(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
08 November 2018 (08.11.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/204689 A1

(51) International Patent Classification:
A61K 31/352 (2006.01) *A61K 31/415* (2006.01)
A61K 31/397 (2006.01)

(21) International Application Number:
PCT/US2018/030944

(22) International Filing Date:
03 May 2018 (03.05.2018)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
62/501,536 04 May 2017 (04.05.2017) US

(71) Applicant: **THE BOARD OF REGENTS OF THE UNIVERSITY OF TEXAS SYSTEM** [US/US]; 201 West 7th Street, Austin, TX 78701 (US).

(72) Inventor: **MCMAHON, Lance, R.**; The University Of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78229 (US).

(74) Agent: **MARTY, Scott D.** et al.; Ballard Spahr LLP, 999 Peachtree Street, Suite 1000, Atlanta, GA 30309 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report (Art. 21(3))*

WO 2018/204689 A1

(54) Title: METHODS OF TREATING SYNTHETIC CANNABINOID TOXICITY OR OVERDOSE WITH RIMONABANT

(57) Abstract: The disclosure relates to compositions and methods of preventing or treating a subject suffering from a synthetic cannabinoid overdose. The method comprises administering to a patient in need of treatment an effective amount of rimonabant.

METHODS OF TREATING SYNTHETIC CANNABINOID TOXICITY OR OVERDOSE WITH RIMONABANT

CROSS REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Application No. 62/201,536, filed on May 4, 2017, the entire content of which is hereby incorporated by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH

This invention was made with government support under grant no. DA019222 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND

Consumption of synthetic cannabinoids results in adverse events and toxicity. Synthetic cannabinoid overdose often requires emergency medical intervention and hospitalization, and can result in cardiovascular toxicity, seizures, and severe psychiatric reactions that can cause significant harm to the use or to others. Currently, no pharmacological interventions are available that can effectively reverse adverse effects and toxicity resulting from synthetic cannabinoid overdose.

SUMMARY

Disclosed herein are methods of treating or preventing synthetic cannabinoid toxicity or overdose in a subject, the method comprising: administering to a subject a therapeutically effective amount of rimonabant.

Disclosed herein are methods of treating or preventing synthetic cannabinoid toxicity or overdose in a subject, the method comprising: (a) identifying a subject in need of treatment; and (b) administering to the subject a therapeutically effective amount of rimonabant.

Disclosed herein are methods of ameliorating one or more symptoms of synthetic cannabinoid toxicity or overdose in a subject, the method comprising: administering to a subject a therapeutically effective amount of rimonabant.

Disclosed herein are methods of ameliorating one or more symptoms of synthetic cannabinoid toxicity or overdose in a subject, the method comprising: (a) identifying a subject in need of treatment; and (b) administering to the subject a therapeutically effective amount of rimonabant.

Other features and advantages of the present compositions and methods are illustrated in the description below, the drawings, and the claims.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows the effects of AM-2201, JWH-122, CP-47,497, JWH-250 and Δ9-THC, as a function of dose (left) and time (right) in rhesus monkeys discriminating Δ9-THC. Abscissae: vehicle (VEH) or dose in milligram per kilogram of body weight (left) and time (right). Ordinates: mean (± S.E.M.) percentage of responding on the Δ9-THC lever (top) and mean (± S.E.M) response rate expressed as a percentage of the control rate (bottom).

FIG. 2 shows the effects of AM-2201, JWH-122, CP 47,497, and JWH-250 in rhesus monkeys discriminating Δ9- THC: antagonism by rimonabant. Abscissae: dose in milligram per kilogram of body weight or vehicle (VEH). Ordinates: mean (±S.E.M.) percentage of responding on the Δ9-THC lever (left) and mean (±S.E.M) response rate expressed as a percentage of the control rate (right). The control dose-response functions for AM-2201, JWH-122, CP 47,497, and JWH-250 are re- plotted from Fig.1.

FIG. 3 shows the effects of AM-2201, JWH-122, CP 47,497, and JWH-250 in Δ9-THC treated rhesus monkeys discriminating rimonabant. Abscissae: dose of rimonabant in milligram per kilogram of body weight or vehicle (VEH). Ordinates: mean (±S.E.M.) percentage of responding on the rimonabant lever (left) and mean (±S.E.M) response rate expressed as a percentage of the control rate (right).

FIG. 4 shows the magnitude of rightward shift in the rimonabant dose-response function expressed as a function of AM-2201, JWH-122, CP 47,497, and JWH-250 dose. Abscissae: dose in milligram per kilogram of body weight. Ordinate: mean (±S.E.M.) rightward shift in the rimonabant dose- response function, calculated as the rimonabant ED50 value after pretreatment with a cannabinoid agonist divided by the control rimonabant ED50 value.

DETAILED DESCRIPTION

The present disclosure can be understood more readily by reference to the following detailed description of the invention, the figures and the examples included herein.

Before the present compositions and methods are disclosed and described, it is to be understood that they are not limited to specific synthetic methods unless otherwise specified, or to particular reagents unless otherwise specified, as such may, of course, vary. It is also to be understood that the terminology used herein is for the purpose of describing particular aspects only and is not intended to be limiting. Although any methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, example methods and materials are now described.

Moreover, it is to be understood that unless otherwise expressly stated, it is in no way intended that any method set forth herein be construed as requiring that its steps be performed in a specific order. Accordingly, where a method claim does not actually recite an order to be followed by its steps or it is not otherwise specifically stated in the claims or descriptions that the steps are to be limited to a specific order, it is in no way intended that an order be inferred, in any respect. This holds for any possible non-express basis for interpretation, including matters of logic with respect to arrangement of steps or operational flow, plain meaning derived from grammatical organization or punctuation, and the number or type of aspects described in the specification.

All publications mentioned herein are incorporated herein by reference to disclose and describe the methods and/or materials in connection with which the publications are cited. The publications discussed herein are provided solely for their disclosure prior to the filing date of the present application. Nothing herein is to be construed as an admission that the present invention is not entitled to antedate such publication by virtue of prior invention. Further, the dates of publication provided herein can be different from the actual publication dates, which can require independent confirmation.

DEFINITIONS

As used in the specification and the appended claims, the singular forms "a," "an" and "the" include plural referents unless the context clearly dictates otherwise.

The word “or” as used herein means any one member of a particular list and also includes any combination of members of that list.

Throughout the description and claims of this specification, the word "comprise" and variations of the word, such as "comprising" and "comprises," means "including but not limited to," and is not intended to exclude, for example, other additives, components, integers or steps. In particular, in methods stated as comprising one or more steps or operations it is specifically contemplated that each step comprises what is listed (unless that step includes a limiting term such as "consisting of"), meaning that each step is not intended to exclude, for example, other additives, components, integers or steps that are not listed in the step.

Ranges can be expressed herein as from "about" or "approximately" one particular value, and/or to "about" or "approximately" another particular value. When such a range is expressed, a further aspect includes from the one particular value and/or to the other particular value. Similarly, when values are expressed as approximations, by use of the antecedent "about," or "approximately," it will be understood that the particular value forms a further aspect. It will be further understood that the endpoints of each of the ranges are significant both in relation to the other endpoint and independently of the other endpoint. It is also understood that there are a number of values disclosed herein and that each value is also herein disclosed as "about" that particular value in addition to the value itself. For example, if the value "10" is disclosed, then "about 10" is also disclosed. It is also understood that each unit between two particular units is also disclosed. For example, if 10 and 15 are disclosed, then 11, 12, 13, and 14 are also disclosed.

As used herein, the terms "optional" or "optionally" mean that the subsequently described event or circumstance may or may not occur and that the description includes instances where said event or circumstance occurs and instances where it does not.

As used herein, the term "subject" refers to the target of administration, e.g., a human. Thus, the subject of the disclosed methods can be a vertebrate, such as a mammal, a fish, a bird, a reptile, or an amphibian. The term "subject" also includes domesticated animals (e.g., cats, dogs, etc.), livestock (e.g., cattle, horses, pigs, sheep, goats, etc.), and laboratory animals (e.g., mouse, rabbit, rat, guinea pig, fruit fly, etc.). In one aspect, a subject is a mammal. In another aspect, the subject is a human. The term does not denote a particular age or sex. Thus, adult, child, adolescent and newborn subjects, as well as fetuses, whether male or female, are intended to be covered.

As used herein, the term "patient" refers to a subject afflicted with a disease, disorder or condition. The term "patient" includes human and veterinary subjects. In some aspects of

the disclosed methods, the "patient" has been diagnosed with a need for treatment for preventing or treating synthetic cannabinoid toxicity or overdose, such as, for example, prior to the administering step.

As used herein, the term "side effect" refers to adverse effects or toxic effects produced by a drug including but not limited to on a tissue or organ system. Such conditions, for example, can include altered mental status (e.g., hallucinations), tachycardia, agitation, loss of consciousness, seizures, kidney damage, nausea, vomiting, hypokalemia, hypothermia and death.

As used herein, the terms "synthetic cannabinoid toxicity" or "synthetic cannabinoid overdose" refers to the effects of synthetic cannabinoids that are toxic to a subject, resulting in effects that may be mild, moderate or severe including but not limited to mental status (e.g., hallucinations), tachycardia, agitation, loss of consciousness, seizures, kidney damage, nausea, vomiting, hypokalemia, hypothermia and death. Synthetic cannabinoid toxicity can be assessed by any appropriate method known to a clinical physician or skilled artisan. The term "overdose" refers to a subject that takes a dose larger than originally intended that results in one or more adverse effects.

As used herein, the term "treating" refers to partially or completely alleviating, ameliorating, relieving, delaying onset of, inhibiting or slowing progression of, reducing severity of, and/or reducing incidence of one or more symptoms or features of a particular disease, disorder, and/or condition. Treatment can be administered to a subject who does not exhibit signs of a disease, disorder, and/or condition and/or to a subject who exhibits only early signs of a disease, disorder, and/or condition for the purpose of decreasing the risk of developing pathology associated with the disease, disorder, and/or condition. For example, the disease, disorder, and/or condition can be toxicity or an overdose relating to the administration of one or more synthetic cannabinoids.

