Published in final edited form as:

Psychopharmacology (Berl). 2016 July ; 233(13): 2469–2478. doi:10.1007/s00213-016-4298-6.

Effects of zolpidem alone and in combination with nabilone on cannabis withdrawal and a laboratory model of relapse in cannabis users

Evan S. Herrmann, Ziva D. Cooper, Gillinder Bedi, Divya Ramesh, Stephanie C. Reed, Sandra D. Comer, Richard W. Foltin, and Margaret Haney

Division on Substance Abuse, New York State Psychiatric Institute, Department of Psychiatry, Columbia University Medical Center, New York, NY, USA

Abstract

Rationale—Each year over 300,000 individuals in the U.S. enter treatment for Cannabis Use Disorder (CUD). The development of effective pharmacotherapy for CUD is a priority.

Objective—This placebo-controlled study examined the effects of zolpidem alone and in combination with nabilone on cannabis withdrawal and a laboratory measure of relapse.

Methods—Eleven daily, non-treatment-seeking cannabis users completed three, 8-day inpatient phases; each phase tested a different medication condition in counter-balanced order. On the first day of each phase, participants were administered placebo capsules t.i.d. and smoked experimenter-administered active cannabis (5.6% THC). On days 2–8, participants were administered capsules containing either placebo (0 mg at 0900, 1800, and 2300), zolpidem (0 mg at 0900 and 1800 and 12.5 mg at 2300) or zolpidem (12.5 mg at 2300) and nabilone (3 mg at 0900 and 1800). Cannabis withdrawal, subjective capsule effects, and cognitive performance were examined on days 3–4, when only inactive cannabis (0.0% THC) was available for self-administration. ‘Relapse’ was measured on days 5–8, when participants could self-administer active cannabis.

Results—Both medication conditions decreased withdrawal-related disruptions in sleep, but only zolpidem in combination with nabilone decreased withdrawal-related disruptions in mood and food intake relative to placebo. Zolpidem in combination with nabilone, but not zolpidem alone, decreased self-administration of active cannabis. Zolpidem in combination with nabilone also produced small increases in certain abuse-related subjective capsule ratings, while zolpidem alone did not. Neither medication condition altered cognitive performance.

Conclusions—Clinical testing of nabilone, either alone, or in combination with zolpidem is warranted.

Introduction

Cannabis is the most widely used illicit drug, with almost 150 million annual users globally (World Health Organization, n.d.). In 2012–2013, 9.5% of US adults used cannabis in the past year, and ~31% of these individuals met DSM-IV criteria for a Cannabis Use Disorder (CUD) (Hasin et al. 2015). CUD is associated with other mental illnesses, decreased school performance and lifetime achievement, negative effects on brain development, and respiratory problems (Volkow et al. 2014). More than 300,000 individuals enter treatment for CUD in the U.S. each year (Substance Abuse and Mental Health Services Administration 2014). There are currently no FDA-approved pharmacotherapies for CUD, and even with the most effective behavioral treatments most patients are unable to achieve sustained abstinence (see Budney et al. 2006; Carroll et al. 2012).

Withdrawal may be one factor contributing to the persistence of problematic cannabis use. Human laboratory and clinical outpatient studies have demonstrated that individuals who abruptly cease frequent, heavy cannabis use often experience withdrawal symptoms, notably disturbances in mood (e.g., irritability, increased anger), sleep (e.g., increased sleep latency, awakening at night, strange dreams), and gastrointestinal function (e.g., nausea, decreased food intake) (Budney et al. 2003; Haney et al. 1999). These symptoms usually begin after at least 24 hours of abstinence, peak within the first week, and resolve within 2–3 weeks, with the exception of sleep disturbances, which may persist for a month or longer (Budney et al. 2003, 2004; Haney et al. 2005). Cannabis withdrawal is similar in severity to nicotine withdrawal (Budney et al. 2008; Vandrey et al. 2008), and is associated with functional impairment and relapse (Allsop et al. 2012; Budney et al. 2008). These findings suggest that medications that suppress cannabis withdrawal may also improve treatment outcomes among individuals with CUD.

Many classes of medications have been examined as potential treatments for CUD, including cannabinoid agonists (Balter et al. 2014). Oral administration of synthetic ⁹-tetrahydrocannabinol (THC; dronabinol; Marinol®) has been shown to dose-dependently decrease withdrawal symptoms both in laboratory (Budney et al. 2007; Haney et al. 2004; Vandrey et al. 2013) and clinical outpatient (Levin et al. 2011) settings. Despite these effects on withdrawal, dronabinol may be a less than promising treatment for CUD: Dronabinol did not reduce cannabis self-administration in abstinent (Haney et al. 2008) or ongoing (Hart et al. 2002) cannabis smokers in the human laboratory, nor did it reduce cannabis use in clinical outpatients (Levin et al. 2011). Furthermore, dronabinol produces the same metabolites as cannabis, making biochemical verification of cannabis abstinence during dronabinol maintenance difficult.

The synthetic cannabinoid agonist nabilone (Cesamet®) may be a more promising treatment for CUD than dronabinol. Nabilone, an FDA-approved medication primarily used to relieve nausea and vomiting caused by chemotherapy, has been shown to reduce both cannabis withdrawal and self-administration in abstinent cannabis smokers in the laboratory (Haney et al. 2013a). Nabilone is well-tolerated among cannabis users, and has better bioavailability and a longer duration of action than dronabinol, allowing for withdrawal suppression with once-daily dosing (Bedi et al. 2013; Glass et al. 1981; Haney et al. 2013a). Also, nabilone

has lower abuse liability than cannabis and dronabinol (Lemberger et al., 1982; Mendelson and Mello, 1984) and produces urinary biomarkers distinct from those of cannabis (Fraser and Meatherall 1989), which allows for abstinence monitoring using standard urine toxicology during nabilone maintenance. These characteristics make nabilone amenable to application as a pharmacotherapy for CUD.

