Neuropharmacology 124 (2017) 73–83

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Invited review

# The endocannabinoid system as a target for addiction treatment: Trials and tribulations

Matthew E. Sloan [a], Joshua L. Gowin [a], Vijay A. Ramchandani [a], Yasmin L. Hurd [b], Bernard Le Foll [c, d, e, f, *]

[a] Section on Human Psychopharmacology, National Institute on Alcohol Abuse and Alcoholism, 10 Center Drive (10CRC, 2-2352), Bethesda, MD, 20892-1540, USA
[b] Departments of Psychiatry, Neuroscience, Pharmacology, and Systems Therapeutics, Icahn School of Medicine at Mount Sinai, Hess CSM Building, Floor 10, Rm 105, Office 1470, Madison Avenue, New York, NY, 10029, USA
[c] Translational Addiction Research Laboratory, Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, 33 Russell Street, Toronto, Ontario, M5S 2S1, Canada
[d] Addiction Medicine Service, Ambulatory Care and Structured Treatments, Centre for Addiction and Mental Health, Toronto, Ontario, Canada
[e] Departments of Family and Community Medicine, Pharmacology and Toxicology, and Psychiatry, Institute of Medical Science, University of Toronto, Toronto, Ontario, Canada
[f] Campbell Family Mental Health Research Institute, Centre for Addiction and Mental Health, Toronto, Ontario, Canada

ARTICLE INFO

*Article history:*
Received 22 February 2017
Received in revised form
24 May 2017
Accepted 26 May 2017
Available online 28 May 2017

*Keywords:*
Dronabinol
Cannabidiol
Cannabinoid antagonists
Endocannabinoids
Substance use disorders
Smoking cessation
Withdrawal
Clinical trial

ABSTRACT

Addiction remains a major public health concern, and while pharmacotherapies can be effective, clinicians are limited by the paucity of existing interventions. Endocannabinoid signaling is involved in reward and addiction, which raises the possibility that drugs targeting this system could be used to treat substance use disorders. This review discusses findings from randomized controlled trials evaluating cannabinergic medications for addiction. Current evidence suggests that pharmacotherapies containing delta-9-tetrahydrocannabinol, such as dronabinol and nabiximols, are effective for cannabis withdrawal. Dronabinol may also reduce symptoms of opioid withdrawal. The cannabinoid receptor 1 (CB1) inverse agonist rimonabant showed promising effects for smoking cessation but also caused psychiatric side effects and currently lacks regulatory approval. Few trials have investigated cannabinergic medications for alcohol use disorder. Overall, the endocannabinoid system remains a promising target for addiction treatment. Development of novel medications such as fatty acid amide hydrolase inhibitors and neutral CB1 antagonists promises to extend the range of available interventions.

This article is part of the Special Issue entitled "A New Dawn in Cannabinoid Neurobiology".



**Contents**



* Corresponding author. Centre for Addiction and Mental Health, 33 Russell Street, Toronto, Ontario, M5S 2S1. Canada.
*E-mail address:* bernard.lefoll@camh.ca (B. Le Foll).

http://dx.doi.org/10.1016/j.neuropharm.2017.05.031
0028-3908/

## 1. Introduction

Despite the toll that addictions continue to take on public health (Forouzanfar et al., 2016; Rudd et al., 2016), only a small number of pharmacological treatment strategies are available. Although these treatments have been shown to reduce substance-related mortality (Degenhardt et al., 2009), existing pharmacotherapies are only effective for a subset of patients and several substance use disorders lack a single FDA-approved medication (Le Foll, 2016). Many existing pharmacotherapies function as either long-term or temporary substitution strategies, which replace the drug of abuse with a medication targeting the same receptor system that serves to reduce withdrawal and craving. There is an urgent need to develop pharmacotherapies with novel mechanisms of action for patients who are unresponsive to drugs targeting traditional receptor systems as well as for those who have substance use disorders which lack effective treatments.

Over the past three decades, the development of pharmacotherapies targeting the endocannabinoid system (Box 1) has produced a range of compounds that have been studied as treatments for substance use disorders. Many of these medications target cannabinoid receptor 1 (CB1), the primary cannabinoid receptor in the central nervous system (Box 2). CB1 is densely expressed in brain regions involved in the development and maintenance of addictive behaviors including the ventral striatum, the dorsal striatum, and the amygdala (Parsons and Hurd, 2015). Modulation of CB1 receptor activity in each of these regions leads to downstream behavioral effects. For example, CB1 receptor activity moderates alcohol consumption and alcohol-induced dopamine release in the ventral striatum (Caille et al., 2007; Hungund et al., 2003), gates habit formation in the dorsal striatum (Gremel et al., 2016), and regulates fear extinction in the amygdala (Gunduz-Cinar et al., 2013). Thus, pharmacological treatments which alter endocannabinoid signaling could be expected to change addictive behaviors across substance use disorders by directly impinging on the neurobiological underpinnings of addiction.

Pharmacotherapies targeting the endocannabinoid system may also have substance-specific effects. For cannabis use disorder, as delta-9-tetrahydrocannabinol ($\Delta^9$-THC) is a partial CB1 agonist, CB1 agonists and partial agonists may serve as a substitution therapy analogous to methadone and buprenorphine for opioid use disorder or the nicotine patch for nicotine use disorder. For substances

**Box 1**
The Endocannabinoid System: Key Components

Cannabinoid Receptors:

**CB1**: A G-protein coupled cannabinoid receptor that is widely distributed in the human brain. Its activation is thought to be primarily responsible for the psychoactive effects of cannabinoids.

**CB2**: A cannabinoid receptor primarily expressed in peripheral immune cells, where it is thought to modulate immune function. Recent preclinical evidence suggests that it is also expressed in the central nervous system.

Endocannabinoid Neurotransmitters:

**Anandamide**: An endogenous cannabinoid neurotransmitter which functions as a cannabinoid receptor partial agonist.

**2-arachidonoylgylcerol (2-AG)**: An endogenous cannabinoid neurotransmitter which functions as a full cannabinoid receptor agonist.

Cannabinoid metabolizing enzymes:

**Fatty Acid Amide Hydrolase (FAAH)**: A membrane-bound serine hydrolase which inactivates anandamide by converting it to arachidonic acid and ethanolamine.

**Monoacylglycerol Lipase (MAGL)**: A cytosolic serine hydrolase which inactivates 2-AG by converting it to arachidonic acid and glycerol.

**Box 2**
Selected Compounds Targeting the CB1 Receptor

**Delta-9 Tetrahydrocannabinol ($\Delta^9$-THC)**: Cannabinoid primarily responsible for the psychoactive effects of cannabis. Functions as a partial CB1 agonist.

**Cannabidiol (CBD)**: Cannabinoid found in many strains of cannabis. Reduces CB1 activity, possibly through an allosteric mechanism, and has diverse pharmacodynamic effects on other receptor systems.

**Dronabinol (Marinol®)**: Encapsulated oral formulation of $\Delta^9$-THC. FDA-approved for the management of anorexia with weight loss in patients with AIDS and treatment-resistant nausea and vomiting associated with cancer chemotherapy.

**Nabilone (Cesamet®)**: Synthetic analogue of $\Delta^9$-THC. FDA-approved for the management of treatment-resistant nausea and vomiting associated with cancer chemotherapy.

**Nabiximiols (Sativex®)**: An oromucosal spray containing both $\Delta^9$-THC and cannabidiol (2.7 mg $\Delta^9$-THC and 2.5 mg CBD per spray). Approved in Canada and the United Kingdom for adjunctive treatment of multiple sclerosis and in Canada for adjunctive treatment of pain associated with advanced cancer.

**Rimonabant (Acomplia®)**: A CB1 receptor inverse agonist which was initially approved for the treatment of obesity in the European Union. Marketing approval was withdrawn in 2009 due to concerns about adverse psychiatric side effects.

for which the CB1 receptor is not the primary pharmacological target, CB1 modulation could still prove effective. For instance, alcohol and heroin increase extracellular endocannabinoid levels in the nucleus accumbens (Caille et al., 2007), therefore CB1 antagonism could potentially alter the reinforcing properties of these drugs. Modulating endocannabinoid signaling could also have effects on non-cannabinoid signaling pathways relevant to specific substances. For example, reducing CB1 activity increases cholinergic neurotransmission (Kathmann et al., 2001), which may have implications for cannabinergic treatments for nicotine use disorder.

Recent reviews have summarized the role of the endocannabinoid system in brain reward signaling (Parsons and Hurd, 2015) and explored the behavioral effects of endocannabinoid modulation in animal models of addiction (Serrano and Parsons, 2011; Trigo and Le Foll, 2017). To determine whether these preclinical findings can be successfully translated to clinical settings, it is necessary to evaluate the evidence obtained from clinical trials testing cannabinoid modulating treatments. Here we will attempt to comprehensively review the evidence from randomized placebo-controlled clinical trials investigating whether pharmacotherapies that target the endocannabinoid system can be helpful in the management of substance use disorders. We will focus on the three most commonly reported clinically relevant outcomes: withdrawal severity, relapse rates, and drug self-administration. Most studies have examined the effects of these pharmacotherapies in nicotine, cannabis, alcohol, and opioid use disorders, therefore we will focus on these four disorders. Important details from each study, including sample size, medication dose, and treatment duration, will be reported in the accompanying tables. We will also briefly discuss compounds with encouraging preclinical evidence that have not yet been tested clinically in populations with addiction, including inhibitors of endocannabinoid metabolism.

## 2. Cannabinoid modulating treatments for addiction

### 2.1. Nicotine use disorder

Nicotine replacement, bupropion, varenicline, and cytisine have all been found to improve smoking cessation rates (Cahill et al., 2013, 2016). Nicotine, varenicline, and cytisine work by activating the $\alpha4\beta2^*$ nicotinic acetylcholine receptor (Morales-Perez et al., 2016; Papke and Heinemann, 1994), a ligand-gated ion channel which is thought to be centrally involved in the reinforcing effects of nicotine (Picciotto et al., 1998; Tapper et al., 2004). By contrast, bupropion and its metabolites have a more complex mechanism of action involving both blockade of $\alpha4\beta2^*$ nicotinic acetylcholine receptors and inhibition of dopamine and norepinephrine reuptake (Damaj et al., 2004; Slemmer et al., 2000), which may reduce relapse rates by diminishing symptoms of nicotine withdrawal (Warner and Shoaib, 2005). The endocannabinoid system interacts with both the cholinergic and dopaminergic systems, and could therefore be a promising target for smoking cessation.

