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A randomised controlled trial of vaporised Δ9-tetrahydrocannabinol and cannabidiol alone and in combination in frequent and infrequent cannabis users: acute intoxication effects

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Abstract

Access to cannabis and cannabinoid products is increasing worldwide for recreational and medicinal use. Two primary compounds within cannabis plant matter, Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), are both psychoactive, but only THC is considered intoxicating. There is significant interest in potential therapeutic properties of these cannabinoids and of CBD in particular. Some research has suggested that CBD may ameliorate adverse effects of THC, but this may be dose dependent as other evidence suggests possible potentiating effects of THC by low doses of CBD. We conducted a randomised placebo controlled trial to examine the acute effects of these compounds alone and in combination when administered by vaporisation to frequent and infrequent cannabis users. Participants (n = 36; 31 male) completed 5 drug conditions spaced one week apart, with the following planned contrasts: placebo vs CBD alone (400 mg); THC alone (8 mg) vs THC combined with low (4 mg) or high (400 mg) doses of CBD. Objective (blind observer ratings) and subjective (self-rated) measures of intoxication were the primary outcomes, with additional indices of intoxication examined. CBD showed some intoxicating properties relative to placebo. Low doses of CBD when combined with THC enhanced, while high doses of CBD reduced the intoxicating effects of THC. The enhancement of intoxication by low-dose CBD was particularly prominent in infrequent cannabis users and was consistent across objective and subjective measures. Most effects were significant at $p < .0001$. These findings are important to consider in terms of recommended proportions of THC and CBD in cannabis plant matter whether used medicinally or recreationally and have implications for novice or less experienced cannabis users.

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A randomised controlled trial of vaporised Δ^9-tetrahydrocannabinol and cannabidiol alone and in combination in frequent and infrequent cannabis users: acute intoxication effects.

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Abridged title: Acute effects of vaporised THC and CBD alone and in combination

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Abstract (250 words)

Access to cannabis and cannabinoid products is increasing worldwide for recreational and medicinal use. Two primary compounds within cannabis plant matter, Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), are both psychoactive, but only THC is considered intoxicating. There is significant interest in potential therapeutic properties of these cannabinoids, and of CBD in particular. Some research has suggested that CBD may ameliorate adverse effects of THC, but this may be dose-dependent as other evidence suggests possible potentiating effects of THC by low doses of CBD. We conducted a randomised placebo controlled trial to examine the acute effects of these compounds alone and in combination when administered by vaporisation to frequent and infrequent cannabis users. Participants (n=36; 31 male) completed 5 drug conditions spaced one week apart, with the following planned contrasts: Placebo vs CBD alone (400mg); THC alone (8mg) vs THC combined with low (4mg) or high (400mg) doses of CBD. Objective (blind observer ratings) and subjective (self-rated) measures of intoxication were the primary outcomes, with additional indices of intoxication examined. CBD showed some intoxicating properties relative to Placebo. Low doses of CBD when combined with THC enhanced, while high doses of CBD reduced the intoxicating effects of THC. The enhancement of intoxication by low dose CBD was particularly prominent in infrequent cannabis users and was consistent across objective and subjective measures. Most effects were significant at $p<.0001$. These findings are important to consider in terms of recommended proportions of THC and CBD in cannabis plant matter whether used medicinally or recreationally, and have implications for novice or less experienced cannabis users.

Trial registration ISRCTN Registry Identifier: ISRCTN24109245

Keywords (4-6)

Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), cannabis, cannabinoids, intoxication, synergistic effects

Introduction

Cannabis and cannabinoid products are increasingly becoming available as jurisdictions around the world ease restrictions on use recreationally and medicinally. There is significant interest currently in the therapeutic application of cannabinoids, while the focus of attention of the scientific and medical community in the recent past has been on harms associated with exposure, including the development of psychosis [1]. The two primary constituents of cannabis plant matter, Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), are thought to show opposing effects in this regard. THC is a partial agonist at CB1 receptors, while CBD is a low-affinity CB1 and CB2 receptor ligand and negative allosteric modulator of CB1, that reduces the binding of CB1 agonists, while augmenting endocannabinoid tone in an indirect manner [2,3]. THC has been shown to be psychotogenic [4,5], and responsible for cognitive impairment and brain structural alterations in long term users of cannabis [6-8]. High potency THC cannabis products are thought to underlie the development of psychotic-like symptoms or overt psychosis in vulnerable individuals who use cannabis [9]. CBD is considered to be non-intoxicating, but is psychoactive in that it can induce brain functional alterations that are opposite to those induced by THC [10]. CBD has also been shown to possess neuroprotective and antipsychotic properties [11-13]. A by-product of the development of high potency strains of cannabis has been the breeding out of CBD in plant matter, such that either nil or very low levels of CBD are now present in typical street cannabis [14]. It has been posited that this absence of CBD in cannabis of high THC potency may contribute to psychosis-like outcomes [9,15], and a lack of protection from brain harms [8]. Recommendations have been made for the reinstatement of CBD into cannabis-plant matter and cannabis products as a harm minimisation strategy and for maximising benefits therapeutically [15,16].

A number of animal and human studies have shown that CBD may ameliorate some of the adverse effects of THC [12]. In human studies of naturalistic exposure, greater concentrations of CBD determined by hair analysis in regular cannabis users, by analysis of plant matter, or by estimation of proportional exposure, have been associated with better cognitive performance, especially memory [17], and fewer psychotic symptoms [18,19]. Controlled administration studies have shown that pre-treatment with oral CBD reduced the cognitively impairing and paranoia-inducing effects of intravenously administered THC [20] and simultaneous infusion of THC and CBD blocked THC-related anxiety and subjective alterations [21]. In the preclinical literature, CBD has been shown to reverse THC-induced adverse effects on social and cognitive tasks [2,12,22]. Co-administration of CBD with THC, 3mg each, daily for 3 weeks during adolescence prevented the development of THC-induced cognitive and behavioural impairments in mice [23], and an open-label trial of prolonged CBD administration in humans (200mg/day for 10 weeks) improved psychological symptoms and cognition, and increased hippocampal subfield volumes in cannabis users [24,25].

While many studies have focused on the amelioration of THC effects by CBD, there is also evidence to suggest that CBD can potentiate the effects of THC. Antinociceptive and some neuroendocrine effects of THC in mice or rats were exacerbated by CBD [26-28]. Medium and high doses of CBD (10 and 50mg/kg) exacerbated the impairing effects of low (1mg/kg) dose THC on spatial memory, hypoactivity and hypothermia in mice via a CB1 receptor mechanism [29]. CBD co-administered with THC did not reverse THC-induced spatial working memory impairment in rhesus monkeys, and may have exacerbated it, although it did ameliorate impairments on other cognitive tasks [30]. Klein and colleagues [31] demonstrated pre-treatment with CBD to potentiate weight gain, anxiogenic and locomotor suppressant effects of THC when both were administered to adolescent rats over 21 days in ascending matched doses (1, 3 and 10 mg/kg); CBD was administered 20 min prior to each THC injection. Todd and Arnold [32] also showed that CBD potentiated the locomotor suppressant effects of THC, while simultaneously diminishing other neuropharmacological effects of THC, and in a subsequent study suggested that the potentiating effect of CBD on THC-induced locomotor suppression was due to prolongation of those effects over time [33]. This study also demonstrated synergistic interactions between CBD and THC at 1:1 and 5:1 ratios on epigenetic and neuroadaptive changes in the mesolimbic pathway, suggesting long-term molecular changes that may be supra-additive, and the authors suggested that potentiating effects of CBD may be observable in measures sensitive to changes in the mesolimbic pathway, including the rewarding effects of cannabis. CBD has been reported not to modulate the subjective high induced by THC [34,35], although with prolonged administration of high doses of CBD (200mg/day for 10 weeks), we reported a subjective lowering of intoxication experienced from cannabis use external to the trial [25].

Many biphasic effects of THC and of CB1 receptor stimulation have been demonstrated (e.g. [36-38] and an inverted bell-shaped dose-response curve for CBD has been reported in a number of acute administration studies. In animal models of anxiety, Guimaraes et al [39] showed that low doses of CBD (2.5-10mg/kg), but not higher doses, reduced anxiety, and in models of anxiety and depression, Campos and Guimaraes [40] showed the involvement of differing neurochemistry and receptor activation at higher doses (e.g. TRPV1 receptors) compared to lower doses (e.g. 5-HT1A or CB1). In human studies using the Simulated Public Speaking Test, doses of 100-150, 300, and 600- 900mg CBD given orally produced an inverted bell-shaped curve response with the medium dose showing greatest efficacy in reducing anxiety [41,42]. The authors highlighted the need to establish accurate therapeutic dose ranges for CBD in treating individual clinical conditions.

Interactions between THC and CBD appear to be highly complex, and the ability of CBD to block or potentiate the effects of THC has been explained by a range of potential mechanisms, largely involving the endocannabinoid system

[2,3,43-45]. Importantly, these differential effects are thought to be dependent upon absolute dose, ratio of CBD:THC, route of administration, and timing (in terms of temporal proximity to exposure to THC, whether as a pre-treatment, simultaneous or subsequent) [46-49] but no definitive pattern has yet emerged. As one example, pulmonary administration of THC+CBD to rats increased, while oral administration decreased, an index of anxiety relative to THC or CBD alone, however only subcutaneous and oral co-administration of these compounds, and not pulmonary, resulted in increased serum and brain levels of THC relative to THC alone [50]. Both high and low doses of CBD have been shown to raise THC concentrations in blood and brain, prolonging THC disposition in the central nervous system [28,31,51,52] and suggesting that CBD inhibits the metabolism of THC [32,49].

Intrapulmonary administration of cannabinoids (e.g. by smoking or vaporising) is considered to be an effective mode of delivery in humans due to high systemic bioavailability, fast onset of action, short duration of peak effects and time limited duration of effects relative to other noninvasive methods (oral, sublingual, transdermal) [53]. Vaporisation has been suggested as a safer intrapulmonary delivery system than smoking, since by heating rather than combusting plant matter or pure compounds it avoids the formation of pyrolytic toxic compounds [54], but see [55,56]. Vaporisation of cannabinoid compounds provides an efficient means of administering cannabinoid compounds simultaneously for experimental purposes, producing immediate effects, and emulating the effects of smoked cannabis while avoiding the harms of smoking. Vaporisation is increasing in popularity among recreational cannabis users, and being applied medicinally in clinical trials. Few studies in humans have examined interactive effects of vaporised THC and CBD.