It is also possible to target specific cannabis withdrawal symptoms using non-cannabinoid compounds. A prior laboratory study demonstrated that zolpidem (Ambien®), a non-benzodiazepine GABA_A receptor agonist used primarily for the treatment of insomnia, reduced cannabis-withdrawal-related disruptions in sleep (Vandrey et al. 2011). Several clinical trials examining zolpidem for the treatment of chronic insomnia demonstrate that the medication is well-tolerated, and remains effective for up to twelve months without evidence of significant tolerance or rebound insomnia upon discontinuation (Krystal et al. 2008; Randall et al. 2012; Roehrs et al. 2012; Scharf et al. 1994). Furthermore, zolpidem appears to have low abuse liability at doses commonly used to treat insomnia (e.g., Hajak et al. 2003; Rush et al. 1999). Thus, zolpidem may also hold promise as a treatment for the prominent sleep disruptions observed during cannabis withdrawal.

Dronabinol and nabilone also reduce cannabis-related disruptions in sleep (Bedi et al. 2010; Haney et al. 2013a), however, tolerance to somnolent effects can occur with a week of daily dosing (e.g., Bedi et al. 2010; Gorelick et al. 2013). Given that withdrawal-related sleep disturbances may persist for longer than other symptoms, pharmacotherapies for CUD based on cannabinoid agonists alone may be insufficient. Approaches that employ cannabinoid agonists during daytime and hypnotics like zolpidem before bedtime may be effective, while minimizing total agonist exposure. Controlled human laboratory studies are an important first step in examining the efficacy of such combination treatments.

The primary aims of this study were to determine if nightly zolpidem administered alone, or in combination with twice-daily low dose nabilone, suppresses cannabis withdrawal and a laboratory measure of relapse, defined as self-administration after a three-day period of abstinence, among non-treatment-seeking daily cannabis users. We used a well-established human laboratory model of cannabis withdrawal and self-administration (see Haney 2009; Haney et al. 2008, 2013a,b) to build upon prior findings that zolpidem and nabilone attenuate some symptoms of cannabis withdrawal when administered alone (Haney et al. 2013a; Vandrey et al. 2011). Here, we provide a placebo-controlled examination of the effects of zolpidem alone and zolpidem plus nabilone on 1) cannabis withdrawal symptoms during abstinence, including measures of mood, sleep, and food intake, and 2) 'relapse' to cannabis self-administration after a short period of abstinence. As secondary aims, we also examine abuse-liability related subjective effects of the medications tested (e.g., rating of 'good drug effect,' 'like drug effect,' 'take drug again') and effects on a battery of computerized cognitive tasks that measure learning, memory, vigilance, and psychomotor ability.

Materials and Methods

Participants

Healthy cannabis users were recruited from New York, NY through advertisements in local newspapers. Study eligibility was assessed by an initial telephone screening, followed by an in-person interview and medical examination. Inclusion criteria were: (1) 21–50 years of age, (2) reporting use of at least three cannabis cigarettes (or equivalent in blunts, etc.) per day, at least five days per week, for the past four weeks, (3) positive urine tests for recent cannabis use, (4) being able to perform all study procedures, and (5) currently practicing an effective form of birth control (women only). Primary exclusion criteria were: (1) meeting DSM-IV-TR criteria for an Axis I disorder requiring medical intervention, (2) dependence on substances other than cannabis and nicotine, (3) medical history, physical examination, or laboratory tests performed during the screening process revealing any significant illness, (4) currently interested in stopping cannabis use or seeking treatment for cannabis use, (5) currently using any prescription medications daily, (6) reporting ever losing consciousness after cannabis use, or (7) having allergies to hypnotic medications. All participants provided informed consent and all study procedures were approved by the New York State Psychiatric Institute (NYSPI) Institutional Review Board and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

Laboratory Procedures

Participants completed three inpatient phases in a residential laboratory at NYSPI in groups of three or four. The residential laboratory is described in detail elsewhere (see Haney et al., 1999). Each 8-day inpatient phase consisted of active and/or placebo study medication, experimenter-administered active (5.6% THC) and inactive (0.0% THC) cannabis, and opportunities to self-administer active and inactive cannabis at a financial cost (see Table 1). Inpatient phases were separated by at least seven outpatient days to allow participants to resume their normal patterns of behavior (e.g., cannabis use) and for medication washout. Participants completed two 3–4 hour training sessions before starting the first inpatient phase to prepare them for study procedures.

Study days were highly structured. Participants were woken at 0815, and completed subjective measures of sleep and mood shortly after waking. Participants spent the majority of their time between 0915 and 1700 hours in their private rooms, where they completed subjective effects and cognitive/behavioral task batteries (described below). They had free time from 1215–1245 for lunch and from 1700–2200 hours, when they could socialize in the recreation area if they chose to do so. Participants completed final subjective effects and mood scales at 2200 and were given \$70 in faux money representing part of their daily study earnings. They were told that they could use this money to purchase inhalations of cannabis cigarettes on self-administration days or exchange it for cash after completing the study. Lights went out at 0000 hours. Tobacco smokers were provided with their usual brand of cigarettes at a cost of \$0.50 per cigarette, and permitted to smoke *ad libitum*.

