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Short Communication

Cannabidiol reduces cigarette consumption in tobacco smokers: Preliminary findings



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HIGHLIGHTS

- We examined whether cannabidiol could impact on cigarette consumption.
- Ad hoc use of CBD but not placebo reduced cigarette consumption over a week.
- Drugs that alter the endocannabinoid system may be effective treatments for nicotine addiction.

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ABSTRACT

The role of the endocannabinoid system in nicotine addiction is being increasingly acknowledged. We conducted a pilot, randomised double blind placebo controlled study set out to assess the impact of the ad-hoc use of cannabidiol (CBD) in smokers who wished to stop smoking. 24 smokers were randomised to receive an inhaler of CBD ($n = 12$) or placebo ($n = 12$) for one week, they were instructed to use the inhaler when they felt the urge to smoke. Over the treatment week, placebo treated smokers showed no differences in number of cigarettes smoked. In contrast, those treated with CBD significantly reduced the number of cigarettes smoked by ~40% during treatment. Results also indicated some maintenance of this effect at follow-up. These preliminary data, combined with the strong preclinical rationale for use of this compound, suggest CBD to be a potential treatment for nicotine addiction that warrants further exploration.

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1. Introduction

Cannabidiol (CBD) is a non-psychoactive component of the cannabis plant. CBD has a complex action at a number of receptors including antagonistic action at the cannabinoid 1 and 2 (CB1 and CB2) receptors and inhibition of the uptake and enzymatic hydrolysis of the endogenous cannabinoid ligand, anandamide. CBD has recently attracted interest for its anxiolytic (Crippa et al., 2011) and antipsychotic (Leweke et al., 2012) properties. The endocannabinoid system is now thought to be intrinsic to reward and reinforcement (Serrano & Parsons, 2011) and several lines of evidence suggest that CBD may also be a useful treatment in nicotine dependence.

A variety of sources have shown that CB1 receptors modulate the rewarding effects of nicotine and other drugs. Conditioned place preference (CPP) is absent in both CB1-knockout mice (Cossu et al., 2001) and rats treated with a systemic dose of the CB1 antagonist rimonabant (Le Foll & Goldberg, 2004). Pretreatment with rimonabant also reduced

nicotine, ethanol, methamphetamine, and morphine self-administration in rodents (Arnone et al., 1997; Cohen, Perrault, Voltz, Steinberg, & Soubrie, 2002; Navarro et al., 2001; Vinklerova, Novakova, & Sulcova, 2002). Rimonabant blocks reinstatement of drug seeking following withdrawal from nicotine (Cohen, Perrault, Griebel, & Soubrie, 2005). Perhaps most significantly however a Cochrane review that included 3 clinical trials of rimonabant for smoking cessation concluded that "...20 mg may increase the chances of quitting (nicotine) approximately 1.5-fold..." (Cahill & Ussher, 2007, pp. 3). These effects were attributed to its capacity to regulate the endocannabinoid system which has been suggested in turn to regulate dopamine (Rodriguez De Fonseca et al., 2001). Rimonabant has, however, been withdrawn from clinical use in humans due to increased depression and suicide in some patients. But CBD, unlike rimonabant, has an excellent safety profile (Bergamaschi, Queiroz, Zuardi, & Crippa, 2011), and is an alternative strategy for normalising the endocannabinoid system as recent research has shown that regular dosing with CBD raises depleted levels of anandamide: the main neurotransmitter of the endocannabinoid system (Leweke et al., 2012).

Although no research has been conducted specifically in cigarette smokers addiction, other sources of evidence suggest that CBD may be an effective treatment in addiction. In heroin-addicted rats, CBD reduces cue-related drug seeking, and this effect was still evident

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14 days after a single CBD injection (Ren, Whittard, Higuera-Matas, Morris, & Hurd, 2009). Parker, Burton, Sorge, Yakiwchuk, and Mechoulam (2004) found that systemic administration of CBD prior to exposure to a previously cocaine- or amphetamine-paired environment facilitated extinction of cocaine and amphetamine CPP. Naturalistic studies in humans have shown that CBD reduces the salience of THC stimuli in cannabis dependent humans. Those smoking cannabis low in CBD showed a marked bias towards drug and food-related images which was absent, or reversed, in those smoking high CBD cannabis (Morgan, Freeman, Schafer, & Curran, 2010). CBD is also a potentially excellent treatment of addiction due to its anxiolytic properties, as anxiety is a key symptom often observed in withdrawal from nicotine and other drugs (Hughes, Higgins, & Bickel, 1994). No research as yet has examined the effects of directly administered CBD in addiction in humans.

