Cannabidiol reverses attentional bias to cigarette cues in a human experimental model of tobacco withdrawal

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ABSTRACT

Background and Aims Cannabidiol (CBD), a non-intoxicating cannabinoid found in cannabis, may be a promising novel smoking cessation treatment due to its anxiolytic properties, minimal side effects and research showing that it may modify drug cue salience. We used an experimental medicine approach with dependent cigarette smokers to investigate if (1) overnight nicotine abstinence, compared with satiety, would produce greater attentional bias (AB), higher pleasantness ratings of cigarette-related stimuli and increased craving and withdrawal; and (2) CBD in comparison to placebo, would ameliorate AB, pleasantness of cigarette-related stimuli, craving and withdrawal and not produce any side effects.

Design Randomized, double-blind cross-over study with a fixed satiated session followed by two overnight abstinence sessions.

Setting UK laboratory. Participants Thirty non-treatment-seeking, dependent cigarette smokers recruited from the community.

Intervention and comparator 800 mg oral CBD, or matched placebo (PBO) in a counterbalanced order.

Measurements AB to pictorial tobacco cues was recorded using a visual probe task and an explicit rating task. Withdrawal, craving, side effects, heart rate and blood pressure were assessed repeatedly.

Findings When participants received PBO, tobacco abstinence increased AB (P = 0.001, d = 0.789) compared with satiety. However, CBD reversed this effect, such that automatic AB was directed away from cigarette cues (P = 0.007, d = 0.704) and no longer differed from satiety (P = 0.82). Compared with PBO, CBD also reduced explicit pleasantness of cigarette images (P = 0.011; d = 0.514). Craving (Bayes factor = 7.08) and withdrawal (Bayes factor = 6.95) were unaffected by CBD, but greater in abstinence compared with satiety. Systolic blood pressure decreased under CBD during abstinence.

Conclusions A single 800-mg oral dose of cannabidiol reduced the salience and pleasantness of cigarette cues, compared with placebo, after overnight cigarette abstinence in dependent smokers. Cannabidiol did not influence tobacco craving or withdrawal or any subjectively rated side effects.

Keywords Abstinence, attentional bias, cannabidiol, cigarette dependence, craving, withdrawal.

INTRODUCTION

More than 1.1 billion people smoke worldwide [1]. A primary addictive driver of cigarette smoking is nicotine withdrawal. Withdrawal occurs upon cessation and includes physiological symptoms (headaches, nausea), affective symptoms (anxiety, depression and irritability) and impaired cognitive performance (delay discounting, response inhibition) [2], which peak within the first few days [3]. Some evidence suggests withdrawal severity predicts relapse [3–6], prevention of which is a major challenge in the treatment of addiction [7]. Even when using the currently most effective smoking cessation drug (varenicline), a majority still fail to maintain long-term abstinence [8]. Nicotinic medications may also have unpleasant side effects, e.g. nausea [9].

There is mounting evidence that the endogenous cannabinoid (eCB) system is involved in motivation for rewards, including modulating the rewarding effects of drugs [10–15]. In relation to nicotine dependence,
cannabinoid receptor 1 (CB1R) antagonists, such as rimonabant, decrease nicotine conditioned place preference and self-administration in pre-clinical models of addiction [16,17]. In human clinical trials, rimonabant increased smoking abstinence rates 1.6-fold [18,19]. Although potentially effective, rimonabant was withdrawn from the market due to serious neuropsychological side effects.

Cannabidiol (CBD) is the second most abundant cannabinoid in cannabis. It has been shown to have broad therapeutic benefits [20,21] and is showing initial promise as a treatment for addiction, anxiety and schizophrenia. The psychological properties of CBD are suggestive of a potentially ideal drug for smoking cessation. These include its lack of intoxicating and subjective effects [22-24], alongside its anxiolytic [25,26] effects in humans. Its anxiolytic properties are particularly relevant, as anxiety is a primary symptom of tobacco withdrawal [27]. The first human pilot study to investigate CBD as a treatment for nicotine dependence randomized participants to either 1 week of ad-hoc CBD or placebo inhaler to be used when they had the urge to smoke. CBD reduced the number of cigarettes reportedly smoked by almost 40%, in comparison to placebo, but did not affect craving [28]. No neurocognitive mechanisms through which CBD may assist with the treatment of smoking cessation were investigated. On the basis of previous findings [29], the authors proposed that a reduction in the salience of drug cues could be one candidate mechanism.