Study Medication Administration—Study medication was packaged by the NYSPI Research Pharmacy in size 00 capsules. Administration was double-blind, and each

participant completed all three medication phases in randomized order. Capsules were administered at 0900, 1800, and 2300 during all eight days of each inpatient phase. All three capsules were placebo during day 1 of each inpatient phase. During the placebo phase, all three capsules on days 2–8 were also placebo. During the zolpidem alone phase, capsules administered at 0900 and 1800 contained placebo and capsules administered at 2300 contained zolpidem (12.5 mg). During the zolpidem plus nabilone phase, capsules administered at 0900 and 1800 contained nabilone (3 mg) and capsules administered at 2300 contained zolpidem (12.5 mg). We chose to administer 3mg b.i.d. because a previous study in our laboratory demonstrated that 6mg administered once daily can produce minor impairments in performance on cognitive tasks (Bedi et al., 2013).

Experimenter Administered Cannabis

Participants completed two cannabis ‘sampling’ sessions before the beginning of each inpatient phase to familiarize them with the doses of cannabis available during the inpatient stay. Participants received a single cannabis cigarette, at no cost, during each sampling session. In one session they smoked an active cannabis cigarette (5.6% THC; labeled ‘Dose A’), and in the other they smoked an inactive cannabis cigarette (0.0% THC; labeled ‘Dose B’) in randomized order. Cannabis was administered using a cued-smoking procedure, with inhalation duration, time spent holding smoke in lungs, and inter-puff interval standardized (see Foltin et al., 1987). Participants were asked to focus on the effects of these doses because they would later make decisions about purchasing individual inhalations of Dose A and Dose B. During the first day of each inpatient phase, participants smoked three inhalations of an active cannabis cigarette at 1000, 1130, 1300, 1430, 1600, and 2200 hours (18 inhalations total) in order to standardize levels of cannabis exposure prior to abstinence and collect data on subjective drug effects and behavioral/cognitive performance under conditions of active cannabis use.

Laboratory Measure of Cannabis Relapse

During study days 2–8, participants had the option to purchase 0, 1, 2, or 3 inhalations from cannabis cigarettes at 1000, 1130, 1300, 1430, 1600, and 2200 hours (max 18 inhalations/day). The first inhalation of the day cost participants \$9, with each subsequent inhalation available for \$2. The first inhalation of the day had a higher cost in order to model clinical relapse by requiring participants to make a costly financial decision to resume cannabis use (see Haney et al., 2008). During study days 2–4, the cannabis available for purchase was inactive (0.0% THC; labeled ‘Dose B’), allowing us to collect data on cannabis withdrawal. During days 5–8, active cannabis was available for purchase (5.6% THC; labeled ‘Dose A’), allowing us to assess ‘relapse,’ defined as self-administration of active cannabis after a period of abstinence.

Assessments

Cannabis Withdrawal—Measures of mood, sleep, and food intake were collected during study days 3–4 (described below).

Mood: Participants completed a 44-item computerized mood scale questionnaire 8 times each day. They viewed mood, physical symptom, and drug effect descriptors and used a 100-

mm visual analog scale (VAS) to rate the extent to which each descriptor applied to how they felt at that moment, ranging from ‘not at all’ (0 mm) to ‘extremely’ (100 mm). Based on a cluster analysis conducted previously (see Haney et al., 2013a), we used arithmetic means of individual item scores to reduce 32 of the 44 items into six subscales: (1) irritable (‘irritable,’ ‘miserable’), (2) anxious (e.g., ‘anxious,’ ‘restless’), (3) bad effect (e.g., ‘depressed,’ ‘upset stomach’), (4) tired (e.g., ‘tired,’ ‘sedated’), (5), social (e.g., ‘friendly,’ ‘talkative’) and (6) high (‘high,’ ‘good effect’). We also analyzed four individual VAS items (‘hunger,’ ‘I want marijuana,’ ‘I want alcohol,’ ‘I want cigarettes’).

Sleep: Objective data on sleep were obtained using the wrist-worn Actiwatch® Activity Monitoring System (Respironics Company, Bend OR). From these data, we calculated total sleep time during the lights out period, sleep latency (time from lights out until falling asleep), and sleep efficiency (proportion of time asleep from initially falling asleep until awakening in the morning). Participants also completed a 7-item VAS sleep questionnaire each morning (‘slept well,’ ‘fell asleep easily,’ ‘woke often,’ etc.; see Haney et al., 2004) to collect subjective ratings of sleep quality.

Food intake and body weight: Participants were weighed each morning shortly after waking and then received a box of food containing a wide variety of meal items, snacks and beverages. Frozen meals (~20 varieties) and additional units of any item were available by request. Participants scanned custom-designed bar codes whenever they ate or drank, specifying substance and portion, to provide detailed data on food intake. Food was not available between 2330 and 0800 hours.

Cannabis ‘Relapse’—The number of inhalations purchased on study days 5–8 (5.6% THC; labeled ‘Dose A’) was recorded as a laboratory measure of relapse to active cannabis after a period of abstinence.

Subjective Capsule Effects—Participants completed a Drug Effect Questionnaire (DEQ; Evans et al., 1995) twice each day to assess the subjective effects of study medications. The questionnaire asked them to rate (1), how ‘strong’ of a drug effect they were feeling on a five-point scale of 0 (‘no effect at all’) to 4 (‘very strong effect’), (2) if they were feeling ‘good effects,’ and ‘bad effects,’ and the degree to which they would be willing to take the drug again on a five-point scale ranging from 0 (‘not at all’) to 4 (‘very much’), (3) whether the drug effects they were feeling were sedative-like, stimulant-like, or absent, and (4) if they disliked or liked the way the drug made them feel, using a nine-point scale ranging from -4 (‘dislike very much’) to 4 (‘like very much’).

Cognitive Tasks—Participants completed a computerized battery of tasks five times each day that measured learning, memory, vigilance, and psychomotor ability (Foltin et al., 1996). This task battery consisted of a 3-min digit-symbol substitution task (DSST), a 3-min repeated acquisition task (RAT), a 10-min divided attention task (DAT), a 10-min rapid information task (RIT), and an immediate and delayed digit-recall task (IDDRT).

