite</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nabiximols</td>
<td>3.56 (3.31)</td>
<td>2.12 (2.88)</td>
<td>$F_{8,357.5} = 2.52^f$ $F_{1,76.81} = 5.09^p$ $F_{8,357.5} = 1.13$</td>
<td>0.61</td>
<td>2248.24</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.95 (2.96)</td>
<td>2.34 (2.62)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviation: AIC, Akaike information criterion.

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

* $P = .001$.
† $P = .01$.
‡ $P = .05$. 

(Table 4).
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-naive 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...
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), craving, 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.

ARTICLE INFORMATION

Submitted for Publication: May 21, 2013; final revision received July 10, 2013; accepted August 8, 2013.


Author Affiliations: National Cannabis Prevention and Information Centre, National Drug and Alcohol Research Centre, Faculty of Medicine, University of New South Wales, Sydney, Australia (Allsop); Drug and Alcohol Services, South Eastern Sydney Local Health District New South Wales Ministry of Health, Sydney, Australia (Lintzeris); Addiction Medicine, Central Clinical School, Faculty of Medicine, University of Sydney, Sydney, Australia (Lintzeris); Drug and Alcohol Clinical Services, Hunter New England Local Health District, New South Wales Ministry of Health, Newcastle, Australia (Dunlop, Sadler, Holland, Muhleisen); School of Medicine and Public Health, Faculty of Health, University of Newcastle, Newcastle, Australia (Dunlop); Department of Psychology, Macquarie University, Sydney, Australia (Norberg); School of Psychology, University of Sydney, Sydney, Australia (Booth, McGregor).

Author Contributions: Dr Allsop had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Allsop, Copeland, Lintzeris, Dunlop, Sadler, Rivas, Holland, Muhleisen, Norberg, McGregor.

Acquisition of data: Allsop, Lintzeris, Montebello, Sadler, Rivas, Holland, Norberg, Booth, McGregor.

Analysis and interpretation of data: Allsop.

Table 4. 28-Day Follow-up Measures

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

Abbreviations: CPQ, Cannabis Problems Questionnaire; SDS, Severity of Dependence Scale.

$^a P < .001$. 

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).

Conflict of Interest Disclosures: Dr Allsop’s institution received funding for his salary from the National Health and Medical Research Council (NHMRC) and the Australian Government Department of Health and Aging, and he received funding from the National Institute on Drug Abuse to attend a conference in the United States in November 2011. No other conflicts were reported.

Funding/Support: This study was funded by project grant T06036 from the NHMRC. Study drugs (nabiximols and placebo) were provided free of charge by GW Pharmaceuticals, UK.

Role of the Sponsor: The NHMRC and GW Pharmaceuticals, UK, had no role in the design and conduct of the study; the collection, management, analysis, or interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional Contributions: Deborah Zador, MD, Bas Dall, MD, Hester Wilson, MD, and Victoria Hayes, MD, medically screened study participants. Sarah Kezelman, BPsych (Hons), Lucy Albertella, MSC, Sherrilyn Thomson, BPsych (Hons), and Claudia Sannibale, PhD, administered the Structured Clinical Interview for Drug Dependence (all SCID-RV interviewers were remunerated for their services). Julie Spencer, RN, MPH, Jackie O’Mahony, MSN (nurse practitioner), and the nursing staff at Ward 2 East, Sydney Hospital and Sydney Eye Hospital, and Cathy Fisk, RN, Lynne Robertson, RN AAS, and the nursing staff at Lakeside Detox Unit, Belmont Hospital, Newcastle, provided daily patient care, medication delivery, and clinical data collection. Celia Weight, BPharm, and Judith Hampson, BPharm, MHA, provided pharmaceutical services for managing medications and randomization (all pharmaceutical services were reimbursed). Ryan Vandrey, PhD, provided suggestions on the manuscript. Tim Slade, PhD, Mathew Sunderland, PhD, Raimondo Bruno, PhD, and Barbara Tozon BSc (Hons) contributed statistical support and advice. The toxicology unit of Pacific Laboratory Medicine Services coordinated the urinalysis studies, and toxicology services were reimbursed. All named individuals without a financial disclosure here did not receive any reimbursement from project funds for their contributions to the study.

Correction: This article was corrected on March 14, 2014, to provide additional data in Table 1.

REFERENCES


15. Levin FR, Mariani JJ, Brodie DJ, Xie S, Murray KA. Delta-9-tetrahydrocannabinol testing may have the sensitivity to detect marijuana use among individuals ingesting dronabinol. Drug Alcohol Depend. 2010;106(1):65-68.


Nabiximols in Cannabis Withdrawal


