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Antagonist-Elicited Cannabis Withdrawal in Humans

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Abstract

Cannabinoid CB1 receptor antagonists have potential therapeutic benefits, but antagonist-elicited cannabis withdrawal has not been reported in humans. Ten male daily cannabis smokers received 8 days of increasingly frequent 20-mg oral Δ^9 -tetrahydrocannabinol (THC) dosages (40–120 mg/d) around-the-clock to standardize cannabis dependence while residing on a closed research unit. On the ninth day, double-blind placebo or 20- (suggested therapeutic dose) or 40-mg oral rimonabant, a CB1-cannabinoid receptor antagonist, was administered. Cannabis withdrawal signs and symptoms were assessed before and for 23.5 hours after rimonabant. Rimonabant, THC, and 11-hydroxy-THC plasma concentrations were quantified by mass spectrometry. The first 6 subjects received 20-mg rimonabant (1 placebo); the remaining 4 subjects received 40-mg rimonabant (1 placebo). Fourteen subjects enrolled; 10 completed before premature termination because of withdrawal of rimonabant from clinical development. Three of 5 subjects in the 20-mg group, 1 of 3 in the 40-mg group, and none of 2 in the placebo group met the prespecified withdrawal criterion of 150% increase or higher in at least 3 visual analog scales for cannabis withdrawal symptoms within 3 hours of rimonabant dosing. There were no significant associations between visual analog scale, heart rate, or blood pressure changes and peak rimonabant plasma concentration, area-under-the-rimonabant-concentration-by-time curve (0–8 hours), or peak rimonabant/THC or rimonabant/(THC + 11-hydroxy-THC) plasma concentration ratios. In summary, prespecified criteria for antagonist-elicited cannabis withdrawal were not observed at the 20- or 40-mg rimonabant doses. These data do not preclude antagonist-elicited withdrawal at higher rimonabant doses.

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Drs Bonnet and Ortemann-Renon work for the study sponsor, Sanofi-Aventis. The other authors are NIDA or Maryland Psychiatric Research Center scientists and have no conflicts to declare. The sponsor contributed to study design and data management but played no role in data analysis or the decision to submit the article for publication. The NIDA investigators collected all data; NIDA and Maryland Psychiatric Research Center investigators prepared the article. The sponsor controlled the rimonabant allocation schedule and reviewed the article.

AUTHOR DISCLOSURE INFORMATION

Drs. Ortemann-Renon and Bonnet are employees of Sanofi-Aventis Recherche. The other authors declare no conflicts of interest.

Keywords

antagonist; cannabis; marijuana; rimonabant; withdrawal

The endogenous cannabinoid (endocannabinoid) system, comprising cannabinoid receptors on neurons and other cell types and endogenous ligands for these receptors, modulates a variety of important physiological functions,^{1,2} including food and drug intake, body weight, fat metabolism, body temperature, blood pressure, and cognition.^{3–7} Animal and human studies indicated therapeutic potential for antagonists at the cannabinoid CB1 receptor.^{8–10} Several such antagonists were in advanced clinical development for the treatment of obesity, metabolic syndrome, and nicotine and alcohol dependence.^{11–15} One antagonist, rimonabant, was marketed in several dozen countries around the world for the treatment of obesity.

One potential limitation to widespread clinical use of CB1 antagonists might be elicitation of cannabis withdrawal. Cannabis is the most widely used illicit psychoactive substance, with up to 190 million users worldwide.¹⁶ An estimated 10% of cannabis smokers are dependent. Ingestion of a receptor antagonist by substance-tolerant individuals can elicit a substance-specific withdrawal syndrome, as occurs with opioids after naloxone, a mu-opioid receptor antagonist, or benzodiazepines after flumazenil, a benzodiazepine receptor antagonist. Antagonist-elicited withdrawal is typically qualitatively similar to abstinence-elicited (ie, spontaneous) withdrawal but has a more rapid onset and greater intensity of symptoms.

In cannabinoid-tolerant rodents and dogs, administration of rimonabant elicited a cannabis withdrawal syndrome, with quicker onset and greater intensity than after spontaneous cannabis withdrawal.¹⁷ Rimonabant-elicited cannabis withdrawal has recently been demonstrated in rhesus monkeys made dependent with chronic subcutaneous Δ^9 -tetrahydrocannabinol (THC) (1 mg/kg per 12 hours).¹⁸ However, antagonist-elicited cannabis withdrawal has not been reported in humans.

We present here data from the first human study of antagonist-elicited cannabis withdrawal, after administration of the selective CB1 antagonist rimonabant to cannabis-tolerant individuals.

MATERIALS AND METHODS

Subjects

Adult (18–45 years old), non—treatment-seeking cannabis smokers recruited from the community by advertising and word-of-mouth met the following inclusion criteria: cannabis use for at least 1 year, with daily use for the 3 months before unit admission; a urine specimen positive for cannabinoids in the 30 days before study enrollment; sitting blood pressure (BP) of 140/90 mm Hg or less and heart rate of 100 beats per minute or less; and estimated IQ of 85 or higher (Wechsler Abbreviated Scale of Intelligence). Applicants were excluded for any of the following: past or present clinically significant medical condition that might interfere with safe study participation; current physical dependence on any substance other than cannabis, nicotine, or caffeine; 6 or more standard alcohol drinks per day 4 or more times per week in the month before study entry; history of a clinically significant adverse event associated with cannabis intoxication or withdrawal; history of epileptic seizures or head trauma with loss of consciousness greater than 3 minutes; history of psychosis or any current *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*, Axis I disorder (other than cannabis, caffeine, or nicotine dependence or simple phobia); Attention Deficit/Hyperactivity Disorder Screening Rating Scale score of 24 or

higher on either the A or B subscale. Women could not be pregnant or breast-feeding. Women with childbearing potential had to use an intrauterine device or hormonal contraceptive and have a negative serum pregnancy test.

Applicants underwent a comprehensive medical and psychological evaluation, including medical history and physical examination, psychiatric and drug use history, clinical laboratory tests, 12-lead electrocardiography (ECG) with 3-minute rhythm strip, tuberculosis skin test, structured psychiatric diagnostic interview, and psychological testing. Qualified applicants gave written informed consent when not acutely intoxicated or in withdrawal and were compensated for their time and inconvenience. The institutional review boards of the National Institute on Drug Abuse (NIDA) Intramural Research Program, the University of Maryland School of Medicine, and the Maryland Department of Health and Mental Hygiene approved the study.