As used herein, the phrase "non-dependent" refers to a subject that has taken any cannabinoid or synthetic cannabinoid at least once without becoming dependent prior to the instance for which treatment is sought.

INTRODUCTION

Synthetic cannabinoid CB1 and CB2 receptor agonists marketed under various brand names (e.g., Spice or K2) have been sold and abused worldwide since 2008. These products typically contain at least one synthetic cannabinoid and do not contain cannabis or its primary

psychoactive drug Δ9-tetrahydrocannabinol (Δ9-THC). A rise in synthetic cannabinoid abuse has been due to several factors, e.g., prior to regulation by the Drug Enforcement Agency synthetic cannabinoids provided legal alternatives to cannabis (Auwärter, 2009; Vardakou et al., 2010). Several countries have since prohibited the possession of many of the synthetic cannabinoids originally detected in Spice/K2 and related products including JWH-018, JWH-073, CP-47,497, and HU-210, as well as chemical analogs to JWH-018 and JWH-073 such as AM-2201, JWH-122, and JWH-250 (Makriyannis and Deng, 2001; Huffman et al., 2005; Lapoint et al., 2011; Nakajima et al., 2011; Simmons et al., 2011; Rosenbaum et al., 2012). There are hundreds of structurally diverse synthetic cannabinoids and the *in vivo* effects of many have not been widely characterized.

AM-2201 (1-(5-fluoropentyl)-3-(1-naphthoyl)indole), JWH-122 (4-methyl-1-naphthyl)- (1-pentylindol-3-yl)methanone, JWH-250 (2-(2-methoxyphenyl)-1-(1-pentylindol-3- yl)ethanone), and CP-47,497 ([2-(1R,3S)-3-hydroxy-cyclohexyl]-5-(2-methyloctan-2-yl)phenol) are divided into three distinct chemical groups. AM-2201 and JWH-122 are naphthoylindoles (Makriyannis and Deng, 2001; 2007; Huffman et al., 2003) and JWH-250 is a phenylacetylindole (Huffman et al., 2005). CP-47,497 is a cyclohexylphenol and lacks the pyran ring of Δ9-THC and other tricyclic terpenoid derivatives (Palmer et al., 2002). CP-47,497 is a cannabinoid CB1 and CB2 receptor agonist that produces effects typical of cannabinoid agonists such as hypolocomotion, analgesia, hypothermia, catalepsy, and discriminative stimulus effects in rodents (Weissman et al. 1982). JWH-250 does not have the naphthalene ring present in JWH-122 and AM-2201, but instead has a 2'-methoxy-phenylacetyl group in that position (Huffman et al., 2005). AM-2201, JWH-122, and JWH-250 were demonstrated to produce Δ9-THC like discriminative stimulus effects in rodents (Gatch and Forster, 2014; 2016), suggesting that they produce cannabis-like subjective in humans.

Described herein are the results of a study comparing the pharmacology of synthetic cannabinoids including CP-47,497, which was detected in herbal blends as early as 2008. Others included AM-2201, JWH-122, and JWH-250, which became more prevalent after 2010 when CP-47,497 and other "first generation" synthetic cannabinoids (e.g., JWH-018 and JWH-073) were banned (DEA Schedules of Controlled Substances: Temporary Placement of Five Synthetic Cannabinoids into Schedule I, 2011). CP-47,497, AM-2201, JWH-122, and JWH-250 substituted for the discriminative stimulus effects of Δ9-THC. AM-

2201 and JWH-122 were 10- and 3.3-fold more potent than Δ9- THC, respectively, whereas JWH-250, CP-47,497, and Δ9-THC were equipotent. CP-47,497 and Δ9-THC had a similar duration of action (4-5 h) whereas that of AM-2201, JWH-122, and JWH- 250 (1-2 h) was longer. As disclosed below, rimonabant (1 mg/kg) antagonized the discriminative stimulus and rate-decreasing effects of the agonists. Quantitative analysis of the magnitude of antagonism of discriminative stimulus effects by rimonabant was similar for all cannabinoid agonists tested. AM-2201, JWH-122, CP-47,497, and JWH-250 dose-dependently attenuated the discriminative stimulus effects of rimonabant in monkeys receiving 1 mg/kg/12 h of Δ9-THC. These data show that three synthetic cannabinoids placed under Schedule 1 of the United States Controlled Substances Act (AM-2201, JWH-122, and JWH-250) are more potent and have a shorter duration of action than Δ9-THC. All cannabinoids tested here, however, appear to produce subjective effects through a common CB1-receptor mechanism.

Before 2010 the synthetic cannabinoids JWH-018 and JWH-073 were the primary ingredients in Spice/K2 and related herbal blend products (Huffman et al., 1994; Atwood et al., 2009; Huffman, 2009). JWH-018 and JWH-073 were demonstrated to share discriminative stimulus effects with Δ9-THC in monkeys and mice (Ginsburg et al, 2012; Wiley et al., 2012). JWH-018 and JWH073 were banned and replaced by various aminoalkylindole, phenacetylindole, and naphthoylpyrolles cannabinoids designed by J. W. Huffman and benzoylindole cannabinoids designed by A. Makriyannis (Hudson and Ramsey, 2011; Järbe et al., 2011; Carroll et al., 2012). The emergence of AM-2201, JWH-122, and JWH-250 as drugs of abuse occurred in the absence of extensive pharmacological and toxicological data. All three were eventually shown to share discriminative stimulus effects with Δ9-THC in rats (Gatch and Forster 2014; 2016; Järbe et al., 2016). Disclosed herein are methods of preventing and reversing discriminative stimulus effects of Δ9-THC and synthetic cannabinoids by administering rimonabant.

COMPOSITIONS

As disclosed herein, rimonabant can be useful for preventing or treating toxicity or overdose due to the administration of one or more synthetic cannabinoids. Currently, there are no established treatments for preventing or treating toxicity or overdose due to the administration of one or more synthetic cannabinoids. Rimonabant is a selective CB1 receptor blocker or antagonist. Rimonabant is also known as SR141716, Acomplia™ and Zimulti™.

Rimonabant can be useful in the treatment of synthetic cannabinoids toxicity or overdose resulting from synthetic cannabinoids including but not limited to cannabicyclohexanol, JWH-018, JWH-073, JWH-398, JWH-250, CP-47,497 and HU-210, homologous thereof and any mixtures thereof.

Rimonabant can also be useful for the treatment of subjects that are non-dependent subjects suffering from synthetic cannabinoid toxicity or overdose. For example, those subjects who have used any cannabinoid or synthetic cannabinoid in the past and have not developed tolerance or dependence to any of the synthetic cannabinoids can be treated for synthetic cannabinoid toxicity or overdose. The time period of therapeutic effectiveness of rimonabant from a single (or multiple) dose(s) administration can last from about 15 minutes to over 4 hours. In an aspect, a time period of therapeutic effectiveness of rimonabant can be between 15 minutes to 30 minutes or 30 minutes to 1 hour. In an aspect, the time period of therapeutic effectiveness of rimonabant can be at least 1 hour, at least 2 hours, at least 3 hours or at least 4 hours or any time period in between.

In some aspects, the rimonabant can be used in combination with other therapeutic drugs used to treats subjects suffering from cannabinoid toxicity, synthetic cannabinoid toxicity or overdose. For example, in some aspects, rimonabant can be administered with one or more synthetic cannabinoid receptor agonists.

METHODS OF TTREATMENT

Disclosed herein, are methods of treating or preventing synthetic cannabinoid toxicity or overdose in a subject, the method comprising: (a) identifying a subject in need of treatment; and (b) administering to the subject a therapeutically effective amount of rimonabant. Also, disclosed herein, are methods of ameliorating one or more symptoms of synthetic cannabinoid toxicity or overdose in a subject, the method comprising: (a) identifying a subject in need of treatment; and (b) administering to the subject a therapeutically effective amount of rimonabant.

In an aspect, a therapeutically effective amount of a pharmaceutical composition comprising rimonabant and a pharmaceutically acceptable carrier can be administered to the subject. In an aspect, the synthetic cannabinoid toxicity or overdose results from synthetic cannabinoid administration to a non-dependent subject. In an aspect, the subject can be a synthetic cannabinoid user. In an aspect, the administration of rimonabant can reduce one or more symptoms of drug toxicity or overdose. In an aspect, one or more of the symptoms of

drug toxicity or overdose can be reduced over a period of at least 15 to about 30 minutes. In an aspect, one or more of the symptoms of drug toxicity or overdose can be reduced over a period of at least 1 hour, at least 2 hours, at least 3 hours, at least 4 hours or more. In an aspect, the one or more symptoms of synthetic cannabinoid toxicity or overdose can be selected from seizures, tachycardia, hypokalemia, nausea and vomiting.

The pharmaceutical compositions described herein can be formulated to include a therapeutically effective amount of a rimonabant. In an aspect, rimonabant can be contained within a pharmaceutical formulation. In an aspect, the pharmaceutical formulation can be a unit dosage formulation. In an aspect, rimonabant can administered on an as-needed basis.

Therapeutic administration encompasses prophylactic applications. Based on genetic testing and other prognostic methods, a physician in consultation with their patient can choose a prophylactic administration where the patient has a clinically determined predisposition or increased susceptibility (in some cases, a greatly increased susceptibility) to one or more side effects associated with synthetic cannabinoid use.