Rimonabant, a selective CB1 blocker with inverse agonist activity (Landsman et al., 1997; Rinaldi-Carmona et al., 1994), was once a promising candidate as a smoking cessation therapy. It was initially developed as a weight-loss medication and received European regulatory approval for the treatment of obesity in 2006 (EMA, 2007). In addition to its anti-obesity effects, preclinical studies found that rimonabant reduced nicotine self-administration (Cohen et al., 2002), conditioned place preference (Forget et al., 2005; Le Foll and Goldberg, 2004), and cue-induced relapse (Forget et al., 2009), possibly by reducing nicotine and nicotine-cue induced dopamine release (Cohen et al., 2002). These studies suggested that rimonabant could be effective for smoking cessation in humans while reducing smoking cessation related weight gain.

A series of clinical trials known as the Studies with Rimonabant and Tobacco Use (STRATUS) tested rimonabant for nicotine use disorder (Table 1). Although unpublished, the results of three of the STRATUS trials have been summarized in a review (Cahill and Ussher, 2011). Pooled results from two smoking cessation trials found that the 20 mg dose of rimonabant, but not the 5 mg dose, substantially increased abstinence rates and reduced smoking cessation related weight gain relative to placebo. In a third trial investigating long-term relapse prevention, smokers were initially randomized to receive rimonabant 5 mg or 20 mg. Those who quit smoking were then re-randomized to be maintained on rimonabant or placebo. Participants who successfully quit smoking using the 20 mg dose of rimonabant and were then maintained on the medication had improved odds of remaining abstinent at 1 year follow up. The only published rimonabant trial, the CIRRUS trial, investigated a combination of rimonabant with the nicotine patch (Rigotti et al., 2009). Those randomized to the nicotine patch plus rimonabant combination had higher rates of continuous abstinence than those receiving placebo patch plus rimonabant (39.0% versus 21.3%), but the trial was limited by the lack of a nicotine patch monotherapy group and a placebo-only control group. Nonetheless, the abstinence rate in the combined group compares favorably to the reported abstinence rate following nicotine patch monotherapy in a recent well-powered study (Baker et al., 2016), suggesting a possible synergistic effect. Unfortunately, rimonabant's promising findings may not extend to other CB1 antagonists and inverse agonists. Trials testing the CB1 blockers surinabant and taranabant have been negative, although this may have been related to insufficient dosages (Morrison et al., 2010; Tonstad and Aubin, 2012).

Post-hoc analyses of rimonabant trials for obesity and metabolic disorders eventually began to show worrisome patterns of adverse events. Meta-analyses of the four Rimonabant in Obesity (RIO) trials demonstrated higher rates of mood and anxiety symptoms in patients receiving rimonabant versus placebo (Christensen et al., 2007; Rucker et al., 2007). This was a concern in the CIRRUS smoking cessation trial as well, as 17 participants discontinued treatment due to depression or anxiety and one participant attempted suicide (Rigotti et al., 2009). In 2008, the CRESCENDO trial, a massive study evaluating rimonabant for prevention of cardiovascular events, was stopped prematurely by regulatory authorities due to concerns about higher rates of completed suicide (4 versus 1) and psychiatric adverse events in the rimonabant versus placebo group (Topol et al., 2010). Shortly afterwards, the European Medicines Agency decided to withdraw the marketing authorization for rimonabant in the European Union (EMA, 2009). There are currently no CB1 antagonists or inverse agonists with regulatory agency approval. The problems observed in these trials pose a dilemma for the development of novel CB1 antagonists. If new compounds are eventually tested in clinical trials, excluding participants with current or past mood and anxiety disorders as well as those with a history of suicidal behavior may improve the risk-to-benefit ratio.

There is evidence that cannabidiol (CBD), a cannabinoid found in many strains of cannabis, decreases CB1 receptor activity without the side effects of CB1 inverse agonists (Bergamaschi et al., 2011; Rohleder et al., 2016). CBD's mechanism of action at the CB1 receptor is not yet clear, but it may function as a negative allosteric modulator (Laprairie et al., 2015) or antagonize the CB1 receptor (Thomas et al., 2007). The pharmacodynamic effects of CBD are complex. For example, CBD may act on $5HT_{1A}$ receptors (Russo et al., 2005), TRPV cation channels (Bisogno et al., 2001; Qin et al., 2008), and may modulate endocannabinoid metabolism and reuptake (Bisogno et al., 2001). A small, one-week pilot study

**Table 1**
Cannabinoid modulating treatments for nicotine use disorder.

| Study | Endpoint of Interest | Treatment (N) | Treatment Duration | Outcome | Treatment Effective[a] |
|---|---|---|---|---|---|
| STRATUS-EU (Cahill and Ussher, 2011) | Smoking Cessation | Rimonabant 5 mg[b] (N = 256) Rimonabant 20 mg (N = 267) Placebo (N = 260) | 10 wks | 20 mg dose effective (1.50 RR[c] vs. placebo for prolonged abstinence at week 50) in pooled STRATUS-EU + US analysis | Yes |
| STRATUS-US (Cahill and Ussher, 2011) | Smoking Cessation | Rimonabant 5 mg (N = 262) Rimonabant 20 mg (N = 261) Placebo (N = 261) | 10 wks | See above | – |
| STRATUS-WW (Cahill and Ussher, 2011) | Prolonged Relapse Prevention | Rimonabant 5 mg (N = 2026): 644 quitters re-randomized to treatment or placebo for relapse prevention phase[d] Rimonabant 20 mg (N = 3029): 1017 quitters re-randomized for relapse prevention phase[d] | First Phase: 10 wks, Second Phase: 42 wks | Quitters from 20 mg group maintained on treatment had higher abstinence rates (RR of 1.3 for either dose vs. placebo) | Yes |
| CIRRUS (Rigotti et al., 2009) | Smoking Cessation | Rimonabant 20 mg + 21 mg Nicotine Patch (N = 369) Rimonabant 20 mg + Placebo Patch (N = 366) | 8 wks[e] | Combined treatment more effective than rimonabant monotherapy (39.0% vs. 21.3% abstinence rate) | Yes |
| (Morrison et al., 2010), | Smoking Cessation | Taranabant 2-8 mg[f] (N = 159) Placebo (N = 158) | 8 wks | No effect of treatment on continuous abstinence rates (7.5% active treatment group vs. 6.3% placebo group) | No |
| (Tonstad and Aubin, 2012), | Smoking Cessation | Surinabant 2.5 mg (N = 199) Surinabant 5 mg (N = 204) Surinabant 10 mg (N = 205) Placebo (N = 202) | 8 wks | No effect of treatment on continuous abstinence rates (21.5%–22.6% and 25.2% for active treatment groups & placebo group respectively) | No |
| (Morgan et al., 2013), | Smoking Reduction | Cannabidiol inhaler[g] (N = 12) Placebo (N = 12) | 1 wk | Reduced no. of cigarettes smoked in CBD but not placebo group | Yes |

[a] As compared to placebo group.
[b] All dosages expressed as total daily dose.
[c] RR = Risk Ratio.
[d] Rimonabant 5 mg quitters re-randomized to rimonabant 5 mg (N = 322) or placebo (N = 322); rimonabant 20 mg quitters re-randomized to rimonabant 20 mg (N = 340), rimonabant 5 mg (N = 335), or placebo (N = 342).
[e] 1-week lead-in treatment period in which participants were given rimonabant 20 mg prior to randomization to nicotine patch or placebo, 8-week of combination treatment, and two-week nicotine patch taper (nicotine patch 14 mg/daily x 1 week and 7 mg/daily x 1 week).
[f] Dose was titrated from 2 mg to 8 mg daily with the goal of limiting adverse events. If a patient experienced significant side effects, the dose was not increased and could be adjusted downward.
[g] Participants were instructed to use the inhaler whenever they felt like smoking. The inhaler administered 400mcg of CBD dissolved in absolute ethanol per dose.

that randomized treatment-seeking smokers to a CBD or placebo inhaler found modest reductions in self-reported smoking (Morgan et al., 2013), but it is unclear which of CBD's pharmacological effects produced this reduction. Further studies of CBD are warranted.

CB1 antagonists and inverse agonists have been studied for smoking cessation more than for any other substance use disorder indication and the current evidence indicates that rimonabant improves continuous abstinence rates and reduces relapse rates. However, any future consideration of CB1 antagonists will need to carefully weigh the risks and benefits of treatment. If low risk groups are prespecified and patients are carefully monitored for psychiatric symptoms, the potential for harm may be minimized. Alternatively, development of novel CB1 antagonists with better side effect profiles could resolve this issue. In either of these scenarios, the use of CB1 antagonists to improve smoking cessation rates and reduce relapse risk could offer substantial benefits, especially in patients for whom smoking cessation-induced weight gain poses a significant barrier to treatment.

### 2.2. Cannabis use disorder

Only a small proportion of individuals with cannabis use disorder receive any type of treatment for their problematic cannabis use (Hasin et al., 2016). One of the reasons for the low treatment rate may be the lack of effective pharmacotherapies. There are currently no FDA approved medications for cannabis use disorder and there is insufficient evidence that any of the medications that have been tested effectively promote abstinence (Gorelick, 2016; Marshall et al., 2014). Drugs targeting the endocannabinoid system would be a logical strategy for the treatment of this disorder.

Chronic cannabis use leads to CB1 receptor downregulation (D'Souza et al., 2016; Hirvonen et al., 2012), and these signaling alterations may lead to withdrawal symptoms when an individual decides to suddenly cut down or abstain from use. Treatment with CB1 agonists could be used to reduce these signaling alterations and therefore suppress withdrawal symptoms. Three CB1 agonists have been studied: dronabinol, which is encapsulated oral $\Delta^9$-THC, nabilone, an oral synthetic analogue of $\Delta^9$-THC that exhibits dose linearity (Lemberger et al., 1982) and has a slower time to peak subjective effect than dronabinol (Bedi et al., 2013), and nabiximols, an oromucosal spray containing both $\Delta^9$-THC and CBD (Collin et al., 2007). A series of human laboratory trials have tested these three medications in non-treatment seeking cannabis users by employing designs in which individuals are instructed to smoke cannabis for one or more days and then abstain from use while receiving either CB1 agonist or placebo. These studies have found that dronabinol (Budney et al., 2007; Haney et al., 2004, 2008; Vandrey et al., 2013), nabilone (Haney et al., 2013; Herrmann et al., 2016), and nabiximols (Trigo et al., 2016) are all effective for cannabis withdrawal (Table 2). The effectiveness of both dronabinol and nabiximols for cannabis withdrawal has been verified in larger clinical trials involving treatment-seeking participants (Allsop et al., 2014; Levin et al., 2011). Since withdrawal seems to be one of the factors that leads cannabis-dependent individuals to relapse (Allsop et al., 2012), it was then hypothesized that prescribing CB1 agonists could also lower relapse rates.