Hindocha and colleagues [35] administered vaporised doses of 8mg THC and 16 mg CBD, each alone and combined, and examined effects on an emotional facial recognition task in frequent and infrequent cannabis users, who scored high or low on schizotypy. CBD alone improved emotional facial affect recognition, while THC was detrimental, and THC+CBD produced no impairment. Subjective intoxication was equivalent between the THC and THC+CBD conditions, and no interactions with frequency of cannabis use or schizotypy were observed. Most recently, Morgan and colleagues [57] reporting on the same sample as Hindocha et al [35], showed no attenuation by the 16mg CBD of psychotomimetic or cognitively impairing effects of the 8mg THC. They conclude that at a ratio of 2:1, CBD does not attenuate the acute psychotic and memory impairing effects of vaporised THC. They also reported a blunted antipsychotic response to CBD in frequent users, while infrequent users showed reduced scores on the Psychotomimetic States Inventory (PSI) following CBD alone. No interactions with schizotypy were found. The dose of CBD administered in these studies may be considered low-medium. It is at the higher end of what may be present in cannabis plant matter, but far lower than doses of CBD that have been shown to have therapeutic (e.g. antipsychotic and anxiolytic) efficacy or modulate brain function (e.g. 600mg [10]).

In the double-blind randomised placebo controlled trial that we report here, we tested a substantially higher dose of CBD alone and co-administered with 8mg THC, as well as a substantially lower dose of CBD co-administered with 8mg THC. The low dose of CBD that we selected, 4mg, was chosen to emulate the 2:1 THC:CBD ratio that had been more common in street level cannabis, before the development of high potency THC strains [58,59]. For the high dose CBD we aimed to vaporise doses equivalent to those that had been demonstrated to have antipsychotic efficacy and to show opposite effects on brain function (e.g. 600mg, administered orally) [10,11]. As one of the first studies of vaporised high doses of CBD, significant protocol development was undertaken toward refining methods for this trial [60]. Our pilot work showed that 200mg CBD was the maximum that could be vaporised into a single balloon; as such, we administered two balloons to deliver 400mg CBD.

The overall aim of this randomised controlled trial was to examine effects of vaporised high dose CBD, and low and high doses of CBD delivered simultaneously with THC, on a broad range of measures pertinent to understanding associations between cannabis or cannabinoid compounds and psychotic-like outcomes. These included assessments of electroencephalography, cognition and neurochemistry, to be reported elsewhere. This paper reports subjective and objective intoxication outcomes, and their association with psychotic-like, depressive and anxiety symptoms. We investigated the effects of these cannabinoids in a sample comprised of frequent and infrequent cannabis users and non-naïve nonusers, with an aim to examine any differential effects of these compounds according to the extent of prior experience with cannabis. Based on mixed findings from animal and human studies, we formulated the following hypotheses: 1) that high dose CBD alone would not be intoxicating relative to placebo; 2) that low dose CBD combined with THC may potentiate the intoxicating effects of THC; and 3) that high dose CBD combined with THC may attenuate the intoxicating effects of THC. In further support of our second hypothesis, we note that in human studies, users of low CBD strains of cannabis perform significantly worse on cognitive tests [57], show higher psychotic-like symptoms [19] and reduced grey matter concentration in hippocampus [61] than users of higher CBD strains. While the interpretation that these observations indicate a protective nature of higher concentrations of CBD may indeed be correct, whether these data might indicate a possibility of low doses potentially exacerbating effects of THC has not been considered. Given the range of evidence in the literature reviewed above, we sought to test this hypothesis.

Methods

Participants

Current cannabis users and non-naïve nonusers were recruited via flyers and advertisements placed around the University of Wollongong, in local newspapers, and through word of mouth. Current cannabis users must have used cannabis at least once per month for 2 years. Non-naïve nonusers were required to have used at least once in the past 2 years with 5-10 lifetime uses. Self-reported substance use, other than cannabis, alcohol or tobacco, in the 2 weeks prior to testing and positive urine drug screens on days of testing were exclusionary. Further exclusion criteria were: any previous adverse reaction to cannabis (i.e., that required medical attention or induced subjective distress), having a first degree relative with a history of any psychotic disorder, personal psychiatric diagnoses or medications, significant head injuries, neurological conditions, cardiovascular disease, asthma, pregnancy, alcohol dependence and significant use of any illicit substance other than cannabis (>50 occasions in the past 12 months; the final sample had a median of 2 occasions of other illicit drug use, range 0-35). Participants were required to abstain from cannabis and alcohol for at least 12 hrs prior to testing and nicotine and caffeine during test sessions.

Thirty-six participants (31 male; median age 21, range 18 – 51) were subsequently divided into groups of Frequent users (n=18; 17 male; median age 21.8, range 21-44) and Infrequent users/non-naïve nonusers (henceforth referred to as Infrequent users; n=18; 14 male; median age 20.5, range 18-51) via median split on lifetime cannabis use (128 occasions). Frequent users had 133-~8000 lifetime occasions of use, were currently using cannabis on a median 10 days per month (range 2-28) and had been using at least once/month for a median 3 years (range 1.4-25.5). Infrequent users had 6-123 lifetime occasions of use, were currently using cannabis on a median 0 days per month (range 0-5) and had a median 0 years of at least monthly use (range 0-4.5). Participants were required to attend 6 sessions in total at the University: a baseline assessment session and five drug administration sessions, during which a range of outcome measures were obtained (e.g. electroencephalography, neuropsychological testing; to be reported elsewhere). They provided written consent prior to each session and were reimbursed AUD$80 per session for their time involvement. The trial was approved by the University of Wollongong and Illawarra Shoalhaven Local Health District Human Research Ethics Committee.

Clinical, cannabis and other substance use and demographic measures

Participants were telephone screened for exclusion criteria. Eligible participants were invited to attend a substantive baseline assessment at the University. This involved a semi-structured interview to assess demographic information, medical history and detailed history of current and previous substance use, including a 30-day timeline follow-back (TLFB) [62] and the Alcohol Use Disorders Identification Test (AUDIT) [63]. The M.I.N.I. International Neuropsychiatric Interview – PLUS [64] screened for psychiatric disorders, whilst symptoms of anxiety and mood dysregulation were assessed by the State-Trait Anxiety Index (STAI) [65] and Beck Depression Inventory (BDI) [66]. Participants completed the Community Assessment of Psychic Experiences (CAPE) [67] and Schizotypal Personality Questionnaire (SPQ) [68] to assess psychosis liability. Any participants scoring in the very high range of psychosis liability on the CAPE (>50) were excluded from proceeding with drug sessions. They completed the Severity of Dependence Scale (SDS) [69] for cannabis, and Cannabis Experiences Questionnaire (CEQ) [70] to retrospectively assess symptoms experienced whilst intoxicated. Height and weight were measured and used to calculate body mass index (BMI).

Drug administration sessions

There were five drug administration sessions in which the following compounds were administered by vaporisation, with a one week washout: Placebo (ethanol vehicle 400 μl), THC alone (8 mg), CBD_{high} alone (400 mg), THC+CBD_{low} (THC: 8 mg, CBD: 4 mg) and THC+CBD_{high} (THC: 12 mg; CBD: 400 mg). THC and CBD were dissolved in an ethanol solution, 4% for THC and 10% for CBD. Ethanol was blown off by vaporisation at a lower temperature prior to vaporising the cannabinoids at a higher temperature for administration to participants (see [60]). All solutions were purchased from STI Pharmaceuticals (Essex, UK) and administered via a Volcano Vaporiser® (Storz and Bickel, Tuttlingen, Germany). The THC+CBD_{low} dose was equivalent to proportions found in some strains of cannabis plant matter [71] while the high dose of CBD was selected to approximate therapeutic oral doses from the literature (see [60] for dose and protocol development).

Following consent signing at each session, participants provided a urine sample to corroborate self-reported abstinence from substances other than cannabis. Females were pregnancy tested for exclusion. To minimise individual differences in drug metabolism, all participants were requested to refrain from eating the morning of their session and were provided a standardised light meal on arrival. An intravenous cannula was placed in the non-dominant arm for collecting blood samples at regular intervals. Plasma was analysed by LC-MS/MS for CBD, THC, and THC metabolite concentrations [72]. Heart rate (HR) and blood pressure (BP) were measured using an automated cuff placed on the

opposite arm to blood sampling cannulation. Participants were seated in an upright position for a minimum of 2 min prior to recording HR and BP. Three consecutive measurements were recorded at each timepoint (Fig. 1) and the median was analysed.

The order of drug conditions was pseudo-counterbalanced between groups and randomly assigned for each participant. Administration procedures included a 'main dose' and two 'top-up' doses approximately 65 and 120 min following the main dose to maintain intoxication across all experimental protocols (not reported here). To ensure blinding to drug conditions, participants were administered two normal sized Volcano® Easy Valve balloons to deliver the main dose and one balloon to deliver top-up doses at each session, with the balloon covered by opaque fabric to prevent identification of vapour colour or density (see [60] for further details). Drug doses were discretely prepared and vaporised into the balloons by the principal investigator, and handed to research staff with the opaque cover to administer to participants. In this way, the research staff responsible for data collection were blinded to the drug conditions. Participants were instructed to inhale a comfortable amount and hold their breath for 10 seconds before exhaling. Drug administration for the main dose took ~10 min, involving 6-10 inhalations from each balloon. Fig. 1 provides a schematic showing protocols across the entire session, which lasted approximately 3.5 hrs. The primary focus of this manuscript is on the first hour after administration of the main dose. Baseline measures, prior to drug administration, are referred to as Time 0, with outcomes of interest at Time 1, Time 2, Time 3 and during Recovery (approximately 3 hrs after the main dose), as described further below. In between times, participants underwent electroencephalography while watching a silent film or button pressing to auditory stimuli, and performed cognitive tasks after the second top-up dose.

Fig. 1 about here

Intoxication measures

Primary outcomes were objective and subjective measures of intoxication. The objective measures were obtained by independent observers blinded to drug condition and group, rating participants from 0 (not at all) to 4 (extremely) on the 8 observer items of the Clinician Administered Dissociative States Scale (CADSS) [73]. Scores on the 8 items were summed to produce a composite score out of a total possible 32, reflecting the extent to which they observed the participant to be intoxicated. Example items include: “Did the subject appear to be separated or detached from what is going on, as if not a part of the experience or not responding in a way that you would expect?” and “Did the subject say something bizarre or out of context, or not speak when you would have expected it?”. The independent observers were trained psychologist members of the research team, assisting with daily project management, but not involved in drug

administration. The CADSS observer items were administered at Time 0, again ~ 55 min after main dose drug administration (Time 2) and during the Recovery period (after two additional top-ups were administered as per Fig. 1).