The pharmaceutical compositions described herein can be administered to the subject (e.g., a human patient) in an amount sufficient to delay, reduce, prevent or reverse the onset or duration of synthetic cannabinoid toxicity or overdose in a subject. Accordingly, in some aspects, the patient is a human patient. In therapeutic applications, compositions are administered to a subject (e.g., a human patient) already expressing or diagnosed with one or more synthetic cannabinoid toxic symptoms in an amount sufficient to at least partially improve a sign or symptom or to inhibit the progression of (and preferably arrest) the symptoms of the condition, its complications, and consequences. An amount adequate to accomplish this is defined as a therapeutically effective amount. A therapeutically effective amount of a pharmaceutical composition can be an amount that achieves a cure or reverses one or more symptoms of synthetic cannabinoid toxicity, but that outcome is only one among several that can be achieved. As noted, a therapeutically effect amount includes amounts that provide a treatment in which the onset, progression or expression of one or more of the side effects associated with synthetic cannabinoid use or toxicity or overdose is delayed, hindered, or prevented, or the one or more symptoms associated with synthetic cannabinoid use or toxicity or overdose is reduced, ameliorated or reversed. One or more of the symptoms can be less severe. Recovery can be accelerated in an individual who has been treated.

Amounts effective for this use can depend on the severity of the symptoms of drug toxicity or overdose and the weight and general state and health of the subject, but generally range from about 0.05 μg to about 1000 μg (e.g., 0.5-100 mg) of an equivalent amount of the rimonabant per dose per subject.

The total effective amount of a rimonabant as disclosed herein can be administered to a subject as a single dose, either as a bolus or by infusion over a relatively short period of time, or can be administered using a fractionated treatment protocol in which multiple doses are administered over a more prolonged period of time. Alternatively, continuous intravenous infusions sufficient to maintain therapeutically effective concentrations in the blood are also within the scope of the present disclosure.

The therapeutically effective amount or dosage of the rimonabant used in the methods as disclosed herein applied to mammals (e.g., humans) can be determined by one of ordinary skill in the art with consideration of individual differences in age, weight, sex, other drugs administered and the judgment of the attending clinician. Variations in the needed dosage may be expected. Variations in dosage levels can be adjusted using standard empirical routes for optimization. The particular dosage of a pharmaceutical composition to be administered to the patient will depend on a variety of considerations (e.g., the severity of side effects of the synthetic cannabinoids), the age and physical characteristics of the subject and other considerations known to those of ordinary skill in the art. Dosages of rimonabant can be in the range of 0.1 mg to 100 mg per kilogram of the subject's body weight. In an aspect, the dosage of rimonabant can be 100, 200, 300 or 400 mg total. In an aspect, the dosage of rimonabant can be 0.1 to 25 mg/kg. It is presently believed that 0.2 mg/kg rimonabant administered intravenously occupies about 50% of cannabinoid receptors in rhesus monkeys. In an aspect, rimonabant can be administered intravenously. The side effects (e.g., behaviorally disruptive effects) of synthetic cannabinoids can be reversed by 0.1-0.32 mg/kg rimonabant i.v. in rhesus monkeys that, for example, also received daily treatment with 2 mg/kg Δ^9-tetrahydrocannabinol. The equivalent range of rimonabant doses in humans assuming a body weight of 70 kg is about 7-25 mg/kg total. In an aspect, the therapeutically effective amount of rimonabant can be between 7 to 25 mg/kg of body weight or any amount in between. In an aspect, smaller therapeutically effective doses may retain the ability to reverse one or more side effects (e.g., behaviorally disruptive effects) of synthetic cannabinoids.

PHARMACEUTICAL COMPOSITIONS

As disclosed herein, are pharmaceutical compositions, comprising rimonabant and a pharmaceutical acceptable carrier described herein. In some aspects, rimonabant can be formulated for intravenous administration. The compositions can be formulated for administration by any of a variety of routes of administration, and can include one or more physiologically acceptable excipients, which can vary depending on the route of administration. As used herein, the term "excipient" means any compound or substance, including those that can also be referred to as "carriers" or "diluents." Preparing pharmaceutical and physiologically acceptable compositions is considered routine in the art, and thus, one of ordinary skill in the art can consult numerous authorities for guidance if needed.

The compositions can be administered directly to a subject. Generally, the compositions can be suspended in a pharmaceutically acceptable carrier (e.g., physiological saline or a buffered saline solution) to facilitate their delivery. Encapsulation of the compositions in a suitable delivery vehicle (e.g., polymeric microparticles or implantable devices) may increase the efficiency of delivery.

The compositions can be formulated in various ways for parenteral or nonparenteral administration. Where suitable, oral formulations can take the form of tablets, pills, capsules, or powders, which may be enterically coated or otherwise protected. Sustained release formulations, suspensions, elixirs, aerosols, and the like can also be used.

Pharmaceutically acceptable carriers and excipients can be incorporated (e.g., water, saline, aqueous dextrose, and glycols, oils (including those of petroleum, animal, vegetable or synthetic origin), starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monosterate, sodium chloride, dried skim milk, glycerol, propylene glycol, ethanol, and the like). The compositions may be subjected to conventional pharmaceutical expedients such as sterilization and may contain conventional pharmaceutical additives such as preservatives, stabilizing agents, wetting or emulsifying agents, salts for adjusting osmotic pressure, buffers, and the like. Suitable pharmaceutical carriers and their formulations are described in "Remington's Pharmaceutical Sciences" by E.W. Martin, which is herein incorporated by reference. Such compositions will, in any event, contain an effective amount of the compositions together with a suitable

amount of carrier so as to prepare the proper dosage form for proper administration to the patient.

The pharmaceutical compositions as disclosed herein can be prepared for oral or parenteral administration. Pharmaceutical compositions prepared for parenteral administration include those prepared for intravenous (or intra-arterial), intramuscular, subcutaneous, intraperitoneal, transmucosal (e.g., intranasal, intravaginal, or rectal), or transdermal (e.g., topical) administration. Aerosol inhalation can also be used. Thus, compositions can be prepared for parenteral administration that includes rimonabant dissolved or suspended in an acceptable carrier, including but not limited to an aqueous carrier, such as water, buffered water, saline, buffered saline (e.g., PBS), and the like. One or more of the excipients included can help approximate physiological conditions, such as pH adjusting and buffering agents, tonicity adjusting agents, wetting agents, detergents, and the like. Where the compositions include a solid component (as they may for oral administration), one or more of the excipients can act as a binder or filler (e.g., for the formulation of a tablet, a capsule, and the like). Where the compositions are formulated for application to the skin or to a mucosal surface, one or more of the excipients can be a solvent or emulsifier for the formulation of a cream, an ointment, and the like.

The pharmaceutical compositions can be sterile and sterilized by conventional sterilization techniques or sterile filtered. Aqueous solutions can be packaged for use as is, or lyophilized, the lyophilized preparation, which is encompassed by the present disclosure, can be combined with a sterile aqueous carrier prior to administration. The pH of the pharmaceutical compositions typically will be between 3 and 11 (e.g., between about 5 and 9) or between 6 and 8 (e.g., between about 7 and 8). The resulting compositions in solid form can be packaged in multiple single dose units, each containing a fixed amount of the above-mentioned agent or agents, such as in a sealed package of tablets or capsules.

ARTICLES OF MANUFACTURE

The composition described herein can be packaged in a suitable container labeled, for example, for use as a therapy to treat or prevent synthetic cannabinoid toxicity or overdose. Accordingly, packaged products (e.g., sterile containers containing the composition described herein and packaged for storage, shipment, or sale at concentrated or ready-to-use concentrations) and kits, including at least rimonabant as described herein and instructions for use, are also within the scope of the disclosure. A product can include a container (e.g., a

vial, jar, bottle, bag, or the like) containing the composition described herein. In addition, an article of manufacture further may include, for example, packaging materials, instructions for use, syringes, buffers or other control reagents for treating or monitoring the condition for which prophylaxis or treatment is required. The product may also include a legend (e.g., a printed label or insert or other medium describing the product's use (e.g., an audio- or videotape)). The legend can be associated with the container (e.g., affixed to the container) and can describe the manner in which the compound therein should be administered (e.g., the frequency and route of administration), indications therefor, and other uses. The compounds can be ready for administration (e.g., present in dose-appropriate units), and may include a pharmaceutically acceptable adjuvant, carrier or other diluent. Alternatively, the compounds can be provided in a concentrated form with a diluent and instructions for dilution.

EXAMPLES

Example 1: Effects of AM-2201, JWH-122, JWH-250 and CP-47,497 in Rhesus Monkeys Discriminating Δ9-THC.

Drug discrimination assays in non-human primates were used to assess the potency, time course, and CB1 receptor mediated effects of CP-47,497, AM-2201, JWH-122, and JWH-250. One group of rhesus monkeys (n=4) discriminated Δ9-THC (0.1 mg/kg i.v.).

Materials and Methods

Subjects. Two female and two male adult rhesus monkeys (*Macaca mulatta*) discriminated Δ9-THC from vehicle and one female and three male adult rhesus monkeys discriminated rimonabant while receiving chronic Δ9-THC (1 mg/kg/12 h, s.c.). The monkeys were housed individually in stainless-steel cages on a 14-h light/10-h dark schedule (lights on at 6:00 AM). They were maintained at 95% free-feeding weight (range 6.0–11.8 kg) with a diet consisting of primate chow (High Protein Monkey Diet; Harlan Teklad, Madison, WI), fresh fruit, and peanuts; water was provided in the home cage. Monkeys received cannabinoids in previous studies (Ginsburg et al., 2012; Hruba and McMahon, 2014).

Surgery. Monkeys were anesthetized with ketamine (10 mg/kg i.m.) followed by isoflurane (1.5–3.0% inhaled via facemask). A catheter (heparin-coated polyurethane; o.d. = 1.68 mm; i.d. = 1.02 mm; Instech Laboratories, Plymouth Meeting, PA) was inserted into a subclavian or femoral vein and secured to the vessel with suture silk (coated vicryl; Ethicon

Inc., Somerville, NJ). The catheter extended from the vessel to the midscapular region of the back and was attached to a vascular access port located s.c. (Mida-cbas-c50; Instech Laboratories).