Study Design

This study was designed to determine the lowest dose of CB1 receptor antagonist that would reliably elicit withdrawal in cannabis-dependent individuals. Subjects were admitted in the evening to either of 2 closed clinical research units within approximately 24 hours of last cannabis use. Starting the next afternoon, after collection of all baseline measures, they received escalating daily doses of oral synthetic THC (dronabinol) for 8 days to maintain and standardize cannabis tolerance and dependence. On the morning of the ninth day, immediately after the last oral dronabinol dose, they were randomly assigned to receive a double-blind single oral dose of rimonabant or placebo. Subjects were discharged from the research unit on the 10th day, 24 hours after rimonabant or placebo dosing. Psychological and physiological measures of cannabis intoxication and withdrawal, safety measures such as vital signs, ECG, and adverse effects checklists, and biologic specimens for assay of cannabinoids were obtained periodically throughout the 10 days on the research unit.

Subjects were randomized in blocks of six. Within each block, 5 subjects received rimonabant and 1 received placebo. The first medication block was completed with a 20-mg oral rimonabant dose. Rimonabant dosing started at 20 mg because this was the marketed dose of rimonabant for treatment of obesity. The protocol was terminated prematurely during the second (40-mg) medication block. Three subjects had received 40-mg rimonabant and 1 received placebo when the rimonabant manufacturer stopped worldwide clinical trials, ending clinical development efforts.¹⁹

Research Setting

Subjects were housed on either the Behavioral Pharmacology Research Unit at the Johns Hopkins Bayview Medical Center, Baltimore, Md, or at the Maryland Psychiatric Research Center, Catonsville, Md. Behavioral Pharmacology Research Unit and Maryland Psychiatric Research Center are closed units with 24-hour staffing, ensuring that subjects had no access to drugs except those provided in the study.

Medication

Subjects received open-label oral synthetic THC (dronabinol) on days 2 to 9, in the form of 20-mg capsules of Marino® (Unimed, Marietta, Ga), to maintain and standardize cannabis dependence and tolerance across subjects, while minimizing short-term adverse effects. Dronabinol was given in increasing total daily dosage, but always in 20-mg individual doses, with increasing frequency every 4 to 6 hours around the clock. Dronabinol doses were given twice on day 2 (40-mg total), 5 times on days 3 to 6 (100-mg total), 6 times on days 7 to 8 (120-mg total), and twice (40-mg total) on day 9, before rimonabant on day 9. A

dronabinol dose was held if the subject had an abnormal ECG, BP greater than 140/90 mm Hg, or heart rate more than 100 beats per minute.

Rimonabant and matching placebo were provided by Sanofi-Aventis (Malvern, Pa). Rimonabant or placebo was given at 9:30 A.M. on day 9, immediately after the second (and last) dronabinol dose of the day. To reduce subjects' expectancy of withdrawal, single-blind rimonabant placebo was given on days 3 (8 A.M.), 5 (10 A.M.), and 7 (10 A.M.) immediately after a dronabinol dose.

Pharmacodynamic Assessments

Common signs and symptoms of cannabis intoxication and withdrawal, drawn from the published literature,^{20–24} were assessed periodically, starting the evening of admission (day 1), with 2 batteries of self-report items. The batteries combined items typical of intoxication and withdrawal to minimize cueing of subjects. The short battery (subjective effects scale, taking approximately 3.5 minutes to complete) was administered twice daily (10 A.M., 8 P.M.), plus every 30 minutes for 3 hours after administration of placebo rimonabant on days 3, 5, and 7; every 30 minutes for 7 hours after administration of rimonabant or placebo on day 9; and 8 A.M. on day 10. This short battery consisted of eleven 100-mm visual analog scales (VASs) and thirteen 5-point Likert scale items (none, slight, mild, moderate, severe). The VAS assessed good drug effect, high, stoned, stimulated, sedated, anxious, depressed, irritable, restless, craving for marijuana, and angry/aggressive. Visual analog scales were anchored on the left with “not at all” and on the right with “most ever.” The score for each VAS was the number of mm the subject marked to the right of the left anchor point. The Likert scales assessed the following: difficulty concentrating, altered sense of time, slowed or slurred speech, body feels sluggish or heavy, feel hungry, feel thirsty, shakiness/tremulousness, nausea, headache, palpitations, upset stomach, dizzy, and dry mouth or throat.

The longer battery, administered twice daily at approximately 10 A.M. and 8 P.M. and taking approximately 20 minutes, consisted of the SCL-90R²⁵ and a cannabis checklist of twentyfour 5-point Likert scale items. The Likert scales assessed: shaky/tremulous, decreased appetite, diarrhea/loose stools, nauseous, sweating, hiccups, decreased sexual arousal, stuffy nose, strange or vivid dreams, hot flashes, chills, increased appetite, fatigue/tiredness, yawning, increased sexual arousal, muscle aches or pains, heaviness in limbs, noises seem louder than usual, talkative, stomach pain, mellow, clumsy, muscle spasms, and blurred vision. As part of the longer battery, the St. Mary's Hospital Sleep Questionnaire²⁶ was given every morning and the 12-item Marijuana Craving Questionnaire²⁷ every evening.

Safety Assessments

Vital signs were checked thrice daily (generally 8 A.M., 4 P.M., 11 P.M.) and every 2 hours for 8 hours after the first dose of dronabinol on day 2; every 30 minutes for 3 hours, then every hour for the next 5 hours after the placebo rimonabant dose on days 3, 5, and 7 (to preserve the single blind); and every 30 minutes for 3 hours, then every hour for the next 8 hours after rimonabant or placebo on day 9. A 12-lead ECG with 3-minute rhythm strip was done on day 2 (8 A.M.), then twice daily (7:00–8:30 A.M., 7 P.M.) on days 3, 5, 7, and 9. Continuous peripheral monitoring of heart rate, heart rhythm (2-lead ECG), blood pressure, and pulse oximetry was done for 3 hours (or until vital signs returned to within 20% of baseline values) after a placebo rimonabant or rimonabant dose on days 3, 5, 7, and 9.

Before unit discharge on day 10, vital signs, mental status, and motor coordination were evaluated to establish that it was safe for subjects to return home.

Pharmacokinetic Assessments

Peripheral blood was collected periodically through an indwelling venous catheter for the assay of THC and metabolites and rimonabant. Specimens were collected in heparinized tubes, stored on ice no more than 2 hours before centrifugation, and separated plasma stored frozen at -20°C (rimonabant specimens) or refrigerated at 4°C (cannabinoid specimens) until analysis. Specimens were assayed for THC, its psychoactive metabolite, 11-hydroxy-THC (11-OH-THC), and inactive metabolite 11-nor-9-carboxy-THC (THCCOOH) by 2-dimensional gas chromatography–mass spectrometry with cryofocusing, with a limit of quantification of 0.25 ng/mL for THC and THCCOOH and 0.5 ng/mL for 11-OH-THC. Specimens were collected the evening of admission and thrice daily (8:00 or 10:00 A.M., 8:00 or 8:30 P.M., and 10:00 or 10:30 P.M.) on days 2 to 9, plus at 1, 1.5, 2, 2.5, 3.5, 4.5, 5.5, 7.5, 10.5, 12.5, and 22.5 hours after the last dronabinol administration on day 9.