The current study set out to assess the impact of ad-hoc use of low dose CBD in an inhaler form on nicotine addiction in tobacco smokers who wished to stop smoking. We hypothesised that the use of CBD, via mediation of the endocannabinoid system, would reduce cigarette smoking.

2. Methods and materials

2.1. Design and participants

In a double-blind placebo controlled study, 24 smokers were recruited from the community and were randomised to receive an inhaler of CBD ($n = 12$; 6 females) or placebo ($n = 12$; 6 females). Inclusion criteria were that participants smoked > 10 cigarettes per day, and expressed an intention to quit smoking using a brief screen ('Taking Steps to Quit': Etter, Laszlo, Zellweger, Perrot, & Perneger, 2002); were aged 18–35 years old; had no history of psychiatric, substance misuse or physical health problems; and were not pregnant. The study was approved by the institutional ethics committee (UCL Graduate School) and was conducted in accordance with the Declaration of Helsinki. All participants gave written, witnessed, and informed consent.

2.2. Procedure

Participants were screened prior to randomisation. They responded to an SMS with their daily cigarette use for the week prior to their first visit to the study centre. Participants attended the study centre on two days separated by one week. On the first testing session ('pre'-testing), demographic data, premorbid IQ (Wechsler Test of Adult Reading: WTAR) and exhaled carbon monoxide levels were recorded following 1 hour abstinence, participants also completed the baseline measures detailed below and were given brief counselling on smoking reduction. This consisted of around ten minutes of simple psychoeducational information on relapse prevention focused around 'urge surfing' (Bowen & Marlatt, 2009). Participants were then given the inhaler and trained in how to use it to maximise inhalation of the drug. They were instructed to use the inhaler whenever they felt like smoking in the intervening week and given a diary in which to record their daily cigarette and inhaler use. During the week between the two testing days (pre- and post-testing) participants were reminded via daily text message at the same time each day, which was agreed with the participant. They were reminded to enter details of cigarette and inhaler use in their diary and required to respond via text message with the number of cigarettes, level of craving for cigarettes and number of times they had used the inhaler. On the 'post'-testing day at the study centre they returned, and repeat measures of mood and craving were conducted (see below). Participants kept a daily diary for the two weeks following the second testing session and were telephoned at the end of this period to assess their cigarette use over this period.

2.3. Drug administration

CBD (STI Pharmaceuticals: Brentwood, UK) or placebo was administered via a pressurised Metered Dose Inhaler (pMDI). Each depress of the solution aerosol in the inhaler administered a dose of 400 μ g CBD dissolved in absolute ethanol \approx 5%; or placebo (ethanol alone). Initial studies suggest a bioavailability of CBD following administration through this delivery device of > 65% (Davies, STI pharmaceuticals, *personal communication*).

2.4. Assessments

2.4.1. Baseline measures

Dependence was assessed with the 4 item severity of dependence scale (SDS). Trait anxiety and depressive symptoms were assessed using the Spielberger Trait Anxiety Inventory (STAI: Spielberger & Gorsuch, 1970) and Beck Depression Inventory (BDI: Beck, Ward, Mendelson, Mock, & Erbaugh, 1961), respectively. Trait impulsivity was assessed using the Behaviour Impulsivity Scale (BIS: Gest, 1997).

2.4.2. Interim measures

In the days between testing participants were required to text the number of uses of inhaler each day, and the number of cigarettes consumed. They also responded to the question "on a scale of 1–100, at this moment in time, how much do you want a cigarette?". The VAS craving measure assesses momentary subjective craving.

2.4.3. Repeated measures on Day 1 and Day 7

Recorded number of cigarettes smoked was the key outcome variable. Exhaled carbon monoxide levels were taken on both testing days as an indicator of smoking status. Craving was assessed using the Tiffany Craving Questionnaire (TCQ: 11). The 16-item Mood Rating Scale (MRS: Bond and Lader, 1974) was used to assess key side effects (pre- and 1 hour post-placebo/DCS). Principle component analysis of this measure yields factors for sedation, depression and anxiety.