Apparatus. Monkeys were seated in chairs (model R001; Primate Products, Miami, FL) and placed in ventilated, sound-attenuating chambers equipped with two levers and two lights, one positioned above each lever. Their feet were placed in shoes containing brass electrodes to which a brief electric stimulus (3 mA, 250 ms) could be delivered from an A/C generator (Coulbourn Instruments, Allentown, PA). The chambers were connected to a computer with an interface (MED Associates, St. Albans, VT); experimental events were controlled and recorded with Med-PC software (MED Associates).

Drug Discrimination Training. Monkeys discriminated Δ9-THC (0.1 mg/kg i.v.) from vehicle (1 part absolute ethanol, 1 part Emulphor-620, and 18 parts saline) while responding under a fixed ratio 5 (FR5) schedule of stimulus-shock termination. Four other monkeys received 1 mg/kg s.c. Δ9-THC at 6:15 AM and again at 6:15 PM and discriminated rimonabant (1 mg/kg i.v.) from vehicle at 12:15 PM under an FR5 schedule of stimulus-shock termination.

The experimental sessions were divided into consecutive 10-min, multiple cycles; each cycle began with a 5-min timeout. Responses during the timeout had no programmed consequence. The timeout was followed by a 5-min schedule of stimulus-shock termination, the beginning of which was signaled by illumination of red lights. Five consecutive responses on the correct lever extinguished the red lights, prevented delivery of an electric stimulus, and initiated a 30-s timeout. Otherwise, an electric stimulus was scheduled for delivery every 40 s in monkeys discriminating Δ9-THC and 10 s in monkeys discriminating rimonabant. Responding on the incorrect lever reset the response requirement on the correct lever. Determination of correct levers varied among monkeys (e.g. left lever associated with the training dose of the training drug; right lever associated with vehicle) and remained the same for that monkey for the duration of the study.

Training sessions consisted of a minimum of three and a maximum of six cycles. Drug training consisted of administration of Δ9-THC (0.1 mg/kg i.v.) or rimonabant (1 mg/kg i.v.) within the first min of the first of three cycles; sham (dull pressure applied to the skin overlying the vascular access port) was administered within the first minute of the subsequent cycles. Vehicle training involved administration of vehicle within the first min of the first

cycle followed by vehicle or sham in subsequent cycles for a maximum of six cycles. Zero to three vehicle-training cycles immediately preceded three Δ9-THC or rimonabant training cycles. Completion of the FR on the correct lever was required for reinforcement during each training cycle. Monkeys had previously satisfied the criteria for testing, i.e., at least 80% of the total responses occurred on the correct lever and fewer than five responses occurred on the incorrect lever before completion of the first FR on the correct lever within a cycle for all cycles during five consecutive or six of seven training sessions. Tests were conducted after performance satisfied the test criteria for consecutive training sessions, including both vehicle and drug training sessions. The order of training with drug or vehicle was non-systematic.

Drug Discrimination Testing. During test sessions, five consecutive responses on either lever postponed the shock schedule. In monkeys discriminating Δ9-THC, dose-effect functions for cannabinoid agonists were determined by administering vehicle in the first cycle followed by doses increasing by 0.5 log unit in subsequent cycles. The dose-effect function included an ineffective dose (i.e., dose resulting in less than 20% of responses on the training drug-appropriate lever) up to a dose producing greater than 80% of responses on the Δ9-THC lever. To establish a time course, the smallest dose producing greater than 80% Δ9-THC appropriate responding was administered at the beginning of a cycle; on the same day, subsequent 5-min tests were conducted at 30 min, 1 h, and in 1-h increments thereafter until Δ9-THC appropriate responding was less than 20%. Monkeys discriminating Δ9-THC also received rimonabant (1 mg/kg i.v.) in the first cycle followed by cumulative doses of the cannabinoid agonists in subsequent cycles.

In Δ9-THC-treated monkeys discriminating rimonabant, vehicle or a dose of CP-47,497 (0.32, 1.0 and 3.2 mg/kg) was administered in the first cycle followed by doses of rimonabant increasing by 0.5 log unit in subsequent cycles. AM-2201, JWH-122, and JWH-250 had a relatively short duration of action. Therefore, the combined effects of rimonabant with a dose of AM-2201 (0.1 and 0.32 mg/kg), JWH-122 (0.32 and 1.0 mg/kg), and JWH-250 (0.32 and 1.0 mg/kg) were examined single-cycle test sessions conducted on different days. Rimonabant was studied from ineffective doses up to doses that produced greater than 80% of responses on the rimonabant lever or up to a dose of 5.6 mg/kg, whichever occurred first. Due to limitations in the solubility of rimonabant in the vehicle and volume used for i.v. administration, 5.6 mg/kg was the largest dose studied. The order of testing with the

cannabinoid agonists (AM-2201, JWH-122, JWH-250 and CP-47,497) or rimonabant was non-systematic.

Drugs. D9-tetrahydrocannabinol (Δ9-THC; 100 mg/ml in absolute ethanol) and rimonabant (The Research Technology Branch, National Institute on Drug Abuse, Rockville, MD); AM-2201 ([1-(5-fluoropentyl)-1H-indol-3-yl]-1-naphthalen-methanone; Cayman Chemical Company, Ann Arbor, MI); JWH-122 ((4-methyl-1-naphthalenyl)(1-pentyl-1H-indol-3-yl)-methanone; Cayman Chemical Company); CP-47,497 (rel-2[(1S,3R)-3-hydroxycyclohexyl]-5-(2-methyloctan-2- yl)phenoland; Cayman Chemical Company) and JWH-250 (2-(2-methoxyphenyl)-1-(1- pentylindol-3-yl)ethanone; Arch Pharm, Inc., Libertyville, IL) were dissolved in a mixture of 1 part absolute ethanol, 1 part Emulphor-620 (Rhodia Inc., Cranbury, NJ), and 18 parts physiologic saline and administered intravenously in a volume of 0.1 to 1 ml/kg. Doses were expressed as the weight of the forms listed above in milligrams per kilogram of body weight.

Data Analyses. Discrimination data were expressed as a percentage of responses on the drug lever out of the total number of responses on both the drug and vehicle levers. Rate of responding on both levers (i.e., drug and vehicle) was calculated as responses per second excluding responses during timeouts. Rate of responding during a test was expressed as the percentage of the control response rate for individual animals. The control was defined as the average response rate for all cycles during the five previous vehicle training sessions excluding sessions during which the test criteria were not satisfied. Discrimination and rate data were averaged among subjects, separately per training drug, and were plotted as a function of dose and time.

To estimate the ED50 value or dose producing 50% responding on the drug lever, individual dose-response data were analyzed with linear regression (Prism version 5.0 for Windows; GraphPad Software Inc., San Diego, CA). The analyses included doses spanning the linear portion of the dose-response function, and a common, best-fitting slope was used for further analyses (Kenakin, 1997). Doses corresponding to the 50% level of effect (ED50 value), potency ratios, and their 95% confidence limits were calculated by parallel line analyses of data from individual subjects (Tallarida, 2000). The ED50 values were compared by calculating potency ratios for individual subjects. ED50 values were considered significantly different when the 95% confidence limits of the potency ratio did not include 1. For antagonism by rimonabant in monkeys discriminating Δ9-THC, a single-dose apparent

affinity estimate was calculated for individual monkeys with the following equation: pKB=−log(B/dose ratio −1), with B expressed in moles per kilogram of body weight. Significant differences among pKB values were assessed with repeated measures one way analysis of variance (ANOVA). Time course data were converted to area under the function per animal, and differences among cannabinoid agonists were analyzed with repeated measures one way analysis of variance (ANOVA) followed by post-hoc Tukey's multiple comparison test ($p<0.05$).

In Δ9-THC-treated monkeys discriminating rimonabant, the potencies of AM-2201, JWH-122, JWH-250, and CP-47,497 were calculated by expressing the mean shift in the rimonabant dose-response function (i.e., ED50 value of rimonabant determined in the presence of agonist divided by the ED50 of rimonabant alone) as a function of dose for individual monkeys. Linear regression of the individual data was used to estimate the dose of agonist producing a 2-fold rightward shift in the rimonabant dose-response function. Effects on response rate were examined with a one-way analysis of variance (ANOVA) separately per drug followed by post- hoc Tukey's multiple comparison test.

Results

AM-2201, JWH-122, CP-47,497, and JWH-250 dose-dependently increased mean Δ9-THC lever responding (Fig. 1, top left). AM-2201 and JWH-122 produced 100% drug lever responding at a dose of 0.0032 mg/kg; a larger dose (0.1 mg/kg) was required for Δ9-THC, JWH-250, and CP-47,497 to produce 100% responding on the drug lever. After vehicle, mean responding on the Δ9-THC lever was 0% (Fig. 1, top left, leftmost symbols above VEH). The slopes of the five dose-response functions were not significantly different from each other ($F_{4,39} = 0.56$; $p = 0.75$). The ED50 values and 95% confidence limits calculated from the common slope are shown in Table 1. AM-2201 and JWH-122 were 10- and 3.3-fold more potent than Δ9-THC, respectively, whereas CP-47,497 and JWH-250 were equipotent with Δ9-THC. Up to the largest doses tested, Δ9-THC, AM-2201, JWH-122, JWH-250, and CP-47,497 did not significantly modify response rate (Fig. 1, bottom left).

Table 1.