Peripheral venous blood for assay of rimonabant was collected 1.5 hours before and 1, 1.5, 2, 2.5, 3.5, 4.5, 5.5, 7.5, 10.5, 12.5, and 22.5 hours after rimonabant administration on day 9. Rimonabant was quantified in specimens by a validated liquid chromatography–tandem mass spectrometry method with a 1.0-ng/mL limit of quantification. Intra-assay bias was -7.4% to 6.0% , and intra-assay imprecision (%CV) was 1.8% to 5.7%. The interassay bias ranged from -1.8% to 1.5% , with interassay imprecision of 2.5% to 10.1% (Sanofi-Aventis). The internal standard was $[^2\text{H}]_{10}$ –rimonabant and linearity extended from 1 to 200 ng/mL. Rimonabant was extracted from plasma on 96-well Varian SPEC PLUS C19AR solid-phase extraction plates (Agilent Technologies, Santa Clara, Calif) before injection onto a Phenomenex IB-SIL 5 C8 BD (50×4.6 mm; $5\ \mu\text{m}$) column. The mobile phase was (A) 2 mM ammonium acetate/0.2% formic acid and (B) 2 mM ammonium acetate/0.2% formic acid acetonitrile/water (98/2, vol/vol) at 0.5 mL/min. The initial gradient was 60% A/40% B for 3 minutes, increasing to 100% B by 5 minutes and returning to 60% A at 5.1 minutes. A Finnigan TSQ 7000 triple quadrupole mass spectrometer (Thermo/Finnigan Ltd, Waltham, Mass) monitored precursor ions m/z 463 and m/z 473 for rimonabant and $[^2\text{H}]_{10}$ –rimonabant, respectively, and the product ion m/z 363 for both analytes.

Statistical Analysis

The original study design called for 20-, 40-, 60-, and 80-mg doses of rimonabant in each successive block of 6 subjects until robust, reliable cannabis withdrawal was observed in all subjects treated with a given dose. Blinded safety reviews after each rimonabant dose level were conducted before proceeding to the next dose. Reliable withdrawal was defined as all 5 subjects receiving rimonabant (the sixth received placebo) in the block showing at least 150% (2.5-fold) increases (or 1.5-point increase when baseline value was 0) over prrimonabant baseline in at least 3 of 6 primary VAS items: “anxious,” “depressed,” “irritable,” “restless,” “angry-aggressive,” and “craving for marijuana” within 3 hours after rimonabant dosing. This criterion for withdrawal was based on published human experimental studies of spontaneous cannabis withdrawal.^{20,29} χ^2 tests were used to compare the proportion of subjects receiving rimonabant or placebo who showed significant postrimonabant change on any of the 6 primary VAS items.

The study was prematurely terminated when rimonabant was withdrawn from clinical development by the manufacturer, Sanofi-Aventis, after marketing authorization in the European Union was suspended because of increased rates of depression and suicidality in outpatients. Termination occurred after only 10 subjects completed, of whom only 8 received rimonabant. Therefore, to supplement this prespecified analysis, we performed 4 additional sets of post hoc analyses using data from all 10 completing subjects (8 rimonabant, 2 placebo). First, a within-subjects comparison of the maximum change from baseline for the 6 primary VAS items on day 7 (single-blind rimonabant placebo) and day 9

(double-blind active rimonabant) was performed for the 8 subjects who received active rimonabant on day 9. This comparison was done in 2 ways: (1) as a non-parametric test for differences in average maximum changes, using Cochran-Mantel-Haenszel statistics, and (2) as a comparison of the frequency distribution of maximum changes, using the χ^2 test. Second, a fixed-effects multiple regression model (SAS Proc Mixed, SAS Institute, Cary, NC) evaluated the association, for all 10 subjects, between peak rimonabant plasma concentration (placebo rimonabant = 0) and peak change from primonabant baseline in each of the 6 primary VAS items, heart rate, and systolic and diastolic blood pressure. The same procedure evaluated the association between rimonabant/THC or rimonabant/(THC + 11-OH-THC) plasma concentration ratios or area-under-the-rimonabant-concentration-by-time curve (0–8 hours) (AUC_{0-8}) and these withdrawal measures. Third, repeated-measure analysis of covariance (SAS Proc Mixed) was used to evaluate the trend over time of each primary VAS item and cardiovascular measure, with baseline (primonabant or preplacebo) value as a covariate. A spatial power covariance structure with correlation decreasing with increasing time was used to account for the correlation between repeated measures collected over unequally spaced time intervals. Fourth, nonpara-metric Wilcoxon rank tests (SAS NPAR1WAY procedure) were used to compare the peak change from primonabant baseline, and the time to peak change, between rimonabant and placebo groups for each primary VAS item and cardiovascular measure.

A power analysis based on a between-subjects, placebo-controlled design, assuming use of a rimonabant dose identified by the prespecified criteria as eliciting cannabis withdrawal, yielded a power of at least 0.8 to detect cannabis withdrawal, assuming 18 subjects received rimonabant and 18 received placebo, with a withdrawal effect size of 0.7 (based on means and SDs of VAS changes during spontaneous withdrawal in human experimental studies²⁹ and a 2-tailed $\alpha = 0.05$). Thus, the post hoc analyses, which included only 10 subjects (8 rimonabant, 2 placebo), were underpowered to detect cannabis withdrawal.

Comparisons of pharmacokinetic parameters between the 2 rimonabant dose groups used independent *t* tests. Correlations between rimonabant dose and pharmacokinetic parameters were analyzed with Pearson *r*.

All statistical tests used 2-tailed $\alpha = 0.05$. Pharmacodynamic analyses used SAS statistical software version 9.1 (SAS Institute, Cary, NC). Pharmacokinetic analyses used SPSS statistical software version 15.0 (SPSS, Inc, Chicago, Ill).

RESULTS

Subject Characteristics

A total of 596 individuals were screened for the study, of whom 14 subjects (all men) were considered eligible and offered enrollment. Most unsuccessful subjects did not keep their screening appointment (63%). Other reasons for applicant exclusion included women not using acceptable contraception (9%), abnormalities on medical screening (9%), IQ less than 85 (8%), and substance use outside protocol eligibility limits (5%). All 14 eligible subjects enrolled and 10 completed the study. Of the remaining 4 subjects, 1 subject withdrew for personal reasons before receiving rimonabant, 2 subjects were discharged because of adverse events before receiving rimonabant (1 subject because of psychological reactions to dronabinol, 1 subject because of premature ventricular contractions), and 1 subject had not yet been admitted when the study was terminated.

