Effects of fixed or self-titrated dosages of Sativex on cannabis withdrawal and cravings

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Abstract

Background—There is currently no pharmacological treatment approved for cannabis dependence. In this proof of concept study, we assessed the feasibility/effects of fixed and self-

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Contributors

Jose M. Trigo (Project scientist) coordinated the implementation of the study and performed the analysis of results and wrote the first draft of the manuscript. Dina Lagzdins (clinician) was involved in medical assessments. Jürgen Rehm, Peter Selby, Islam Gamaleddin, Benedikt Fischer were involved in the study design. Allan J. Barnes and Marilyn A. Huestis performed the analysis of THC and THC metabolites and contributed to the interpretation of those results. Bernard Le Foll is the Principal investigator and Qualified Investigator for the study. He was involved in all aspects of the study. All authors contributed to interpretation of results, manuscript writing and gave final approval of the version to be published.

Conflict of interest

None.

titrated dosages of Sativex (1:1, Δ^9 -tetrahydrocannabinol (THC)/cannabidiol (CBD)) on craving and withdrawal from cannabis among nine community-recruited cannabis-dependent subjects.

Methods—Participants underwent an 8-week double-blind placebo-controlled trial (an ABACADAE design), with four smoke as usual conditions (SAU) (A) separated by four cannabis abstinence conditions (B–E), with administration of either self-titrated/fixed doses of placebo or Sativex (up to 108 mg THC/100 mg CBD). The order of medication administration during abstinence conditions was randomized and counterbalanced. Withdrawal symptoms and craving were assessed using the Cannabis Withdrawal Scale (CWS), Marijuana Withdrawal Checklist (MWC) and Marijuana Craving Questionnaire (MCQ). Medication use was assessed during the study by means of self-reports, vial weight control, toxicology and metabolite analysis. Cannabis use was assessed by means of self-reports.

Results—High fixed doses of Sativex were well tolerated and significantly reduced cannabis withdrawal during abstinence, but not craving, as compared to placebo. Self-titrated doses were lower and showed limited efficacy as compared to high fixed doses. Participants reported a significantly lower “high” following Sativex or placebo as compared to SAU conditions. Cannabis/medication use along the study, as per self-reports, suggests compliance with the study conditions.

Conclusions—The results found in this proof of concept study warrant further systematic exploration of Sativex as a treatment option for cannabis withdrawal and dependence.

Keywords

Cannabis; Marijuana; Withdrawal; THC; Cannabidiol; Clinical trials.gov ID# NCT01748799

1. Introduction

Cannabis is the most widely used illicit substance worldwide (United Nations Office on Drugs and Crime, 2010). Research indicates that about 7–9% of those who ever use cannabis develop cannabis dependence (Anthony et al., 1994; Lev-Ran et al., 2013). In spite of the demonstrated risks and harms to individuals and society posed by cannabis dependence (Fergusson and Boden, 2008; Fischer et al., 2016; Lubman et al., 2014; van Gastel et al., 2014; Volkow et al., 2014), few research teams have explored the possibility of developing medications for its treatment (Budney et al., 2007a; Elkashef et al., 2008; Marshall et al., 2014; Nordstrom and Levin, 2007; Vandrey and Haney, 2009), and currently there is no available approved pharmacological therapy (Marshall et al., 2014).

Agonist assisted treatment is currently a promising approach for pharmacological treatment of cannabis dependence. Indeed, there has been growing interest in the use of Δ^9 -tetrahydrocannabinol (THC) to reduce cannabis withdrawal symptoms and/or modulate self-administration behavior (Budney et al., 2007b; Haney et al., 2008, 2004; Hart et al., 2002; Levin et al., 2011; Vandrey et al., 2013). However, despite promising effects on cannabis withdrawal and treatment retention, THC did not reduce marijuana use more than placebo in a randomized clinical trial (Levin et al., 2011). Additionally, the studies using THC have still not addressed other important factors as testing a sufficient range of doses. Rather, a combination of THC and cannabidiol (CBD) might be more promising, as CBD might modulate THC's euphoric (Dalton et al., 1976), appetitive (Morgan et al., 2010), anxiogenic