Drug alone	ED_{50} Value (95% CL)	Potency Ratio (95% CL) vs. Δ^9-THC	
Δ^9-THC	0.050 (0.035-0.069)		
AM-2201	0.005 (0.002-0.013)	10 (3.4-16) vs. Δ^9-THC*	
JWH-122	0.015 (0.010-0.023)	3.3 (2.8-3.8) vs. Δ^9-THC*	
CP-47,497	0.025 (0.012-0.054)	2.0 (0.7-3.5) vs. Δ^9-THC	
JWH-250	0.033 (0.021-0.053)	1.5 (0.7-2.4) vs. Δ^9-THC	
Drug in combination with rimonabant	**ED_{50} Value (95% CL)**	**Potency Ratio (95% CL) vs. drug alone**	**pK_B (95% CL)**
AM-2201	0.053 (0.037-0.074)#	10.6 (3.2-18.5)	6.61 (6.20-7.02)
JWH-122	0.161 (0.108-0.239)#	10.7 (9.9-11.3)	6.65 (6.62-6.69)
CP-47,497	0.274 (0.119-0.631)#	11.0 (9.7-11.9)	6.66 (6.61-6.71)
JWH-250	0.517 (0.278-0.963)#	15.7 (4.9-28.7)	6.83 (6.50-7.17)

ED50 values, potency ratios, and pKB values, and 95% confidence limits (CL) for AM-2201, JWH-122, CP-47,497, and JWH-250 in rhesus monkeys discriminating Δ9-THC (0.1 mg/kg i.v.).

Potency ratios are the ED50 values of the agonist versus Δ9-THC (top) or the ED50 values of the agonist in combination with rimonabant (1 mg/kg) divided by the ED50 value of the agonist alone (bottom). *Significantly more potent than Δ^9-THC; #Significantly different from the ED50 values of the drugs alone.

The duration of action of JWH-250, JWH-122, and AM 2201 to produce Δ9-THC lever responding was shorter than that of Δ9-THC and CP-47,497 ($F_{4,15} = 47.53$; $p < 0.0001$) (Fig.1, top right). Monkeys switched their response choice from predominantly on the drug lever to the vehicle lever 1-2 h after administration of AM 2201, JWH-122, and JWH-250 and 4-5 h after CP-47,497 and Δ9-THC. The cannabinoid agonists did not significantly modify response rate as a function of time (Fig. 1, bottom right).

Rimonabant (1 mg/kg) alone produced 0% responding on the Δ9-THC lever and antagonized the discriminative stimulus effects of each cannabinoid agonist (Fig. 2, left panels). Rimonabant (1 mg/kg) increased the ED50 value 10.6-fold for AM-2201, 10.7-fold for JWH-122, 11.0-fold for CP-47,497, and 15.7-fold for JWH-250 (Table 1). The single-dose apparent affinity estimates calculated for rimonabant were 6.61 in the presence of AM-

2201, 6.65 in the presence of JWH-122, 6.66 in the presence of CP-47,497, and 6.83 in the presence of JWH-250. The pKB values calculated for each cannabinoid agonist were not significantly different from each other ($F_{3,9} = 0.34$, $p = 0.79$). Rate of responding was not significantly altered after rimonabant (1 mg/kg) alone or in combination with AM-2201, JWH-122, CP-47,497, or JWH-250 (Fig. 2, right panels).

The results demonstrated that AM-2201, JWH-122, JWH-250, and CP-47,497 shared discriminative stimulus effects with Δ9-THC; rank order potency was AM-2201<JWH-122<JWH-250=CP-47,497=Δ9-THC. Weismann et al. (1982) showed that CP-47,497 was 7-fold more potent than Δ9-THC in rats, which could reflect the differences in route of administration (i.v. versus i.p.) and species (monkeys versus rats). AM-2201, JWH-122, and JWH-250 had a shorter duration of action (1-2 h) than CP-47,497 and Δ9-THC (4-5 h). Under experimental conditions identical to those of the current study, JWH-018 and JWH-073 had a duration of action of 1-2 h (Ginsburg et al., 2012). Many cannabinoids from the JWH series including JWH-122 and JWH-250 contain an indole ring, and AM-2201 is a benzoylindole that differs from JWH-018 by the presence of a fluorine atom in the pentyl chain (Nakijama et al., 2011). The bicyclic cannabinoid CP-47,497 has a longer duration of action (4-5 h). An indole ring appears to confer a relatively short *in vivo* half-life, which is supported by previous results demonstrating that the aminoalkylindole WIN-55,212-2 has a short duration of action (i.e., 1-2 h; Hruba and McMahon, 2014).

Example 2: Effects of AM-2201, JWH-122, CP-47,497, and JWH-250 in Δ9-THC Treated Monkeys Discriminating Rimonabant.

To identify the extent to which CB_1 receptors mediate the effects of each agonist, they were studied in combination with rimonabant (1 mg/kg). A second group of rhesus monkeys (n=4) discriminated rimonabant (1 mg/kg i.v.) while receiving chronic Δ9- THC (1 mg/kg/12 h s.c.). Quantitative analysis of antagonism by rimonabant was conducted.

Previously, Schild analysis and single-dose apparent affinity estimates using rimonabant as the antagonist suggested that Δ9-THC, JWH-018, and JWH-073 produced subjective effects through a common receptor site (Ginsburg et al., 2012; Rodriguez and McMahon, 2014). HU-210, on the other hand, required significantly larger doses of rimonabant to both prevent and reverse its effects (Hruba and McMahon, 2014). These results, in conjunction with the long duration of action of HU-210 (i.e., 24-48 h), were attributed to pseudo-irreversible cannabinoid receptor binding. As disclosed herein,

rimonabant was administered prior to synthetic cannabinoids and pKB values were calculated in monkeys discriminating Δ9-THC. Reversal of the effects by rimonabant was examined in monkeys discriminating rimonabant while receiving Δ9-THC daily.

Methods and materials used are described herein and above.

Results

Rimonabant dose-dependently increased drug-lever responding, with 0.1 mg/kg producing 0% responding on the drug lever and 1 mg/kg producing 100% responding on the drug lever (Fig. 3 left panels, circles). The ED50 value was 0.25 mg/kg when rimonabant was administered in cumulative doses (i.e., the control function for experiments with CP-47,497) and 0.21 mg/kg when rimonabant was administered in a single dose per test session (Table 2). Rimonabant alone did not significantly modify rate of responding (Fig. 3, left panels, circles). Responding was 0% on the rimonabant lever when monkeys received i.v. vehicle or a dose of AM-2201 (0.1 and 0.32 mg/kg), JWH-122 (0.32 and 1 mg/kg), CP-47,497 (0.32, 1, and 3.2 mg/kg), or JWH-250 (1 and 3.2 mg/kg) 6 h after 1 mg/kg of Δ9-THC s.c. The largest doses of AM-2201 (0.32 mg/kg) and JWH-122 (1 mg/kg) produced emesis and ataxia. Response rate was significantly decreased to 14% of the vehicle control by 0.32 mg/kg AM-2201, 16% of the vehicle control by 1 mg/kg JWH-122, 16% of the vehicle control by 3.2 mg/kg CP-47,497, and 15% of the vehicle control by 3.2 mg/kg JWH-250 ($p<0.05$) (Fig. 3, right panels, symbols above VEH).

Table 2.

Drug	**ED_{50} Value (95% CL)**	**Potency Ratio (95% CL)**
Rimonabant (cumulative dosing)	0.25 (0.16-0.39)	
+ CP 47,497 (0.32 mg/kg)	0.51 (0.37-0.71)*	2.0 (1.2-3.6)
+ CP 47,497 (1.0 mg/kg)	1.02 (0.82-1.27)*	4.1 (2.0-8.5)
+ CP 47,497 (3.2 mg/kg)	2.66 (1.92-3.68)*	10.6 (2.9-39.3)
Rimonabant (single bolus dosing)	0.21 (0.12-0.46)	
+ AM-2201 (0.1 mg/kg)	0.77 (0.44-1.33)*	3.7 (1.6-8.3)
+ AM-2201 (0.32 mg/kg)	1.88 (1.67-2.11)*	9.0 (1.8-42.4)
+ JWH-122 (0.32 mg/kg)	0.49 (0.36-0.67)*	2.3 (1.3-4.1)
+ JWH-122 (1.0 mg/kg)	1.80 (1.78-1.82)*	8.6 (1.8-38.8)
+ JWH-250 (1.0 mg/kg)	0.56 (0.54-0.58)*	2.7 (1.3-5.2)
+ JWH-250 (3.2 mg/kg)	2.21 (1.74-2.82)*	10.5 (3.4-31.5)

ED50 values and 95% CLs for rimonabant, alone and in combination with AM-2201, JWH-122, CP-47,497, and JWH-250, in Δ9 -THC (1 mg/kg/12 h) treated rhesus monkeys discriminating rimonabant (1 mg/kg i.v.). Potency ratios and 95% CLs are the ED50 values of rimonabant in combination with the agonist divided by the ED50 value of rimonabant alone. Indicates significantly different from rimonabant alone.

AM-2201, JWH-122, CP-47,497, and JWH-250 significantly and dose-dependently attenuated the discriminative stimulus effects of rimonabant in monkeys receiving 1 mg/kg/12 h Δ9-THC. CP-47497, at doses of 0.32, 1, and 3.2 mg/kg, increased the ED50 value of rimonabant by 2.0-, 4.1-, and 10.6-fold, respectively (Table 2). AM-2201 (0.1 and 0.32 mg/kg) increased the ED50 value of rimonabant by 3.7 and 9.0-fold, respectively, JWH-122 (0.32 and 1.0 mg/kg) increased the ED50 value of rimonabant by 2.3- and 8.6-fold, respectively, and JWH-250 (1.0 and 3.2 mg/kg) increased the ED50 value of rimonabant by 2.7- and 10.5-fold, respectively (Table 2). Rimonabant significantly antagonized the rate-decreasing effects of each cannabinoid agonist. In the presence of rimonabant (1 mg/kg), AM-2201 (0.32 mg/kg) and JWH-122 (1.0 mg/kg) no longer produced emesis and ataxia.