Three randomized controlled trials have tested CB1 agonists as relapse prevention strategies. Two dronabinol trials, one using dronabinol monotherapy and another using a combination of dronabinol and the alpha-2 adrenergic agonist lofexidine, employed six weeks of medication maintenance but found no reduction in abstinence rates when treatment groups were

**Table 2**
Cannabinoid modulating treatments for cannabis use disorder.

| Study | Endpoint(s) of Interest | Treatment (N) | Treatment Duration | Outcome | Treatment Effective[a] |
|---|---|---|---|---|---|
| (Haney et al., 2004) | Withdrawal Severity | Dronabinol 50 mg[b] Placebo (Within-Subject, N = 7) | 6 days[c] | Significant reduction in withdrawal severity with dronabinol treatment. | Yes |
| (Budney et al., 2007) | Withdrawal Severity | Dronabinol 30, 90 mg Placebo (Within-Subject, N = 8) | 5 days[d] | Significant reduction in withdrawal severity with dronabinol treatment. | Yes |
| (Haney et al., 2008) | Withdrawal Severity, Self-Administration | Dronabinol 60 mg Lofexidine 2.4 mg Dronabinol + Lofexidine[e] Placebo (Within-Subject, N = 8) | 7 days[f] | All active treatments reduced withdrawal symptoms. Lofexidine alone and in combination reduced self-administration. | Yes |
| (Vandrey et al., 2013) | Withdrawal Severity | Dronabinol 30, 60, 120 mg Placebo (Within-Subject, N = 13) | 5 days[d] | Dose-dependent reduction in withdrawal severity with dronabinol. | Yes |
| (Levin et al., 2011) | Relapse Prevention, Withdrawal Severity | Dronabinol 40 mg (N = 79) Placebo (N = 77) | 9 wks[g] | Dronabinol had no effect on abstinence rates (17.7% active treatment group vs. 15.6% placebo group) but reduced withdrawal severity. | No[h] |
| (Levin et al., 2016) | Relapse Prevention, Withdrawal Severity | Dronabinol + Lofexidine[e] (N = 61) Placebo (N = 61) | 10 wks[g] | No effect of active treatment on abstinence rates (27.9% active treatment group vs. 29.5% placebo group) or withdrawal severity. | No |
| (Haney et al., 2013) | Withdrawal Severity, Self-Administration | Nabilone 6, 8 mg Placebo (Within-Subject, N = 11) | 7 days[f] | Nabilone treatment reduced withdrawal severity and self-administration. | Yes |
| (Herrmann et al., 2016) | Withdrawal Severity, Self-Administration | Zolpidem 12.5 mg Nabilone + Zolpidem[i] Placebo (Within-Subject, N = 11) | 7 days[f] | Combination treatment reduced withdrawal severity and self-administration. | Yes |
| (Allsop et al., 2014) | Withdrawal Severity, Cannabis Use | Nabiximols[j] (N = 27) Placebo (N = 24) | 6 days | Reduced withdrawal severity in nabiximols group but no change in weekly cannabis use at 28-day follow up. | Yes[k] |
| (Trigo et al., 2016) | Withdrawal Severity | Fixed-dose Nabiximols[l] Self-titrated Nabiximols Fixed-dose Placebo Self-titrated Placebo (Within-Subject, N = 9) | 4 days[m] | Both active treatments suppressed abstinence-induced withdrawal. | Yes |

[a] As compared to placebo group.
[b] All dosages expressed as total daily dose.
[c] Participants lived in a residential laboratory for two 15-day inpatient phases, one while receiving only placebo and one while receiving placebo for the first 9 days and dronabinol for the last 6 days. On days 5–8, a standardized dose of cannabis was given to the participants. On days 9–14 (6 days), placebo cannabis was given and effects of treatment on withdrawal severity were observed. The two inpatient phases were separated by an outpatient washout period.
[d] (Budney et al., 2007) and (Vandrey et al., 2013) had similar designs. Participants engaged in 7–9 day periods of smoking cannabis as usual separated by 5-day periods of abstinence from cannabis in which they received treatment (placebo or dronabinol at doses ranging from 30 to 120 mg).
[e] For (Haney et al., 2008), daily doses of dronabinol and lofexidine were 60 mg and 2.4 mg respectively. For (Levin et al., 2016), daily doses of dronabinol and lofexidine were 60 mg and 1.8 mg respectively or maximum tolerated dose.
[f] (Haney et al., 2008), (Haney et al., 2013), and (Herrmann et al., 2016) had similar designs. Subjects lived in a residential laboratory for 8 days under different treatment conditions. During each stay, participants smoked 6 doses of cannabis on day 1. Participants started each active treatment on day 2 while simultaneously being withdrawn from cannabis for 3 days (withdrawal phase, days 2–4). Finally, they were given the opportunity to pay to self-administer cannabis for 4 days (relapse phase, days 5–8). Therefore, each active treatment was given for 7 days' duration. Each inpatient phase was separated by an outpatient washout period.
[g] (Levin et al., 2011) and (Levin et al., 2016) had similar designs. The full trials were 11–12 weeks: a 1 week placebo lead-in phase, a 1–2-week medication titration phase, a 6-week medication maintenance phase, a 2-week tapering phase, and a 1–2-week placebo lead-out phase.
[h] No treatment effect for primary endpoint of relapse prevention, but the treatment was effective at suppressing cannabis withdrawal symptoms.
[i] Daily doses of nabilone and zolpidem were 6 mg and 12.5 mg respectively.
[j] Maximum dose was 86.4 mg $\Delta^9$-THC + 80 mg CBD, dose was tapered until discontinuation during treatment.
[k] No treatment effect with respect to self-reported weekly cannabis use at 28-day follow up.
[l] Fixed dose was 40 sprays (108 mg $\Delta^9$-THC and 100 mg CBD) and self-titrated strategy was up to 40 sprays.
[m] Participants competed four smoking-cannabis-as-usual conditions followed by each of the four treatment conditions for 4 days.

compared to placebo groups (Levin et al., 2011, 2016). Furthermore, although dronabinol monotherapy improved treatment retention, the combination of dronabinol and lofexidine did not improve withdrawal or increase treatment retention. A trial testing nabiximols employed a different approach. Cannabis-dependent participants were randomized to a 6-day nabiximols taper or placebo during a nine-day inpatient stay to provide initial management of cannabis withdrawal (Allsop et al., 2014). Relapse rates were then examined 28 days later. Nabiximols reduced cannabis withdrawal and increased treatment retention for the duration of medication administration, but 3 days after discontinuation there was no longer a difference in retention. At 28-day follow-up, there was no significant difference in cannabis use between treatment groups. Thus, the available evidence suggests that management of cannabis withdrawal is not sufficient to reduce relapse to cannabis use. Longer-term maintenance with dronabinol appears ineffective, but trials investigating long-term administration of nabiximols are necessary to confirm whether combined $\Delta^9$-THC and CBD maintenance strategies could prove effective.

It is possible that long-term use of cannabinoid antagonists could help reduce relapse rates. This strategy is used for opioid use disorder, as the mu-opioid antagonist naltrexone reduces relapse to

heroin use (Krupitsky et al., 2011; Lee et al., 2016). CB1 antagonists and inverse agonists have been found to block acute cannabis-induced subjective and physiological effects (Huestis et al., 2001, 2007; Klumpers et al., 2013; Zuurman et al., 2010). This blockade could translate to reduced cannabis use as CB1 antagonists have been found to reduce cannabis self-administration and reinstatement of cannabis use in non-human primates (Justinova et al., 2008; Schindler et al., 2016). However, these drugs have not been tested for relapse prevention in humans to date. If new CB1 antagonists without adverse psychiatric side effects are developed, they would warrant testing for relapse prevention in cannabis use disorder. CBD may also have potential as a relapse prevention strategy given its ability to inhibit CB1 receptor activity and its favorable side effect profile. However, although CBD has been shown to attenuate the psychotogenic and anxiogenic effects of $\Delta^9$-THC in humans (Bhattacharyya et al., 2010; Zuardi et al., 1982), a recent trial demonstrated that CBD does not block $\Delta^9$-THC-induced hedonic or physiological effects (Haney et al., 2016). CBD may therefore prove ineffective as a relapse prevention strategy.

The endocannabinoid system remains a logical target for the treatment of cannabis use disorder. Cannabinoid treatments with CB1 agonist activity such as dronabinol, nabilone, and nabiximols can be used to effectively manage cannabis withdrawal. Trials directly comparing these medications are necessary to determine whether any of them produce superior clinical outcomes or have a more favorable side effect profile. Longer term maintenance with dronabinol for relapse prevention has thus far proven ineffective, however nabilone and nabiximols have yet to be tested. Non-human primate studies suggest that CB1 antagonists may have potential as novel treatments, but human trials will likely depend on the development of compounds with less harmful side effect profiles.

### 2.3. Alcohol use disorder

There are currently three FDA-approved medications for alcohol use disorder with distinct mechanisms of action: naltrexone, acamprosate, and disulfiram. Although acamprosate and naltrexone are effective treatment strategies for some patients (Jonas et al., 2014), predicting who will respond has been a major challenge (Oslin et al., 2015). Additionally, no new treatments have been approved by the FDA for over a decade. Recent evidence suggests that human endocannabinoid metabolism can affect alcohol dependence vulnerability and severity (Sloan et al., 2017), thus treatments targeting this system may prove effective.

CB1 modulation has been shown to alter alcohol consumption in animal models. CB1 agonists dose-dependently increase alcohol consumption in rats and these effects are blocked by pre-treatment with CB1 antagonists (Colombo et al., 2002). Conversely, rimonabant and other CB1 antagonists suppress rodent alcohol consumption (Arnone et al., 1997; Colombo et al., 1998; Femenia et al., 2010; Wang et al., 2003), possibly by blunting alcohol-induced dopamine release (Hungund et al., 2003). Rimonabant may also have antagonist activity at the mu-opioid receptor (Seely et al., 2012), which calls into question whether the suppression of alcohol consumption is exclusively related to its CB1 activity. Nevertheless, the preclinical literature provides strong evidence that the endocannabinoid system influences alcohol intake in rodents.