The primary measure of subjective intoxication was participant self-rated response to the question "On a scale from 1 – 10, where 10 is the most stoned you've ever been, how stoned do you feel now?". The participant was provided with a visual analogue scale (VAS) with end points marked as "Not at all stoned" at 1 and "The most stoned you've ever been" at 10 and asked to verbally report a score between 1 and 10. This item was administered at Time 0, immediately after administration of the main dose (Time 1), again ~55 min later at Time 2 (at the same time as the CADSS), and during the Recovery period. (Raw scores from additional administration time points across the session for this measure are depicted in Fig. 4a, but were not analysed for this paper).

Further self-report measures of intoxication were included to aid interpretation of the nature of the primary subjective intoxication score. Other VAS items (adapted from, [74]) rated from 0 (not at all) to 4 (extremely) measured internal perception (6 items), reflecting inner feelings that do not correspond with reality, external perception (6 items), reflecting misperception of external stimuli or changes in the awareness of the environment [75], and drowsiness (1 item). The CADSS provided 19 self-report ratings from 0 (not at all) to 4 (extremely) contributing to subscales that measure depersonalisation, derealisation and amnesia. The VAS and the CADSS were administered at Time 0, Time 2 and during Recovery, and the VAS was also administered at Time 1. One further measure of intoxication was obtained at a different time point to the VAS and CADSS: the 48-item Psychotomimetic States Inventory (PSI) [76]) was administered at Time 0, ~15 min after the first top-up dose (Time 3), and at Recovery. The items, rated from 0 (not at all) to 3 (strongly), form six sub-scales: delusional thinking, perceptual distortion, cognitive disorganisation, anhedonia, mania and paranoia.

The Brief Psychiatric Rating Scale (BPRS) [77], BDI and STAI were administered at the start of each weekly drug session to monitor change or variations in psychiatric symptom status over the course of participation in the trial, but not immediately following drug administration. No significant changes were observed over the course of the trial. These measures were examined in association with intoxication outcomes within each drug session.

Participants were retained beyond the recovery period indicated in Fig. 1 until their score on the primary VAS item of subjective intoxication returned to baseline levels.

Data analysis

All analyses utilised change scores from Time 0 to Time 1, Time 2, Time 3 and/or Recovery (as appropriate for each measure). Missing values (of which there were few) were not replaced. Spearman's correlations tested associations between dose delivered and plasma concentrations at Time 1. HR and BP changes were examined at Time 1 only, using simple and linear contrasts as described below. In the Results, we report outcomes from statistical analysis in the following order: hypothesis 1 (CBD_{high} vs Placebo); hypotheses 2 and 3 (contrasts between the three THC conditions), each explored also as interacting with group (Frequent vs Infrequent users/non-naïve nonusers). Effect sizes are reported as partial eta-squared (ηp2), where values >.02, >.13 and >.26 are considered small, medium and large, respectively.

Primary experimental analyses

We tested the hypotheses that CBD_{high} would not be more intoxicating than placebo, and that low and high doses of CBD when added to THC would respectively increase or attenuate intoxication, by analysing change scores from baseline for the objective and subjective measures of intoxication. We used planned simple or linear contrasts within repeated measures analyses of variance (rmANOVAs), with drug Condition the within-subject factor and Group the between-subjects factor (using SPSS Version 24). Many of the outcome measures were not normally distributed and could not be adequately transformed to normality. However, as the above parametric analyses provide greater flexibility with which to address the research hypotheses, and as rmANOVA is generally robust (in terms of Type I error) to normality violations, the above parametric approach was used, and significant results confirmed using equivalent non-parametric analyses (Friedman's, Wilcoxon signed-rank, Kruskal-Wallis and Mann-Whitney U tests). The pattern of results reported below did not change when conducting confirmatory non-parametric tests. For each of the following, both the contrast and the interaction between the contrast and Group from the rmANOVA were examined. Simple contrasts compared Placebo vs THC (to verify that the experimental design was appropriate for eliciting THC-induced intoxication), and Placebo vs CBD_{high} (to determine whether high dose CBD induces intoxication; hypothesis 1). In line with our hypotheses (2 and 3) that, relative to THC alone, low doses of CBD added to THC would increase intoxication whereas high doses of CBD would reduce intoxication, a linear contrast was conducted where the drug conditions were entered in the order THC+CBD_{low}, THC then THC+CBD_{high}. Tests for interactions with Group do not directly test the hypotheses set out in the Introduction, but are included here due to their strong relevance to the literature described above. To account for any potential order effects, analyses were first conducted on data sorted by session (drug sessions 1 – 5, to which drug conditions were randomised). For both primary objective and subjective intoxication measures, the linear contrast for session and its interaction with group were nonsignificant (both $p>.91$ and $p>.41$, respectively). Age did not differ between Frequent and Infrequent users ($p=.47$)

and was not correlated with objective or subjective intoxication outcomes in any drug condition (all p>.14); age was therefore not included as a covariate or considered further.

Exploratory Analyses

Exploratory analyses using additional self-report measures of intoxication (VAS, CADSS, PSI) were conducted using planned contrasts as described in the primary experimental analysis section. Spearman's rho tested associations between the primary objective and subjective measures of intoxication and these additional self-report measures to inform the qualitative nature of intoxication. Additional correlations between the primary objective and subjective intoxication change scores at Time 1 and/or 2, and both cannabis use measures (lifetime occasions of use, hours since last use of cannabis) and BMI, as well as between intoxication and CAPE total frequency and distress scores, SPQ total score, CEQ subscales, BPRS, BDI and STAI (State and Trait) were conducted to determine whether psychosis-proneness or mood measures may predict intoxication effects for any drug condition.

Results

Doses and plasma concentrations

Drug conditions with doses loaded into the vaporiser, estimates of actual dose delivered, and plasma concentrations of THC, THC-metabolites and CBD are provided in Table 1. Some participants experienced difficulty in inhaling the full contents of the balloons administered, either due to feeling too intoxicated already from the dose inhaled, or due to throat irritation, particularly in the high dose CBD conditions. Actual dose delivered was estimated from the proportion of the balloon inhaled, confirming clear separation between the drug conditions of our experimental design, as intended. That is, despite lesser doses being consumed by some participants, the drug conditions nevertheless clearly represented Placebo, high dose CBD alone, THC alone, THC with low dose CBD and THC with high dose CBD. The estimated dose of THC (mg) delivered did not differ between the THC and THC+CBD_{low} conditions (Z=1.07, p=.29), while that in the THC+CBD_{high} condition was significantly lower than in the THC condition (Z=4.13, p<.0001). Despite this, Infrequent and Frequent users did not differ in the estimated dose delivered in any condition (CBD: Z=1.73, p=.09; THC: Z=1.0, p=.32; THC+CBD_{low}: Z=0.04, p=.97; THC+CBD_{high}: Z=1.51, p=.13), indicating that between group comparisons were unconfounded by any dose differences. For between condition contrasts, analyses were repeated on a subsample who did not differ in proportional dose consumed in the THC and THC+CBD_{high} conditions (n=16; 5 Infrequent users, 11 Frequent users) to confirm condition effects.

Plasma CBD concentration correlated with the estimated dose of CBD delivered in the CBD_{high} condition (*rho*=.425, p=.012) and in the THC+CBD_{high} condition (*rho*=.415, p=.016), but not in the THC+CBD_{low} condition (p=.38). Plasma concentrations of THC or THC metabolites, however, did not correlate with the estimated dose of THC delivered in any condition (all p>.10). Strong positive correlations were observed between plasma THC and CBD concentrations in both of the combined conditions (THC+CBD_{low}: *rho*= .726, p<.0001; THC+CBD_{high}: *rho*=.920, p<.0001).

Heart rate and blood pressure

HR across the session for each drug condition is depicted in Fig. 2. There was no Condition effect for the simple contrast between Placebo and CBD_{high} conditions and no main effect or interaction with Group (all p>.10). The simple contrast between Placebo and THC showed a highly significant Condition effect (F(1,34)=100.86, p<.0001) which interacted with Group (F(1,34)=10.20, p=.003), while the main effect of Group was not significant (p=.12). This indicated that THC significantly elevated HR relative to Placebo, and did so more strongly in Infrequent users. For the

three THC conditions, the linear contrast showed a Condition effect ($F(1,34)=34.97$, $p<.0001$), with greater change in HR for the THC and THC+CBD_{low} conditions than in the THC+CBD_{high} condition. There was a main effect of Group ($F(1,34)=8.57$, $p=.006$) with Infrequent Users showing greater HR change than Frequent, which tended to be more evident in the THC and THC+CBD_{low} conditions ($p=.075$). The linear contrast between the three THC conditions remained significant, showing the same pattern, in the subsample matched for dose in the THC and THC+CBD_{high} conditions ($F(1,14)=7.37$, $p=.017$), but did not interact with Group ($p=.52$).

There were no significant differences in blood pressure (BP) across conditions (all $p>.37$). Frequent users showed an overall increase in diastolic BP in the simple contrast between CBD_{high} and Placebo ($F(1,34)=7.11$, $p=.012$) and a trend level reduction in systolic BP in the THC conditions ($p=.057$), but there were no Condition by Group interactions (both $p>.23$).

Fig. 2 about here

Objective and subjective measures of intoxication

Objective intoxication scores

There were no significant differences between CBD_{high} and Placebo; CBD_{high} showed a trend toward a higher intoxication rating than Placebo ($p=.092$), which did not interact with Group ($p=.67$) (Fig. 3a). No effects were observed at Recovery (all $p>.16$). Whilst the contrast between CBD_{high} and THC was not planned at the outset, a significant intoxicating effect of CBD_{high} relative to placebo was found in the analysis of subjective intoxication scores as reported below. It was therefore deemed prudent to examine further the degree of intoxication from CBD_{high} by contrasting it with THC, and this contrast was therefore also performed on the objective measure. Objectively measured intoxication was rated significantly higher for THC than for CBD_{high} ($F(1,34)=22.58$, $p<.0001$, $\eta p2=.399$), with a tendency for this contrast to be greater in Infrequent users ($p=.067$). No difference between THC and CBD_{high} was evident during Recovery (both $p>.49$).