The relationship between magnitude of shift in the rimonabant dose-response function and dose of cannabinoid agonist is shown in Fig 4. The slopes of the lines were not significantly different from each other (p=0.20). Linear regression was used to estimate the dose of each agonist producing a 2-fold rightward shift in the rimonabant dose-response function; the values were 0.06 for AM-2201, 0.24 for JWH-122, 0.44 for CP-47,497, and 0.64 for JWH-250. The relative potencies of AM-2201, JWH-122, CP-47,497, and JWH-250 to attenuate the rimonabant discriminative stimulus and substitute for the Δ9-THC discriminative stimulus effect were similar.

Rimonabant pretreatment resulted in surmountable antagonism of the discriminative stimulus effects of AM-2201, JWH-122, JWH-250, and CP-47,497. Under experimental conditions identical to the current study, rimonabant produced dose-dependent rightwards shifts in the dose-response functions of other cannabinoid agonists (McMahon, 2009; Ginsburg et al., 2012). The results of Schild analysis from these previous studies suggested that antagonism was simple, competitive, and reversible. The surmountable antagonism obtained at one dose of rimonabant here and elsewhere (McMahon, 2009) has been assumed to reflect a simple, competitive, and reversible interaction, i.e., the slope of a Schild plot was assumed to be not different from unity. Based on that assumption, a dose- ratio calculated

from a rightward shift is sufficient to calculate a single-dose apparent affinity estimate (i.e., pKB value). The pKB values calculated for rimonabant in the presence of AM-2201, JWH-122, JWH-250, and CP-47,497 did not significantly differ from each other. The current results add to existing data (McMahon, 2006; McMahon, 2009; Ginsburg et al., 2012; Hruba and McMahon, 2014) that evidences a common receptor mechanism (i.e., CB1) mediates the capacity of drugs to substitute for the discriminative stimulus effects of intravenously administered Δ9-THC in rhesus monkeys.

A quantitative analysis of the capacity of an antagonist to reverse the effects of synthetic cannabinoids not only provides insight into receptor mechanisms of action, but also could inform novel clinical applications. In Δ9-THC treated monkeys, pretreatment with AM-2201, JWH-122, JWH-250, and CP-47,497 resulted in a decrease in the potency of rimonabant to produce discriminative stimulus effects. That is, rimonabant reversed the effects of each synthetic cannabinoid. The capacity of rimonabant to reverse the effects of each synthetic cannabinoid was decreased as a function of increasing the dose of AM-2201, JWH-122, JWH-250, and CP- 47,497. Figure 4, which shows the magnitude of rightward shift in the rimonabant dose-effect function as a function of synthetic cannabinoid agonist dose, demonstrates that the relative potencies of AM-2201, JWH-122, JWH-250, and CP-47,497 are similar to their relative potencies in substituting for the discriminative stimulus effects of Δ9-THC (compare Fig. 4 to Fig. 1, top left). Collectively, these results demonstrate that rimonabant is equally effective in either preventing or reversing the effects of AM-2201, JWH-122, JWH-250, and CP-47,497. These data evidence that rimonabant can be an effective medication for reversing the CB1 receptor mediated effects of synthetic cannabinoids. Although the use of rimonabant (Acomplia™, Zimulti™) for treatment of obesity-related illness was discontinued in 2009 due to concerns over adverse effects, its limited (i.e., acute) use to reverse synthetic cannabinoid overdose in emergency situations can be beneficial.

Synthetic cannabinoids were originally synthesized as research tools and for potential therapeutic applications such as pain control. However, several of them have become drugs of abuse and it is becoming increasingly clear that many synthetic cannabinoid agonists can produce undesired effects that pose a significant hazard to human health. As described herein, for example, intravenous administration of relatively large doses of AM-2201 and JWH-122 produced vomiting and ataxia in rhesus monkeys. These adverse effects were not

observed in the presence of rimonabant or after intravenous administration of JWH-250 and CP-47,497 alone. AM-2201 and JWH-122 had the greatest potency for producing CB1 receptor-mediated effects, suggesting that high potency (i.e., greater than Δ9-THC) carries the greatest risk for adverse effects. The strikingly similar CB1 receptor pharmacology of most synthetic cannabinoids studied to date could be exploited by using CB1 receptor antagonists to antagonize adverse effects resulting from overdose.

It will be apparent to those skilled in the art that various modifications and variations can be made in the present invention without departing from the scope or spirit of the invention. Other aspects of the invention will be apparent to those skilled in the art from consideration of the specification and practice of the invention disclosed herein. It is intended that the specification and examples be considered as exemplary only, with a true scope and spirit of the invention being indicated by the following claims.

REFERENCES

Auwärter V, Dresen S, Weinmann W, Müller M, Pütz M, and Ferreirós N (2009) 'Spice' and other herbal blends: harmless incense or cannabinoid designer drugs? *J. Mass Spectrom* 44:832-837.

Atwood BK, Huffman J, Straiker A, and Mackie K (2009) JWH018, common constituent of 'Spice' herbal blends, is a potent and efficacious cannabinoid CB receptor agonist. *Br J Pharmacol* 160:585-593.

Balster RL and Prescott WR (1992) Δ^9-tetrahydrocannabinol discrimination in rats as a model for cannabis intoxication. *Neurosci Biobehav Rev* 16:55-62.

Carroll FI, Lewin AH, Mascarella SW, Seltzman HH, and Reddy PA (2012) Designer drugs: a medicinal chemistry perspective. *Ann N Y Acad Sci* 1248:18-38.

DEA Schedules of Controlled Substances: Temporary Placement of Five Synthetic Cannabinoids into Schedule I (2011) *Fed Reg* 76:11075-11078.

Gatch MB and Forster MJ (2014) Δ^9-Tetrahydrocannabinol-like discriminative stimulus effects of compounds commonly found in K2/Spice. *Behav Pharmacol* 25:750-757.

Gatch MB and Forster MJ (2016) Δ^9-Tetrahydrocannabinol-like effects of novel synthetic cannabinoids in mice and rats. *Psychopharmacology* 233:1901-1910.

Ginsburg BC, Schulze DR, Hruba L, and McMahon LR (2012) JWH-018 and JWH-073: Δ^9- tetrahydrocannabinol-like discriminative stimulus effects in monkeys. *J Pharmacol Exp Ther* 340:37-45.

Hruba L, Ginsburg BC, and McMahon LR (2012) Apparent inverse relationship between cannabinoid agonist efficacy and tolerance/cross-tolerance produced by Δ^9- tetrahydrocannabinol treatment in rhesus monkeys. *J Pharmacol Exp Ther* 342:843-849.

Hruba L and McMahon LR (2014) The cannabinoid agonist HU-210: pseudo-irreversible discriminative stimulus effects in rhesus monkeys. *Eur J Pharmacol* 727:35-42.

Hudson S and Ramsey J (2011) The emergence and analysis of synthetic cannabinoids. *Drug Test Anal* 3:466-478.

Huffman JW, Dai D, and Martin BR (1994) Design, synthesis and pharmacology of cannabinomimetic indoles. *Bioorg Med Chem Lett* 4:563-566.

Huffman JW, Mabon R, Wu, MJ Lu J, Hart R, Hurst, DP, Reggio PH, Wiley JL, and Martin BR (2003) 3-Indolyl-1-naphthylmethanes: new cannabimimetic indoles provide evidence for aromatic stacking interactions with the CB_1 cannabinoid receptor. *Bioorg Med Chem* 11:539-549.

Huffman JW, Szklennik PV, Almond A, Bushell K, Selley DE, He H, Cassidy MP, Wiley JL and Martin BR (2005) Pentyl-3-phenylacetylindoles, a new class of cannabimimetic indoles. *Bioorg Med Chem Lett* 15:4110-4113.

Huffman JW (2009) *Cannabinomimetic indoles, pyrroles and indenes: structure-activity relationships and receptor interactions.* In: The cannabinoid receptors (Regio PH, ed), Vol. 1, pp. 49–94. New York: Humana Press.

Järbe TU, Deng H, Vadivel SK, and Makriyannis A (2011) Cannabinergic aminoalkylindoles, including AM678=JWH018 found in 'Spice', examined using drug Δ^9-tetrahydrocannabinol discrimination for rats. *Behav Pharmacol* 22:498-507.

Järbe TU, Gifford RS, Zvonok A, and Makriyannis A (2016) Δ^9-Tetrahydrocannabinol discriminative stimulus effects of AM2201 and related aminoalkylindole analogs in rats. *Behav Pharmacol* 27:211-214.

Kenakin TP (1997) *Pharmacologic Analysis of Drug-Receptor Interaction,* 3rd ed, Raven Press, New York.

Lapoint J, James LP, Moran CL, Nelson LS, Hoffman RS and Moran JH (2011) Severe toxicity following synthetic cannabinoid ingestion. *Clin Toxicol (Phila)* 49:760-764.

Makriyannis A, Deng, H (2001) Cannabimimetic indole derivatives. United States Patent US00/28832 1-25

Makriyannis A and Deng H (2007) Cannabimimetic indole derivates. United States Patent US20080090871A1.

McMahon LR (2006) Characterization of cannabinoid agonists and apparent pA2 analysis of cannabinoid antagonists in rhesus monkeys discriminating Δ^9-tetrahydrocannabinol. *J Pharmacol Exp Ther* 319:1211-1218.

McMahon LR (2009) Apparent affinity estimates of rimonabant in combination with anandamide and chemical analogs of anandamide in rhesus monkeys discriminating Δ^9- tetrahydrocannabinol. *Psychopharmacology (Berl)* 203:219-228.

Nakajima J, Takahashi M, Nonaka R, Seto T, Suzuki J, Yoshida M, Kanai C, Hamano T (2011) Identification and quantitation of a benzoylindole (2-methoxyphenyl)(1-pentyl-1H-indol-3- yl)methanone and a naphthoylindole 1-(5-fluoropentyl-1H-indol-3-yl)-(naphthalene-1- yl)methanone (AM-2201) found in illegal products obtained via the Internet and their cannabimimetic effects evaluated by in vitro [35S]GTPγS binding assays. *Forensic Toxicol* 29:132-141.