2.5. Statistical analysis

Data were analysed using PASW Statistics (v.18.0). t-Tests or where data were non-parametric Mann-Whitney U tests were used to analyse baseline characteristics and a series of repeated measures ANOVA to analyse smoking, craving and mood and anxiety data. Pearson's correlation was used to examine the relationship between inhaler and cigarette use.

Table 1
Baseline and pre- and post-treatment data following CBD and placebo.

	Day 0 CBD	Day 0 placebo	Day 7 CBD	Day 7 placebo
Age	28.00 (4.29)	28.08 (6.17)		
IQ-WTAR	43.93 (4.46)	44.33 (3.42)		
Cigarettes smoked per day	18.20 (3.42)	16.54 (2.67)		
Years smoked cigarettes	14.25 (5.95)	11.33 (4.23)		
Fagerstrom score	5.0 (1.53)	5.17 (1.11)		
Depression: BDI	9.42 (5.98)	10.08 (2.94)		
Dependence: SDS	7.58 (3.61)	9.58 (1.62)		
Trait Anxiety: STAI	35.67 (8.98)	33.58 (8.10)		
Impulsivity: BIS	66.17 (6.95)	67.25 (12.89)		
MRS-Sedation	38.35 (17.01)	29.19 (14.19)	41.68 (16.43)	39.85 (15.00)
MRS-Depression	30.58 (14.57)	34.62 (12.01)	34.67 (11.12)	31.43 (13.05)
MRS-Anxiety	39.08 (23.50)	34.14 (15.96)	25.79 (16.58)	31.96 (14.34)

TCQ: Tiffany Craving Scale; MRS: Mood Rating Scale.

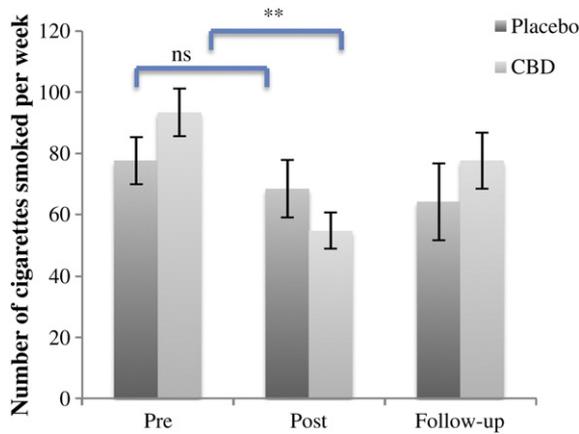


Fig. 1. CBD treatment reduces cigarette consumption in smokers.

3. Results

3.1. Participants

Participants were well-matched demographically, groups were balanced for gender with no differences in age, IQ on the WTAR, baseline smoking variables of cigarettes per day, years of cigarette smoking and Fagerstrom scale of nicotine dependence score and there were no significant group differences in BDI score, BIS score, SDS score or STAI score (Table 1).

3.2. Number of cigarettes smoked (see Fig. 1)

A 2×3 repeated measures ANOVA with a within subjects factor of Time (Pre, Post and Follow-up) and between subjects factor of Treatment (CBD, placebo) found a borderline significant Time \times Treatment interaction [$F(2,42) = 3.12, p = 0.054; \eta_p^2 = 0.13$]. Planned comparisons revealed this to be attributable to a significant reduction in number of cigarettes smoked across the treatment week in the CBD group ($p = 0.002$) but no difference in the placebo group, and a trend, following Bonferroni correction, for a maintenance of this effect in the 2 weeks following the study ($p = 0.034$). Total cigarettes smoked over treatment week were correlated with the total inhaler users in the CBD group however no significant correlation emerged.

3.3. Nicotine craving (Table 2)

Craving assessed by the TCQ on Day 1 and Day 7 and at Follow-up (Day 21) was subjected to a repeated measures ANOVA that found a main effect of Time [$F(2,42) = 3.26, p = 0.048; \eta_p^2 = 0.13$] but no main effect of Treatment or interaction. Planned comparisons revealed a significant reduction in craving in both groups Day 1–Day 7 ($p < 0.001$) but no difference between Day 1 and Follow-up. A 7×2 repeated measures ANOVA of the mean craving reported on SMS across the 7 days of inhaler use also revealed no significant main effects of Time, Treatment or interactions.

Table 2

Pre- and post-treatment data following CBD and placebo.