Higher intoxication ratings were obtained for the THC than Placebo condition ($F(1,34)=26.19$, $p<.0001$, $\eta p2=.435$), with this effect marginally greater in Infrequent users ($F(1,34)=3.78$, $p=.06$). There was a significant linear reduction across the three THC conditions, with intoxication rated highest in the THC+CBD_{low} condition, lower in the THC alone condition, and lowest in the THC+CBD_{high} condition ($F(1,34)=6.87$, $p=.013$, $\eta p2=.168$). This pattern interacted with Group, such that it was greatly accentuated in Infrequent users, and relatively absent in Frequent users

(F(1,34)=5.81, p=.021, ηp2=.146) (Fig.3b). Infrequent users had marginally higher intoxication ratings overall (p=.06). No effects remained at Recovery (all p>.34). Similar results were found using the subsample matched for THC dose, differing only in that the linear contrast over THC conditions was reduced to trend-level (p=.087; Condition by Group F(1,14)=4.59, p=.05, ηp2=.247; main effect of Group p=.09).

Fig. 3 about here

Subjective intoxication scores

Subjective intoxication scores for the entire sample across the testing protocol are depicted graphically in Fig. 4a for each drug condition. Only change from Time 0 to Time 1, Time 2 and Recovery timepoints are considered here. Fig. 4b and Fig. 4c show change scores from Time 0 to Time 1 for subjective intoxication by group for the primary drug condition comparisons.

Fig. 4 about here

Participants' intoxication scores were significantly higher for CBD_{high} than Placebo at Time 1 (F(1,34)=52.55, p<.0001, ηp2=.607), and remained significantly higher one hour later at Time 2 (F(1,34)=20.61, p<.0001, ηp2=.377), as well as during Recovery (F(1,34)=5.49, p=.025, ηp2=.139). There were no interactions with Group (all p>.71) and no main effects of Group (all p>.12) (Fig. 4b). After removing seven participants who had plasma THC concentrations (>5ng/ml) in the CBD alone condition, CBD_{high} remained significantly more intoxicating than Placebo at Time 1 (F(1,27)=31.10, p<.0001, ηp2=.535) and Time 2 (F(1,27)=11.74, p=.002, ηp2=.303), but not at Recovery (p=.109), and there were no Group effects or interactions (all p>.16). Given this unexpected finding of CBD being intoxicating, the simple contrast between CBD_{high} and THC was also tested. The intoxication with CBD_{high} was rated lower that with THC at Time 1 (F(1,34)=17.29, p<.0001) and Time 2 (F(1,34)=87.28, p<.0001, ηp2=.720), both times interacting with Group (F(1,34)=5.16, p=.030, ηp2=.132, and F(1,34)=4.160, p=.049, ηp2=.109, respectively), with a relatively greater degree of intoxication with THC in Infrequent users. This contrast between CBD_{high} and THC remained significant during Recovery (F(1,34)=29.35, p<.0001, ηp2=.463), also interacting with Group (F(1,34)=4.70, p=.037, ηp2=.121).

The THC condition induced significantly higher intoxication ratings than Placebo at Time 1 (F(1,34)=97.89, p<.0001, ηp2=.742) and Time 2 (F(1,34)=201.93, p<.0001, ηp2=.856), and this interacted with Group at both times (F(1,34)=5.75, p=.022, ηp2=.145, and F(1,34)=7.29, p=.011, ηp2=.176, respectively), being greater in Infrequent users. These effects were sustained into the Recovery period (Condition: F(1,34)=39.35, p<.0001, ηp2=.536; Condition by Group: F(1,34)=4.53, p=.041, ηp2=.117).

For the three THC conditions, the linear decrease across Conditions was not significant at Time 1 (p=.30), but an interaction between Condition and Group (F(1,34)=7.906, p=.008, ηp2=.189) indicated a significant linear decrease in intoxication scores from THC+CBD_{low} to THC alone to THC+CBD_{high} in Infrequent users, that was absent in Frequent users (Fig. 4c). At Time 2, this pattern was significant overall with a Condition effect (F(1,34)=20.63, p<.0001, ηp2=.189) that did not interact with Group (p=.11), but a main effect of Group indicated that Infrequent Users were significantly more intoxicated than Frequent users across all three THC conditions (F(1,34)=7.03, p=.012, ηp2=.171). The main effect of Group was not significant at Time 1 (p>.09). There were no significant effects at Recovery (all p>.14). In the subsample matched for THC dose delivered in THC and THC+CBD_{high} conditions, the linear contrast between the three THC conditions continued to show a significant Condition by Group interaction at Time 1 (F(1,14)=7.81, p=.014, ηp2=.358), while the Condition effect at Time 2 was reduced to trend level (p=.064).

Additional measures of subjective effects

VAS

Fig. 5a shows change scores from baseline at Time 2 for each subscale on the VAS, displayed by group separately for CBD_{high} vs Placebo and the three THC conditions.

At Time 1, scores for CBD_{high} were higher than Placebo for *Internal Perception* (F(1,34)=14.32, p=.001, ηp2=.296) only (all other p>.45). At Time 2, both *Internal* and *External Perception* scores were higher for CBD_{high} than Placebo (F(1,34)=8.86, p=.005, ηp2=.207; and F(1,34)=6.48, p=.016, ηp2=.160, respectively). A trend Condition effect for *Drowsiness* at Time 2 (p=.079), marginally significantly interacting with Group (F(1,34)=4.11, p=.051, ηp2=.088), indicated higher drowsiness in Infrequent users with CBD_{high} relative to Placebo, but the reverse pattern in Frequent users; this interaction pattern continued into the Recovery period at trend level (p=.078). *External perception* scores also trended toward being higher for CBD_{high} during Recovery (F(1,34)=4.06, p=.052). No other effects or interactions were significant at any time point (all p>.10).

For the THC conditions, significant linear contrasts were observed for Condition at Time 1 for *Drowsiness* (F(1,34)=5.52, p=.025, ηp2=.140), and at Time 2 for *Internal* and *External Perception* (F(1,34)=9.39, p=.004, ηp2=.216; and (F(1,34)=4.66, p=.038, ηp2=.121, respectively), with highest scores for THC+CBD_{low}, followed by THC, and lowest scores for THC+CBD_{high}. A trend toward a Condition by Group interaction at Time 1 for *Internal*

Perception, supported the above pattern being most prominent in Infrequent users (p=.068). All other effects and interactions were nonsignificant (all p>.12).

Fig. 5 about here

Clinician Administered Dissociative States Scale (CADSS)

Fig. 5b shows change scores from baseline at Time 2 for CADSS total score, derealisation and amnesia subscales, displayed by group separately for CBD_{high} vs Placebo and the three THC conditions.

At Time 2, CBD_{high} scores were higher than for Placebo for *Total score* (F(1,34)=6.52, p=.015, ηp2=.161) and *Amnesia* (F(1,34)=5.49, p=.025, ηp2=.139), trending also for *Derealisation* (p=.058). *Total score* remained elevated at Recovery (p=.079), with no other effects or group interactions (all p>.10).

There was a significant linear reduction across the three THC conditions at Time 2 for *Total score* (F(1,34)=4.89, p=.034, ηp2=.126) and *Derealisation* (F(1,34)=6.63, p=.015, ηp2=.163), with highest scores for $THC+CBD_{low}$, followed by THC alone, and lowest scores for $THC+CBD_{high}$. For *Amnesia* this contrast interacted with Group (F(1,34)=4.29, p=.046), whereby Infrequent users showed the above pattern, whereas Frequent users showed the reverse pattern: highest scores for $THC+CBD_{high}$, followed by THC and lowest scores in $THC+CBD_{low}$. No effects remained at Recovery (all p>.15), and all other effects and interactions were nonsignificant (all p>.22).

Psychotomimetic Symptom Inventory (PSI)

The main drug effects measured by this scale correspond to a different time point (Time 3) to the above scales: ~15 min after a top up dose was given in each condition (as described in the Methods).

In the CBD_{high} vs Placebo contrasts, Condition effects were observed on the *Perceptual Distortion* scale (F(1,33)=5.05, p=.031, ηp2=.133), *Cognitive Disturbance* scale (F(1,33)=4.99, p=.032, ηp2=.131) (which persisted at Recovery, F(1,33)=4.73, p=.037, ηp2=.125), and on the *Mania* scale (F(1,33)=10.31, p=.003, ηp2=.238), with higher scores for CBD_{high} than Placebo. Frequent users had trend-level higher scores on the *Mania* scale than Infrequent users (p=.06). A significant Condition by Group simple contrast was observed on the *Anhedonia* scale (F(1,34)=9.19, p=.005, ηp2=.218) with Infrequent users showing higher scores for CBD_{high} than Placebo, but the reverse pattern evident in Frequent users, and this pattern tended to persist into the Recovery period (p=.064).

For the three THC conditions, two linear contrasts were significant: on the *Perceptual Distortion* scale F(1,33)=9.36, *p*=.004, ηp2=.221) and on the *Mania* scale (F(1,33)=6.44, *p*=.016, ηp2=.163) (for all other scales, Condition *p*>.12). In each case highest scores were observed for THC+CBD_{low}, followed by THC, and lowest scores for THC+CBD_{high}. There were no significant main effects or interactions with Group (all *p*>.088) and no effects at Recovery.

Exploratory correlations

Objective intoxication change scores were positively correlated with subjective intoxication change scores at Time 1 and 2 in the THC+CBD_{low} and THC conditions, only at Time 2 in the THC+CBD_{high} condition (Table 2). In the CBD alone condition, objective measures correlated with subjective measures at Time 1 (*rho*=.395, *p*=.017), but not Time 2 (*p*=.29). HR correlated with all objective and subjective intoxication change scores in the THC+CBD_{low} condition (respectively: *rho*=.370, *p*=.026; Time 1 *rho*=.503, *p*=.002; Time 2 *rho*=.589, *p*=.0002), mostly in the THC condition (respectively: *rho*=.388, *p*=.020; Time 1 *rho*=.304, *p*=.072; Time 2 *rho*=.511, *p*=.001), not in the THC+CBD_{high} condition at Time 1 (all *p*>.30) but at trend level with subjective intoxication at Time 2 (*rho*=.327, *p*=.052). These associations support the validity of the blind observer ratings for the THC and THC+CBD_{low} conditions.

A negative association was observed between lifetime occasions of cannabis use and both objective and subjective intoxication scores at both time points in the THC+CBD_{low} and THC conditions only (Table 2). The associations indicate greater intoxication in those with lesser exposure to cannabis, with the strongest correlations evident in the THC+CBD_{low} condition. These associations were not evident in the THC+CBD_{high} condition (Table 2), nor in the CBD_{high} condition (all *p*>.12).