and other psychological/physical effects (Karniol et al., 1974; Nicholson et al., 2004; Zuardi et al., 1982). THC is a CB_{1/2} partial agonist, whereas CBD is a CB_{1/2} antagonist (Pertwee, 2008). THC and CBD appear to have different properties. THC produces psychotic-like and anxiogenic effects in humans under some conditions (D'Souza et al., 2005, 2004, 2008). Human research suggests that CBD may have anti-psychotic properties (Zuardi et al., 2006), while some pre-clinical studies suggest that CBD may have anxiolytic (Guimaraes et al., 1990) properties. In addition, CBD seems to exert effects on the extinction of cocaine/amphetamine (Parker et al., 2004) and cue-induced reinstatement of heroin seeking (Ren et al., 2009). However, the possible effects of CBD on cannabis-related addictive behaviors remains unclear (Prud'homme et al., 2015). In spite of evidence indicating that CBD may be useful to curb drug addiction, only one study to date evaluated the efficacy of a 1:1 THC/CBD combination (Sativex) in the treatment of cannabis dependence in humans (Allsop et al., 2014). In the study by Allsop et al. (2014), Sativex (maximum daily dose, 86.4 mg of THC and 80 mg of CBD) was found to reduce cannabis withdrawal and to improve retention in treatment in absence of evident intoxicating effects (Allsop et al., 2014). On other hand, Sativex administration did not result in higher reductions on cannabis use as compared to the placebo group.

Laboratory studies have been used to evaluate the potential of candidate drugs for addiction treatment (Panlilio et al., 2016; Vandrey and Haney, 2009). In this study we focused on cannabis withdrawal and cravings to further explore the therapeutic potential of Sativex. The selection of cannabis withdrawal as an outcome measure was based on studies proposing its participation on relapse (Budney et al., 2008; Cornelius et al., 2008). Notably, participants in treatment studies have reported that cannabis withdrawal contributed to their inability to quit (Budney et al., 1999, 1998; Coffey et al., 2002; Copeland et al., 2001; Copersino et al., 2006; Crowley et al., 1998; Stephens et al., 2002). Relapse to cannabis use is associated with greater severity of withdrawal symptoms (Allsop et al., 2012) and 65% of treatment-seekers report using marijuana to alleviate withdrawal symptoms (Budney et al., 1999; Vandrey et al., 2005). It should be noted that cannabis withdrawal syndrome has also been included, after years of debate, in DSM-5 (APA, 2013). We also selected craving as an outcome measure. Craving, which is also part of the cannabis withdrawal symptomatology, is the most highly endorsed symptom causing relapse in non-treatment-seeking adults (Copersino et al., 2006; Levin et al., 2010) and has been used frequently in clinical trials (Marshall et al., 2014) and in a previous study using a similar design (Budney et al., 2007b). Recent studies have shown that cannabis craving was significantly correlated with current cannabis use and predicted cannabis use-related problems and abstinence (Cousijn et al., 2015). However, the predictive validity of cannabis withdrawal and craving measures in predicting the efficacy of therapeutic interventions in subsequent randomized clinical trials is still unclear (Balter et al., 2014). The clinical significance of cannabis withdrawal and craving are still being debated (Allsop et al., 2012).

In this study, we evaluated the combination of THC/CBD (up to 40 sprays/day, i.e., up to 108 mg THC/100 mg CBD) for its ability to attenuate withdrawal and craving during protocol-induced abstinence for five days in non-treatment seekers. The use of cannabis/medication along the study was assessed by means of participant's self-reports. Urine and blood cannabinoid metabolite concentrations were also determined. We hypothesized that,

due to the tolerance that develops in subjects with regular cannabis use, Sativex should be administered at much higher dosage than those used to treat spasticity or pain in clinical practice; i.e., one spray/day up to 12 sprays/day (Langford et al., 2013; Novotna et al., 2011). We performed this study in cannabis dependent subjects as a first step towards evaluating optimal Sativex dosing for cannabis dependence treatment. The inclusion of “self-titration” conditions in this study, might provide additional information on self-administration of Sativex, and allow establishing useful comparisons in terms of dosage and effectiveness as compared with fixed doses. The present study might extend the literature on Sativex (Allsop et al., 2014) by testing higher doses of Sativex and individual preferences in dosage (i.e., self-titration conditions).

2. Methods

2.1. Study design

The study design was adapted from a published study (Budney et al., 2007b) evaluating oral THC effects on cannabis withdrawal symptoms. In the present study, an eight-week double-blind, placebo-controlled study, all subjects underwent each of eight conditions, lasting five week-days each (an ABACADAE study design): four smoking-as-usual (SAU) conditions and four cannabis abstinence conditions. During each abstinence condition (B–E), subjects were assigned to self-titration of placebo, fixed dose of placebo, self-titration of Sativex (up to a maximum of 40 sprays, equal to 108 mg THC) or a fixed dose of Sativex (40 sprays). Each medication phase (B–D) was followed by a washout period, where individuals were requested to SAU (A condition) with no medication. The study concluded after medication phase E. The order of medication administration during abstinence conditions was randomized and counterbalanced. During SAU conditions, subjects were requested not to change their pattern of ordinary cannabis use but to refrain from taking psychoactive drugs (excluding alcohol, tobacco and caffeine), whereas during the abstinence condition, subjects were requested to abstain from both cannabis and psychoactive drug use (excluding alcohol, tobacco and caffeine). The study was approved by the CAMH REB (#103/2011), Health Canada (# 152698).