The 13 subjects who received study medication had the following sociodemographic characteristics: mean (SD) age, 24.6 (3.7) years; 10 African-American, 2 white, 1 other; 1 Hispanic; body mass index, 26.0 (5.0) kg/m²; years of education, 12.9 (1.7); and IQ, 100.3

(10.9). Subjects had smoked cannabis for 10.6 (3.8) years, starting at age 14.0 (2.4) years. All smoked cannabis at least 500 times, with 5 reporting more than 10,000 episodes. All but 1 subject smoked cannabis plus blunts and/or hashish (1 smoked only blunts). Seven subjects smoked cannabis the day of admission, 5 subjects smoked the day before, and 1 subject smoked 2 days before. Nine subjects were current cigarette smokers and 3 subjects were past smokers. All subjects were lifetime alcohol drinkers but 2 subjects had not drunk in the 2 weeks before study screening. Lifetime use of other illegal drugs was limited: 7 subjects ingested opiates other than heroin and 4 subjects used intranasal cocaine. No subject took other illegal drugs in the 2 weeks before study screening.

Pharmacokinetic Data

There were no significant differences between the 20- and 40-mg rimonabant dose groups in mean peak rimonabant plasma concentration ($C_{\max}$) (195.0 [83.4] vs 288.0 [100.6] ng/mL, respectively, $t = 1.42$, $df = 6$, $P = 0.21$), time to peak concentration ($T_{\max}$) (1.7 [1.0] vs 1.3 [0.3] hours, $t = 0.57$, $df = 6$, $P = 0.59$), area-under-the-time-by-plasma-concentration curve (AUC) (1087.0 [351.6] vs 1490.0 [538.6] h/ng per milliliter, $t = 1.30$, $df = 6$, $P = 0.24$), or half-life (17.4 [6.4] vs 8.8 [4.5] hours, $t = 2.03$, $df = 6$, $P = 0.09$). Because there were no significant dose differences in rimonabant pharmacokinetic variables, data were combined from all 8 subjects receiving rimonabant, yielding $C_{\max} = 229.9$ (95.8) ng/mL, $T_{\max} = 1.6$ (0.8) hours, AUC = 1238.1 (443.9) h/ng per milliliter, and half-life = 14.2 (7.0) hours. There were no significant correlations between rimonabant dose (mg/kg body weight) and any of these pharmacokinetic parameters: $r = 0.38$, $P = 0.35$ for $C_{\max}$, $r = 0.17$, $P = 0.69$ for $T_{\max}$, $r = 0.60$, $P = 0.12$ for AUC, and $r = 0.19$, $P = 0.66$ for half-life.

Cannabinoid plasma pharmacokinetics were previously described for the first 6 subjects in this study.³⁰ All 10 subjects had variable concentrations because of erratic oral absorption and enterohepatic circulation (Table 1). At the time of rimonabant administration (9:30 A.M. on day 9), median THC and 11-OH-THC concentrations were 6.7 ng/mL (range, 4.6–14.2 ng/mL) and 9.5 ng/mL (range, 5.4–20.4 ng/mL), respectively. Median THC and 11-OH-THC concentrations generally peaked approximately 1.5 hours after rimonabant (or placebo) administration at 14.3 and 16.5 ng/mL, respectively. At 22.5 hours after the final dronabinol (and rimonabant) dose, median THC and 11-OH-THC plasma concentrations were 3.2 ng/mL (range, 1.2–5.2 ng/mL) and 2.2 ng/mL (range, 0–6.3 ng/mL), respectively.

Cannabis Withdrawal

The prespecified criterion for cannabis withdrawal was not met in the 20- or 40-mg rimonabant groups (two of three 40-mg subjects did not achieve withdrawal criterion) (Table 2). Three of 5 subjects in the 20-mg rimonabant group, 1 of 3 subjects in the 40-mg rimonabant group, and none of 2 subjects in the placebo group met the prespecified withdrawal criterion, that is, at least 150% increase in at least 3 of the 6 primary VAS items. Individual VAS items showed 150% increases as follows: restless, 6 subjects (four 20 mg and two 40 mg); irritable, 3 subjects (all 20 mg); depressed, 3 subjects (all 20 mg); angry, 3 subjects (two 20 mg and one 40 mg); craving, 3 subjects (two 20 mg and one 40 mg [and 1 of 2 placebo subjects]); and anxious, 2 subjects (one 20 mg and one 40 mg). There was no significant medication group difference in proportion of subjects with increased VAS score for any VAS item (data not shown). There was no significant change in SCL-90 depression subscale score on day 9, that is, before or after rimonabant or during placebo dosing (data not shown). Only 2 subjects had an increase in this subscale score: 1 received placebo and 1 received 20 mg of rimonabant.

The 4 sets of post hoc analyses did not show any evidence of significant cannabis withdrawal. There was no significant difference in mean maximum change from baseline

between the placebo rimonabant day (day 7) and the active rimonabant day (day 9) for any of the 6 primary VAS items and there were no significant differences in the frequency distributions of the maximum change scores (data not shown). There was no significant association between peak rimonabant plasma concentration, rimonabant AUC_{0–8h}, nor rimonabant/THC or rimonabant/ (THC + 11-OH-THC) plasma concentration ratios for any of the 6 primary VAS items (data not shown) or for peak change from prerimonabant baseline in heart rate and systolic or diastolic blood pressure (data not shown). There was no significant effect of rimonabant on the postbaseline time course (continuous variable) or the peak postbaseline change (categorical variable) of any withdrawal measure (data not shown). Diastolic blood pressure achieved its peak increase significantly sooner after rimonabant (median, 5 hours) than after placebo (median, 22.5 hours) ($z = 1.98$, with 0.5 continuity correction, $P = 0.05$) (Table 3). There was no significant difference in time to peak change for any other withdrawal variable (data not shown).

No subject reported symptoms suggestive of cannabis withdrawal during initiation and escalation of dronabinol dosing (days 1–6).

Safety and Tolerability

Both the single dose of rimonabant and the long-term oral dronabinol were well tolerated by subjects. The blinded safety review after completion of the 20-mg dose block showed no reason not to proceed to the next dose block (40 mg). Only 2 adverse events (both in the same subject) were considered possibly related to rimonabant. This subject reported transient (lasting 1 hour) mild intensification of preexisting intermittent sadness, beginning 5.5 hours after receiving 20 mg of rimonabant, and mild nausea lasting 30 minutes beginning 23 hours after dosing (also considered possibly related to dronabinol). Both adverse events resolved without treatment or sequelae. No ECG changes or abnormalities in vital signs, oxygen saturation, or continuous cardiac monitoring occurred after rimonabant administration.