Based on this preclinical evidence, two studies have investigated the effects of rimonabant on human alcohol consumption (Table 3). The only clinical trial in treatment-seeking alcohol-dependent subjects found no significant effect of rimonabant versus placebo on return to any drinking (Soyka et al., 2008). However, there was a non-significant reduction in relapse to heavy drinking in the rimonabant versus placebo group (26.0% and 32.5% respectively), therefore it would be necessary to conduct another trial in a larger sample before concluding that rimonabant is ineffective. The other study, a small between-subject human laboratory investigation, found no effect of rimonabant on alcohol self-administration (George et al., 2010). Thus, the limited evidence from human studies suggests that CB1 inverse agonists may not be a useful treatment for alcohol use disorder, although an effect on relapse to heavy drinking cannot be ruled out.

Although future studies with rimonabant are unlikely given the withdrawal of regulatory approval, preclinical work is still needed to determine whether its mu-opioid receptor activity is primarily responsible for its reduction of alcohol consumption in rodent models. If not, the testing of novel cannabinoid antagonists for the treatment of alcoholism may still be worthwhile. Given that CBD has shown early signs of efficacy in other addictions and has recently been found to reduce alcohol consumption in mice (Viudez-Martínez et al., 2017), investigation of its effects on human alcohol use is also warranted. Much work remains to be done if we are to elucidate whether the endocannabinoid system is a viable treatment target for alcohol use disorder.

### 2.4. Opioid use disorder

There is a range of existing interventions for opioid use disorder. For opioid withdrawal, both alpha-2 adrenergic agonists such as clonidine and lofexidine (Gowing et al., 2016) and opioids including methadone and buprenorphine (Amato et al., 2013; Gowing et al., 2017) reduce withdrawal severity. Long-term methadone, buprenorphine, and naltrexone treatment have been shown to reduce heroin relapse (Krupitsky et al., 2011; Lee et al., 2016; Mattick et al., 2014). Buprenorphine implants also show considerable promise as a novel intervention (Rosenthal et al., 2016). However, all medications currently used to prevent relapse target the mu-opioid receptor. Discovering non-opioid treatments, especially drugs that can be used in combination with current treatment regimens to improve efficacy, could prove helpful in combatting the opioid epidemic.

Dronabinol has been studied as a clinical treatment for opioid

**Table 3**
Cannabinoid modulating treatments for alcohol use disorder.

| Study | Endpoint of Interest | Treatment (N) | Treatment Duration | Outcome | Treatment Effective[a] |
|---|---|---|---|---|---|
| (Soyka et al., 2008) | Relapse Prevention | Rimonabant 20 mg[b] (N = 131)<br>Placebo (N = 127) | 12 wks | No effect on relapse rates (41.1% rimonabant vs. 46.0% placebo) | No |
| (George et al., 2010) | Self-Administration | Rimonabant 20 mg (N = 18)<br>Placebo (N = 21) | 2 wks[c] | No effect of treatment on alcohol self-administration | No |

[a] As compared to placebo group.
[b] All dosages expressed as total daily dose.
[c] Heavy drinkers received rimonabant 20 mg or placebo daily over a period of 14 days and performed an alcohol self-administration on the last day of treatment. During the two-hour self-administration period, participants had the opportunity to drink alcohol or receive three dollars for each drink not consumed.

withdrawal based on the finding that CB1 agonists decrease some withdrawal symptoms in rodents (Lichtman et al., 2001) (Table 4). One clinical trial randomized opioid-dependent participants to dronabinol or placebo while they were undergoing an 8-day inpatient detoxification and injectable naltrexone induction (Bisaga et al., 2015). Dronabinol reduced the symptoms of opioid withdrawal compared to placebo, but this trial did not compare dronabinol to an active treatment. In a second within-subject human laboratory trial, regular opioid users were admitted to an inpatient unit for 5 weeks, maintained on oxycodone, and then withdrawn from oxycodone to experimentally induce withdrawal on seven separate test sessions (Jicha et al., 2015; Lofwall et al., 2016). Oxycodone, but not dronabinol, attenuated physical symptoms of withdrawal, including changes in heart rate, blood pressure, and pupil diameter, whereas the 20 and 30 mg doses of dronabinol induced tachycardia. When using opioid withdrawal scales rather than direct physiological measures, the 20 and 30 mg doses of dronabinol reduced withdrawal compared to placebo but were substantially less effective than oxycodone. (Lofwall et al., 2016). This is a discouraging result, and suggests that dronabinol is likely inferior to opioid-based withdrawal treatments. Additional clinical trials comparing dronabinol to clonidine and lofexidine would help determine whether dronabinol could be used for patients who prefer non-opioid medications for withdrawal management.

There is evidence from a preclinical study that CBD may be a useful treatment for opioid use disorder, particularly for the prevention of cue-induced relapse (Ren et al., 2009). After rats were trained to self-administer heroin and the behavior was subsequently extinguished, CBD attenuated reinstatement of lever pressing induced by a conditioned light cue but not lever pressing induced by a priming dose of heroin. Interestingly, this study also found that CBD attenuated glutamatergic disturbances in the nucleus accumbens which may be associated with drug-seeking behavior. In humans, a study of healthy adults showed that low doses of fentanyl can be safely combined with CBD (Manini et al., 2015), but no studies have been conducted in opioid-dependent participants at higher doses of opioids which are consistent with their daily use patterns. There are no published studies to date investigating CBD treatment in patients with opioid use disorder. Pilot data reported in a recent review suggest that CBD may blunt cue-induced craving in individuals with opioid dependence following a period of abstinence (Hurd et al., 2015). This finding is currently being studied in a larger number of participants. Further safety data as well as results from human laboratory studies are needed before CBD is ready for clinical testing. If CBD specifically reduces cue-induced rather than priming-induced relapse, it may be useful in combination with naltrexone, which could complement the action of CBD by blocking such priming effects.

Medications targeting the endocannabinoid system are just beginning to be studied for opioid use disorders. Preliminary data suggest that dronabinol may reduce opioid withdrawal, but could be inferior to opioid-based medications. Additionally, one preclinical study suggests that CBD may be useful at preventing cue-induced relapse, but whether this effect translates to humans remains to be verified. Interactions between the cannabinoid and opioid systems have been extensively studied in animal models (Fattore et al., 2004). Determining how cannabinoids affect opioid withdrawal, craving, and relapse in individuals with opioid use disorder may also improve our understanding of the reciprocal communication between these systems in humans.

## 3. Future directions

### 3.1. Fatty acid amide hydrolase (FAAH) inhibitors

Fatty acid amide hydrolase (FAAH) is an enzyme that regulates endocannabinoid signaling by metabolizing anandamide, an endocannabinoid neurotransmitter with partial CB1 agonist activity. Compounds have been synthesized capable of selectively inhibiting FAAH, thereby increasing anandamide levels (Kathuria et al., 2003). In rodents, these FAAH inhibitors have been shown to attenuate symptoms of cannabis withdrawal and reduce some, but not all, symptoms of opioid withdrawal (Ramesh et al., 2011; Schlosburg et al., 2009). These effects may translate to humans, as clinical trials with dronabinol suggest that CB1 activation suppresses cannabis withdrawal and may suppress opioid withdrawal (Bisaga et al., 2015; Levin et al., 2011).

Only a few studies testing FAAH inhibitors in humans have been published to date. After an initial trial in healthy subjects (Li et al., 2012), FAAH inhibitors were employed in a neuroimaging study (Boileau et al., 2015) and in a clinical trial to treat pain associated with osteoarthritis of the knee (Huggins et al., 2012). A search of the two largest clinical trial registries found one trial seeking to test a FAAH inhibitor for the treatment of cannabis withdrawal and cannabis use disorder relapse, but this trial is currently on clinical hold. Unfortunately, much of the initial enthusiasm for FAAH inhibitors has been tempered by a recent phase I trial in which the FAAH inhibitor BIA 10-2474 caused an acute neurologic syndrome that killed one participant and led to prolonged neurological impairment in several others (Kerbrat et al., 2016). Based on the safety profile observed in other FAAH inhibitor studies, it is thought that this toxicity is unique to BIA 10-2474 and does not extend to other drugs in this class (FDA, 2016). However, given the fallout from the BIA 10-2474 incident, it is possible that many pharmaceutical companies will suspend the development of these drugs.

**Table 4**
Cannabinoid modulating treatments for opioid use disorder.

| Study | Endpoint of Interest | Treatment (N) | Treatment Duration | Outcome | Treatment Effective[a] |
|---|---|---|---|---|---|
| (Bisaga et al., 2015) | Withdrawal Severity | Dronabinol 30 mg[b] (N = 40) Placebo (N = 20) | 6 wks[c] | Significant reduction in withdrawal severity in dronabinol group. | Yes |
| (Jicha et al., 2015) and (Lofwall et al., 2016) | Withdrawal Severity | Dronabinol 5, 10, 20, 30 mg Oxycodone 30, 60 mg Placebo (Within-Subject, N = 12) | Single dose[d] | Dronabinol 20 and 30 mg reduced withdrawal severity. Both doses of oxycodone were also effective. | Yes |

[a] As compared to placebo group.
[b] All dosages expressed as total daily dose.
[c] Eight-day inpatient detoxification. Participants were initiated on dronabinol 10 mg daily on day 2 and titrated up to 30 mg daily by day 4. The difference in withdrawal severity was only significant on days 2–4. Patients were then given dronabinol for an additional five weeks after discharge, although there was no effect of dronabinol on treatment retention at the end of this period.
[d] Participants were admitted to an inpatient unit for approximately 5 weeks. They were stabilized on oral oxycodone 30 mg four times per day for 5 days prior to testing each medication. The day prior to each test day, participants did not get their last two doses of oxycodone. During test sessions, a single dose of test drug was administered and withdrawal symptoms were monitored for a total of 6 hours. This was repeated 7 times, once for each treatment condition.

### 3.2. Monoacylglycerol lipase (MAGL) inhibitors

Selective inhibitors of monoacylglycerol lipase (MAGL), the enzyme which degrades the endogenous CB1 agonist 2-arachidonoylgylcerol (2-AG), have also been synthesized (Long et al., 2009a). In mice, acute inhibition of MAGL has been shown to reduce nicotine, cannabis, and opioid withdrawal (Muldoon et al., 2015; Ramesh et al., 2011; Schlosburg et al., 2009). Acute inhibition of MAGL also increases cue-induced reinstatement of nicotine seeking behaviors (Trigo and Le Foll, 2016). Interestingly, a dual FAAH and MAGL inhibitor, SA-57, has been shown to not only reduce opioid withdrawal but also opioid seeking behavior (Ramesh et al., 2013; Wilkerson et al., 2017). MAGL inhibitors have not yet been tested in human subjects, but trials for cannabis or opioid withdrawal may be reasonable starting points.