	Day 0 CBD	Day 0 placebo	Day 7 CBD	Day 7 placebo
TCQ	43.83 (15.50)	51.25 (10.65)	37.08 (12.36)	38.75 (12.68)
MRS-Sedation	38.35 (17.01)	29.19 (14.19)	41.68 (16.43)	39.85 (15.00)
MRS-Depression	30.58 (14.57)	34.62 (12.01)	34.67 (11.12)	31.43 (13.05)
MRS-Anxiety	39.08 (23.50)	34.14 (15.96)	25.79 (16.58)	31.96 (14.34)

TCQ: Tiffany Craving Scale; MRS: Mood Rating Scale.

3.4. Anxiety and mood (Table 2)

2×2 repeated measures ANOVA were MRS (Sedation, Depression and Anxiety) scores. For sedation scores on the MRS there was a trend for a main effect of Time [$F(1,22) = 3.88, p = 0.084$] reflecting greater sedation in both groups on the second testing day, but no main effect of Treatment or interaction. Analysis of depression scores revealed no main effects of Time or Treatment or interaction. There was a main effect of Time on anxiety [$F(1,22) = 4.79, p = 0.04$], reflecting lower scores in both groups at Time 2, however there was no interaction or main effect of Treatment.

4. Discussion

This preliminary study set out to assess the impact of the ad-hoc use of an inhaler of the naturally occurring cannabinoid CBD on cigarette smoking in tobacco smokers who wanted to quit. The main finding of this study was a dramatic reduction in the number of cigarettes smoked across a 7 day period in the individuals using the CBD inhaler, compared to no reduction in the placebo group. However, this reduction occurred in the absence of a change in cigarette craving reported daily across the week. There was a reduction in craving in both groups between Day 1 and Day 7 but this reduction was not maintained at follow-up. Both the CBD and placebo groups in this study showed reduced anxiety across the 7 days.

This is the first study, as far as we are aware, to demonstrate the impact of CBD on cigarette smoking. The reduction in smoking observed in this study was striking and occurred in the absence of other specific effects, notably on craving. Given the pivotal role of craving in relapse, this is a potentially very encouraging finding, in that participants using the CBD inhaler reduced the number of cigarettes they smoked without increased craving for nicotine. The decrease in smoking observed here may plausibly relate to the action of CBD at the CB1 receptor, given previous literature on similar reductions following treatment with rimonabant. Neurochemically, another putative mechanism suggested by recent research has shown that the reinforcing and neurochemical effects of nicotine in rats are reduced by fatty acid amide hydrolase (FAAH) inhibition (Gonzalez et al., 2002), as it has been proposed that some of the behavioural effects of CBD are related to its properties as an FAAH-inhibitor (Leweke et al., 2012).

Psychologically, the reduction in smoking may occur via a modulation of the salience of smoking cues by CBD, consistent with preclinical studies (Ren et al., 2009) and a naturalistic study that found CBD to reduce the attentional bias of dependent cannabis users to cannabis stimuli (Morgan et al., 2010). CBD may have acted to weaken the attentional bias of smokers to smoking stimuli. Attentional bias is thought to play a fundamental role in maintaining the cycle of craving and relapse in addiction and therefore a reduction in salience of smoking cues would be predicted to have a powerful effect on substance use, as is seen in this study. CBD has also been recently found to disrupt reconsolidation (Stern et al., 2012), a memory process by which memories are destabilised which has been suggested to have a therapeutic role in addiction (Taylor et al., 2009). Such a disruption with inhaler use on a daily basis might also explain these findings.

This was a preliminary study requiring replication, especially in light of the absence of any other biochemical assays (e.g. cotinine levels). The results reported here are solely based on self-report which is a clear limitation, as is that we only assessed craving once per day which could have been contaminated by recent cigarette use. At the doses used in this study, CBD did not produce changes in self-rated anxiety or increase sedation, both previous noted effects of the drug (Scherma et al., 2008). CBD produced no increase in depression unlike selective CB1 antagonists such as rimonabant, which is encouraging for the use of CBD as a treatment for nicotine addiction should future, larger-scale studies, reinforce the suggestions of this pilot study.

In conclusion, the preliminary data presented here suggest that CBD may be effective in reducing cigarette use in tobacco smokers, however larger scale studies, with longer follow-up are warranted to gauge the implications of these findings. These findings add to a growing literature that highlights the importance of the endocannabinoid system in nicotine addiction.

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Author contributions

CJAM and SJK designed research, CJAM analysed data and wrote manuscript, and AJ and RD performed research.

Conflict of interest

None.

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