Attentional bias is a potentially important in-laboratory predictive marker of the salience of drug cues. It is heightened, as indexed by dot-probe tasks, during acute abstinence [2]; predicts short-term relapse [30]; and is thought to play a causal role in maintaining addiction [31]. Attentional bias to tobacco stimuli at a short (compared to longer) exposure interval is particularly important, as tobacco abstainers show greater bias to these cues only at short exposure [32]. CBD may reduce the salience of smoking cues, which would be consistent with pre-clinical, human experimental and neuroimaging research. In human naturalistic research, cannabis with high, in comparison to low, levels of CBD reduced cue salience to cannabis-related stimuli in a visual probe task [29]. This was again only observed at the short stimulus exposure interval which maps ‘automatic’ bias, i.e. that which is not subject to conscious cognitive control. As such, CBD may target an important implicit process involved in relapse. In a pre-clinical rat model of addiction, Ren et al. [33] showed that CBD (5-20 mg/kg) attenuated cue-induced heroin-seeking behaviour and relapse, which was maintained for 2 weeks after CBD administration. Furthermore, human translational pilot research showed that a single dose of CBD can attenuate cue-induced craving in heroin users during a 24-hour period and this was maintained for 7 days [34]. One neuroimaging study suggests that CBD modulates activity of areas in the brain associated highly with salience attribution, including the striatum, hippocampus and prefrontal cortex [35]. Taken together, the experimental evidence provides a strong rationale to hypothesize that CBD is a potential treatment for substance use disorders where the salience of drug cues is key.

This is the first study, to our knowledge, to investigate the effects of CBD during nicotine withdrawal in humans. We employ an experimental medicine approach to investigate CBD’s potential to target processes relevant to smoking cessation. Human laboratory studies of smoking abstinence provide an efficient, cost-effective, mechanistic evaluation of medications for smoking behaviour [36], which may facilitate translational research. Specifically, we hypothesized that: (1) overnight nicotine abstinence, compared with satiety, will produce a range of nicotine withdrawal symptoms in dependent cigarette smokers which include greater attentional bias (short stimulus exposure), higher pleasantness of cigarette-related stimuli and increased craving and withdrawal; (2) CBD in comparison to placebo, would attenuate attentional bias and pleasantness of cigarette-related stimuli, craving and withdrawal symptomology relative to pre-drug scores; and (3) CBD in comparison to placebo, will not produce any significant cardiovascular or side effects.

**MATERIAL AND METHODS**

**Design and participants**

Thirty participants attended three sessions [mean = 7.85, standard deviation (SD) = 2.77 days between sessions]. Participants smoked as normal before their first (baseline) session, verified with expired carbon monoxide (CO) ≥ 10 parts per million (p.p.m.) (Bedfont Scientific, Harrietsham, UK). Participants then attended two sessions after overnight (~12-hour) abstinence, verified by CO ≤ 10 p.p.m. [37]. A double-blind, placebo-controlled, cross-over design was used to compare the effects of 800 mg oral CBD with matched placebo (PBO) after overnight smoking abstinence. Treatment order for abstinence sessions was randomized and counterbalanced. Participants received the drug based on a randomization code, balanced for gender (www.random.org), which was concealed from experimenters until all data were collected and entered. Drug concealment occurred through participant-numbered, opaque, sealed envelopes. There was a minimum washout period of 1 week between drug sessions to preclude potential CBD carry-over effects following previous research [23,24].

Dependent cigarette smokers were recruited from the community through on-line message boards. Inclusion criteria were: (i) age 18-50 years; (ii) smoking ≥ 10
with post-hoc comparisons, Bonferroni-corrected locally within each omnibus term.

Scaled Jeffreys–Zellner–Siow (JZS) Bayes factors (BF) were calculated when the main effect of drug (CBD versus PBO) was not significant according to frequentist statistics (P > 0.05). We used a scaled-information prior of r = 1 [53].

Carry-over effects were assessed using an additional between-subjects factor of 'order'. No order effects were found for the main analyses (as evidenced by no interactions or main effects involving treatment order). Therefore, we report results without accounting for order. As we did not have any specific a priori hypotheses regarding covariates, we did not include any, as per Kraemer [54].