2.2. Participants

Inclusion criteria were (a) age 18–50 years; (b) current cannabis dependence; (c) cannabis as primary drug of abuse; (d) frequent cannabis use (i.e., at least 5 days per week); (e) have experienced at least 2 withdrawal symptoms during previous cessation periods; (f) cannabis use not for medical purposes (i.e., not a government-approved medical cannabis user); (g) not seeking treatment for cannabis dependence; and (h) willingness to participate in study protocol.

Exclusion criteria were (a) meet criteria for any psychiatric disorder requiring psychiatric intervention; (b) have a history of seizures; (c) have known sensitivity to dronabinol, CBD, propylene glycol, ethanol or peppermint oil (used in Sativex buccal spray); (d) suffer from an unstable medical condition; (e) currently have physical dependence on any other drugs (excluding nicotine) that would require medical detoxification; (f) currently taking psychotropic medication with benefit for any other illness than treatment of insomnia; (g)

pregnant or breast-feeding; (h) operating heavy machinery; (i) currently seeking treatment for cannabis-related problems; (j) family history of psychotic symptoms.

As per the study protocol, reasons for terminating participation in the study included severe side effects; major protocol violation; subject lost to follow-up; withdrawal of consent and/or pregnancy.

2.3. Procedures

Participants were recruited by media advertisements and flyers, indicating basic study parameters, placed within the Greater Toronto area (Canada) over a period of one year. Following a brief telephone screening, prospective participants meeting all eligibility criteria were invited for an in-person interview for consent procedures and assessment which included urine drug screens, a structured medical assessment and the Structured Clinical Interview for DSM-IV Axis I Disorders Research Version (SCID-I/P). Withdrawal, as defined by a participant's experience of three or more symptoms after cessation of prolonged cannabis use or continuing use to avoid withdrawal symptoms, was assessed during the SCID-I/P. Race and ethnicity were documented by self-report.

As each study condition lasted one week, all eligible subjects started the treatment phase on Mondays and completed daily assessment visits (approximately 30 min) Monday through Thursday. Daily assessments included several scales and questionnaires to assess primary outcomes (medication tolerability, SAEs, withdrawal and craving) and other psychosocial/physical outcomes: vital signs and weight; Marijuana Craving Questionnaire (MCQ; Heishman et al., 2001); Cannabis Withdrawal Scale (CWS; Allsop et al., 2011); St. Mary's Hospital Sleep Questionnaire (SMHSQ; Ellis et al., 1981); Drug Effects Questionnaire; Addiction Research Center Inventory (Haertzen and Hickey, 1987); Minnesota Nicotine Withdrawal Scale (Hughes and Hatsukami, 1986). Additionally, on each Monday when the study drug was administered (B–E condition), participants took their first dose in the presence of study staff and were observed for 1 h to ensure medication tolerability, assess for idiosyncratic adverse events and ensure expedited treatment of these issues should they occur. On Fridays, each of the eight weeks in this study, subjects completed a 2 h visit that included all daily assessments described above plus: Addiction Severity Index (ASI); Marijuana Withdrawal Checklist (MWC; Budney et al., 1999); Brief Symptom Inventory (BSI; Derogatis and Melisaratos, 1983); Profiles of Mood States (POMS); Tiffany Questionnaire of Smoking Urges; Hamilton Depression Rating Scale (HAM-D; Hamilton, 1960); Hamilton Anxiety Scale (Hamilton, 1959); Brief Psychiatric Rating Scale; Timeline Followback (TLFB) for cannabis, tobacco, caffeine and alcohol (Sobell et al., 1988). Participants were instructed to continue using study medication until they attended their weekly visit on Friday. Urine samples for THC metabolite analysis were collected three times each week (on Monday, Wednesday and Friday) and initially screened for a 10-panel (Methamphetamine, Amphetamine, Cannabis, Cocaine, Opiates, Barbiturates, Benzodiazepines, Phencyclidine, Methadone, Oxycodone) urine drug test (QuickScreen™ Cup Multi Drug Screening Test, Confirm Biosciences, San Diego, CA, USA). Blood for THC and metabolites analyses was collected by venipuncture each Friday. Specimens were stored on ice for less than 2 h, centrifuged and plasma separated. Specimens were frozen at –20 °C for less than 3 months

prior to 2-dimensional GC–MS analysis or LC–MS/MS for cannabinoids. Participants were also provided with a smoking diary during the first study visit and instructed to complete information regarding the frequency of cannabis or medication use, time feeling “high” and reasons to use cannabis/medication during each study day. Use of cannabis by different routes of administration (smoking joints or pipes, oral ingestion) was recorded (Mason et al., 2012). Participants received a \$900 compensation.