Associations were observed with hours since last use of cannabis prior to drug administration in the THC and THC+CBD_{low} conditions only; for objective and subjective intoxication at Time 2, but only THC+CBD_{low} at Time 1 (Table 2). These findings indicate that greater intoxication was induced the longer ago that cannabis was last used, and particularly so in the THC+CBD_{low} condition. There were no associations with hours since last use of cannabis in the CBD_{high} condition (all *p*>.27).

Neither subjective nor objective intoxication scores correlated with BMI in any condition (all *p*>.09). Objective intoxication was not correlated with CAPE total or subscale scores in any condition (all *p*>.09). For subjective intoxication scores, the only association with CAPE scores was observed at Time 1 in the CBD_{high} condition, with intoxication being greater among those scoring highly on positive symptom frequency and positive symptom distress

(*rho*=.382, *p*=.021 and *rho*=.347, *p*=.038, respectively). SPQ total score was not correlated with objective or subjective intoxication at either time (all *p*>.24, aside from a trend level association for THC+CBD_{low} at Time 1, p=.092). CEQ showed significant associations between psychotic-like effects and subjective intoxication at Time 2 for THC+CBD_{low} (*rho*=-.37, *p*=.028), supported by a trend level association also with objective intoxication (*rho*=-.33, *p*=.051), and between psychotic-like effects and subjective intoxication at Time 1 for THC+CBD_{high} (*rho*=.34, *p*=.045). Of note, these associations were in the opposite direction in these two drug conditions. Trend level associations were also apparent in the THC+CBD_{high} condition between CEQ euphoric effects and objective intoxication (*rho*=.33, *p*=.052), and between CEQ after effects and subjective intoxication at Time 1 (*rho*=.29, p=.082). All other associations in all drug conditions were nonsignificant (all *p*>.10). There were no significant associations between objective or subjective intoxication measures and BPRS, BDI, State or Trait Anxiety scores (all *p*>.10), other than BPRS and objective intoxication in the THC+CBD_{high} condition (rho=.356, p=.046) and a trend for BDI and subjective intoxication at Time 1 in the CBD_{high} condition (*rho*=.309, *p*=.067).

The qualitative nature of objective and subjective intoxication ratings was examined through correlations with the additional measures of intoxication, as depicted in Table 3.

Discussion

This double-blind placebo-controlled study examined two measures of intoxication, one objective and one subjective, following administration of THC and CBD, each alone and in combination, to frequent and infrequent cannabis users (the latter group including non-naïve nonusers). We aimed to test the hypotheses that high dose CBD alone would not be intoxicating relative to placebo, and that when added to THC, low dose CBD would enhance intoxication whereas high dose CBD would attenuate the intoxication due to THC. The results from both objective and subjective measures indicated that the addition of CBD to THC produced differential dose-dependent effects to intoxication. In line with our hypotheses, low dose CBD enhanced intoxication relative to THC alone, whereas high dose CBD reduced intoxication. The potentiation by low dose CBD was most prominent in the infrequent users/non-naïve nonusers. Our first hypothesis was not supported. Contrary to the literature, both frequent and infrequent users subjectively reported feeling intoxicated by high dose CBD administered alone (i.e., not combined with THC), with protracted effects across the 3-hr session relative to placebo, but this was not corroborated by the objective intoxication measure. Subjective intoxication from CBD was nevertheless significantly less than that reported for THC.

High dose CBD alone induced intoxication relative to placebo

Subjective intoxication with CBD manifested largely as a dissociated state, correlating with the depersonalisation and derealisation scores on the CADSS, as well as the CADSS total score, but not the amnesia subscale. Correlations were also observed with the VAS internal and external perception scales, but surprisingly not with drowsiness. CBD has been reported to be sedating in other studies [47,78]. Interestingly, independent observer ratings of intoxication in the high dose CBD condition did correlate with participant ratings of drowsiness immediately after drug administration, as well as participant ratings of changes in external perception and at trend level internal perception and CADSS total score. This suggests that observers' ratings of intoxication may have been based on perceiving participants' drowsiness and behaviours indicating that they were responding differently to their external environment and dissociating. The independent observers inferred intoxication but had no direct insight into the internal world of the participants, who felt intoxicated due to distinct feelings of depersonalisation, derealisation, and altered internal and external perceptions. No such findings have been reported in the literature in relation to high doses of CBD, however most studies have administered high dose CBD orally. Indeed with oral administration, 600mg of CBD was shown to specifically attenuate symptoms of depersonalisation following ketamine administration [79]. It is likely that these dissociating effects were rapidly induced by vaporisation of this compound, delivering CBD with high bioavailability to the bloodstream and hence central nervous system, although this is likely also confounded by dose. While 400mg was

loaded into the vaporiser, we estimate that participants consumed slightly less – 385mg – by not inhaling all of the balloons. Further, our preliminary studies for protocol development suggested that only about 40% of the CBD could be vaporised due to the sticky resin produced in the process, saturation and vaporisation inefficiency [60]. This may therefore have resulted in an actual dose delivered of ~150mg. It is possible that vaporised CBD may also show the bell-shaped dose-response curve that has been demonstrated with oral administration [39-42]. Our protocol development work, however, found 200mg of CBD to be the maximum that could be vaporised into a balloon (and hence we administered two balloons) [60]. The high dose CBD condition induced significant coughing; as such, participants were aware that they were being administered an active condition (as opposed to the ease of inhalation of ethanol-flavoured air in the placebo condition). The changes in intoxication might therefore be surmised to be a placebo effect, however, the fact that heart rate did not change (which would have provided participants with a physical cue to endorsing psychological effects) and the specificity of the reported effects, suggests that indeed medium-high doses of CBD when vaporised induce a dissociation-driven intoxication that may be dose-dependent, and is long lasting, as subjective intoxication scores remained elevated one hour later and at the Recovery time point.

Low and high doses of CBD added to THC respectively enhance and attenuate intoxication

A consistent pattern of effects was observed across almost all measures in this study, whereby highest levels of intoxication were evident in the THC+CBD_{low} condition, followed by THC alone, and lowest levels of intoxication were observed in the THC+CBD_{high} condition. Intoxication in all three THC conditions was associated with dissociation, largely CADSS total scores driven by the subjective experiences of derealisation, and to some extent depersonalisation. This also appeared to drive the objective ratings of intoxication. Clearly observers rated participants on the basis of their behaviour, which reflected their internal world, and provided slightly differing perspectives on what was more or less prominent for observers versus participants themselves in rating degree of intoxication in the different drug conditions. For example, self-reported anhedonia was only associated with subjective intoxication in the THC alone condition, not surprisingly not driving any observer ratings of intoxication (as it is difficult to infer from behaviour, particularly in a laboratory setting). Subjectively experienced amnesia was prominent in association with subjective intoxication scores in the THC alone condition, less so in the THC+CBD_{low} condition and minor in the THC+CBD_{high} condition, behaviourally influencing observer ratings in the former two conditions, but not the latter. In relation to this, the cognitive disorganisation scale of the PSI was only mildly sensitive to self-reported intoxication in the THC alone condition, yet was associated with observer ratings for all conditions, and self-reported intoxication in both the THC+CBD_{low} and THC+CBD_{high} conditions. Observer ratings of intoxication were further associated with subjective reports of perceptual distortion across all THC conditions, most prominently in the THC+CBD_{high} and THC

alone conditions, whereas subjective intoxication ratings were less associated with perceptual distortion in the THC alone condition, and more prominently in the THC+CBD_{low} condition. Both subjective and objective intoxication ratings were associated with changes to VAS internal and external perception in the THC and THC+CBD_{low} conditions, less so for external perception in the THC+CBD_{high} condition. Drowsiness did not feature prominently in association with intoxication measures, but perhaps more so in the THC+CBD_{low} condition. Participants did not strongly endorse PSI delusions and paranoia in any condition, while mania showed associations with subjective and objective intoxication in THC and THC+CBD_{low} conditions, but not THC+CBD_{high}.

It is interesting that paranoia is often cited as a frequent experience when people are intoxicated from cannabis, yet this was not elevated in the sample of this study, even though half of the sample was comprised of infrequent users or nonusers. This may be due to our screening and exclusion criteria, but we also tested the hypothesis that measures of psychosis-proneness (CAPE, SPQ, BPRS), other psychological symptoms (BDI: depressive; STAI: state and trait anxiety) and experiences when using cannabis (CEQ) may predict response in differing drug conditions, and this was not upheld, at least in the current sample of relatively psychologically healthy individuals. Of note, none of these qualitative aspects of intoxication differed between frequent and infrequent users (other than amnesia), and there was little specific and strong differentiation between the three THC conditions according to these additional qualifiers of the experience. Therefore, the linear contrast patterns of increasing intoxication effects from THC+CBD_{high} to THC to THC+CBD_{low} conditions across almost all measures, and that were most prominent in infrequent users for primary measures of subjective and objective intoxication, appear to reflect general composite effects of these experiences for the overall experience of intoxication, or some unmeasured qualitative aspects. There appears to be some synergism in the potentiating effects of adding low dose CBD to THC, and potential antagonistic effects by the addition of high doses of CBD to THC.

Possible mechanisms

A potential mechanism to explain our findings may be via the allosteric modulation of CB1 receptors by CBD. As a negative allosteric modulator [3,80], CBD may interfere with CB1R activation in terms of the kinetics of orthosteric binding by THC, or receptor activation and signalling [81]. Straiker and colleagues [81] showed that CBD inhibits endogenous CB1-mediated signalling in a concentration-dependent manner. Positive allosteric modulators can enhance the binding, potency and efficacy of orthosteric modulators, such as THC, and CBD is known to act as a positive allosteric modulator at opioid receptors [82] and has recently been demonstrated to show orthosteric partial agonism at CB2 receptors, while a CBD synthetic derivative showed partial agonist activity and positive allosteric modulation at

CB1 and CB2 receptors [80]. Tham and colleagues [80] suggested that this synthetic CBD derivative may enhance the binding of orthosteric ligands dose-dependently, reducing binding at higher concentrations to produce a bell-shaped curve (which may explain the bell-shaped dose-response curve observed for CBD in a number of animal and human administration studies [83]). Other cannabinoid receptor ligands (e.g. Org27569 and fenofibrate) have been shown to have both negative and positive allosteric or agonist properties at CB1 receptors that vary at low and high concentrations [80,84,85]. There is evidence to suggest that a yet-to-be discovered high affinity CBD binding site exists on CB1 receptors that is distinct from the orthosteric site [80]; Tham and colleagues showed that CBD shared a binding site with the CB1 agonist CP55,940. We were unable to assay for plasma CBD metabolites in this study, some of which represent 97% of CBD-related plasma concentrations (following repeat oral administration of high doses [86]; the activity of these metabolites interacting with THC and THC-metabolites remains unknown. Much remains to be learned regarding the allosteric mechanisms of CBD and the conditions under which they operate differentially. For example, simultaneous but not sequential inhalation of THC and CBD was shown to attenuate some effects of THC [87]. While simultaneous inhalation is pertinent to this study, it was pure compounds that we administered, and mechanistically much could change in the presence of the multiple other cannabinoids in plant matter. Understanding these mechanisms is highly pertinent to the development of novel pure allosteric modulators that lack agonist or inverse agonist activity to minimise side effects and optimise benefits in therapeutic applications of cannabinoids. Tham et al [80] warn that ligand interaction with the allosteric and orthosteric sites of cannabinoid receptors is highly fluid and flexible, making drug design challenging. However, there are lessons here as well for consideration of plant matter and edible products (see below) that are used medicinally or recreationally.