RESULTS

Participant characteristics (Tables 1 & 2)

Thirty participants (14 female) took part. The sample had a mean (SD) age of 28.07 (8.66) years, with an FTND score of 5.56 (1.13) demonstrating moderate dependence. They smoked 13.5 (2.39) cigarettes per day, which is slightly more than the national adult average of 11.5 [55]. Further demographics, trait scores and cigarette smoking information can be found in Table 1. Use of other drugs was minimal in this population (Table 2). For confirmation of both self-reported and CO level indexed abstinence: see Supporting Information.

Table 1 Participants' demographic and trait variables. Results are displayed as mean (standard deviation).

<p>| | |</p>
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>n</td>
<td>30</td>
</tr>
<tr>
<td>Age (years)</td>
<td>28.07 (8.66)</td>
</tr>
<tr>
<td>FTND score</td>
<td>5.56 (1.13) range 4–8</td>
</tr>
<tr>
<td>Cigarettes per day</td>
<td>13.5 (2.39) range 10–20</td>
</tr>
<tr>
<td>Time to first cigarette (mins)</td>
<td>25.5 (15.87)</td>
</tr>
<tr>
<td>Years smoked</td>
<td>9.55 (7.36)</td>
</tr>
<tr>
<td>Years smoking &gt; 10+ cigarettes/day</td>
<td>8.17 (7.08)</td>
</tr>
<tr>
<td>Life-time quit attempts (n = 25)</td>
<td>3.2 (3.91)</td>
</tr>
<tr>
<td>Most successful quit attempt (days)</td>
<td>100.48 (163.47)</td>
</tr>
<tr>
<td>Body mass index</td>
<td>23.98 (7.78)</td>
</tr>
<tr>
<td>Spot the Word</td>
<td>48.03 (4.15)</td>
</tr>
<tr>
<td>STAI</td>
<td>40.53 (9.4)</td>
</tr>
<tr>
<td>BDI</td>
<td>10.36 (7.54)</td>
</tr>
</tbody>
</table>

FTND = Fagerström Test for Nicotine Dependence; STAI = State–Trait Inventory; BDI = Beck Depression Inventory.

Table 2 Drug use history (n = the number of people who used the drug in the past year). Results are displayed as mean (standard deviation).

<table>
<thead>
<tr>
<th></th>
<th>Alcohol</th>
<th>Cannabis</th>
<th>MDMA</th>
<th>Cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>26</td>
<td>17</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Days since last use</td>
<td>6.39 (10.13)</td>
<td>100 (68.30)</td>
<td>84.66 (82.22)</td>
<td>100 (56.12)</td>
</tr>
<tr>
<td>Number of years used</td>
<td>13.08 (8.68)</td>
<td>8.29 (4.61)</td>
<td>4.55 (1.59)</td>
<td>3.33 (2.12)</td>
</tr>
<tr>
<td>Days per month</td>
<td>11.43 (8.85)</td>
<td>0.75 (1.30)</td>
<td>0.67 (1.32)</td>
<td>0.5 (1.15)</td>
</tr>
<tr>
<td>Typical amount per session</td>
<td>7.1 units (3.23)</td>
<td>0.87 joints (0.69)</td>
<td>258.33 mg (144.70)</td>
<td>800 mg (0.83)</td>
</tr>
</tbody>
</table>

MDMA = 3,4-methylenedioxymethamphetamine.

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**Figure 2**  Attentional bias across satiated (30 min post-cigarette) and abstinent (180 min post-drug administration) for both short and long exposure times. Estimated marginal means are presented with 95% confidence interval error bars. *p ≤ 0.05; **p ≤ 0.01; ***p ≤ 0.001. SAT=satiated; CBD=cannabinol; PBO=placebo.

There was no difference between CBD and PBO, pre-drug administration (P = 0.99) confirmed by a Bayesian analysis, showing that the null was 7.08 more likely than the alternative given the data (JZS BF = 7.08). To investigate if CBD attenuated craving in comparison to PBO on abstinent sessions, we conducted an ANOVA that showed a main effect of time (F(2,54) = 8.34, P < 0.001, η²p = 0.22); however, there was no main effect of drug (P = 0.81) confirmed by a Bayesian analysis (JZS BF = 6.87) or drug × time interaction, suggesting no difference between CBD and PBO.

**Withdrawal (Fig. 5)**

Pre-drug MPSS scores was greater under abstinent conditions versus satiation (F1,29) = 29.88, P < 0.001, η²p = 0.51), suggesting that abstinence increased withdrawal. There was no difference between CBD and PBO.