Selective FAAH and MAGL inhibitors can be used to elucidate specific pharmacological effects of anandamide and 2-AG. For example, a rodent study found that selective MAGL but not FAAH inhibition causes hypomotility, both FAAH and MAGL inhibition are antinociceptive (although dual inhibition leads to much larger antinociceptive effects), and dual but not single enzyme inhibition causes catalepsy (Long et al., 2009b). Use of selective and dual FAAH and MAGL inhibitors could also be employed to help clarify the specific contributions of anandamide and 2-AG to addictive behavior and determine which of these inhibitors would have the greatest potential as addiction treatments.

### 3.3. Neutral CB1 antagonists

CB1 blockers which lack inverse agonist activity, known as neutral CB1 antagonists, have been hypothesized to retain the therapeutic efficacy of inverse agonists with reduced adverse side effects (Meye et al., 2013). There is evidence that a neutral CB1 antagonist, AM4113, reduces nicotine self-administration, cue- and priming-induced reinstatement of nicotine use, and body weight in rats without significantly inducing anxiety or depression-like behavior (Gueye et al., 2016; Sink et al., 2010). In non-human primates, AM4113 was found to reduce nicotine and cannabis self-administration as well as both cue- and priming-induced reinstatement of drug seeking behavior (Schindler et al., 2016). These results are promising and indicate that neutral CB1 antagonists should be considered for the treatment of nicotine and cannabis use disorders in humans, although close monitoring for psychiatric adverse events is still warranted.

### 3.4. CB2 receptor modulation

CB2 receptors were originally thought to be solely located in peripheral immune cells, but subsequent animal research has demonstrated that they are also located in the central nervous system (Van Sickle et al., 2005), including in the ventral tegmental area (VTA) where they may modulate dopamine release (Zhang et al., 2014). Administration of selective CB2 agonists inhibits VTA dopamine neuron firing and leads to reductions in cocaine self-administration in mice (Xi et al., 2011; Zhang et al., 2014). These effects are blocked by pre-administration of a selective CB2 antagonist and are not observed in mice lacking the CB2 receptor. The impact of CB2 ligands may be species-specific (Zhang et al., 2015). For example, CB2 ligands affect nicotine seeking behaviors in mice (Ignatowska-Jankowska et al., 2013; Navarrete et al., 2013) but not in rats (Gamaleddin et al., 2012). Whether CB2 receptors play a prominent role in reward signaling in the human brain remains unclear. Clinical trials testing CB2 agonists for pain-related indications and have thus far been negative (Dhopeshwarkar and Mackie, 2014; Ostenfeld et al., 2011), but no trials have tested CB2 receptor modulation for addiction. More preclinical evidence will be necessary before such trials should be considered.

## 4. Conclusions

In recent years, there have been exciting advances in the treatment of addiction using drugs targeting the endocannabinoid system. Numerous clinical studies have been published, and human laboratory research has paved the way for cannabinoids to be tested for new indications. Meanwhile, compounds with novel mechanisms of action are being developed and tested in animal models. So far, available evidence suggests CB1 agonists such as dronabinol and nabiximols are effective in the treatment of cannabis withdrawal. The preclinical literature indicates that CB1 antagonists and inverse agonists may be effective across many substance use disorders. Although human studies of rimonabant for alcohol use disorder have thus far been negative, large smoking cessation trials have demonstrated encouraging results. Hopefully, as the evidence continues to accumulate, drugs targeting the endocannabinoid system will demonstrate their clinical utility for a range of substance use indications. These drugs could then be used to reduce the public health burden of addiction, which remains the top priority of this line of research.

## Declarations of interest

The authors report no conflicts of interest.

## Acknowledgements

This work was supported by the Division of Intramural Clinical and Biological Research of the National Institute on Alcohol Abuse and Alcoholism (Z1A AA000466). The authors thank Jenna Gale for her comments and suggestions during manuscript preparation.

## References

Allsop, D.J., Copeland, J., Lintzeris, N., Dunlop, A.J., Montebello, M., Sadler, C., Rivas, G.R., Holland, R.M., Muhleisen, P., Norberg, M.M., Booth, J., McGregor, I.S., 2014. Nabiximols as an agonist replacement therapy during cannabis withdrawal: a randomized clinical trial. JAMA psychiatry 71, 281–291.

Allsop, D.J., Copeland, J., Norberg, M.M., Fu, S., Molnar, A., Lewis, J., Budney, A.J., 2012. Quantifying the clinical significance of cannabis withdrawal. PLoS One 7, e44864.

Amato, L., Davoli, M., Minozzi, S., Ferroni, E., Ali, R., Ferri, M., 2013. Methadone at tapered doses for the management of opioid withdrawal. Cochrane database Syst. Rev. Cd003409.

Arnone, M., Maruani, J., Chaperon, F., Thiebot, M.H., Poncelet, M., Soubrie, P., Le Fur, G., 1997. Selective inhibition of sucrose and ethanol intake by SR 141716, an antagonist of central cannabinoid (CB1) receptors. Psychopharmacol. (Berl.) 132, 104–106.

Baker, T.B., Piper, M.E., Stein, J.H., Smith, S.S., Bolt, D.M., Fraser, D.L., Fiore, M.C., 2016. Effects of nicotine patch vs varenicline vs combination nicotine replacement therapy on smoking cessation at 26 Weeks: a randomized clinical trial. JAMA 315, 371–379.

Bedi, G., Cooper, Z.D., Haney, M., 2013. Subjective, cognitive and cardiovascular dose-effect profile of nabilone and dronabinol in marijuana smokers. Addict. Biol. 18, 872–881.

Bergamaschi, M.M., Queiroz, R.H., Zuardi, A.W., Crippa, J.A., 2011. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr. drug Saf. 6, 237–249.

Bhattacharyya, S., Morrison, P.D., Fusar-Poli, P., Martin-Santos, R., Borgwardt, S., Winton-Brown, T., Nosarti, C., CM, O.C., Seal, M., Allen, P., Mehta, M.A., Stone, J.M., Tunstall, N., Giampietro, V., Kapur, S., Murray, R.M., Zuardi, A.W., Crippa, J.A., Atakan, Z., McGuire, P.K., 2010. Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology. Neuropsychopharmacology 35, 764–774.

Bisaga, A., Sullivan, M.A., Glass, A., Mishlen, K., Pavlicova, M., Haney, M., Raby, W.N., Levin, F.R., Carpenter, K.M., Mariani, J.J., Nunes, E.V., 2015. The effects of dronabinol during detoxification and the initiation of treatment with extended release naltrexone. Drug Alcohol Depend. 154, 38–45.

Bisogno, T., Hanus, L., De Petrocellis, L., Tchilibon, S., Ponde, D.E., Brandi, I., Moriello, A.S., Davis, J.B., Mechoulam, R., Di Marzo, V., 2001. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors

and on the cellular uptake and enzymatic hydrolysis of anandamide. Br. J. Pharmacol. 134, 845–852.
Boileau, I., Rusjan, P.M., Williams, B., Mansouri, E., Mizrahi, R., De Luca, V., Johnson, D.S., Wilson, A.A., Houle, S., Kish, S.J., Tong, J., 2015. Blocking of fatty acid amide hydrolase activity with PF-04457845 in human brain: a positron emission tomography study with the novel radioligand [(11)C]CURB. J. Cereb. Blood Flow. Metab. 35, 1827–1835.
Budney, A.J., Vandrey, R.G., Hughes, J.R., Moore, B.A., Bahrenburg, B., 2007. Oral delta-9-tetrahydrocannabinol suppresses cannabis withdrawal symptoms. Drug Alcohol Depend. 86, 22–29.
Cahill, K., Lindson-Hawley, N., Thomas, K.H., Fanshawe, T.R., Lancaster, T., 2016. Nicotine receptor partial agonists for smoking cessation. Cochrane database Syst. Rev. Cd006103.
Cahill, K., Stevens, S., Perera, R., Lancaster, T., 2013. Pharmacological interventions for smoking cessation: an overview and network meta-analysis. Cochrane database Syst. Rev. Cd009329.
Cahill, K., Ussher, M.H., 2011. Cannabinoid type 1 receptor antagonists for smoking cessation. Cochrane database Syst. Rev. Cd005353.
Caille, S., Alvarez-Jaimes, L., Polis, I., Stouffer, D.G., Parsons, L.H., 2007. Specific alterations of extracellular endocannabinoid levels in the nucleus accumbens by ethanol, heroin, and cocaine self-administration. J. Neurosci. 27, 3695–3702.
Christensen, R., Kristensen, P.K., Bartels, E.M., Bliddal, H., Astrup, A., 2007. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. Lancet 370, 1706–1713.
Cohen, C., Perrault, G., Voltz, C., Steinberg, R., Soubrie, P., 2002. SR141716, a central cannabinoid (CB(1)) receptor antagonist, blocks the motivational and dopamine-releasing effects of nicotine in rats. Behav. Pharmacol. 13, 451–463.
Collin, C., Davies, P., Mutiboko, I.K., Ratcliffe, S., 2007. Randomized controlled trial of cannabis-based medicine in spasticity caused by multiple sclerosis. Eur. J. Neurol. 14, 290–296.
Colombo, G., Agabio, R., Fa, M., Guano, L., Lobina, C., Loche, A., Reali, R., Gessa, G.L., 1998. Reduction of voluntary ethanol intake in ethanol-preferring sP rats by the cannabinoid antagonist SR-141716. Alcohol Alcohol 33, 126–130.
Colombo, G., Serra, S., Brunetti, G., Gomez, R., Melis, S., Vacca, G., Carai, M.M., Gessa, L., 2002. Stimulation of voluntary ethanol intake by cannabinoid receptor agonists in ethanol-preferring sP rats. Psychopharmacol. (Berl.) 159, 181–187.
D'Souza, D.C., Cortes-Briones, J.A., Ranganathan, M., Thurnauer, H., Creatura, G., Surti, T., Planeta, B., Neumeister, A., Pittman, B., Normandin, M., Kapinos, M., Ropchan, J., Huang, Y., Carson, R.E., Skosnik, P.D., 2016. Rapid changes in CB1 receptor availability in cannabis dependent males after abstinence from cannabis. Biol. Psychiatry Cognitive Neurosci. Neuroimaging 1, 60–67.
Damaj, M.I., Carroll, F.I., Eaton, J.B., Navarro, H.A., Blough, B.E., Mirza, S., Lukas, R.J., Martin, B.R., 2004. Enantioselective effects of hydroxy metabolites of bupropion on behavior and on function of monoamine transporters and nicotinic receptors. Mol. Pharmacol. 66, 675–682.
Degenhardt, L., Randall, D., Hall, W., Law, M., Butler, T., Burns, L., 2009. Mortality among clients of a state-wide opioid pharmacotherapy program over 20 years: risk factors and lives saved. Drug Alcohol Depend. 105, 9–15.
Dhopeshwarkar, A., Mackie, K., 2014. CB2 Cannabinoid receptors as a therapeutic target-what does the future hold? Mol. Pharmacol. 86, 430–437.
EMA, 2007. EUROPEAN PUBLIC ASSESSMENT REPORT (EPAR) ACOMPLIA: EPAR Summary for the Public (London, United Kingdom).
EMA, 2009. European Medicines Agency: PUBLIC STATEMENT on Acomplia (Rimonabant) WITHDRAWAL of the MARKETING AUTHORISATION IN the EUROPEAN UNION.
Fattore, L., Cossu, G., Spano, M.S., Deiana, S., Fadda, P., Scherma, M., Fratta, W., 2004. Cannabinoids and reward: interactions with the opioid system. Crit. Rev. Neurobiol. 16, 147–158.
FDA, 2016. FDA Finds Drugs under Investigation in the U.S. Related to French BIA 10-2474 Drug Do Not Pose Similar Safety Risks.
Femenia, T., Garcia-Gutierrez, M.S., Manzanares, J., 2010. CB1 receptor blockade decreases ethanol intake and associated neurochemical changes in fawn-hooded rats. Alcohol. Clin. Exp. Res. 34, 131–141.
Forget, B., Coen, K.M., Le Foll, B., 2009. Inhibition of fatty acid amide hydrolase reduces reinstatement of nicotine seeking but not break point for nicotine self-administration–comparison with CB(1) receptor blockade. Psychopharmacol. (Berl.) 205, 613–624.
Forget, B., Hamon, M., Thiebot, M.H., 2005. Cannabinoid CB1 receptors are involved in motivational effects of nicotine in rats. Psychopharmacol. (Berl.) 181, 722–734.
Forouzanfar, M.H., Afshin, A., Alexander, L.T., Anderson, H.R., Bhutta, Z.A., Biryukov, S., et al., 2016. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388, 1659–1724.
Gamaleddin, I., Zvonok, A., Makriyannis, A., Goldberg, S.R., Le Foll, B., 2012. Effects of a selective cannabinoid CB2 agonist and antagonist on intravenous nicotine self administration and reinstatement of nicotine seeking. PLoS One 7, e29900.
George, D.T., Herion, D.W., Jones, C.L., Phillips, M.J., Hersh, J., Hill, D., Heilig, M., Ramchandani, V.A., Geyer, C., Spero, D.E., Singley, E.D., O'Malley, S.S., Bishai, R., Rawlings, R.R., Kunos, G., 2010. Rimonabant (SR141716) has no effect on alcohol self-administration or endocrine measures in nontreatment-seeking heavy alcohol drinkers. Psychopharmacol. (Berl.) 208, 37–44.
Gorelick, D.A., 2016. Pharmacological treatment of cannabis-related disorders: a narrative review. Curr. Pharm. Des. 22 (42), 6409–6419.
Gowing, L., Ali, R., White, J.M., Mbewe, D., 2017. Buprenorphine for managing opioid withdrawal. Cochrane database Syst. Rev. 2, Cd002025.
Gowing, L., Farrell, M., Ali, R., White, J.M., 2016. Alpha(2)-adrenergic agonists for the management of opioid withdrawal. Cochrane database Syst. Rev. Cd002024.
Gremel, C.M., Chancey, J.H., Atwood, B.K., Luo, G., Neve, R., Ramakrishnan, C., Deisseroth, K., Lovinger, D.M., Costa, R.M., 2016. Endocannabinoid modulation of orbitostriatal circuits gates habit formation. Neuron 90, 1312–1324.
Gueye, A.B., Pryslawsky, Y., Trigo, J.M., Poulia, N., Delis, F., Antoniou, K., Loureiro, M., Laviolette, S.R., Vemuri, K., Makriyannis, A., Le Foll, B., 2016. The CB1 neutral antagonist AM4113 retains the therapeutic efficacy of the inverse agonist rimonabant for nicotine dependence and weight loss with better psychiatric tolerability. Int. J. Neuropsychopharmacol. 19.
Gunduz-Cinar, O., MacPherson, K.P., Cinar, R., Gamble-George, J., Sugden, K., Williams, B., Godlewski, G., Ramikie, T.S., Gorka, A.X., Alapafuja, S.O., Nikas, S.P., Makriyannis, A., Poulton, R., Patel, S., Hariri, A.R., Caspi, A., Moffitt, T.E., Kunos, G., Holmes, A., 2013. Convergent translational evidence of a role for anandamide in amygdala-mediated fear extinction, threat processing and stress-reactivity. Mol. Psychiatry 18, 813–823.
Haney, M., Cooper, Z.D., Bedi, G., Vosburg, S.K., Comer, S.D., Foltin, R.W., 2013. Nabilone decreases marijuana withdrawal and a laboratory measure of marijuana relapse. Neuropsychopharmacology 38, 1557–1565.
Haney, M., Hart, C.L., Vosburg, S.K., Comer, S.D., Reed, S.C., Foltin, R.W., 2008. Effects of THC and lofexidine in a human laboratory model of marijuana withdrawal and relapse. Psychopharmacol. (Berl.) 197, 157–168.
Haney, M., Hart, C.L., Vosburg, S.K., Nasser, J., Bennett, A., Zubaran, C., Foltin, R.W., 2004. Marijuana withdrawal in humans: effects of oral THC or divalproex. Neuropsychopharmacology 29, 158–170.
Haney, M., Malcolm, R.J., Babalonis, S., Nuzzo, P.A., Cooper, Z.D., Bedi, G., Gray, K.M., McRae-Clark, A., Lofwall, M.R., Sparenborg, S., Walsh, S.L., 2016. Oral cannabidiol does not alter the subjective, reinforcing or cardiovascular effects of smoked cannabis. Neuropsychopharmacology 41, 1974–1982.
Hasin, D.S., Kerridge, B.T., Saha, T.D., Huang, B., Pickering, R., Smith, S.M., Jung, J., Zhang, H., Grant, B.F., 2016 Jun 1. Prevalence and correlates of DSM-5 cannabis use disorder, 2012-2013: findings from the national epidemiologic survey on alcohol and related conditions–III. Am. J. Psychiatry 173 (6), 588–599.
Herrmann, E.S., Cooper, Z.D., Bedi, G., Ramesh, D., Reed, S.C., Comer, S.D., Foltin, R.W., Haney, M., 2016. Effects of zolpidem alone and in combination with nabilone on cannabis withdrawal and a laboratory model of relapse in cannabis users. Psychopharmacol. (Berl.) 233, 2469–2478.
Hirvonen, J., Goodwin, R., Li, C.-T., Terry, G., Zoghbi, S., Morse, C., Pike, V., Volkow, N., Huestis, M., Innis, R., 2012. Reversible and regionally selective downregulation of brain cannabinoid CB1 receptors in chronic daily cannabis smokers. Mol. Psychiatry 17, 642–649.
Huestis, M.A., Boyd, S.J., Heishman, S.J., Preston, K.L., Bonnet, D., Le Fur, G., Gorelick, D.A., 2007. Single and multiple doses of rimonabant antagonize acute effects of smoked cannabis in male cannabis users. Psychopharmacol. (Berl.) 194, 505–515.
Huestis, M.A., Gorelick, D.A., Heishman, S.J., Preston, K.L., Nelson, R.A., Moolchan, E.T., Frank, R.A., 2001. Blockade of effects of smoked marijuana by the CB1-selective cannabinoid receptor antagonist SR141716. Arch. Gen. Psychiatry 58, 322–328.
Huggins, J.P., Smart, T.S., Langman, S., Taylor, L., Young, T., 2012. An efficient randomised, placebo-controlled clinical trial with the irreversible fatty acid amide hydrolase-1 inhibitor PF-04457845, which modulates endocannabinoids but fails to induce effective analgesia in patients with pain due to osteoarthritis of the knee. Pain 153, 1837–1846.
Hungund, B.L., Szakall, I., Adam, A., Basavarajappa, B.S., Vadasz, C., 2003. Cannabinoid CB1 receptor knockout mice exhibit markedly reduced voluntary alcohol consumption and lack alcohol-induced dopamine release in the nucleus accumbens. J. Neurochem. 84, 698–704.
Hurd, Y.L., Yoon, M., Manini, A.F., Hernandez, S., Olmedo, R., Ostman, M., Jutras-Aswad, D., 2015. Early phase in the development of cannabidiol as a treatment for addiction: opioid relapse takes initial center stage. Neurotherapeutics 12, 807–815.
Ignatowska-Jankowska, B.M., Muldoon, P.P., Lichtman, A.H., Damaj, M.I., 2013. The cannabinoid CB2 receptor is necessary for nicotine-conditioned place preference, but not other behavioral effects of nicotine in mice. Psychopharmacol. (Berl.) 229, 591–601.
Jicha, C.J., Lofwall, M.R., Nuzzo, P.A., Babalonis, S., Elayi, S.C., Walsh, S.L., 2015. Safety of oral dronabinol during opioid withdrawal in humans. Drug Alcohol Depend. 157, 179–183.
Jonas, D.E., Amick, H.R., Feltner, C., Bobashev, G., Thomas, K., Wines, R., Kim, M.M., Shanahan, E., Gass, C.E., Rowe, C.J., Garbutt, J.C., 2014. Pharmacotherapy for adults with alcohol use disorders in outpatient settings: a systematic review and meta-analysis. JAMA 311, 1889–1900.
Justinova, Z., Munzar, P., Panlilio, L.V., Yasar, S., Redhi, G.H., Tanda, G., Goldberg, S.R., 2008. Blockade of THC-seeking behavior and relapse in monkeys by the cannabinoid CB(1)-receptor antagonist rimonabant. Neuropsychopharmacology 33, 2870–2877.
Kathmann, M., Weber, B., Zimmer, A., Schlicker, E., 2001. Enhanced acetylcholine release in the hippocampus of cannabinoid CB(1) receptor-deficient mice. Br. J. Pharmacol. 132, 1169–1173.
Kathuria, S., Gaetani, S., Fegley, D., Valino, F., Duranti, A., Tontini, A., Mor, M., Tarzia, G., La Rana, G., Calignano, A., Giustino, A., Tattoli, M., Palmery, M., Cuomo, V., Piomelli, D., 2003. Modulation of anxiety through blockade of