Implications regarding proportional exposure to THC and CBD for medicinal and recreational cannabis use

While precise mechanisms remain to be elucidated, the finding that low doses of CBD may potentiate effects of THC has significant implications for consideration of proportions of THC and CBD that may be recommended within plant matter. With cannabis increasingly being used for medicinal purposes, it is important to ensure that harms are minimised in favour of boosting therapeutic properties. While intoxication per se is not necessarily harmful overall, it is not welcome by many clinical patients, and it may be harmful in situations such as driving under the influence of cannabis. Further research is required to replicate the findings here, and indeed to establish a greater efficacy base for specific cannabinoid compounds in treating specific symptoms or conditions. This would inform the development of guidelines to recommend appropriate proportions of THC and CBD, and indeed other cannabinoids, in cannabis for medicinal purposes. As cannabis is increasingly legalised for recreational use, clinicians, patients and recreational users alike should be mindful that low doses of CBD in plant matter may be more intoxicating than using cannabis without

CBD, and also be mindful that the vaporisation route of administration also induces stronger effects than smoking, as recently reported [56]. Given that this study used vaporisation of pure compounds, it is important to see whether our findings would be replicated in a study of smoked cannabis with and without CBD, at low and high CBD levels. It would not be possible to utilise doses of CBD as high as that administered here in a smoked cannabis study. Although relatively high-CBD grade cannabis products are available, their absolute amount of CBD may be too low to attenuate the THC intoxication. Further, this study examined acute effects of combined vaporised THC and CBD; whether the effects we report would also be pertinent to longer-term administration by this or other routes (e.g. smoked or oral formulations) remains to be investigated. We reported previously that prolonged oral administration of high dose CBD appeared to diminish intoxication induced by cannabis smoked externally to the trial [25].

A further important finding here was that infrequent cannabis users and nonusers showed the greatest degree of potentiation of THC effects by the addition of low dose CBD. This was further substantiated with the associations observed between intoxication and lifetime occasions of cannabis use, and intoxication and hours since last use of cannabis. Whilst not surprising, less experienced cannabis users, and those who use less frequently experienced greater intoxication. But that these effects were most evident in the THC+CBD_{low} condition, indicates that less experienced or novice users are most at risk of experiencing greater intoxication than may have been expected when CBD is present at low levels within cannabis. Further public health concerns may arise with the proliferation of non-cannabis products containing low levels of CBD on the general market, including hemp dietary products, oils, pastes, confectionary, and drinks [88]. The general message to the community currently is that “CBD is good for you”. Just how this has come about is unclear but likely stems from the anecdotal and lay dissemination of information about CBD’s therapeutic potential. But little is currently known about the doses and their biphasic nature, to correct such potential misinformation. The longer term health effects of low levels of CBD being consumed in those forms remains to be determined, as does the question of whether CBD from such, mostly orally consumed, products may interact with THC from smoked cannabis. The findings of this study suggest there could potentially be interactive synergistic effects in terms of intoxication.

Limitations

Although this study provides helpful data and description around low and high doses of CBD simultaneously inhaled with THC, there are important aspects to be cognisant of in the interpretation and translation of the data. For some participants, blood concentrations indicated the presence of THC or metabolites, or CBD, respectively, in drug administration conditions where none would be expected. It is possible that this may reflect exposure from cannabis

used externally to the study, or that there may have been some low level contamination occurring between conditions from the vaporiser equipment, despite following manufacturer cleaning protocols and providing each participant a new balloon and mouthpiece for every drug condition. A recent rat study also reported the presence of THC in serum and brain when only CBD had been administered [50], adding to an ongoing debate about the potential conversion of CBD to THC in vivo, which was considered unlikely. But this phenomenon was only observed following oral and subcutaneous administration, not pulmonary. In any case, only a few participants showed these unexpected compounds in plasma, the median plasma concentrations showed clear separation between drug conditions and mostly the effects reported would have been diminished rather than enhanced by these extraneous potential sources of compounds. We showed that the intoxicating effect of CBD remained after exclusion of participants with THC in plasma. Further, this study was not designed specifically for pharmacokinetic investigation and the blood concentrations reported here are only those from a sample collected immediately after administration of the main dose. They may not reflect the peak concentrations reached, nor were collections optimised for examining metabolism of the compounds over time. Related to this, there was a great deal of variation in the time that participants took to inhale the doses from the balloons, ranging from a few minutes to ~20 minutes for some participants in some conditions, particularly those containing high dose CBD due to throat irritation and coughing. Such delays would also have affected the various measures of intoxication, since some would have been obtained at different points within the time course of intoxication between participants. There is much individual variability in any case in terms of metabolism and experiences with cannabis, making complete standardisation problematic; protocols were as standardised as feasible in this study. It would have been unethical to force participants to take the full dose when they reported that they had had enough and were already intoxicated beyond their comfort levels. This, and the throat irritation and coughing led to a lesser dose of THC being consumed in the THC+CBD_{high} condition, and as such, the findings that high dose CBD added to THC reduces intoxication, must be tempered by the fact that less THC was consumed in that condition. However, the follow up analyses on the smaller sample matched for THC dose in this and the THC alone condition, showed that this confounder was not responsible for the reduced intoxication. It should further be noted that although the primary hypotheses were restricted to account for Type 1 error, exploratory analyses were not, which makes replication important for the results from the exploratory analyses. The predominance of males in our sample precluded examination of sex differences; future studies should investigate whether the response to these cannabinoids may differ in males and females.

Comparison with previous findings

One final consideration must be made and that is how or why our findings differ from those of Morgan and colleagues [57] in a study using similar measures. Both studies used the same dose of THC – 8mg; Morgan et al report increased scores on the PSI, whereas effects in this study were minimal. It is not clear why this may be, as similar inhalation protocols were followed. The biggest differences between studies are in relation to effects of CBD added to THC. The CBD:THC ratio in Morgan et al's study was 2:1 (16mg CBD), whereas here we applied a 1:2 ratio in the THC+CBD_{low} condition (4mg CBD) and a 50:1 ratio in the THC+CBD_{high} condition (400mg CBD). It is possible that if CBD shows biphasic effects, with synergism at low doses and antagonism at high doses when combined with THC, the low-medium dose applied in the Morgan et al study may have fallen into the mid-range between these two divergent actions.

Conclusion

In conclusion, this study reports two novel findings: 1) that high doses of CBD when vaporised led to an intoxication characterised by a dissociative state; 2) that low doses of CBD when added to THC potentiated intoxication relative to THC alone, particularly in infrequent cannabis users, while high doses of CBD when added to THC reduced the intoxication. These findings, while specific to vaporisation and requiring replication, may have implications for recommended proportions of THC and CBD in cannabis being used medicinally or recreationally within the community.

Ethical standards

This study was approved by the University of Wollongong and Illawarra Shoalhaven Local Health District Health and Medical Human Research Ethics Committee and registered as a clinical trial (ISRCTN24109245 [89]). Participants provided written informed consent prior to participating in the study and at the start of each drug session.

Conflict of interest

The authors declare that they have no conflict of interest.

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Figure Captions

Fig. 1. Schematic of the time points of various measures throughout each drug session. CADSS: Clinician Administered Dissociative States Scale; HR+BP: heart rate and blood pressure; PSI: Psychotomimetic States Inventory; VAS: Visual Analogue Scale. Time 0: baseline, ~15 min prior to drug administration; Time 1: ~1 min after inhalation of main dose; Time 2: ~55 min later; Top up 1, TU1[a]: ~1 min following a top-up dose; Time 3: ~15 min after inhalation of TU1; Pre-Top up 2, Pre-TU2[a]: ~45 min after TU1; Top up 2, TU2[a]: ~1 min after a second top-up dose; Recovery: ~1 hr after TU2; [a] Data points not analysed in this paper.

Fig. 2 Heart rate (bpm) averaged over the entire sample across the testing protocol. The x-axis depicts approximate time in min (not to scale) from the completion of inhalation of the main dose. Time 0: baseline, ~15 min prior to drug administration; Time 1: ~1 min after inhalation of main dose; Time 2: ~55 min later; Top up 1, TU1[a]: ~1 min following a top-up dose; Pre-Top up 2, Pre-TU2[a]: ~45 min after TU1; Top up 2, TU2[a]: ~1 min after a second top-up dose; Recovery: ~1 hr after TU2. [a] Data points not analysed in this paper.

Fig. 3. Objective ratings of intoxication by a blind observer, rating participants on the 8 observer items of the Clinician Administered Dissociative States Scale (change scores from Time 0 to Time 2), for a) Placebo vs CBD_{high} by group; b) the three THC conditions by group. Error bars indicate SEM; and △, mean change or difference score.

Fig. 4 a) Subjective rating of intoxication (scale range 1-10) for the entire sample across the testing protocol. The x-axis depicts approximate time in minutes (min; not to scale) from the completion of inhalation of the main dose; b) Change scores for subjective intoxication (change from baseline) at Time 1 by group for Placebo vs CBD_{high}; c) Change scores for subjective intoxication (change from baseline) at Time 1 by group for the three THC conditions. Time 0: baseline, ~15 min prior to drug administration; Time 1: ~1 min after inhalation of main dose; Time 2: ~55 min later; Top up 1, TU1[a]: ~1 min following a top-up dose; Pre-Top up 2, Pre-TU2[a]: ~45 min after TU1; Top up 2, TU2[a]: ~1 min after a second top-up dose; Recovery: ~1 hr after TU2. Error bars indicate SEM; and △, mean change or difference score. [a] Data points not analysed in this paper.