2.4. Sativex dosing

Participants were required to bring their vials to each study session to assess usage (i.e., vial weight loss). Medication intake was assessed by means of recordings of medication use on the smoking diary, and by weighing each vial before delivering it to participants, during regular study visits and once the used vial was returned. Measures of THC and metabolite concentrations were determined in urine and plasma specimens (see below) and compared with medication use self-reports.

2.4.1. Fixed dose—For the fixed-dose regime, participants were instructed to take four sprays of medication every hour (up to a maximum of 40 sprays/day, which is equivalent to 108 mg THC/100 mg CBD). Participants were also instructed to wait one hour prior to taking another dose if they were experiencing any adverse events due to study medication. On the Friday visit, participants were instructed to administer 4 Sativex sprays upon arrival, after which medication vials were weighed and returned to the pharmacy.

2.4.2. Self-titrated dose—Participants were informed to administer study medication as needed with a limit to four sprays every hour up to a maximum of 40 sprays/day. At the Friday visit, participant’s dosing patterns for the week were assessed through the smoking diary. Participants were instructed to administer the average usage dose (not exceeding four sprays), after which medication vials were weighed and returned to the pharmacy.

2.5. THC metabolites

Urine samples for THC and metabolites analyses were collected three times each week—on Monday, Wednesday and Friday, and blood for analysis of plasma THC and metabolites was collected each Friday. Subjects were considered abstinent based on self-reports from TLFB and smoking diaries. Urine and plasma samples also were analyzed for multiple cannabinoid markers at the Chemistry and Drug Metabolism Section, Intramural Research Program, National Institute on Drug Abuse using previously described methodology (Lowe et al., 2007; Schwoppe et al., 2011) (see Supplementary information S.1–2 for detailed methods). Urine concentrations for the cannabinoids of interest were normalized to creatinine.

2.6. Abstinence and use of drugs verification

Verification of abstinence from cannabis was based on self-reports (smoking diary and TLFB). Abstinence from other drugs was based on self-reports and urine drug tests. Daily cannabis (and other drugs) use was self-reported using the TLFB questionnaire (see Fig. 1a and S1 in Supplementary information) and the smoking diary. Figures for TLFB represent cannabis use and other substances use during the actual abstinence conditions.

2.7. Blinding/randomization

The CAMH research pharmacy generated the randomization list using random block sizes. Participants, investigators and outcome assessors were blinded to treatment allocation until all research procedures were completed.

2.8. Statistical analysis

We aimed for ten participants to determine the tolerability and effect size of Sativex on cannabis withdrawal outcomes. Data collected during each week-day, within each condition, were averaged to obtain a mean of each of the eight conditions. For each variable, we first reported the overall results of a condition effect in eight-cell repeated measures analyses of variance (ANOVA). When initial ANOVA yielded a significant effect, pair-wise comparisons between abstinence conditions and corresponding SAU conditions and between Sativex and placebo conditions were performed, with differences considered statistically significant when significance was $p < 0.05$. No specific instructions were provided to subjects related to the use of cannabis prior to the baseline visit. Therefore, there may have been variability between subjects in terms of their cannabis use or their withdrawal status during this baseline visit and this data is provided as information only in the main manuscript. SPSS 20.0 statistical package was used for analysis.

3. Results

3.1. Demographics

A total of 54 participants were screened and selected for baseline assessment: 22 participants did not attend baseline assessment and were lost to contact, 10 participants did not meet criteria for cannabis dependence, 2 had a negative cannabinoid urine test, 2 met criteria for drugs other than cannabis, 1 was taking medication for another psychiatric disorder, 1 was eligible but no longer interested in participating. The remaining 16 participants were deemed eligible and randomized to receive, in a counterbalanced order, placebo or Sativex in either self-titrated or fixed dose regimen (total of 4 conditions) during each abstinence condition (B, C, D and E conditions). A total of 9 participants completed the entire experimental sequence (see Table 1 for demographics). Two withdrew and five were excluded before completing the eight weeks (two were positive for cocaine, one for incompatible schedule, one disclosed not meeting inclusion criteria after enrollment, and one became pregnant). Study completers reported using cannabis 6.4 days (SD = 0.9) per week, consuming on average 4.5 g (SD = 3.3) per week. Data regarding cannabis use along the study was based on self-reports. Exposure to drugs and medication was assessed by 10-panel urine drug tests performed on site at the time of the assessment and on later analysis of the plasma and urine specimens collected (see Section 3.6).