anandamide hydrolysis. Nat. Med. 9, 76–81.
Kerbrat, A., Ferré, J.-C., Fillatre, P., Ronzière, T., Vannier, S., Carsin-Nicol, B., Lavoué, S., Vérin, M., Gauvrit, J.-Y., Le Tulzo, Y., Edan, G., 2016. Acute neurologic disorder from an inhibitor of fatty acid amide hydrolase. N. Engl. J. Med. 375, 1717–1725.
Klumpers, L.E., Roy, C., Ferron, G., Turpault, S., Poitiers, F., Pinquier, J.L., van Hasselt, J.G., Zuurman, L., Erwich, F.A., van Gerven, J.M., 2013. Surinabant, a selective cannabinoid receptor type 1 antagonist, inhibits Delta9-tetrahydrocannabinol-induced central nervous system and heart rate effects in humans. Br. J. Clin. Pharmacol. 76, 65–77.
Krupitsky, E., Nunes, E.V., Ling, W., Illeperuma, A., Gastfriend, D.R., Silverman, B.L., 2011. Injectable extended-release naltrexone for opioid dependence: a double-blind, placebo-controlled, multicentre randomised trial. Lancet 377, 1506–1513.
Landsman, R.S., Burkey, T.H., Consroe, P., Roeske, W.R., Yamamura, H.I., 1997. SR141716A is an inverse agonist at the human cannabinoid CB1 receptor. Eur. J. Pharmacol. 334, R1–R2.
Laprairie, R.B., Bagher, A.M., Kelly, M.E., Denovan-Wright, E.M., 2015. Cannabidiol is a negative allosteric modulator of the cannabinoid CB1 receptor. Br. J. Pharmacol. 172, 4790–4805.
Le Foll, B., 2016. What does addiction medicine expect from neuroscience? From genes and neurons to treatment responses. Prog. Brain Res. 224, 419–447.
Le Foll, B., Goldberg, S.R., 2004. Rimonabant, a CB1 antagonist, blocks nicotine-conditioned place preferences. Neuroreport 15, 2139–2143.
Lee, J.D., Friedmann, P.D., Kinlock, T.W., Nunes, E.V., Boney, T.Y., Hoskinson Jr., R.A., Wilson, D., McDonald, R., Rotrosen, J., Gourevitch, M.N., Gordon, M., Fishman, M., Chen, D.T., Bonnie, R.J., Cornish, J.W., Murphy, S.M., O'Brien, C.P., 2016. Extended-release naltrexone to prevent opioid relapse in criminal justice offenders. N. Engl. J. Med. 374, 1232–1242.
Lemberger, L., Rubin, A., Wolen, R., DeSante, K., Rowe, H., Forney, R., Pence, P., 1982. Pharmacokinetics, metabolism and drug-abuse potential of nabilone. Cancer Treat. Rev. 9 (Suppl. B), 17–23.
Levin, F.R., Mariani, J.J., Brooks, D.J., Pavlicova, M., Cheng, W., Nunes, E.V., 2011. Dronabinol for the treatment of cannabis dependence: a randomized, double-blind, placebo-controlled trial. Drug Alcohol Depend. 116, 142–150.
Levin, F.R., Mariani, J.J., Pavlicova, M., Brooks, D., Glass, A., Mahony, A., Nunes, E.V., Bisaga, A., Dakwar, E., Carpenter, K.M., Sullivan, M.A., Choi, J.C., 2016. Dronabinol and lofexidine for cannabis use disorder: a randomized, double-blind, placebo-controlled trial. Drug Alcohol Depend. 159, 53–60.
Li, G.L., Winter, H., Arends, R., Jay, G.W., Le, V., Young, T., Huggins, J.P., 2012. Assessment of the pharmacology and tolerability of PF-04457845, an irreversible inhibitor of fatty acid amide hydrolase-1, in healthy subjects. Br. J. Clin. Pharmacol. 73, 706–716.
Lichtman, A.H., Sheikh, S.M., Loh, H.H., Martin, B.R., 2001. Opioid and cannabinoid modulation of precipitated withdrawal in delta(9)-tetrahydrocannabinol and morphine-dependent mice. J. Pharmacol. Exp. Ther. 298, 1007–1014.
Lofwall, M.R., Babalonis, S., Nuzzo, P.A., Elayi, S.C., Walsh, S.L., 2016. Opioid withdrawal suppression efficacy of oral dronabinol in opioid dependent humans. Drug Alcohol Depend. 164, 143–150.
Long, J.Z., Li, W., Booker, L., Burston, J.J., Kinsey, S.G., Schlosburg, J.E., Pavon, F.J., Serrano, A.M., Selley, D.E., Parsons, L.H., Lichtman, A.H., Cravatt, B.F., 2009a. Selective blockade of 2-arachidonoylglycerol hydrolysis produces cannabinoid behavioral effects. Nat. Chem. Biol. 5, 37–44.
Long, J.Z., Nomura, D.K., Vann, R.E., Walentiny, D.M., Booker, L., Jin, X., Burston, J.J., Sim-Selley, L.J., Lichtman, A.H., Wiley, J.L., Cravatt, B.F., 2009b. Dual blockade of FAAH and MAGL identifies behavioral processes regulated by endocannabinoid crosstalk in vivo. Proc. Natl. Acad. Sci. U. S. A. 106, 20270–20275.
Manini, A.F., Yiannoulos, G., Bergamaschi, M.M., Hernandez, S., Olmedo, R., Barnes, A.J., Winkel, G., Sinha, R., Jutras-Aswad, D., Huestis, M.A., Hurd, Y.L., 2015. Safety and pharmacokinetics of oral cannabidiol when administered concomitantly with intravenous fentanyl in humans. J. Addict. Med. 9, 204–210.
Marshall, K., Gowing, L., Ali, R., Le Foll, B., 2014. Pharmacotherapies for cannabis dependence. Cochrane database Syst. Rev. Cd008940.
Mattick, R.P., Breen, C., Kimber, J., Davoli, M., 2014. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. Cochrane database Syst. Rev. Cd002207.
Meye, F.J., Trezza, V., Vanderschuren, L.J., Ramakers, G.M., Adan, R.A., 2013. Neutral antagonism at the cannabinoid 1 receptor: a safer treatment for obesity. Mol. Psychiatry 18, 1294–1301.
Morales-Perez, C.L., Noviello, C.M., Hibbs, R.E., 2016. X-ray structure of the human alpha4beta2 nicotinic receptor. Nature 538, 411–415.
Morgan, C.J., Das, R.K., Joye, A., Curran, H.V., Kamboj, S.K., 2013. Cannabidiol reduces cigarette consumption in tobacco smokers: preliminary findings. Addict. Behav. 38, 2433–2436.
Morrison, M.F., Ceesay, P., Gantz, I., Kaufman, K.D., Lines, C.R., 2010. Randomized, controlled, double-blind trial of taranabant for smoking cessation. Psychopharmacol. (Berl.) 209, 245–253.
Muldoon, P.P., Chen, J., Harenza, J.L., Abdullah, R.A., Sim-Selley, L.J., Cravatt, B.F., Miles, M.F., Chen, X., Lichtman, A.H., Damaj, M.I., 2015. Inhibition of monoacylglycerol lipase reduces nicotine withdrawal. Br. J. Pharmacol. 172, 869–882.
Navarrete, F., Rodriguez-Arias, M., Martin-Garcia, E., Navarro, D., Garcia-Gutierrez, M.S., Aguilar, M.A., Aracil-Fernandez, A., Berbel, P., Minarro, J., Maldonado, R., Manzanares, J., 2013. Role of CB2 cannabinoid receptors in the rewarding, reinforcing, and physical effects of nicotine. Neuropsychopharmacology 38, 2515–2524.
Oslin, D.W., Leong, S.H., Lynch, K.G., Berrettini, W., O'Brien, C.P., Gordon, A.J., Rukstalis, M., 2015. Naltrexone vs placebo for the treatment of alcohol dependence: a randomized clinical trial. JAMA psychiatry 72, 430–437.
Ostenfeld, T., Price, J., Albanese, M., Bullman, J., Guillard, F., Meyer, I., Leeson, R., Costantin, C., Ziviani, L., Nocini, P.F., Milleri, S., 2011. A randomized, controlled study to investigate the analgesic efficacy of single doses of the cannabinoid receptor-2 agonist GW842166, ibuprofen or placebo in patients with acute pain following third molar tooth extraction. Clin. J. Pain 27, 668–676.
Papke, R.L., Heinemann, S.F., 1994. Partial agonist properties of cytisine on neuronal nicotinic receptors containing the beta 2 subunit. Mol. Pharmacol. 45, 142–149.
Parsons, L.H., Hurd, Y.L., 2015. Endocannabinoid signalling in reward and addiction. Nat. Rev. Neurosci. 16, 579–594.
Picciotto, M.R., Zoli, M., Rimondini, R., Lena, C., Marubio, L.M., Pich, E.M., Fuxe, K., Changeux, J.P., 1998. Acetylcholine receptors containing the beta2 subunit are involved in the reinforcing properties of nicotine. Nature 391, 173–177.
Qin, N., Neeper, M.P., Liu, Y., Hutchinson, T.L., Lubin, M.L., Flores, C.M., 2008. TRPV2 is activated by cannabidiol and mediates CGRP release in cultured rat dorsal root ganglion neurons. J. Neurosci. 28, 6231–6238.
Ramesh, D., Gamage, T.F., Vanuytsel, T., Owens, R.A., Abdullah, R.A., Niphakis, M.J., Shea-Donohue, T., Cravatt, B.F., Lichtman, A.H., 2013. Dual inhibition of endocannabinoid catabolic enzymes produces enhanced antiwithdrawal effects in morphine-dependent mice. Neuropsychopharmacology 38, 1039–1049.
Ramesh, D., Ross, G.R., Schlosburg, J.E., Owens, R.A., Abdullah, R.A., Kinsey, S.G., Long, J.Z., Nomura, D.K., Sim-Selley, L.J., Cravatt, B.F., Akbarali, H.I., Lichtman, A.H., 2011. Blockade of endocannabinoid hydrolytic enzymes attenuates precipitated opioid withdrawal symptoms in mice. J. Pharmacol. Exp. Ther. 339, 173–185.
Ren, Y., Whittard, J., Higuera-Matas, A., Morris, C.V., Hurd, Y.L., 2009. Cannabidiol, a nonpsychotropic component of cannabis, inhibits cue-induced heroin seeking and normalizes discrete mesolimbic neuronal disturbances. J. Neurosci. 29, 14764–14769.
Rigotti, N.A., Gonzales, D., Dale, L.C., Lawrence, D., Chang, Y., 2009. A randomized controlled trial of adding the nicotine patch to rimonabant for smoking cessation: efficacy, safety and weight gain. Addiction 104, 266–276.
Rinaldi-Carmona, M., Barth, F., Héaulme, M., Shire, D., Calandra, B., Congy, C., Martinez, S., Maruani, J., Néliat, G., Caput, D., 1994. SR141716A, a potent and selective antagonist of the brain cannabinoid receptor. FEBS Lett. 350, 240–244.
Rohleder, C., Muller, J.K., Lange, B., Leweke, F.M., 2016. Cannabidiol as a potential new type of an antipsychotic. A critical review of the evidence. Front. Pharmacol. 7, 422.
Rosenthal, R.N., Lofwall, M.R., Kim, S., Chen, M., Beebe, K.L., Vocci, F.J., 2016. Effect of buprenorphine implants on illicit opioid use among abstinent adults with opioid dependence treated with sublingual buprenorphine: a randomized clinical trial. JAMA 316, 282–290.
Rucker, D., Padwal, R., Li, S.K., Curioni, C., Lau, D.C., 2007. Long term pharmacotherapy for obesity and overweight: updated meta-analysis. BMJ 335, 1194–1199.
Rudd, R.A., Aleshire, N., Zibbell, J.E., Gladden, R.M., 2016. Increases in drug and opioid overdose Deaths–United States, 2000-2014. MMWR Morb. Mortal. Wkly. Rep. 64, 1378–1382.
Russo, E.B., Burnett, A., Hall, B., Parker, K.K., 2005. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem. Res. 30, 1037–1043.
Schindler, C.W., Redhi, G.H., Vemuri, K., Makriyannis, A., Le Foll, B., Bergman, J., Goldberg, S.R., Justinova, Z., 2016. Blockade of nicotine and cannabinoid reinforcement and relapse by a cannabinoid CB1-receptor neutral antagonist AM4113 and inverse agonist rimonabant in squirrel monkeys. Neuropsychopharmacology 41, 2283–2293.
Schlosburg, J.E., Carlson, B.L., Ramesh, D., Abdullah, R.A., Long, J.Z., Cravatt, B.F., Lichtman, A.H., 2009. Inhibitors of endocannabinoid-metabolizing enzymes reduce precipitated withdrawal responses in THC-dependent mice. AAPS J. 11, 342–352.
Seely, K.A., Brents, L.K., Franks, L.N., Rajasekaran, M., Zimmerman, S.M., Fantegrossi, W.E., Prather, P.L., 2012. AM-251 and rimonabant act as direct antagonists at mu-opioid receptors: implications for opioid/cannabinoid interaction studies. Neuropharmacology 63, 905–915.
Serrano, A., Parsons, L.H., 2011. Endocannabinoid influence in drug reinforcement, dependence and addiction-related behaviors. Pharmacol. Ther. 132, 215–241.
Sink, K.S., Segovia, K.N., Sink, J., Randall, P.A., Collins, L.E., Correa, M., Markus, E.J., Vemuri, V.K., Makriyannis, A., Salamone, J.D., 2010. Potential anxiogenic effects of cannabinoid CB1 receptor antagonists/inverse agonists in rats: comparisons between AM4113, AM251, and the benzodiazepine inverse agonist FG-7142. Eur. Neuropsychopharmacol. 20, 112–122.
Slemmer, J.E., Martin, B.R., Damaj, M.I., 2000. Bupropion is a nicotinic antagonist. J. Pharmacol. Exp. Ther. 295, 321–327.
Sloan, M.E., Gowin, J.L., Yan, J., Schwandt, M.L., Spagnolo, P.A., Sun, H., Hodgkinson, C.A., Goldman, D., Ramchandani, V.A., 2017 Feb 1. Severity of alcohol dependence is associated with the fatty acid amide hydrolase Pro129Thr missense variant. Addict. Biol. http://dx.doi.org/10.1111/adb.12491 [Epub ahead of print].
Soyka, M., Koller, G., Schmidt, P., Lesch, O.M., Leweke, M., Fehr, C., Gann, H., Mann, K.F., 2008. Cannabinoid receptor 1 blocker rimonabant (SR 141716) for treatment of alcohol dependence: results from a placebo-controlled, double-blind trial. J. Clin. Psychopharmacol. 28, 317–324.
Tapper, A.R., McKinney, S.L., Nashmi, R., Schwarz, J., Deshpande, P., Labarca, C., Whiteaker, P., Marks, M.J., Collins, A.C., Lester, H.A., 2004. Nicotine activation of alpha4* receptors: sufficient for reward, tolerance, and sensitization. Science 306, 1029–1032.