Fig. 5. a) Change scores from baseline on self-report measures of intoxication at Time 2 for the Internal Perception subscale, External Perception subscale and Drowsiness subscale of the Visual Analogue Scale (VAS), displayed by group separately for Placebo vs CBD_{high}, and THC conditions; b) Change scores from baseline on self-report measures

of intoxication at Time 2 for Total score, Amnesia subscale and Derealisation subscale of the Clinician Administered Dissociative States Scale (CADSS). Error bars indicate SEM; and △, mean change or difference score from baseline.

Tables

Table 1. Drug conditions defined by doses loaded into the vaporiser and estimates of actual dose delivered (mg), and plasma concentrations of THC, THC-metabolites and CBD (ng/ml) at Time 1; median (range).

Drug Condition (dose loaded)	**Placebo**	**CBD (400mg)**	**THC (8mg)**	**THC+CBD$_{low}$ (8mg+4mg)**	**THC+CBD$_{high}$ (8mg+400mg)***
Proportion of balloon inhaled	1.0 (1.0 – 1.0)	0.963 (0.25 – 1.0)	1.0 (0.80 – 1.0)	1.0 (0.50 – 1.0)	0.625 (0.15 – 1.0)
Proportion inhaled x dose loaded	0.0	385mg (100 – 400)	8mg (6.4 – 8)	8mg THC (4 – 8) 4mg CBD (2 – 4)	5mg THC (1.2 – 8) 250mg CBD (60 – 400)
Plasma concentrations (ng/ml)					
THC	0.50 (0 – 27.6)	0.0 (0 – 44.6)	87.8 (19.7 – 275.1)	91.2 (16.9 – 173.7)	30.0 (7.2 – 127.8)
OH-THC	0.0 (0 – 10.9)	0.0 (0 – 19.4)	6.6 (1.8 – 22.1)	6.0 (2.4 – 33.7)	2.6 (0 – 18.1)
COOH-THC	0.70 (0 – 328.0)	0.70 (0 – 489.2)	20.0 (1.9 – 283.8)	18.6 (1.5 – 346.4)	11.0 (0 – 429.9)
CBD	1.2 (0 – 73.8)	525.9 (114 – 2783)	2.6 (0 – 32.2)	24.6 (4.9 – 92.1)	379.3 (89.0 – 2102.5)

* The actual dose loaded in the THC+CBD$_{high}$ condition was 12mg THC with 400mg CBD to achieve equivalence following vaporisation to the 8mg THC loaded in the THC and THC+CBD$_{low}$ conditions, due to inefficiency of vaporisation of THC in the presence of high doses of CBD (see [60]).

OH-THC: 11-hydroxy-Δ^9-tetrahydrocannabinol; COOH-THC: 11-nor-9-carboxy-Δ^9-tetrahydrocannabinol

Table 2. Spearman's correlations (*rho*) between objective and subjective intoxication measures (change scores from baseline), lifetime occasions of cannabis use and hours since last use of cannabis.

		Subjective Intoxication Time 1	Subjective Intoxication Time 2	Lifetime Use	Last Use
Observer					
Intoxication Time 2					
	$THC+CBD_{low}$	.638***	.675***	-.523***	.537***
	THC	.468**	.526***	-.416**	.395*
	$THC+CBD_{high}$	.310	.403*	-.097	.014
Subjective					
Intoxication Time 1					
	$THC+CBD_{low}$		.696***	-.448**	.563***
	THC		.713***	-.374*	.278
	$THC+CBD_{high}$		.607***	.194	-.290
Subjective					
Intoxication Time 2					
	$THC+CBD_{low}$			-.537***	.541***
	THC			-.485**	.430**
	$THC+CBD_{high}$			-.253	.172

* $p<.05$; ** $p<.01$; *** $p<.001$. Trend level associations are presented without asterisks.

Table 3. Spearman's correlations (*rho*) between objective and subjective intoxication measures, and additional measures of intoxication from the CADSS, VAS and PSI.

		Subjective intoxication Time 1	**Subjective intoxication Time 2**	**Objective intoxication Time 2**
CADSS	CBD_{high}	.375*	.404*	-
Total score	$THC+CBD_{low}$	.493**	.616***	.648***
	THC	.535**	.702***	.834***
	$THC+CBD_{high}$	.526**	.699***	.680***
Amnesia	CBD_{high}	.309	-	-
	$THC+CBD_{low}$	-	.463**	.532**
	THC	.551***	.553***	.640***
	$THC+CBD_{high}$	.313	.391*	-
Depersonalisation	CBD_{high}	.388*	.490**	-
	$THC+CBD_{low}$	.378*	.383*	.525**
	THC	.304	.411*	.503**
	$THC+CBD_{high}$	.328	.675***	.493**
Derealisation	CBD_{high}	.348*	.423**	-
	$THC+CBD_{low}$	.466**	.579**	.631***
	THC	.488**	.667***	.837***
	$THC+CBD_{high}$	.447**	.593***	.663***
VAS	CBD_{high}	.350*	.487**	.322
Internal perception	$THC+CBD_{low}$	.453**	.365*	.423**
Time 1	THC	.623***	.651***	.773***
	$THC+CBD_{high}$	.525**	.439**	.330*
Internal perception	CBD_{high}	.504**	.519***	-
Time 2	$THC+CBD_{low}$	.444**	.584***	.537**
	THC	.515**	.683***	.724***
	$THC+CBD_{high}$	.424*	.603***	.587***
External perception	CBD_{high}	.282	.446**	.372*
Time 1	$THC+CBD_{low}$	.379*	-	.288
	THC	.379*	-	.419*
	$THC+CBD_{high}$	-	.461**	.300
External perception	CBD_{high}	-	.387*	-
Time 2	$THC+CBD_{low}$	-	.482**	.539**
	THC	-	.388*	.528**
	$THC+CBD_{high}$	-	-	-
Drowsy Time 1	CBD_{high}	-	-	.367*

	$THC+CBD_{low}$	.338*	.356*	.358*
	THC	.383*	-	-
	$THC+CBD_{high}$	.337*	.310	.371*
Drowsy Time 2	CBD_{high}	-	-	-
	$THC+CBD_{low}$	.329*	.375*	.424**
	THC	.327	.338*	.385
	$THC+CBD_{high}$	-	-	-
PSI	CBD_{high}	-	-	-
Delusional thinking	$THC+CBD_{low}$	-	-	-
	THC	-	-	-
	$THC+CBD_{high}$	-	-	-
Perceptual distortion	CBD_{high}	-	-	-
	$THC+CBD_{low}$	.512**	.421**	.348*
	THC	.309	.376*	.637***
	$THC+CBD_{high}$	.313	.553***	.732***
Cognitive	CBD_{high}	-	-	-
disturbance	$THC+CBD_{low}$	.422**	.471**	.463**
	THC	-	-	.577***
	$THC+CBD_{high}$	.361*	.629***	.337*
Anhedonia	CBD_{high}	-	-	-
	$THC+CBD_{low}$	-	.311	.324
	THC	.333*	.459**	-
	$THC+CBD_{high}$	-	.306	-
Mania	CBD_{high}	-	-	-
	$THC+CBD_{low}$	.391*	.445**	.388*
	THC	-	.400*	.470**
	$THC+CBD_{high}$	-	.301	-
Paranoia	CBD_{high}	-	-.294	-
	$THC+CBD_{low}$	-	-	-
	THC	-	-	.414*
	$THC+CBD_{high}$	.323	-	.313

1 * $p<.05$; ** $p<.01$; *** $p<.001$. Trend level associations are presented without asterisks.