3.2. Abstinence verification and other drug use

Seven of 9 participants remained abstinent during treatment with Sativex (fixed/self-titrated doses). Two participants self-reported using cannabis, on one and three occasions, consuming a total of 0.25 and 1 g of cannabis, respectively, during Sativex conditions. Similarly, two out of 9 participants used cannabis on three occasions (each participant)

during placebo conditions, consuming in total 0.75 g of cannabis (each participant) during that time. The number of occasions participants relapsed and the total amount of cannabis consumed did not statistically differ between Sativex and placebo conditions ($p > 0.05$).

Self-reports on medication use collected in smoking diaries (Fig. 1b) matched the vials' weight recordings (data not shown). Results in TLFB were consistent with the other participant's self-report (smoking diary) and showed steady abstinence of cannabis during placebo and Sativex conditions (Fig. 1a). Repeated measures ANOVA showed significant differences between conditions in the use of cannabis according with the TLFB ($F_{(7,56)} = 14.331$, $p < 0.001$), suggesting compliance with study conditions (Fig. 1a). Additionally, TLFB showed no compensatory increases in use of other substances during cannabis abstinence (Fig. S1).

Participants reported no other illegal drugs use and this was verified through ten-panel drug tests performed on site. Urine screening tests did not show use of other drugs other than cannabis (data not shown).

Altogether these results suggest that the participants were compliant with the study protocol conditions and that cannabis abstinence did not lead to other legal or illegal drug intake (Fig. S1 and toxicology analysis).

3.3. Medication effects

Medication intake was higher on fixed as compared to self-titration conditions. Repeated measures showed significant differences between conditions ($F_{(3,24)} = 8.561$, $p < 0.001$). Pairwise comparisons showed significant differences between fixed and self-titration conditions ($p < 0.05$) (Fig. 1b). Mean time experiencing "high" was clearly higher during SAU (6.6–7.3 h) compared with Sativex (2.4–3.3 h) or placebo (0.1–0.3 h), as self-reported by participants in their smoking diary (Fig. 1c). Repeated measures ANOVA showed significant differences between conditions ($F_{(7,56)} = 18.604$, $p < 0.001$). More specifically, within-subjects contrasts showed significant differences between all experimental conditions as compared with corresponding SAU ($p < 0.05$ – 0.001). The reason to use cannabis (during SAU conditions) or self-titrate medication (during abstinence conditions) was also recorded. Participants reported to smoke cannabis during SAU conditions mainly to experience positive effects. However, there was no clear preference in the reason to self-titrate medication between the three options provided (Fig. 1d). Repeated measures ANOVA showed significant condition effects on reason to use cannabis/self-titrate medication ($F_{(3,24)} = 6.559$, $p < 0.01$). Pair-wise comparisons showed significant differences between the reasons to smoke during SAU conditions ($p < 0.01$ – 0.001) and between SAU and self-titrate medication on the reason "to feel positive effects" ($p < 0.05$).

3.4. Effects of Sativex on cannabis withdrawal

Participants reported less withdrawal during SAU and fixed Sativex as compared to the corresponding placebo conditions. Repeated measures ANOVA showed significant condition effects on CWS scores ($F_{(7,56)} = 3.860$, $p < 0.01$) (Fig. 2a). Pair-wise comparisons showed significant differences between placebo and their corresponding SAU conditions ($p < 0.01$) and between Sativex and placebo fixed conditions ($p < 0.01$). Self-titrated Sativex (but not

placebo) prevented increases in withdrawal scores during abstinence (Fig. 2a). MWC scores further supported CWS results. Repeated measures ANOVA showed significant condition effects on withdrawal ($F_{(7,56)} = 3.792, p < 0.01$), pair-wise comparisons showed reduced total withdrawal symptoms during the fixed Sativex condition as compared with placebo ($p < 0.05$) (Fig. 2b) (see Table S1 for MWC subscales analysis).

3.5. Effects of Sativex on cannabis craving

No significant changes were observed in craving scores on the MCQ between experimental conditions ($F_{(7,56)} = 0.829, NS$) (Table S1).