Data Analysis

Repeated-measures analyses of variance with planned comparisons were used to 1) compare study outcome measures between collected during active cannabis administration and during withdrawal under placebo conditions, and 2) examine the effect of zolpidem alone and zolpidem in combination with nabilone on study outcome measures relative to placebo during withdrawal and relapse phases.

The first primary outcome measure was cannabis withdrawal (changes in mood, sleep food intake, and bodyweight). To assess withdrawal, data collected on day 1 (active cannabis administration) were compared to data collected on days 3–4 during the placebo phase using planned contrasts. Data from day 2 were not analyzed because many symptoms of cannabis withdrawal do not present until 24 hours of abstinence (Budney et al., 2003; Kouri & Pope, 2000). Data collected on days 3–4 were then compared between placebo, zolpidem alone, and zolpidem in combination with nabilone phases in order to examine medication effects on withdrawal relative to placebo.

The second primary outcome measure was the laboratory measure of relapse (number of inhalations of active cannabis purchased). Specifically, the number of inhalations purchased on day 5 and mean number of inhalations purchased on days 6–8 were compared between medication conditions using planned contrasts. Day 5 and days 6–8 were analyzed separately because day 5 represents the first opportunity to self-administer active cannabis after a period of abstinence, while days 6–8 better represent opportunities to continue active cannabis use after initial return to self-administration has occurred (see Haney et al., 2013a).

Our two secondary outcome measures were to examine subjective capsule effects and cognitive task performance. To assess these, we compared data on subjective capsule effects and task performance collected on day 1 (active cannabis administration) and days 3–4 under placebo conditions, and also compared data collected on days 3–4 under placebo, zolpidem alone, and zolpidem in combination with nabilone conditions. All data analyses were performed using SuperANOVA for Macintosh. Statistical significance for all analyses was determined at $\alpha = 0.05$ and Huynh-Feldt corrections were used when appropriate.

Results

Participants

Fifteen participants enrolled in the study. Four participants withdrew prior to completing all three inpatient phases; one was discontinued by the investigators for noncompliance with study procedures, two left on the third day of cannabis abstinence for personal reasons, and one failed to return for the second inpatient phase without explanation. There were no serious adverse events. Analyses were performed on data from study completers only ($n = 11$). Demographic and substance use characteristics of study completers are displayed in Table 2.

Cannabis Withdrawal

Mood—Figure 1 displays mean scores on the ‘irritable,’ ‘anxious,’ and ‘high’ clusters during active cannabis administration and during cannabis withdrawal as a function of medication condition. Under the placebo conditions, mean scores of ‘irritable’ and ‘anxious’ clusters increased during withdrawal relative to active cannabis administration ($F(1,14) = 10.71, p < 0.01$ and $F = 12.74, p < 0.01$, respectively) while mean scores on the ‘high’ cluster decreased ($F = 75.40, p < 0.001$). Scores on the ‘bad effect,’ ‘tired,’ and ‘social’ clusters did not significantly change during withdrawal relative to active cannabis administration.

Zolpidem alone did not produce any changes in mood relative to placebo. Zolpidem plus nabilone significantly decreased scores on the ‘irritable’ and ‘anxious’ clusters ($F = 12.28, p < 0.01$ and $F = 10.17, p < 0.05$, respectively) and significantly increased scores on the ‘high’ cluster ($F = 9.61, p < 0.01$) relative to placebo, but did not significantly change scores on the ‘bad effect,’ ‘tired,’ and ‘social’ clusters.

Sleep—Figure 2 displays sleep latency, sleep efficiency, and ratings of ‘fell asleep easily,’ and ‘woke often’ for the night after active cannabis administration and during cannabis withdrawal. Participants had increased sleep latency ($F = 8.34, p < 0.05$), decreased sleep efficiency ($F = 7.13, p < 0.05$), decreased ratings of ‘fell asleep easily’ ($F = 8.39, p < 0.01$), and increased ratings of ‘woke up often’ ($F = 4.55, p < 0.05$) during withdrawal relative to active cannabis administration.

Zolpidem alone decreased sleep latency ($F = 5.44, p < 0.05$) and increased total sleep time ($F = 9.85, p < 0.05$) sleep efficiency ($F = 4.96, p < 0.05$), ratings of ‘fell asleep easily’ ($F = 16.62, p < 0.001$), and ratings of ‘woke up early’ ($F = 4.85, p < 0.05$) relative to placebo. Zolpidem in combination with nabilone decreased sleep latency ($F = 11.55, p < 0.01$) and ratings of ‘woke up often’ ($F = 15.58, p < 0.001$), and increased total sleep time ($F = 7.49, p < 0.05$), sleep efficiency ($F = 21.21, p < 0.001$), ratings of ‘fell asleep easily’ ($F = 23.05, p < 0.001$), ratings of ‘slept well’ ($F = 11.52, p < 0.05$), and subjective estimates of number of hours slept ($F = 6.05, p < 0.05$) relative to placebo.

Food intake and body weight—Figure 3 displays data on food intake and body weight during active cannabis administration and withdrawal. Participants consumed significantly fewer calories ($F = 23.58, p < 0.001$) and had decreased body weight ($F = 35.82, p < 0.001$) during withdrawal as compared to active cannabis administration.

Zolpidem alone did not have any significant effects on food intake or body weight relative to placebo. Zolpidem in combination with nabilone reversed withdrawal-related disruptions in both food intake ($F = 74.83, p < 0.001$) and body weight ($F = 405.14, p < 0.001$) relative to placebo.

Cannabis ‘Relapse’

Figure 4 displays the mean number of cannabis cigarette puffs purchased for self-administration on the first day of active cannabis availability (top panel) and on the subsequent three days (bottom panel) of availability. Zolpidem alone did not alter cannabis

self-administration relative to placebo. Zolpidem in combination with nabilone did not decrease active cannabis self-administration the first day of availability, but did significantly decreased self-administration on subsequent days relative to placebo ($F = 6.55$, $p < 0.05$).