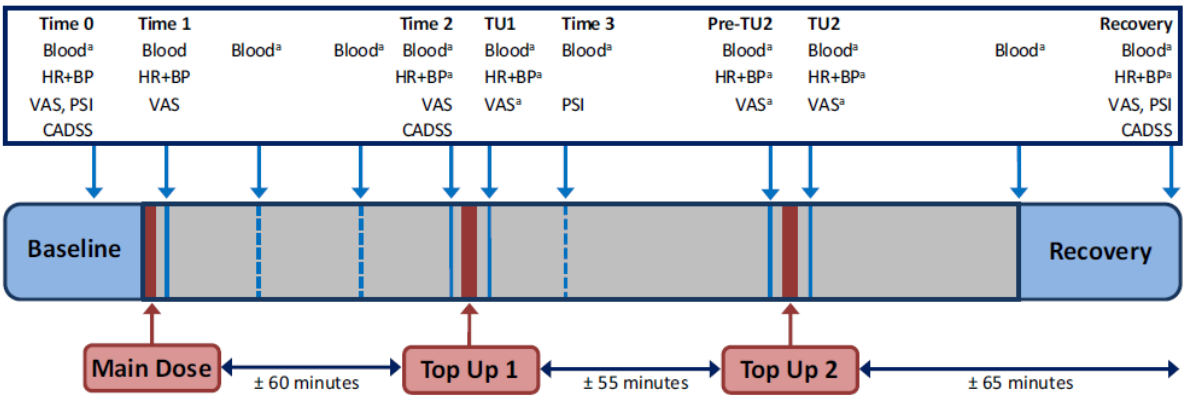

Figure 1

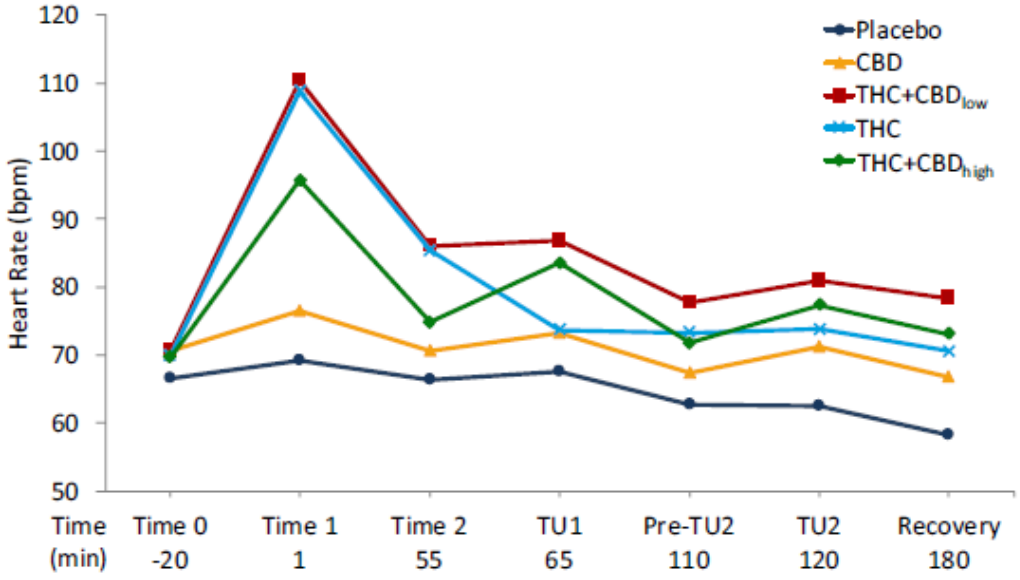

Figure 2

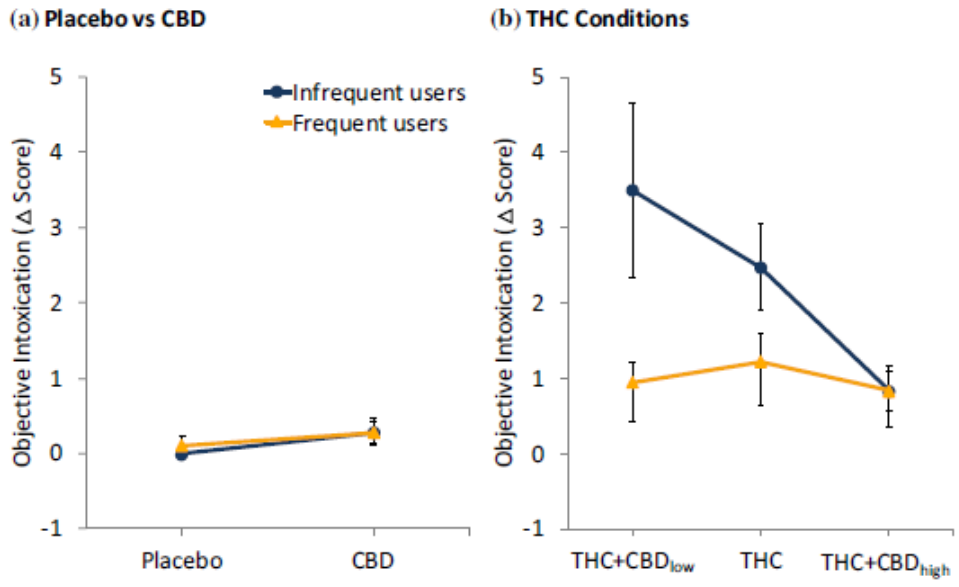

Figure 3

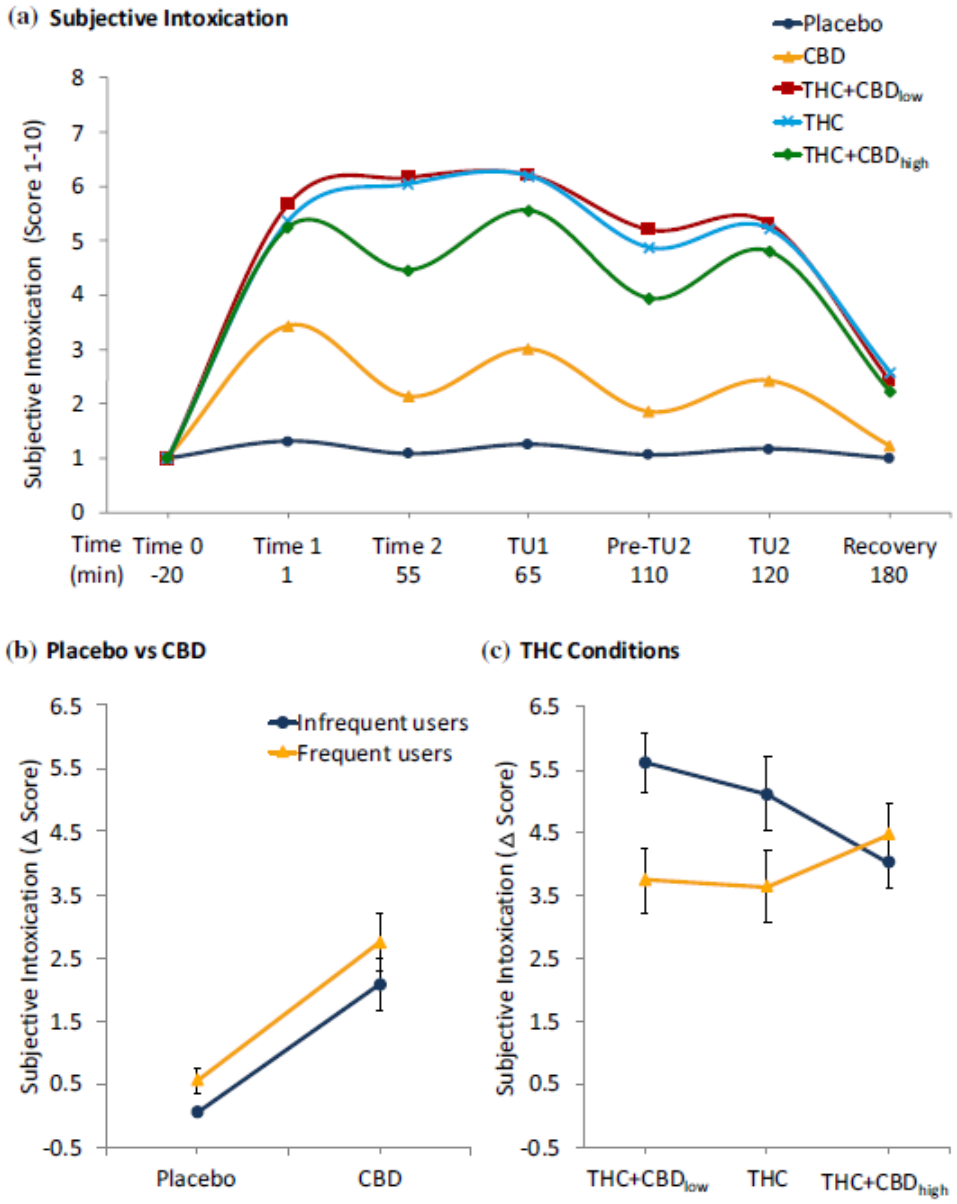
(a) Subjective Intoxication
Placebo
CBD
THC+CBDlow
THC
THC+CBDhigh
Subjective Intoxication (Score 1-10)
0
1
2
3
4
5
6
7
8
Time (min)
Time 0 -20
Time 1 1
Time 2 55
TU1 65
Pre-TU2 110
TU2 120
Recovery 180
(b) Placebo vs CBD
Infrequent users
Frequent users
Subjective Intoxication (Δ Score)
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
Placebo
CBD
(c) THC Conditions
Subjective Intoxication (Δ Score)
6.5
5.5
4.5
3.5
2.5
1.5
0.5
-0.5
THC+CBDlow
THC
THC+CBDhigh

Figure 4

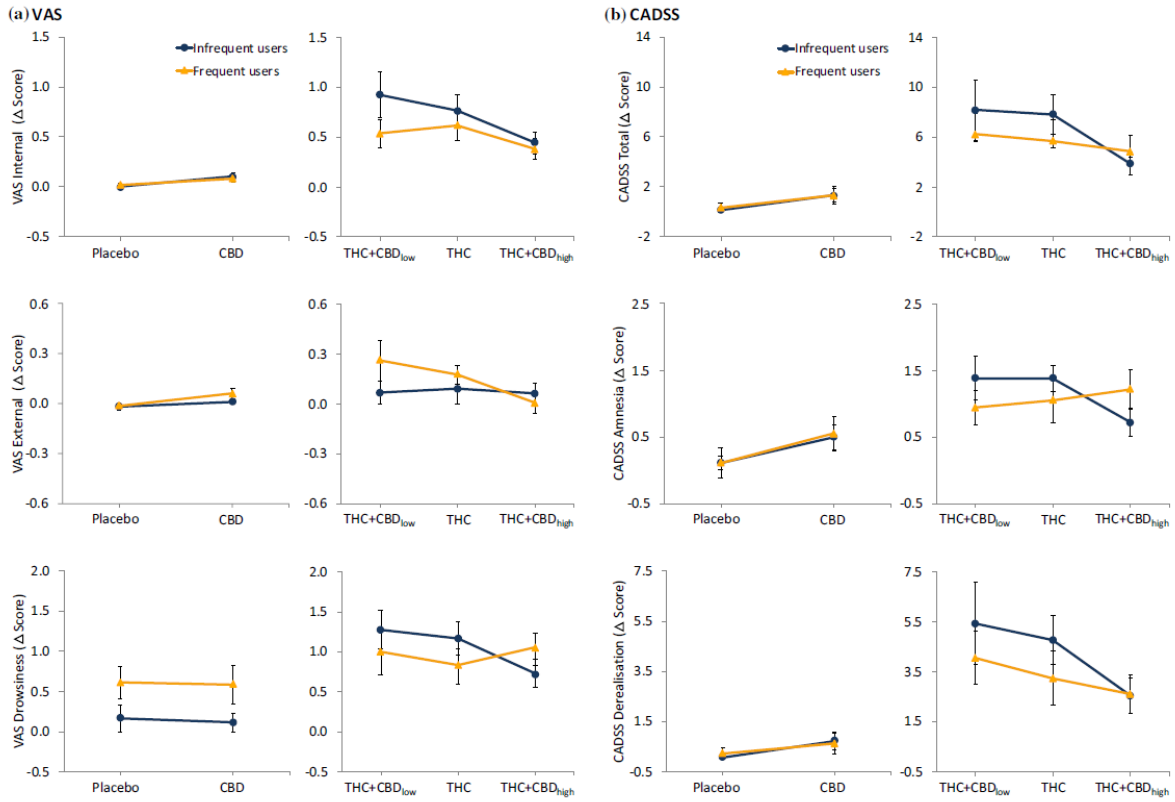
(a) VAS
(b) CADSS
Infrequent users
Frequent users
VAS Internal (Δ Score)
VAS External (Δ Score)
VAS Drowsiness (Δ Score)
CADSS Total (Δ Score)
CADSS Amnesia (Δ Score)
CADSS Derealisation (Δ Score)
Placebo
CBD
THC+CBDlow
THC
THC+CBDhigh

Figure 5