Two subjects were discontinued from the study because of adverse events considered probably due to dronabinol (and before receiving rimonabant). One subject retrospectively reported 30 minutes of depressed mood, suicidal thoughts, and paranoia occurring on the night of day 3, that is, after receiving 6 doses of dronabinol. Dronabinol was discontinued the next day, and he was discharged in good condition. A second subject had 2 hours of occasional premature ventricular contractions on the morning of day 5, which did not recur after dronabinol was discontinued. Other mild and self-limited adverse events possibly related to dronabinol included nausea and vomiting (2 subjects), abdominal pain/discomfort (2 subjects), dry mouth (2 subjects), diarrhea (2 subjects), and euphoria (1 subject). One subject with diarrhea had 2 dronabinol doses withheld on the third dosing day.

There was no apparent association between plasma THC concentration and occurrence of the 3 psychological adverse events (increased sadness, depression with suicidal ideation, euphoria) possibly due to dronabinol. Plasma THC concentrations closest to the onset of the event were 9.6, 23.6, and 47.4 ng/mL, respectively. Mean (SD) concentrations at the comparable time point in subjects without a psychological adverse event were 19.0 (5.6), 24.1 (13.8), and 19.2 (7.0) ng/mL, respectively. The small sample size precluded formal statistical testing.

DISCUSSION

This study was designed to determine the lowest rimonabant dose that reliably produced antagonist-elicited cannabis withdrawal. The first dose evaluated, 20 mg, produced only weak evidence of withdrawal and did not meet the prespecified withdrawal criteria. This 20-

mg dose was widely prescribed in Europe and elsewhere (largely for treatment of obesity and the metabolic syndrome) without apparently generating reports of adverse events due to cannabis withdrawal. This may be related to the plasma (and brain) rimonabant concentrations and CB1 receptor occupancy levels achieved by this dose.

The 20-mg dose in this study generated a peak plasma rimonabant concentration of 195 (83.4) ng/mL with a $T_{\max}$ at 1.7 (1.0) hours. These values are comparable to those reported in 8 healthy men after 21 daily doses of 20-mg rimonabant ($C_{\max} = 196$ [28.1] ng/mL, $T_{\max} = 2.0$ hours [range, 1.5–6 hours]).³¹ We previously reported mean peak rimonabant concentrations of 478.6 ng/mL after a single 90-mg dose and 307.8 and 334.6 ng/mL after 8 or 15 days, respectively, of daily 40-mg doses.³² These higher concentrations were needed to significantly attenuate the short-term effects of a smoked cannabis cigarette. Similar (or greater) concentrations would presumably be needed for rimonabant to displace THC from CB1 receptors to elicit withdrawal.

Higher rimonabant doses could not be evaluated as planned because rimonabant was withdrawn from worldwide clinical development, forcing premature termination of this study. Only 3 of the planned 5 subjects received 40 mg of rimonabant, not meeting the prespecified criteria and providing weak evidence of withdrawal. This dose (0.41–0.45 mg/kg) generated a rimonabant $C_{\max}$ of 288 (100.6) ng/mL and $T_{\max}$ of 1.3 (0.3) hours. These values are comparable to those reported in 8 healthy men after 21 daily doses of 40 mg of rimonabant ($C_{\max} = 326$ [92.5], $T_{\max} = 3.0$ hours [range, 2–6 hours])³¹ but still lower than the concentrations associated with attenuation of acute CB1 receptor agonist effects in humans.³²

We are not aware of any human brain data on rimonabant concentrations or CB1 receptor occupancy. In Wistar rats, 0.1 mg/kg oral rimonabant occupied approximately one quarter of frontal cortex CB1 receptors 1 hour after dosing, as measured by competition with intravenously administered radiolabeled rimonabant.³³ The dose 1 mg/kg occupied approximately half of receptors 1 and 3 hours after dosing but did not immediately reduce food intake. The dose 3 mg/kg occupied approximately two thirds of receptors and did significantly reduce food intake. In Swiss mice, 1 mg/kg oral rimonabant occupied approximately one quarter of brain (minus cerebellum) CB1 receptors after 1 hour and approximately one fifth after 3 hours, as measured by ex vivo displacement of radiolabeled CB1 agonist.³⁴ In a separate mouse study, this same oral dose after 1 and 2 hours blocked approximately 50% of the hypothermic effect of a different CB1 agonist.³⁵ Extrapolating from rodents to humans, these findings suggest that a rimonabant dose at least triple the 20 mg (0.20–0.37 mg/kg) administered in this study might be required to elicit withdrawal.

Our findings suggest that the clinically relevant 20-mg oral rimonabant dose would not have posed a significant risk of eliciting cannabis withdrawal. However, we do not interpret our findings as suggesting that robust antagonist-elicited withdrawal does not exist in humans. Rather, we believe that our failure to demonstrate this phenomenon in the present study was owing to the study's premature termination and resulting inability to adequately evaluate higher rimonabant doses. This interpretation is supported by the fact that we did observe some evidence of cannabis withdrawal. Three of 5 subjects receiving 20 mg of rimonabant and 1 of 3 subjects receiving 40 mg of rimonabant, compared with none of the 2 subjects receiving placebo, met the prespecified withdrawal criterion of at least a 150% increase in at least 3 of the 6 primary VAS items. Five of the 6 VAS items showed 150% or greater increases in at least 3 of the 8 subjects receiving rimonabant, whereas only 1 VAS item showed such an increase in either placebo subject. Diastolic blood pressure achieved its peak increase significantly sooner after rimonabant than after placebo. Had the study been

able to continue as planned to higher rimonabant doses, we believe that robust withdrawal would have been observed.

The failure to observe reliable antagonist-elicited withdrawal was unlikely due to other methodological limitations. Subjects took rimonabant under direct staff observation. Substantial rimonabant plasma concentrations were achieved, peaking 1.6 hours after dosing, well within the 24-hour interval of periodic withdrawal assessments. The prespecified primary VAS items were based on previous studies showing them as significant symptoms during both self-reported and experimentally observed cannabis withdrawal in humans.^{20,21} Thus, our failure to observe reliable antagonist-elicited withdrawal does not cast doubt on the validity of a human cannabis withdrawal syndrome (CWS). The existence of CWS is now widely accepted²⁰ and CWS is included in the proposed fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (www.dsm5.org).

In conclusion, our results, although derived from a small sample size and only 2 doses of rimonabant, suggest that CB1 receptor antagonists with pharmacological profiles similar to rimonabant, should they become clinically available in the future, might be used at therapeutic doses without substantial risk of eliciting clinically significant withdrawal in cannabis-tolerant patients. Future human experimental studies of antagonist-elicited cannabis withdrawal are warranted to more fully evaluate this phenomenon and the dose ranges over which it occurs.