Palmer SL, Thakur GA, and Makriyannis A (2002) Cannabinergic ligands. *Chem Phys Lipids* 121:3-19.

Rajasekaran M, Brents LK, Franks LN, Moran JH, Prather PL (2013) Human metabolites of synthetic cannabinoids JWH-018 and JWH-073 bind with high affinity and act as potent agonists at cannabinoid type-2 receptors. *Toxicol Appl Pharmacol* 269:100–108.

Rodriguez JS and McMahon LR (2014) JWH-018 in rhesus monkeys: differential antagonism of discriminative stimulus, rate-decreasing, and hypothermic effects. *Eur J Pharmacol* 740:151-159.

Rosenbaum CD1, Carreiro SP, and Babu KM (2012) Here today, gone tomorrow…and back again? A review of herbal marijuana alternatives (K2, Spice), synthetic cathinones (bath salts), kratom, Salvia divinorum, methoxetamine, and piperazines. *J Med Toxicol* 8:15-32.

Seely KA, Patton AL, Moran CL, Womack ML, Prather PL, Fantegrossi WE, Radominska-Pandya A, Endres GW, Channell KB, Smith NH, McCain KR, James LP, and Moran JH (2013) Forensic investigation of K2, Spice, and "bath salt" commercial preparations: a three- year study of new designer drug products containing synthetic cannabinoid, stimulant, and hallucinogenic compounds. *Forensic Sci Int* 233:416-422.

Simmons J, Cookman L, Kang C, and Skinner C (2011) Three cases of "spice" exposure. *Clin Toxicol (Phila)* 49:431-433.

Tallarida RJ (2000) *Drug Synergism and Dose-Effect Data Analysis*, Chapman and Hall/CRC, Boca Raton, FL.

Vardakou I, Pistos C, and Spiliopoulou Ch (2010) Spice drugs as a new trend: mode of action, identification and legislation. *Toxicol Lett* 197:157-162.

Weissman A, Milne GM, and Melvin LS (1982) Cannabimimetic activity from CP-47,497, a derivative of 3-phenylcyclohexanol. *J Pharmacol Exp Ther* 223:516-23.

Wiley JL, Marusich JA, Martin BR, and Huffman JW (2012) 1-Pentyl-3-phenylacetylindoles and JWH-018 share in vivo cannabinoid profiles in mice. *Drug and Alcohol Dependence* 123: 148-153.

CLAIMS

WHAT IS CLAIMED IS:

1. A method of treating or preventing synthetic cannabinoid toxicity or overdose in a subject, the method comprising:

(a) identifying a subject in need of treatment; and

(b) administering to the subject a therapeutically effective amount of rimonabant.

2. The method of claim 1, wherein the therapeutically effective amount of rimonabant is 7 to 25 mg/kg of body weight.

3. The method of claim 1, wherein rimonabant is administered intravenously.

4. The method of claim 1, wherein the synthetic cannabinoid toxicity or overdose results from synthetic cannabinoid administration to a non-dependent subject.

5. The method of claim 4, wherein the subject is a synthetic cannabinoid user.

6. The method of claim 1, wherein administration of the rimonabant reduces one or more symptoms of drug toxicity or overdose.

7. The method of claim 6, wherein the symptoms of drug toxicity or overdose are reduced over a period of at least 15 to about 30 minutes.

8. The method of claim 6, wherein the symptoms of drug toxicity or overdose are reduced over a period of at least 1 hour.

9. The method of claim 6, wherein the symptoms of drug toxicity or overdose are reduced over a period of at least 4 hours.

10. The method of claim 1, wherein the symptoms of toxicity or overdose is selected from seizures, tachycardia, hypokalemia, nausea and vomiting.

11. The method of claim 1, wherein rimonabant is contained within a pharmaceutical formulation.

12. The method of claim 11, wherein the pharmaceutical formulation is a unit dosage formulation.

13. The method of claim 1, wherein rimonabant is administered on an as-needed basis.

14. A method of ameliorating one or more symptoms of synthetic cannabinoid toxicity or overdose in a subject, the method comprising:

(a) identifying a subject in need of treatment; and

(b) administering to the subject a therapeutically effective amount of rimonabant.

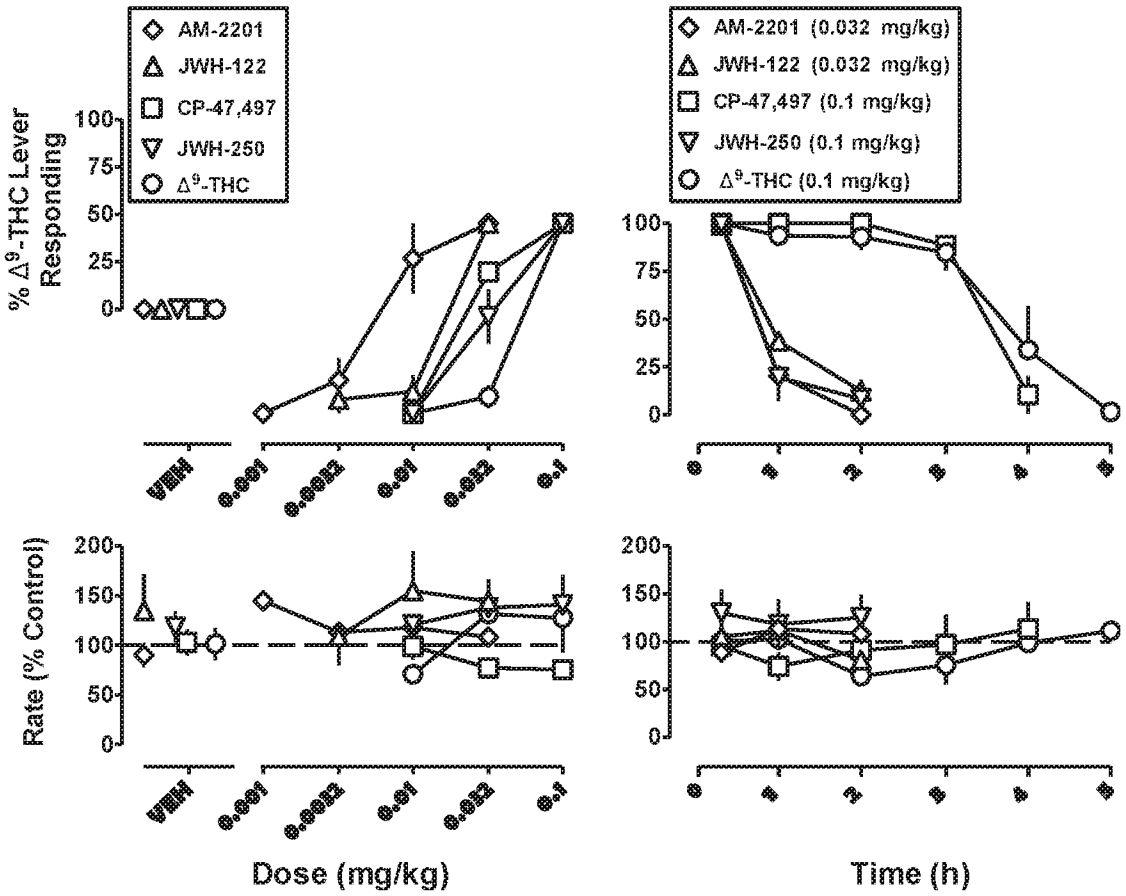
AM-2201
JWH-122
CP-47,497
JWH-250
Δ9-THC
% Δ9-THC Lever Responding
Rate (% Control)
Dose (mg/kg)
AM-2201 (0.032 mg/kg)
JWH-122 (0.032 mg/kg)
CP-47,497 (0.1 mg/kg)
JWH-250 (0.1 mg/kg)
Δ9-THC (0.1 mg/kg)
Time (h)