Subjective Capsule Effects

Under placebo conditions, ratings of 'strong drug effect' (Mean ratings of 0.45 vs. 1.64, $F = 16.06$, $p < 0.01$), 'good drug effect' (0.36 vs. 1.73, $F = 19.04$, $p < 0.001$), 'like drug effect' (0.36 vs. 1.46, $F = 13.97$, $p < 0.01$), 'take drug again' (0.68 vs. 1.73, $F = 12.24$, $p < 0.01$), and identification of the drug as a sedative (0.45 vs. 0.91, $F = 4.54$, $p < 0.05$) were lower during withdrawal relative to active cannabis administration.

Participants were more likely to identify zolpidem as a sedative compared to placebo (Mean ratings of 0.86 vs. 0.45, $F = 5.52$, $p < 0.05$), but there were no other significant differences between zolpidem and placebo during the withdrawal phase. The combination of zolpidem and nabilone significantly increased ratings of 'strong drug effect' (1.04 vs. 0.45, $F = 6.02$, $p < 0.05$), 'good drug effect' (1.00 vs. 0.36, $F = 6.22$, $p < 0.05$), 'bad drug effect' (0.55 vs. 0.45, $F = 7.78$, $p < 0.05$) and identification of drug effect as sedative (1.00 vs. 0.45, $F = 9.81$, $p < 0.01$), but did not alter ratings of 'like drug effect' or 'take drug again' relative to placebo.

Cognitive Task Performance

Under placebo conditions, performance on the IDRT was significantly better during withdrawal than during active cannabis administration, with a greater number of trials correct (7.36 vs. 6.46, $F = 11.95$, $p < 0.01$), percent of trials correct (95% vs. 88%, $F = 10.04$, $p < 0.05$), and percent of digits recognized (100% vs. 82%, $F = 14.27$, $p < 0.05$).

Zolpidem alone significantly increased the total number of trials attempted on the DSST (82.8 vs. 79.7, $F = 4.53$, $p < 0.05$) relative to placebo, but did not change the number of trials completed correctly. There were no other significant effects as a function of medication condition on any other cognitive measures.

Discussion

This report summarizes the first controlled laboratory examination of the effects of zolpidem in combination with nabilone on cannabis withdrawal and a laboratory measure of cannabis relapse, and the first examination of the effects of zolpidem alone on this measure of cannabis relapse. Here we summarize three important findings. First, zolpidem alone reduced cannabis withdrawal-related disturbances in sleep, but did not suppress any other withdrawal symptoms or cannabis relapse as measured in the laboratory. Second, zolpidem in combination with nabilone suppressed a full spectrum of withdrawal symptoms during cannabis abstinence and reduced cannabis 'relapse.' Third, zolpidem in combination with nabilone had robust effects on withdrawal and 'relapse' while producing only minor subjective drug effects associated with abuse liability, and no measurable cognitive impairment.

Consistent with the one prior report on the topic (Vandrey et al., 2011), zolpidem administered shortly before bed significantly improved both objective and self-reported measures of sleep quality relative to placebo during cannabis abstinence, providing further evidence that zolpidem can reduce cannabis withdrawal-related disturbances in sleep. Zolpidem was well tolerated, and produced no residual daytime subjective effects (e.g., sedation) or cognitive impairment. However, zolpidem alone did not suppress withdrawal-related disturbances in mood or food intake, or suppress cannabis self-administration. This is similar to the findings of two studies conducted in our laboratory demonstrating that both mirtazapine (Haney et al., 2010) and quetiapine (Cooper et al., 2013) improved sleep during withdrawal without reducing cannabis self-administration. This suggests that cannabis withdrawal related changes in mood and resumption of cannabis use after a short period of abstinence are not mediated by sleep disturbance, and that improving sleep quality alone is likely insufficient to reduce cannabis use among most cannabis users.

The results of the present study indicate that the combination of zolpidem and nabilone significantly reduced cannabis withdrawal-related disturbances in mood, sleep, and food intake, and reduced self-administration after a short period of abstinence. The observed effects on mood, food intake, cannabis self-administration, and daytime subjective drug effects are likely attributable to nabilone, because they are consistent with effects observed in previous studies administering comparable doses of nabilone alone (e.g., Bedi et al., 2013; Haney et al., 2013a; Lile et al., 2010, 2011). Haney et al. (2013a) demonstrated nabilone alone produced similar improvements in sleep as those observed with zolpidem plus nabilone in the present study, suggesting that zolpidem provided no unique benefit with regard to sleep. Although the similarities between the present study and the results of Haney et al. (2013) are compelling, the fact that we did not examine nabilone alone in the present study undermines our ability to firmly conclude that zolpidem plus nabilone is not superior to nabilone alone.

Despite these results, it would be premature to dismiss the potential utility of zolpidem as a component of combination pharmacotherapy for CUD. As we stated earlier, sleep disturbances appear to be among the most common and protracted symptoms of cannabis withdrawal, and several studies have demonstrated that zolpidem is effective for the long-term treatment on insomnia. Tolerance to dronabinol's effects on sleep develops rapidly (e.g., Bedi et al., 2010; Gorelick et al., 2013). It is unknown if tolerance to nabilone's somnolent effects develops in a similar manner, but if so, zolpidem may be better suited for the treatment of cannabis withdrawal-related sleep disturbance given its protracted time course.