**Figure 3**  Bias in pleasantness rating (calculated as cigarette valence minus neutral valence) for satiated (36 min post-cigarette) and abstinent (188 min post-drug administration) conditions. Estimated marginal means are presented with 95% confidence interval error bars. *p ≤ 0.05

**Figure 4**  Scores for the Questionnaire of Smoking Urges-Brief (QSU-B) (craving). Left panel (a) shows significantly greater craving on abstinent sessions before drug administration, in comparison to satiation scores after a cigarette. Right panel (b) compares cannabinol (CBD) and matched placebo (PBO) across all-time points pre- and post-drug administration (T2 onwards). See Supporting Information, Table S1 for details on timing. Estimated marginal means with 95% confidence interval are presented. ***p ≤ 0.001

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pre-drug administration ($P = 0.85$) confirmed by Bayesian analysis showing the null was 6.95 more likely than the alternative given the data ($JZS \ BF = 6.95$). To investigate if CBD attenuated withdrawal in comparison to PBO on abstinent sessions, we conducted an ANOVA that showed a main effect of time ($F(1,259) = 8.98, P < 0.001$, $\eta^2_{\text{p}} = 0.24$); however, there was no effect of drug ($F(1,293) = 0.22, P = 0.64, \eta^2_{\text{p}} = 0.01$) confirmed by a Bayesian analysis ($JZS \ BF = 6.35$) or drug $\times$ time interaction.

Analysis of the additional MPSS questions (amount of time spent with urges and strength of urges) can be found in Supporting information.

**Cardiovascular effects**

**Heart rate (HR)**

There was a main effect of time ($F(1,39) = 33.73, P < 0.001$, $\eta^2_{\text{p}} = 0.54$) which showed that HR decreased over time. There was no main effect of drug ($P = 0.30$) confirmed by a Bayesian analysis ($JZS \ BF = 4.17$) and no interaction between drug and time.

**Blood pressure (BP)**

A main effect of drug ($F(1,29) = 6.72, P = 0.015$, $\eta^2_{\text{p}} = 0.19$) showed higher systolic BP after PBO than after CBD (+3.40, 95% CI = 0.72–6.08). There was a main effect of time ($F(1,29) = 13.24, P < 0.001$, $\eta^2_{\text{p}} = 0.31$), which showed that systolic BP decreased over time. There were no main effects or interactions for diastolic BP.

**Side effects**

One interaction between drug and time was found for ‘headache’, but no significant pairwise comparisons emerged. No other main effects of drug or interactions were found between drug and time. See Supporting information for more details.

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**DISCUSSION**

This study employed an experimental medicine approach to investigate the effects of a single 800-mg oral dose of CBD on nicotine withdrawal. We found evidence that, compared to placebo, CBD reversed attentional bias to cigarette cues in abstinent smokers, such that it was no longer significantly different from attentional bias when they were satiated. Simultaneously, we observed a reduction in explicit pleasantness during abstinence, such that cigarette stimuli were rated as less pleasant after CBD than placebo. These neurocognitive effects occurred in the absence of any changes in subjective states of craving and withdrawal between CBD and placebo. This suggests that CBD may have specific effects on the evaluative and motivational salience-reducing properties of drug cues, which is consistent with clinical [29,34] and pre-clinical research [33]. Moreover, no significant psychoactive or side effects were observed. These results therefore support the potential of CBD in targeting specific neurocognitive processes in nicotine addiction.

To be specific, a reduction in the implicit salience of drug cues of a large effect size was observed in the CBD condition (versus placebo) after overnight abstinence in dependent cigarette smokers. This is to say that participants were over 40 ms faster to detect probes replacing smoking (versus neutral) cues under placebo than under CBD. This was observed in the short exposure time only, consistent with our initial hypothesis and with previous findings regarding attentional bias [32] and CBD [29]. The short exposure time is related to implicit automatic processing and initial orientation to cues, which occur outside the individual’s explicit awareness [32,56].

These results suggest that one potential candidate mechanism by which CBD may exert anti-addictive effects is by normalizing the salience of drug cues. This is in line with the incentive salience model of drug addiction [57]. Given that attentional bias may predict smoking cessation
outcomes [30]. CBD may be useful in aiding early abstinence by reducing the salience of drug-related cues. However, it is unlikely that attentional bias is the only driver of nicotine addiction, and other mechanisms require investigation.