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Plasma Concentrations of THC, 11-OH-THC, and Rimonabant on the Day of Oral Rimonabant Administration in 10 Daily Cannabis Smokers

TABLE 1

ID		Analyte, ng/mL	Time Point													
			Day 9												Day 10	
			9:30 A.M.	10:30 A.M.	11:00 A.M.	11:30 A.M.	Noon	1:00 P.M.	2:00 P.M.	3:00 P.M.	5:00 P.M.	8:00 P.M.	10:00 P.M.	8:00 A.M.		
1	THC	7.8	5.3	5.2	5.0	4.2	4.5	4.2	3.8	4.2	9.1	4.8	2.6			
	11-OH-THC	11.1	7.0	6.1	5.4	4.6	5.1	4.8	4.9	4.1	8.1	4.3	1.6			
	Rimonabant	<LOQ	30.7	63.0	89.5	101.0	102.0	90.5	76.2	49.6	70.0	49.1	19.2			
2	THC	14.2	42.4	31.3	18.8	17.8	10.9	8.4	7.7	7.6	6.0	7.6	5.2			
	11-OH-THC	20.4	37.8	36.7	29.2	23.8	17.8	14.9	14.6	13.0	10.6	9.7	6.3			
	Rimonabant	<LOQ	157.0	264.0	181.0	143.0	140.0	NR	67.0	37.2	28.8	23.6	17.6			
3	THC	7.7	6.0	5.6	6.3	12.8	11.1	8.5	6.5	8.2	5.8	5.4	4.3			
	11-OH-THC	7.3	5.8	5.7	5.8	11.6	9.9	7.5	7.0	6.6	4.4	4.2	2.2			
	Rimonabant	<LOQ	126.0	98.8	71.8	50.1	46.9	33.6	33.2	17.6	12.8	10.7	8.0			
4	THC	10.8	12.8	12.3	12.1	9.7	7.6	5.2	5.5	4.7	4.9	4.2	3.3			
	11-OH-THC	15.3	16.7	18.9	18.1	16.8	14.1	11.1	10.2	7.8	7.2	5.3	3.4			
	Rimonabant	<LOQ	<LOQ	<LOQ	<OQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ			
5	THC	6.5	28.4	20.3	16.1	11.8	9.8	8.6	6.4	6.7	5.8	4.9	5.0			
	11-OH-THC	9.9	27.4	24.3	18.8	15.4	13.8	11.4	8.6	8.1	6.2	4.6	2.8			
	Rimonabant	<LOQ	187.0	190.0	172.0	120.0	90.5	70.0	54.7	40.1	34.3	27.6	22.6			
6	THC	5.9	16.0	16.3	16.5	11.4	6.8	5.9	4.5	4.0	3.4	3.5	2.4			
	11-OH-THC	9.0	17.7	15.6	13.7	11.1	10.0	7.8	6.0	4.6	2.8	2.6	1.8			
	Rimonabant	<LOQ	293.0	248.0	168.0	131.0	95.3	93.4	61.4	54.2	39.6	44.8	35.6			
10	THC	4.6	6.0	7.1	7.0	5.8	7.0	5.2	5.0	5.2	4.0	4.0	3.1			
	11-OH-THC	5.4	5.6	9.0	7.6	8.2	8.4	5.5	5.2	4.8	4.3	3.3	2.1			
	Rimonabant	<LOQ	185.0	160.0	143.0	115.0	109.0	72.2	67.7	49.9	30.7	23.5	17.3			
11	THC	5.4	6.3	17.3	13.8	7.9	5.3	4.6	4.3	3.6	3.5	2.6	3.7			
	11-OH-THC	10.7	13.2	23.3	26.2	15.5	10.7	8.0	7.0	5.8	5.2	4.5	3.0			
	Rimonabant	<LOQ	316.0	386.0	378.0	305.0	233.0	144.0	111.0	79.1	49.0	45.0	26.9			
12	THC	6.0	4.8	5.0	7.8	8.2	6.4	5.7	6.5	4.2	1.6	1.5	1.3			
	11-OH-THC	7.0	5.7	5.8	7.7	6.9	6.2	6.2	6.6	4.2	1.4	1.1	1.1			

ID		Time Point											
		Day 9						Day 10					
		Analyte, ng/mL	9:30 A.M.	10:30 A.M.	11:00 A.M.	11:30 A.M.	Noon	1:00 P.M.	2:00 P.M.	3:00 P.M.	5:00 P.M.	8:00 P.M.	8:00 A.M.
13	Rimonabant	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
	THC	6.8	11.6	19.8	18.6	9.1	5.2	4.0	3.7	3.2	1.4	1.7	1.2
	11-OH-THC	8.2	13.4	17.5	13.3	9.0	7.5	5.8	4.9	3.9	1.5	1.4	0.0
	Rimonabant	<LOQ	198.0	293.0	187.0	156.0	137.0	78.3	57.2	36.6	28.0	30.3	29.3

Rimonabant 20 mg (subjects 1, 2, 3, 5, and 6), 40 mg (subjects 10, 11, and 13), or placebo (subjects 4 and 12) was given double-blind at 9:30 A.M. on day 9 after 8 days of escalating doses of oral dronabinol (40–120 mg/d). Peripheral venous blood samples were collected at the indicated time points. See text for methodological details.

LOQ indicates limit of quantification.