Fig. 1

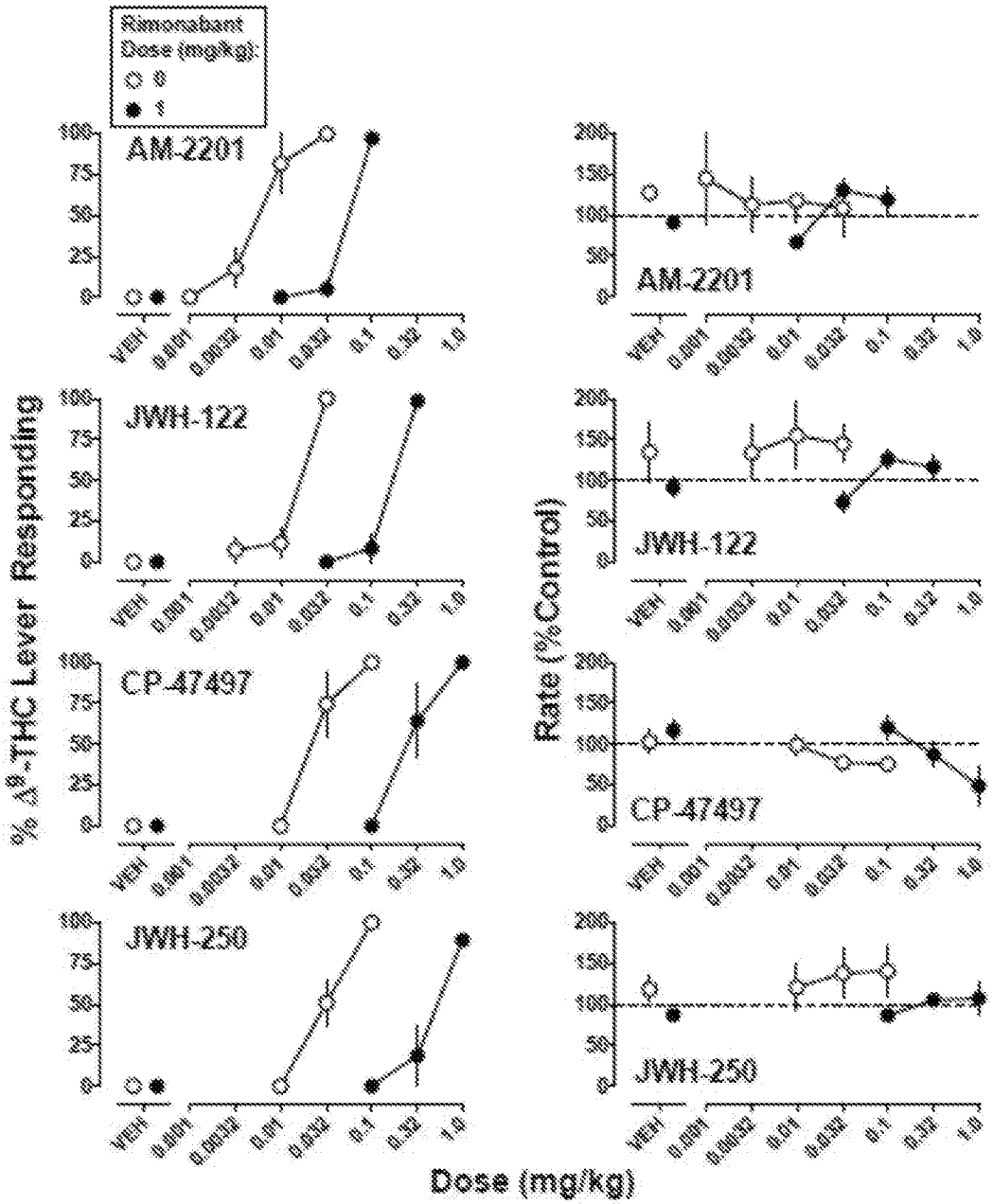
Rimonabant
Dose (mg/kg):
0
1
AM-2201
JWH-122
CP-47497
JWH-250
% Δ9-THC Lever Responding
Rate (% Control)
Dose (mg/kg)

Fig. 2

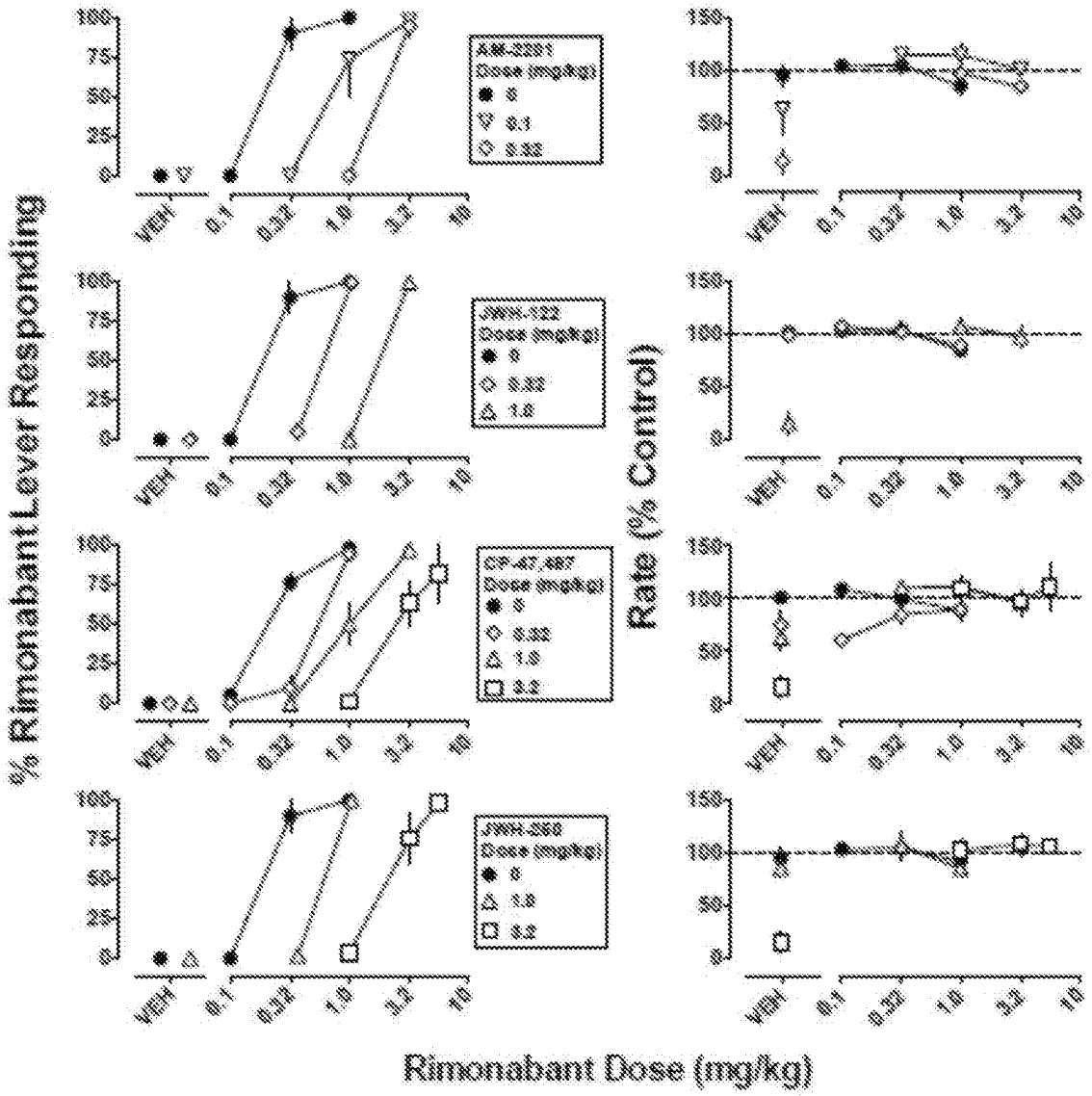
% Rimonabant Lever Responding
Rate (% Control)
Rimonabant Dose (mg/kg)

Fig. 3

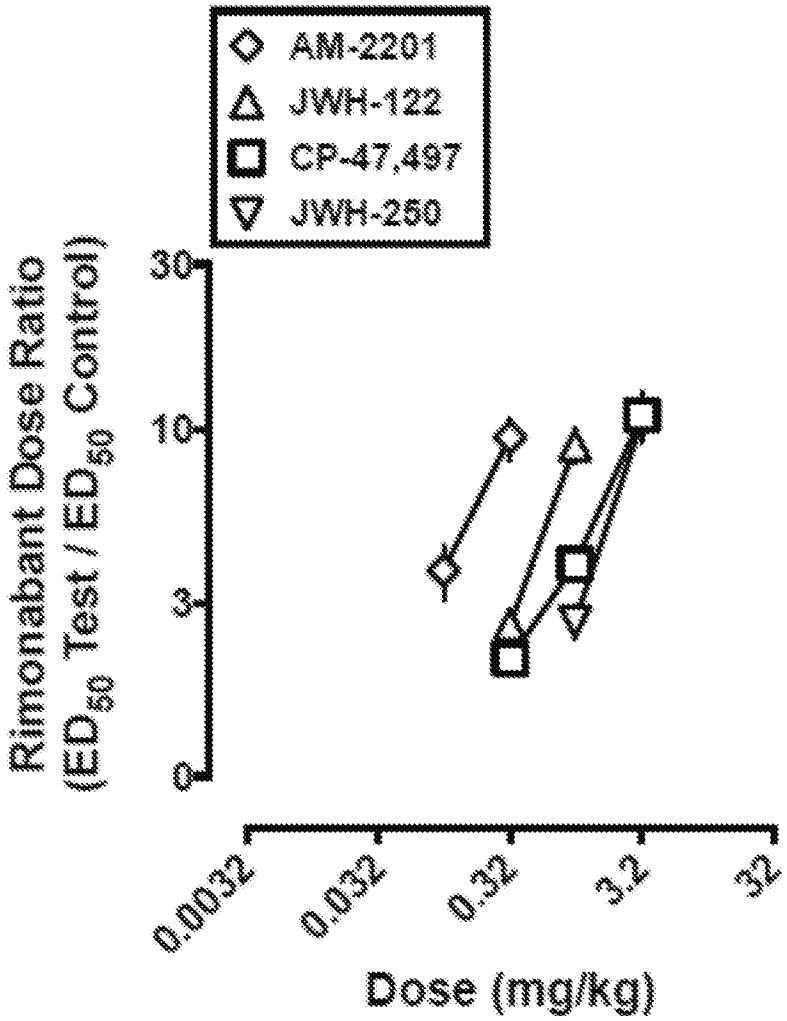
AM-2201
JWH-122
CP-47,497
JWH-250
Rimonabant Dose Ratio
(ED50 Test / ED50 Control)
30
10
3
0
0.0032
0.032
0.32
3.2
32
Dose (mg/kg)

Fig. 4

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 18/30944

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/352, A61K 31/397, A61K 31/415 (2018.01)
CPC - A61K 31/337, A61K 31/352, A61K 31/353

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History Document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History Document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History Document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FORD et al. "Synthetic Pot: NotYour Grandfather's Marijuana", 2016, Trends in Pharacological Science, pg.s 1-20 Pg. 1, Para [1];Pg. 4, Full Para [2]; Pg. 13, Para [3]; Pg. 14, Para [1];	1-14
A	US 2015/0265636A1 (KANE et al.) 24 September 2015 (24.09.2015) Entire Document	1-14
A	US 2015/0342922 A1 (ANKNER et al.) 03 December 2015 (03.12.2015) Entire Document	1-14
A	US 2009/0048232 A1 (CICCOCIOPPO) 19 February 2009 (19.02.2009) Entire Document	1-14

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
09 July 2018	26 JUL 2018
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774