3.6. Urinary and plasma cannabinoids

Creatinine-normalized urine cannabinoid concentrations for the different experimental conditions and the baseline assessment are shown in Fig. 3. Repeated measures ANOVA analysis showed no effects during cannabis abstinence conditions. However, a tendency for decreased THC concentrations was observed during abstinence as compared to the corresponding SAU conditions. Mean CBD concentrations were higher during fixed and self-titrated Sativex (409 and 545 ng/mg, respectively), and almost undetectable during fixed and self-titrated placebo (11.3 and 15.9 ng/mg, respectively). Repeated measures ANOVA showed significant differences on urine CBD concentrations ($F_{(7,56)} = 17.914, p < 0.001$). Pair-wise comparisons showed significantly higher CBD concentrations during Sativex compared to their corresponding SAU or placebo conditions ($p < 0.01$). THC mean concentrations on plasma specimens (Fig. S2) were not significantly different between experimental conditions. Similarly to the results found in urine, a tendency for higher CBD mean concentrations was observed during fixed and self-titrated Sativex (2.6 and 2.7 µg/L, respectively) vs the barely detectable CBD concentrations during fixed and self-titrated placebo (0.5 and 0.8 µg/L, respectively). However, repeated measures ANOVA showed no significant differences in plasma CBD concentrations between conditions.

3.7. Adverse effects

We did not observe serious adverse events (SAEs) associated with the study medication (Sativex/placebo). Some adverse events were not study-related (e.g., mild cold, tension headache or hot flashes) and some expected side effects, such as nausea, sleep problems or diarrhea, were noted. Statistical analysis showed no significant condition effect on the appearance of the adverse events ($F_{(7,56)} = 0.578, NS$). Repeated measures ANOVA showed significant differences for HAM-D scoring ($F_{(7,56)} = 3.592, p < 0.01$). Pair-wise comparisons showed significantly higher HAM-D scores during fixed placebo as compared to the corresponding SAU ($p < 0.01$) and Sativex conditions ($p < 0.05$). Similar findings were observed using the POMS ($F_{(7,56)} = 3.310, p < 0.01$), where significant differences between fixed placebo and corresponding SAU/Sativex conditions were also found ($p < 0.05$). Repeated measures ANOVA showed significant differences for BSI ($F_{(7,56)} = 3.585, p < 0.01$). Pairwise comparisons showed significantly higher scores for BSI during fixed placebo as compared to the corresponding SAU ($p < 0.05$) and self-titrated Sativex as compared to the corresponding SAU ($p < 0.05$). Repeated measures ANOVA showed significant differences for SMHSQ ($F_{(7,56)} = 2.339, p < 0.05$). Pair-wise comparisons showed increases

in sleep latency during self-titrated placebo as compared to the corresponding SAU ($p < 0.05$).

4. Discussion

In this study we explored the tolerability of high Sativex dosages (up to 40 sprays/day) in a non-treatment seeking population with cannabis use disorder. Subjects were instructed to start directly at this high dosage (up to 108 mg THC and 100 mg CBD) when initiating cannabis abstinence. Importantly, we did not observe any significant severe adverse event among the participants. The number of adverse events recorded did not differ between Sativex and placebo conditions. Additionally, we did not observe significant compensatory effects on tobacco, caffeine or other drugs during cannabis abstinence. This suggests that high doses of Sativex can be well tolerated, by subjects with cannabis dependence, during withdrawal.

Another important aspect of the administration of Sativex, in cannabis dependent subjects, is the potential of Sativex to induce intoxication, “high” or loss of control over its use. Subjects using Sativex reported significantly less time being “high” as compared the SAU condition (Fig. 1c). In addition, the duration of “high”, reported by subjects under Sativex condition, was shorter compared to the total time on Sativex, indicating that they were not feeling intoxicated for most of their time using it. THC as delivered via Sativex is associated with a reduced magnitude and duration of “high”. However, we cannot rule out the possibility that Sativex possesses some abuse liability. In fact, previous studies suggest that, when consumed at high rates (i.e., 16 consecutive sprays), Sativex might have certain abuse potential, which appears to have a lower magnitude than that of dronabinol (Schoedel et al., 2011). In our study, subjects could not really distinguish between experiencing positive effects or relief of negative effects when using Sativex vs placebo, suggesting that the intoxicating effects were weak. Another study, in a treatment-seeking population, indicated lack of intoxication and inability of subjects to differentiate between placebo and Sativex treatments (Allsop et al., 2014). Taken together, these findings are reassuring on the tolerability of high dosages in cannabis dependent subjects, but indicate the potential of inducing “high” or loss of control in some subjects when Sativex is taken at high rates. Further studies with larger samples are needed to provide clarity on this issue.