TABLE 2

Cannabis Withdrawal Response to Oral Rimonabant in 10 Daily Cannabis Smokers

ID	VAS Measure	Time Point																	
		Day 9									Day 10								
		8:00 A.M.	9:30 A.M.	10:00 A.M.	10:30 A.M.	11:00 A.M.	11:30 A.M.	Noon	12:30 P.M.	1:00 P.M.	1:30 P.M.	2:00 P.M.	2:30 P.M.	3:00 P.M.	3:30 P.M.	4:00 P.M.	4:30 P.M.	8:00 P.M.	8:00 A.M.
1	Anxious	0	0	1	1	0	0	0	1	1	—	—	—	0	0	0	0	0	0
	Depressed	0	0	0	0	0	1	0	1	0	—	—	—	0	58	39	12	27	0
	Irritable	0	1	1	0	0	0	0	1	0	—	—	—	0	0	25	0	11	0
	Restless	0	1	1	1	0	0	1	1	0	—	—	—	0	0	0	0	0	0
	Marijuana craving	18	1	1	1	0	0	1	2	0	—	—	—	0	0	41	32	0	41
2	Angry-aggressive	0	2	1	1	0	1	1	2	1	—	—	—	0	0	1	0	1	1
	Total VAS score	18	5	5	4	0	2	3	8	2	—	—	—	0	58	106	44	39	43
	Anxious	1	1	0	1	0	0	1	—	0	0	1	0	0	1	1	0	1	0
	Depressed	1	2	1	1	0	1	0	—	0	0	1	0	0	1	1	1	1	1
	Irritable	0	0	1	0	0	1	1	—	0	1	1	1	1	0	0	0	2	0
3	Restless	1	0	0	1	0	1	0	—	0	0	0	0	0	1	0	2	0	1
	Marijuana craving	1	1	2	1	0	1	0	—	1	0	0	0	1	1	1	0	1	1
	Angry-aggressive	1	2	1	1	1	2	0	—	1	1	0	0	3	0	1	1	1	1
	Total VAS score	5	6	5	5	1	6	2	—	2	2	3	1	5	4	4	4	6	4
	Anxious	5	6	6	7	7	8	9	8	9	7	3	7	9	5	7	5	8	7
4	Depressed	8	9	8	6	7	7	8	7	10	6	6	5	7	11	8	4	11	8
	Irritable	60	50	33	58	35	35	34	43	42	72	51	36	31	91	42	51	9	7
	Restless	10	13	9	9	9	9	44	11	16	45	10	48	44	47	29	62	42	51
	Marijuana craving	84	55	48	49	53	47	60	55	51	100	96	63	48	94	61	73	12	32
	Angry-aggressive	39	8	10	8	10	6	10	11	16	12	7	17	16	14	8	11	11	10
	Total VAS score	206	141	114	137	121	112	165	135	144	242	173	176	155	262	155	206	93	115
	Anxious	8	8	6	8	6	7	10	7	6	—	10	6	9	7	8	9	12	7
	Depressed	9	8	4	6	6	7	4	7	5	—	13	8	7	7	5	10	12	7
	Irritable	9	8	12	6	18	7	14	7	13	—	9	7	9	8	17	11	11	7
	Restless	16	9	22	7	10	8	2	7	6	—	7	9	10	11	19	12	9	7
	Marijuana craving	30	26	36	29	28	29	37	23	30	—	32	29	33	31	30	28	48	30

ID	VAS Measure	Time Point																Day 10	
		Day 9																Day 10	
		8:00 A.M.	9:30 A.M.	10:00 A.M.	10:30 A.M.	11:00 A.M.	11:30 A.M.	Noon	12:30 P.M.	1:00 P.M.	1:30 P.M.	2:00 P.M.	2:30 P.M.	3:00 P.M.	3:30 P.M.	4:00 P.M.	4:30 P.M.	8:00 P.M.	8:00 A.M.
5	Angry-aggressive	4	10	15	5	11	9	9	6	8	—	15	13	10	19	18	7	15	9
	Total VAS score	76	69	95	61	79	67	76	57	68	—	86	72	78	83	97	77	107	67
	Anxious	0	0	1	1	2	2	2	2	2	0	0	0	0	0	—	0	0	0
	Depressed	0	0	0	2	1	2	2	3	2	0	0	0	0	0	—	0	0	0
	Irritable	0	0	1	2	1	2	1	3	2	1	0	0	0	0	—	0	0	0
	Restless	0	0	1	2	1	3	2	4	1	1	0	0	0	0	—	0	0	0
	Marijuana craving	0	0	1	3	1	3	2	3	3	0	0	0	0	0	—	0	0	0
	Angry-aggressive	0	1	1	3	3	3	2	5	3	1	0	0	0	0	—	0	0	0
	Total VAS score	0	1	5	13	9	15	11	20	13	3	0	0	0	0	—	0	0	0
	Anxious	10	18	13	13	16	16	12	15	14	16	19	15	20	20	18	18	23	14
6	Depressed	1	2	3	2	1	2	11	10	8	2	8	6	13	4	7	6	4	5
	Irritable	7	12	11	10	11	13	7	10	9	10	13	12	16	18	14	15	17	12
	Restless	0	0	0	0	0	2	1	2	1	4	4	6	5	13	10	10	20	8
	Marijuana craving	5	4	1	2	5	4	5	2	2	4	5	2	4	4	6	5	9	7
	Angry-aggressive	0	0	0	0	0	0	0	0	0	2	1	0	0	1	1	1	1	1
	Total VAS score	23	36	28	27	33	37	36	39	34	38	50	41	58	60	56	55	74	47
	Anxious	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	4
	Depressed	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Irritable	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Restless	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	8
10	Marijuana craving	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	5
	Angry-aggressive	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
	Total VAS score	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	17
	Anxious	0	1	0	0	1	0	0	0	0	1	0	1	0	0	1	0	0	0
	Depressed	0	1	0	0	1	0	0	0	0	0	0	1	0	1	0	0	1	0
	Irritable	0	16	16	3	1	0	0	0	0	0	1	1	0	1	0	0	1	1
	Restless	1	0	0	3	1	0	0	0	1	0	1	1	0	0	0	1	0	3
	Marijuana craving	81	83	80	71	77	69	72	73	76	87	78	75	70	81	79	83	86	94
	Angry-aggressive	1	1	1	1	0	1	0	1	0	0	2	1	0	0	0	1	4	1
	Total VAS score	81	83	80	71	77	69	72	73	76	87	78	75	70	81	79	83	86	94
	Anxious	0	1	0	0	1	0	0	0	0	1	0	1	0	0	1	0	0	0
11	Depressed	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
	Irritable	0	16	16	3	1	0	0	0	0	0	0	1	0	1	0	0	1	1
	Restless	1	0	0	3	1	0	0	0	1	0	1	1	0	0	0	1	0	3
	Marijuana craving	81	83	80	71	77	69	72	73	76	87	78	75	70	81	79	83	86	94
	Angry-aggressive	1	1	1	1	0	1	0	1	0	0	2	1	0	0	0	1	4	1
	Total VAS score	81	83	80	71	77	69	72	73	76	87	78	75	70	81	79	83	86	94
	Anxious	0	1	0	0	1	0	0	0	0	1	0	1	0	0	1	0	0	0
	Depressed	0	1	0	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0
	Irritable	0	16	16	3	1	0	0	0	0	0	0	1	0	1	0	0	1	1
	Restless	1	0	0	3	1	0	0	0	1	0	1	1	0	0	0	1	0	3