The relative lack of mood effects and subjective drug effects associated with abuse liability in the zolpidem plus nabilone condition warrants additional discussion. Although we observed significant increases on the 'High' cluster relative to placebo (mean ratings of 21.4/100.0 vs. 4.6/100.0 on the VAS, respectively), these ratings are markedly less than those reported following active cannabis (62.0/100.0 on the VAS) (see Figure 4). Zolpidem in combination with nabilone also produced minor and inconsistent effects on DEQ items associated with abuse liability. This is generally consistent with previous studies that examined abuse liability of zolpidem (e.g., Hajak et al., 2003; Rush et al., 1999) and prior

studies in our laboratory that administered comparable doses of nabilone (Bedi et al., 2013; Haney et al., 2013a). Earlier research has demonstrated that nabilone has lower abuse liability than smoked cannabis and oral dronabinol (Lemberger et al., 1982; Mendelson and Mello, 1984), and there is little evidence of recreational use or diversion of nabilone despite almost 80,000 prescription users in Canada alone as of 2006 (Ware and St Arnaud-Tempe, 2010). The present study suggests that zolpidem in combination with nabilone also has low abuse liability among heavy cannabis users.

The present report summarizes the first placebo-controlled human laboratory study examining the effects of zolpidem alone on cannabis self-administration, and the first study to examine zolpidem in combination with nabilone on cannabis withdrawal and self-administration. Zolpidem in combination with nabilone suppressed the full spectrum of cannabis withdrawal symptoms and cannabis relapse while producing only minor subjective drug effects associated with abuse liability and no evidence of behavioral/cognitive impairment. In contrast, zolpidem alone reduced sleep disturbance, but did not affect other withdrawal symptoms or reduce relapse. Clinical testing of nabilone, either alone, or in combination with zolpidem or other medications for the treatment of CUD is warranted.

Acknowledgments

This research was supported by P50 DA009236 and T32 DA007294 from the National Institute on Drug Abuse.

References

- Allsop DJ, Copeland J, Norberg MM, Fu S, Molnar A, Lewis J, et al. Quantifying the clinical significance of cannabis withdrawal. *PLoS ONE*. 2012; 7:e44864. [PubMed: 23049760]
- Balter RE, Cooper ZD, Haney M. Novel pharmacologic approaches to treating cannabis use disorder. *Curr Addict Rep*. 2014; 1:137–143. [PubMed: 24955304]
- Bedi G, Cooper ZD, Haney M. Subjective, cognitive and cardiovascular dose-effect profile of nabilone and dronabinol in marijuana smokers. *Addict Biol*. 2013; 18:872–881. [PubMed: 22260337]
- Bedi G, Foltin RW, Gunderson EW, Rabkin J, Hart CL, Comer SD, et al. Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: a controlled laboratory study. *Psychopharmacology*. 2010; 212:675–686. [PubMed: 20824270]
- Budney AJ, Hughes JR, Moore BA, Vandrey R. Review of the validity and significance of cannabis withdrawal syndrome. *Am J Psychiatr*. 2004; 161:1967–1977. [PubMed: 15514394]
- Budney AJ, Moore BA, Rocha HL, Higgins ST. Clinical trial of abstinence-based vouchers and cognitive-behavioral therapy for cannabis dependence. *J Consult Clin Psychol*. 2006; 74:307–316. [PubMed: 16649875]
- Budney AJ, Moore BA, Vandrey RG, Hughes JR. The time course and significance of cannabis withdrawal. *J Abnorm Psychol*. 2003; 112:393–402. [PubMed: 12943018]
- Budney AJ, Vandrey RG, Hughes JR, Moore BA, Bahrenburg B. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. *Drug Alcohol Depend*. 2007; 86:22–29. [PubMed: 16769180]
- Budney AJ, Vandrey RG, Hughes JR, Thostenson JD, Bursac Z. Comparison of cannabis and tobacco withdrawal: Severity and contribution to relapse. *J Subst Abuse Treat*. 2008; 35:362–368. [PubMed: 18342479]
- Carroll KM, Nich C, LaPaglia DM, Peters EN, Easton CJ, Petry NM. Combining cognitive behavioral therapy and contingency management to enhance their effects in treating cannabis dependence: less can be more, more or less. *Addiction*. 2012; 107:1650–1659. [PubMed: 22404223]