The main finding of this study is that high doses of Sativex (fixed condition) were effective to reduce cannabis withdrawal during cannabis abstinence. Lower doses of Sativex (self-titrated condition) were less potent but were still effective preventing cannabis withdrawal during abstinence. It is unclear if CBD is needed to offset cannabis withdrawal, as positive effects were reported with both oral THC at different doses (30–90 mg/day; Budney et al., 2007b; Haney et al., 2004) and with Sativex at daily doses of 86.4 mg THC and 80 mg CBD (Allsop et al., 2014). The concordance of these results provides some guidance on the range of dosages that should be used in cannabis dependent subjects to offset withdrawal symptoms. Our results suggest that Sativex is a safe alternative for an outpatient basis, using either self-titrated or fixed dosage regimen. Higher fixed-doses were more effective than the lower self-titrated dosages, indicating that high doses may be beneficial, as suggested previously with oral THC formulation (Budney et al., 2007b). In this study we found a

preference for lower doses when the participants were given the choice (i.e., self-titration), which might also be considered in the design of future studies.

Here, we found no significant Sativex effects on cannabis craving. It should be noted that in this study we studied symptoms occurring during initial five days of withdrawal. Craving during that time frame is clearly part of the withdrawal symptoms (indeed craving scores are part of the MWC scale; Budney et al., 2001, 2003, 1999). It is also still unclear what the relationship is between withdrawal and drug seeking behavior. On the one hand, relapse to cannabis use during abstinence seems associated with greater withdrawal symptoms severity (Allsop et al., 2012). On the other hand, THC was effective in laboratory studies decreasing the intensity of withdrawal symptoms following cessation of cannabis exposure (Budney et al., 2007b; Haney et al., 2008, 2004; Hart et al., 2002), but ineffective to help subjects quit cannabis use in randomized clinical trials (Allsop et al., 2014; Levin et al., 2011) or in reducing marijuana self-administration in laboratory studies (Hart et al., 2002). Therefore, pharmacotherapies decreasing withdrawal do not seem to guarantee reductions on cannabis use as suggested from previous laboratory studies and recent clinical trials.

CBD, THC and its metabolites' concentrations were measured during the experimental conditions. Urinary and plasma cannabinoids outcomes show higher CBD concentrations during Sativex conditions. CBD concentrations rapidly returned to baseline/placebo levels when no active medication was available. This particular effect of Sativex on CBD concentrations might be of utility to detect Sativex use. We had a clear elevation of CBD, in both urine and plasma samples (although differences between conditions were not statistically significant on the plasma samples), whereas those elevations were not present in subjects reporting cannabis use. Therefore, high CBD concentrations in urine, during Sativex conditions, align with participants' self-reports regarding medication use and vial weight control. Previous studies reported increased CBD and THC metabolites concentrations following treatment with Sativex (Lee et al., 2013; Molnar et al., 2014). Our study further supports that CBD concentrations might be markers indicating exposure to Sativex (Karschner et al., 2011; Lee et al., 2013). Accordingly, almost no CBD was detected during placebo conditions, further suggesting adherence to experimental conditions. On the other hand, our results also show that THC metabolites' concentrations were comparable to baseline concentrations, suggesting that subjects achieved THC doses similar to their usual usage, without the rapid and high peaks that occur after cannabis smoking that increase abuse liability. Cannabinoids' plasma concentrations also point to elevated THC metabolites and CBD concentrations during Sativex conditions, further supporting the results obtained in the analysis of urine specimens.

4.1. Limitations

The major limitation of this trial is the small sample size. However, it was sufficient to detect significant effects. The sample consisted of mostly Caucasian males, which results in a limitation in terms of possible generalization of the data on this study. Another limitation is the fact that participants received different doses during self-titrated conditions, which makes it difficult to compare results between self-titrated and fixed conditions. The ratio of THC/CBD in Sativex is close to 1:1. However, our study did not include experimental

conditions containing THC alone and CBD alone for comparison. Therefore, we cannot be certain of the respective contribution of THC and CBD in the effects observed in this trial. The short duration of the experimental condition is also a limitation, as it did not allow us to evaluate the long-term effects of Sativex/placebo on withdrawal, craving and relapse. Additionally, the large reduction in use under all conditions might have limited the ability to detect reductions in use during active Sativex conditions. Information regarding the use/effects of cannabis and medication was based mostly on self-reports. However, objective measurements (e.g., vial weight changes, and urinary CBD) closely corresponded to the participants' self-reports for Sativex usage. An additional limitation, for the interpretation of the results of this study, is that the experimental conditions might have affected the response of participants regarding Sativex effects (e.g., positive vs. relief of negative effects) due to the imposed abstinence.