		Time Point															
		Day 9								Day 10							
ID	VAS Measure	8:00 A.M.	9:30 A.M.	10:00 A.M.	10:30 A.M.	11:00 A.M.	11:30 A.M.	Noon	12:30 P.M.	1:00 P.M.	1:30 P.M.	2:00 P.M.	2:30 P.M.	3:00 P.M.	3:30 P.M.	4:00 P.M.	8:00 P.M.
12	Total VAS score	83	102	97	78	81	70	72	74	77	88	82	80	70	83	80	99
	Anxious	0	0	0	0	0	0	0	0	0	0	0	0	0	—	0	0
	Depressed	0	0	0	0	0	0	0	0	0	0	0	0	0	—	0	0
	Irritable	0	0	0	0	0	0	0	0	0	0	0	0	0	—	0	0
	Restless	0	0	0	0	0	0	0	0	0	0	0	0	0	—	0	0
13	Marijuana craving	14	0	0	0	0	0	0	0	0	0	0	0	0	—	100	38
	Angry-aggressive	0	0	0	0	0	0	0	0	0	0	0	0	0	—	0	0
	Total VAS score	14	0	0	0	0	0	0	0	0	0	0	0	0	—	100	38
	Anxious	999	0	1	0	1	1	1	—	0	1	0	0	0	0	0	0
	Depressed	999	0	0	1	0	1	0	—	0	0	0	0	0	0	1	0
	Irritable	999	0	0	0	0	1	0	—	0	1	0	0	0	0	0	1
	Restless	999	10	0	0	0	1	0	—	0	0	0	0	0	0	0	0
	Marijuana craving	999	53	63	50	51	44	48	—	45	68	64	54	51	90	66	74
	Angry-aggressive	999	0	0	0	0	0	1	—	0	0	0	0	0	0	0	0
	Total VAS score	999	63	64	51	52	48	50	—	45	70	64	54	51	90	67	75

Rimonabant 20 mg (subjects 1,2,3,5, and 6), 40 mg (subjects 10,11, and 13), or placebo (subjects 4 and 12) was given double-blind at 9:30 A.M. on day 9, after 8 days of escalating doses of oral dronabinol (40–120 mg/d). Six core symptoms of cannabis withdrawal were assessed by 100-mm VAS at the indicated time points. See text for methodological details.

“—” indicates no data.

TABLE 3

Cardiovascular Response to Oral Rimonabant in 10 Daily Cannabis Smokers

ID		Time Point																			
		Day 9																		Day 10	
		8:00 A.M.	9:30 A.M.	10:00 A.M.	10:30 A.M.	11:00 A.M.	11:30 A.M.	Noon	12:30 P.M.	1:30 P.M.	2:30 P.M.	3:30 P.M.	4:00 P.M.	4:30 P.M.	5:30 P.M.	6:30 P.M.	11:00 P.M.	8:00 A.M.			
1	Vitals Measure																				
	Systolic BP	109	110	115	126	107	109	111	124	130	139	141	121	130	124	136	122	118			
	Diastolic BP	65	62	63	52	52	53	64	59	83	86	64	70	85	63	82	76	67			
2	Heart rate	66	60	89	62	60	58	66	62	72	88	73	69	79	70	76	71	61			
	Systolic BP	120	130	119	122	126	130	121	127	140	128	143	136	132	120	128	140	129			
	Diastolic BP	70	74	67	68	70	77	69	77	70	77	81	76	71	74	77	84	77			
3	Heart rate	74	72	65	65	62	64	60	60	60	61	61	63	71	64	67	69	89			
	Systolic BP	119	999	118	126	137	140	152	141	138	147	999	136	148	130	134	135	124			
	Diastolic BP	64	999	56	59	62	60	61	62	55	69	999	59	64	57	73	69	64			
4	Heart rate	65	999	71	68	71	70	64	65	90	68	999	71	78	71	68	71	66			
	Systolic BP	106	999	109	112	110	110	118	116	122	119	123	129	124	116	112	125	127			
	Diastolic BP	50	999	55	64	54	52	54	52	65	61	71	53	65	60	66	60	77			
5	Heart rate	73	999	66	68	70	63	70	62	88	79	65	68	70	67	67	68	70			
	Systolic BP	109	999	98	91	100	102	102	105	113	112	118	116	117	116	118	111	106			
	Diastolic BP	67	999	58	51	51	51	55	58	68	72	61	61	62	76	76	68	71			
6	Heart rate	65	999	74	61	71	65	61	60	68	68	60	64	62	89	66	91	70			
	Systolic BP	111	999	109	111	111	109	112	103	119	122	104	114	110	113	124	117	113			

ID		Time Point																	
		Day 9														Day 10			
		8:00 A.M.	9:30 A.M.	10:00 A.M.	10:30 A.M.	11:00 A.M.	11:30 A.M.	Noon	12:30 P.M.	1:30 P.M.	2:30 P.M.	3:30 P.M.	4:00 P.M.	4:30 P.M.	5:30 P.M.	6:30 P.M.	11:00 P.M.	8:00 A.M.	
Vitals Measure	8:00 A.M.	9:30 A.M.	10:00 A.M.	10:30 A.M.	11:00 A.M.	11:30 A.M.	Noon	12:30 P.M.	1:30 P.M.	2:30 P.M.	3:30 P.M.	4:00 P.M.	4:30 P.M.	5:30 P.M.	6:30 P.M.	11:00 P.M.	8:00 A.M.		
10	Diastolic BP	55	999	55	55	54	62	55	56	67	62	55	54	64	62	66	60	67	
	Heart rate	70	999	65	71	70	65	66	63	74	62	66	69	59	73	65	68	67	
	Systolic BP	132	131	133	142	148	145	132	130	139	149	140	150	131	140	144	147	132	
	Diastolic BP	78	66	73	73	73	74	73	63	80	71	70	71	74	75	79	72	69	
	Heart rate	66	73	69	61	66	72	85	71	81	81	92	105	71	106	77	99	80	
	Systolic BP	126	124	124	147	138	153	131	144	148	144	149	148	126	138	151	134	135	
	Diastolic BP	81	87	75	81	78	90	79	75	88	88	89	82	89	76	79	80	86	
	Heart rate	89	75	78	85	98	84	89	83	88	93	80	113	91	92	93	93	83	
	Systolic BP	123	123	140	140	127	120	123	135	128	143	129	142	137	144	151	130	140	
12	Diastolic BP	66	53	61	61	50	51	60	61	57	63	58	58	62	70	67	63	76	
	Heart rate	58	57	54	58	61	56	60	55	58	57	56	71	83	86	93	93	58	
	Systolic BP	104	98	120	109	122	123	111	116	121	132	134	145	125	128	127	131	117	
13	Diastolic BP	57	51	66	56	51	65	54	54	63	84	71	67	68	60	69	67	62	
	Heart rate	62	64	65	54	63	78	68	67	68	57	59	64	64	70	59	73	55	

Rimonabant 20 mg (subjects 1, 2, 3, 5, and 6), 40 mg (subjects 10, 11, and 13), or placebo (subjects 4 and 12) was given double-blind at 9:30 A.M. on day 9 after 8 days of escalating doses of oral dronabinol (40–120 mg/d). Systolic and diastolic blood pressure (BP; mm Hg) and heart rate (beats per minute) were assessed at the indicated time points. See text for methodological details.