- Cooper ZD, Foltin RW, Hart CL, Vosburg SK, Comer SD, Haney M. A human laboratory study investigating the effects of quetiapine on marijuana withdrawal and relapse in daily marijuana smokers. *Addict Biol.* 2013; 18:993–1002. [PubMed: 22741619]
- Evans SM, Foltin RW, Levin FR, Fischman MW. Behavioral and subjective effects of DN-2327 (pazinaclone) and alprazolam in normal volunteers. *Behav Pharmacol.* 1995; 6:176–186. [PubMed: 11224325]
- Foltin RW, Fischman MW, Pedrosa JJ, Pearlson GD. Marijuana and cocaine interactions in humans: cardiovascular consequences. *Pharmacol Biochem Behav.* 1987; 28:459–464. [PubMed: 2829241]
- Foltin RW, Haney M, Comer SD, Fischman MW. Effect of fenfluramine on food intake, mood, and performance of humans living in a residential laboratory. *Physiol behav.* 1996; 59:295–305. [PubMed: 8838609]
- Fraser AD, Meatherall R. Lack of Interference by Nabilone in the EMIT® and Cannabinoid Assay, Abbott TDx® Cannabinoid Assay, and a Sensitive TLC Assay for 9-THC-Carboxylic Acid. *J Anal Toxicol.* 1989; 13:240–240. [PubMed: 2550703]
- Glass RM, Uhlenhuth EH, Hartel FW, Schuster CR, Fischman MW. Single-Dose Study of Nabilone in Anxious Volunteers. *J Clin Pharmacol.* 1981; 21:383S–396S. [PubMed: 6117576]
- Gorelick DA, Goodwin RS, Schwilke E, Schwoppe DM, Darwin WD, Kelly DL, et al. Tolerance to Effects of High-Dose Oral 9-Tetrahydrocannabinol and Plasma Cannabinoid Concentrations in Male Daily Cannabis Smokers. *J Anal Toxicol.* 2013; 37:11–16. [PubMed: 23074216]
- Hajak G, Müller WE, Wittchen HU, Pittrow D, Kirch W. Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data. *Addiction.* 2003; 98:1371–1378. [PubMed: 14519173]
- Haney M. The marijuana withdrawal syndrome: diagnosis and treatment. *Curr Psychiat Rep.* 2005; 7:360–366.
- Haney M. Self-administration of cocaine, cannabis and heroin in the human laboratory: benefits and pitfalls. *Addict Biol.* 2009; 14:9–21. [PubMed: 18855806]
- Haney M, Cooper ZD, Bedi G, Vosburg SK, Comer SD, Foltin RW. Nabilone decreases marijuana withdrawal and a laboratory measure of marijuana relapse. *Neuropsychopharmacology.* 2013a; 38:1557–1565. [PubMed: 23443718]
- Haney M, Bedi G, Cooper ZD, Glass A, Vosburg SK, Comer SD, Foltin RW. Predictors of marijuana relapse in the human laboratory: robust impact of tobacco cigarette smoking status. *Biol psychiatry.* 2013b; 73:242–248. [PubMed: 22939992]
- Haney M, Hart CL, Vosburg SK, Comer SD, Reed SC, Foltin RW. Effects of THC and lofexidine in a human laboratory model of marijuana withdrawal and relapse. *Psychopharmacology.* 2008; 197:157–168. [PubMed: 18161012]
- Haney M, Hart CL, Vosburg SK, Nasser J, Bennett A, Zubarán C, Foltin RW. Marijuana withdrawal in humans: effects of oral THC or divalproex. *Neuropsychopharmacology.* 2004; 29:158–170. [PubMed: 14560320]
- Haney M, Ward AS, Comer SD, Foltin RW, Fischman MW. Abstinence symptoms following oral THC administration to humans. *Psychopharmacology.* 1999; 141:385–394. [PubMed: 10090646]
- Hart CL, Haney M, Ward AS, Fischman MW, Foltin RW. Effects of oral THC maintenance on smoked marijuana self-administration. *Drug Alcohol Depend.* 2002; 67:301–309. [PubMed: 12127201]
- Hasin DS, Saha TD, Kerridge BT, Goldstein RB, Chou SP, Zhang H, et al. Prevalence of Marijuana Use Disorders in the United States Between 2001–2002 and 2012–2013. *JAMA psychiatry.* 2015; 72:1–9.
- Kouri EM, Pope HG Jr. Abstinence symptoms during withdrawal from chronic marijuana use. *Exp Clin Psychopharmacol.* 2000; 8:483–492. [PubMed: 11127420]
- Krystal AD, Erman M, Zammi GK, Soubrane C, Roth T. Long-term efficacy and safety of zolpidem extended-release 12.5 mg, administered 3 to 7 nights per week for 24 weeks, in patients with chronic primary insomnia: a 6-month, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. *Sleep.* 2008; 31:79–90. [PubMed: 18220081]
- Lemberger L, Rubin A, Wolen R, DeSante K, Rowe H, Forney R, et al. Pharmacokinetics, metabolism and drug-abuse potential of nabilone. *Cancer Treat Rev.* 1982; 9:17–23. [PubMed: 6299550]

- Levin FR, Mariani JJ, Brooks DJ, Pavlicova M, Cheng W, Nunes EV. Dronabinol for the treatment of cannabis dependence: a randomized, double-blind, placebo-controlled trial. *Drug Alcohol Depend.* 2011; 116:142–150. [PubMed: 21310551]
- Lile JA, Kelly TH, Hays LR. Substitution profile of the cannabinoid agonist nabilone in human subjects discriminating 69-tetrahydrocannabinol. *Clin Neuropharmacol.* 2010; 33:235–242. [PubMed: 20838217]
- Lile JA, Kelly TH, Hays LR. Separate and combined effects of the cannabinoid agonists nabilone and 9-THC in humans discriminating 9-THC. *Drug Alcohol Depend.* 2011; 116:86–92. [PubMed: 21227600]
- Mendelson JH, Mello NK. Reinforcing properties of oral 9-tetrahydrocannabinol, smoked marijuana, and nabilone: Influence of previous marijuana use. *Psychopharmacology.* 1984; 83:351–356. [PubMed: 6149589]
- Randall S, Roehrs TA, Roth T. Efficacy of eight months of nightly zolpidem: a prospective placebo-controlled study. *Sleep.* 2012; 35:1551–1557. [PubMed: 23115404]
- Roehrs TA, Randall S, Harris E, Maan R, Roth T. Twelve months of nightly zolpidem does not lead to rebound insomnia or withdrawal symptoms: a prospective placebo-controlled study. *Journal of Psychopharmacology.* 2012; 26(8):1088–1095. [PubMed: 22004689]
- Rush CR, Baker RW, Wright K. Acute behavioral effects and abuse potential of trazodone, zolpidem and triazolam in humans. *Psychopharmacology.* 1999; 144:220–233. [PubMed: 10435388]
- Scharf MB, Rot T, Vogel GW, Walsh JK. A multicenter, placebo-controlled study evaluating zolpidem in the treatment of chronic insomnia. *J Clin Psychiatry.* 1994; 55:192–199. [PubMed: 8071269]
- Substance Abuse and Mental Health Services Administration, Center for Behavioral Health Statistics and Quality. National Admissions to Substance Abuse Treatment Services. BHSIS Series S-71, HHS Publication No. (SMA) 14-4850. Rockville, MD: 2014. Treatment Episode Data Set (TEDS): 2002–2012.
- Vandrey RG, Budney AJ, Hughes JR, Liguori A. A within-subject comparison of withdrawal symptoms during abstinence from cannabis, tobacco, and both substances. *Drug Alcohol Depend.* 2008; 92:48–54. [PubMed: 17643868]
- Vandrey R, Smith M, McCann UD, Budney AJ, Curran EM. Sleep disturbance and the effects of extended-release zolpidem during cannabis withdrawal. *Drug Alcohol Depend.* 2011; 117:38–44. [PubMed: 21296508]
- Vandrey R, Stitzer ML, Mintzer MZ, Huestis MA, Murray JA, Lee D. The dose effects of short-term dronabinol (oral THC) maintenance in daily cannabis users. *Drug Alcohol Depend.* 2013; 128:64–70. [PubMed: 22921474]
- Volkow ND, Baler RD, Compton WM, Weiss SR. Adverse health effects of marijuana use. *N Engl J Med.* 2014; 370:2219–2227. [PubMed: 24897085]
- Ware MA, Arnaud-Trempe S. The abuse potential of the synthetic cannabinoid nabilone. *Addiction.* 2010; 105:494–503. [PubMed: 20402993]
- World Health Organization. Management of substance abuse: Cannabis. (n.d.). Retrieved from http://www.who.int/substance_abuse/facts/cannabis/en/