5. Conclusion

This pilot study demonstrates the feasibility of our approach and suggests that Sativex might be an effective replacement therapy for cannabis dependence. As also reported in previous studies (Allsop et al., 2014), Sativex reduced cannabis withdrawal, but we cannot predict yet if that will allow reduction in cannabis use in treatment-seeking individuals. These data further provide basis for a systematic rigorous evaluation of Sativex effectiveness, especially given large number of cannabis users and the current limited treatment options.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.drugalcdep.2016.02.020>.

Fig. 1.

Cannabis/Sativex use and reasons to smoke/self-medicate. Participants self-reported cannabis/Sativex use along the study using the smoking diary and timeline followback (TLFB), in (a) columns represent average total consumption (+SEM) of cannabis during baseline (BS) (white bars) and the different experimental conditions (black bars) (Monday to Friday) as reported on the TLFB. In (b) columns represent average number of sprays (+SEM) during the different abstinence conditions (black bars represents Sativex intake Monday to Thursday according to the smoking diary). In (c) time spent high (in hours) during the different experimental conditions (smoking diary), in (d) reasons to smoke/take medication during self-titrated and corresponding smoke as usual (SAU) conditions (smoking diary). In (a) cannabis intake was lower during all abstinence conditions compared to SAU, ** ($p < 0.01$). In (b) # ($p < 0.05$) vs the corresponding fixed condition. In (c) * ($p < 0.05$), ** ($p < 0.01$), *** ($p < 0.001$) vs SAU. In (d) * ($p < 0.05$) vs SAU, ## ($p < 0.01$), ### ($p < 0.001$) vs reason to smoke: to feel positive effects. FP = fixed placebo, FS = fixed Sativex, StP = self-titrated placebo, StS = self-titrated Sativex.

Fig. 2.

Cannabis withdrawal. Columns represent average (+SEM) withdrawal scores as measured using (a) Cannabis Withdrawal Scale (CWS) (maximum possible score: 190) and (b) Marijuana Withdrawal Checklist (MWC) (maximum possible score: 48) during baseline (BS) (white bars) and the different experimental conditions (black bars). * ($p < 0.05$), ** ($p < 0.01$) vs smoke as usual (SAU). # ($p < 0.05$), ## ($p < 0.01$) vs corresponding placebo. FP = fixed placebo, FS = fixed Sativex, StP = self-titrated placebo, StS = self-titrated Sativex.

Fig. 3.

Average creatinine-normalized urine ⁹-tetrahydrocannabinol (THC) and cannabidiol (CBD). Cannabinoids of interest in urine were quantified using two-dimensional a gas chromatography–mass spectrometry method (2D-GCMS) (see Supplementary information for detailed methodology). Mean (+SEM) values for (a) THC and (b) CBD. ** ($p < 0.01$) vs corresponding smoke as usual (SAU). ## ($p < 0.01$) vs corresponding placebo. FP = fixed placebo, FS = fixed Sativex, StP = self-titrated placebo, StS = self-titrated Sativex.

Table 1**Demographics.**

Characteristics	Completers <i>n</i> = 9
Demographics, no. (%)	
Age, years, mean (SD)	35.9 (11.5)
Male	8 (88.9%)
White, Non-hispanic	9 (100%)
Latin American	0 (0%)
Aboriginal	0 (0%)
Mixed	0 (0%)
College degree	4 (44.4%)
Full-time employed	1 (11.1%)
Married	1 (11.1%)
Substance abuse assessment, mean (SD)	
Addiction Severity Index	
Employment	0.4 (0.3)
Medical status	0.0 (0.1)
Psychiatric status	0.0 (0.1)
Family/Social	0.1 (0.1)
Alcohol use	0.1 (0.1)
Drug use	0.1 (0.0)
Legal status	0.0 (0.0)
Addiction Research Centre Inventory	12.8 (4.2)
Questionnaire on Smoking Urges	20.6 (14.7)
Minnesota Nicotine Withdrawal Scale	4.6 (5.7)
Psychological functioning scores, mean (SD)	
Brief Symptom Inventory	12.2 (19.6)
Hamilton Anxiety	1.8 (2.6)
Hamilton Depression Rating Scale	1.6 (2.6)
Brief Psychiatric Rating Scale	18.1 (0.3)
Profile of Mood States	0.8 (19.1)
St. Mary's Sleep Questionnaire	
Sleep latency (min)	35.0 (35.8)
Sleep duration (min)	427.3 (124.2)
Sleep quality	17.3 (3.9)