As well as effects of CBD on implicit attentional bias, a reduction in explicit pleasantness for cigarettes under CBD compared to placebo was also observed. Explicit pleasantness is important with regard to addiction because it partly indexes the reinforcing value of a drug. In humans, users of high, in comparison to low CBD : THC ratio cannabis showed lower self-reported pleasantness of cannabis stimuli, which follows the same pattern as the present study [29] and may be related to endocannabinoid involvement in hedonic experiences [58]. However, there was no difference between abstinence and satiated sessions, which was unexpected, as it was hypothesized and has been shown previously [59].

The absence of CBD effects on withdrawal and craving are surprising because, theoretically, the incentive salience model of Robinson & Berridge [57] would suggest that a reduction in attentional bias would be accompanied by a reduction in craving. Moreover, Hurst et al. [34] found that CBD reduced cue-induced craving and anxiety which was maintained for 24 hours in heroin users (however, a different paradigm was used). It is notable that both Morgan et al. [28] and the present study did not find effects on tonic craving, therefore CBD may not be effective for all smokers but only those suffering from heightened attentional bias to drug cues. The incentive salience model equates craving with wanting a drug, not liking a drug, and argues that craving reflects the attribution of intense incentive salience to reward-associated stimuli. In the present research, CBD reduced attentional bias, arguably an index of incentive salience, but had no impact on craving. Given that craving and attentional bias are dissociated here, with CBD specifically attenuating attentional bias, this research seems to be inconsistent with the model. It may be the observed reduction in attentional bias is a result of a general motivational effect in that CBD may be reducing general orienting to salient cues, thus explaining the observed dissociation. Future research should investigate whether CBD also modifies orientating to other salient stimuli such as food cues. This has been investigated with street cannabis, where individuals smoking cannabis high (in comparison to low) in CBD had significantly lower attentional bias to both cannabis and food-related cues [29].

The neurobiological mechanism by which CBD may exert these effects is unclear; however, a promising candidate is through normalization of extracellular anandamide, via inhibition of fatty acid amide hydrolase (FAAH). FAAH inhibitors have been shown to reduce nicotine self-administration and conditioned place preference (CPP) in rats and monkeys as well as nicotine-induced dopamine release in the nucleus accumbens [60–63]. Here, we were unable to measure anandamide levels; however, this putative mechanism requires further research, as more potent FAAH inhibitors may provide more anti-addictive effects than CBD. This may also be the mechanism by which CBD may alleviate psychotic symptoms in people with schizophrenia [40].

Limitations

First, we used an experimental medicine approach to investigate mechanistic effects of single-dose CBD during overnight tobacco withdrawal, therefore it is unclear whether these effects will translate to the clinic and how long they might last. The visual probe task provided only a cross-sectional snapshot of attentional bias in a laboratory setting, and may suffer from low internal reliability [64]. In this case, ecological momentary assessment may be more indicative of attentional bias in actual drug-taking environments. Additionally, use of eye tracking, functional magnetic resonance imaging (fMRI) or electroencephalogram (EEG) would provide additional information on the time-course and neural correlates of attentional bias. Moreover, only a single dose of CBD was given; future research needs to investigate repeated dosing and a range of doses [65]. Finally, compliance with tobacco smoking abstinence instructions was verified with breath CO, but abstinence from other nicotine products was based on self-report, therefore we could not verify objectively that participants had not used other nicotine products. However, craving and withdrawal scores were markedly higher under abstinence than satiation, suggesting that self-report was reliable.

CONCLUSIONS

This is the first study, to our knowledge, to investigate effects of CBD on nicotine withdrawal. After overnight tobacco abstinence, cigarette smokers administered 800 mg CBD, in comparison to placebo, showed a reduced salience and pleasantness of cigarette cues, in the absence of any reductions in withdrawal or craving. This study highlights the potential utility of CBD as a treatment for specific neurocognitive components of tobacco use disorder, and suggests that one potential mechanism by which CBD may exert its effects on addiction is via a reduction in the salience of drug cues. These results support the growing literature regarding CBD in the treatment of addictive disorders.

Declaration of interests

None.
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References


Supporting Information

Additional Supporting Information may be found online in the supporting information tab.

Figure S1 Flow diagram for study recruitment and assessments. The final sample included 30 participants who completed all three sessions.

Table S1 Schedule of assessments on the satiated and abstinence sessions.