Thomas, A., Baillie, G.L., Phillips, A.M., Razdan, R.K., Ross, R.A., Pertwee, R.G., 2007. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. Br. J. Pharmacol. 150, 613–623.

Tonstad, S., Aubin, H.J., 2012. Efficacy of a dose range of surinabant, a cannabinoid receptor blocker, for smoking cessation: a randomized controlled clinical trial. J. Psychopharmacol. Oxf. Engl. 26, 1003–1009.

Topol, E.J., Bousser, M.G., Fox, K.A., Creager, M.A., Despres, J.P., Easton, J.D., Hamm, C.W., Montalescot, G., Steg, P.G., Pearson, T.A., Cohen, E., Gaudin, C., Job, B., Murphy, J.H., Bhatt, D.L., 2010. Rimonabant for prevention of cardiovascular events (CRESCENDO): a randomised, multicentre, placebo-controlled trial. Lancet 376, 517–523.

Trigo, J.M., Lagzdins, D., Rehm, J., Selby, P., Gamaleddin, I., Fischer, B., Barnes, A.J., Huestis, M.A., Le Foll, B., 2016. Effects of fixed or self-titrated dosages of Sativex on cannabis withdrawal and cravings. Drug Alcohol Depend. 161, 298–306.

Trigo, J.M., Le Foll, B., 2016. Inhibition of monoacylglycerol lipase (MAGL) enhances cue-induced reinstatement of nicotine-seeking behavior in mice. Psychopharmacol. (Berl.) 233, 1815–1822.

Trigo, J.M., Le Foll, B., 2017. The role of the endocannabinoid system in addiction. In: Murillo-Rodriguez (Ed.), The Endocannabinoid System: Genetics Biochemistry, Brain Disorders, and Therapy. Academic Press.

Van Sickle, M.D., Duncan, M., Kingsley, P.J., Mouihate, A., Urbani, P., Mackie, K., Stella, N., Makriyannis, A., Piomelli, D., Davison, J.S., Marnett, L.J., Di Marzo, V., Pittman, Q.J., Patel, K.D., Sharkey, K.A., 2005. Identification and functional characterization of brainstem cannabinoid CB2 receptors. Science 310, 329–332.

Vandrey, R., Stitzer, M.L., Mintzer, M.Z., Huestis, M.A., Murray, J.A., Lee, D., 2013. The dose effects of short-term dronabinol (oral THC) maintenance in daily cannabis users. Drug Alcohol Depend. 128, 64–70.

Viudez-Martínez, A., García-Gutiérrez, M.S., Navarrón, C.M., Morales-Calero, M.I., Navarrete, F., Torres-Suárez, A.I., Manzanares, J., 2017 Feb 13. Cannabidiol reduces ethanol consumption, motivation and relapse in mice. Addict. Biol. http://dx.doi.org/10.1111/adb.12495 [Epub ahead of print].

Wang, L., Liu, J., Harvey-White, J., Zimmer, A., Kunos, G., 2003. Endocannabinoid signaling via cannabinoid receptor 1 is involved in ethanol preference and its age-dependent decline in mice. Proc. Natl. Acad. Sci. U. S. A 100, 1393–1398.

Warner, C., Shoaib, M., 2005. How does bupropion work as a smoking cessation aid? Addict. Biol. 10, 219–231.

Wilkerson, J.L., Ghosh, S., Mustafa, M., Abdullah, R.A., Niphakis, M.J., Cabrera, R., Maldonado, R.L., Cravatt, B.F., Lichtman, A.H., 2017. The endocannabinoid hydrolysis inhibitor SA-57: intrinsic antinociceptive effects, augmented morphine-induced antinociception, and attenuated heroin seeking behavior in mice. Neuropharmacology 114, 156–167.

Xi, Z.X., Peng, X.Q., Li, X., Song, R., Zhang, H.Y., Liu, Q.R., Yang, H.J., Bi, G.H., Li, J., Gardner, E.L., 2011. Brain cannabinoid CB(2) receptors modulate cocaine's actions in mice. Nat. Neurosci. 14, 1160–1166.

Zhang, H.Y., Bi, G.H., Li, X., Li, J., Qu, H., Zhang, S.J., Li, C.Y., Onaivi, E.S., Gardner, E.L., Xi, Z.X., Liu, Q.R., 2015. Species differences in cannabinoid receptor 2 and receptor responses to cocaine self-administration in mice and rats. Neuropsychopharmacology 40, 1037–1051.

Zhang, H.Y., Gao, M., Liu, Q.R., Bi, G.H., Li, X., Yang, H.J., Gardner, E.L., Wu, J., Xi, Z.X., 2014. Cannabinoid CB2 receptors modulate midbrain dopamine neuronal activity and dopamine-related behavior in mice. Proc. Natl. Acad. Sci. U. S. A. 111, E5007–E5015.

Zuardi, A.W., Shirakawa, I., Finkelfarb, E., Karniol, I.G., 1982. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. Psychopharmacol. (Berl.) 76, 245–250.

Zuurman, L., Roy, C., Schoemaker, R.C., Amatsaleh, A., Guimaeres, L., Pinquier, J.L., Cohen, A.F., van Gerven, J.M., 2010. Inhibition of THC-induced effects on the central nervous system and heart rate by a novel CB1 receptor antagonist AVE1625. J. Psychopharmacol. Oxf. Engl. 24, 363–371.