Fig. 1.

Mean effects on mood under placebo conditions during experimenter administered active cannabis ('Active'), and during cannabis withdrawal ('Withdrawal') under placebo ('Placebo'), zolpidem alone ('Zolp'), and zolpidem plus nabilone ('Zolp+Nab') conditions. Number signs indicate significant differences between active cannabis administration and cannabis withdrawal under placebo conditions, and asterisks indicate differences between placebo and medication conditions during withdrawal. Significance determined at $\alpha = 0.05$. Error bars represent standard error of the mean

Fig. 2.

Mean effects on measures of sleep under placebo conditions during experimenter administered active cannabis ('Active'), and under placebo, zolpidem alone ('Zolp'), and zolpidem plus nabilone ('Zolp+Nab') conditions during withdrawal (Withdrawal'). Number signs indicate significant differences between active cannabis and cannabis withdrawal under placebo conditions, and asterisks indicate differences between placebo and medication conditions during withdrawal. Significance determined at $\alpha = 0.05$. Error bars represent standard error of the mean

Fig. 3. Mean effects on caloric intake and body weight under placebo conditions during experimenter administered active cannabis ('Active'), and during cannabis withdrawal ('Withdrawal') under placebo, zolpidem alone ('Zolp'), and zolpidem plus nabilone ('Zolp+Nab') conditions. Number signs indicate significant differences between active cannabis administration and withdrawal under placebo conditions, and asterisks indicate differences between placebo and medication conditions during withdrawal. Significance determined at $\alpha = 0.05$. Error bars represent standard error of the mean

Fig. 4.

Average number of cannabis cigarette inhalations self-administered on the first day of active cannabis availability (day 5) and on the subsequent three days of active cannabis availability (days 6–8) as a function of medication condition ('Zolp' = zolpidem alone, 'Zolp+Nab' = zolpidem in combination with nabilone). Asterisks represent significant differences from placebo. Significance determined at $\alpha = 0.05$. Error bars represent standard error of the mean

Table I**Study design**

Study Day	Cannabis Strength (THC)	Cannabis Administration	Medication Condition	Outcome(s) reported
1	5.6%	Experimenter	Placebo	W/D, subjective, cognitive
2	0.0%	Self	Placebo, Zolp, or Zolp/Nab	none *
3	0.0%	Self	Placebo, Zolp, or Zolp/Nab	W/D, subjective, cognitive
4	0.0%	Self	Placebo, Zolp, or Zolp/Nab	W/D, subjective, cognitive
5	5.6%	Self	Placebo, Zolp, or Zolp/Nab	Self-administration
6	5.6%	Self	Placebo, Zolp, or Zolp/Nab	Self-administration
7	5.6%	Self	Placebo, Zolp, or Zolp/Nab	Self-administration
8	5.6%	Self	Placebo, Zolp, or Zolp/Nab	Self-administration

Note. 'Self' = participants could purchase inhalations off of cannabis cigarettes at financial cost; \$9 for the first inhalation each day, and \$2 for each subsequent inhalation. 'Placebo' = placebo capsules at 0900, 01800, and 2300 hours, 'Zolp' = placebo capsules at 0900 and 1800, and zolpidem capsules (12.5mg) at 2300. 'Zolp/Nab' = Nabilone capsules (3mg) at 0900 and 1800, and zolpidem capsules (12.5mg) at 2300. 'W/D' = cannabis withdrawal measures (mood, sleep, food intake and body weight).

* We do not report data from Day 2 because cannabis withdrawal symptoms generally take >24 hours to appear.

Table II**Participant Demographics and Substance Use Characteristics**

Characteristic	n = 11
Demographics	
Age (years)	27.5 (6.1)
Sex (male/female)	11/0
Race (black/white)	10/11
Ethnicity (Hispanic/non-Hispanic)	1/11
Education (years)	11.2 (1.3)
Substance Use	
Cannabis	
Age of first use (years)	12.8 (2.4)
Years of regular use	12.0 (4.6)
Days used per week	6.8 (0.4)
Cannabis cigarettes/day	9.6 (4.6)
Tobacco	
Smoke tobacco cigarettes	9
Cigarettes/day among smokers	3.9 (2.3)
Alcohol	
Drink alcohol	5
Drinks per week among drinkers ^a	4.9 (3.9)

Note. Data are presented as means ($\pm$ SD) or as frequency.

Participants did not use any substances other than cannabis, alcohol, and tobacco.

^aIncludes only those reporting at least 1 drink per week.