Drug and Alcohol Dependence xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

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

Full length article

Dronabinol and lofexidine for cannabis use disorder: A randomized, double-blind, placebo-controlled trial☆

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ARTICLE INFO

Article history:
Received 19 August 2015
Received in revised form 4 November 2015
Accepted 5 November 2015
Available online xxx

Trial registration:
NCT01020019

Keywords:
Marinol
Dronabinol
Lofexidine
Cannabis use disorder
Marijuana dependence
Cannabis withdrawal

ABSTRACT

Background: Cannabis use disorder is associated with substantial morbidity and, after alcohol, is the most common drug bringing adolescents and adults into treatment. At present, there are no FDA-approved medications for cannabis use disorder. Combined pharmacologic interventions might be particularly useful in mitigating withdrawal symptoms and promoting abstinence.
Objective: The purpose of this study was to evaluate the safety and efficacy of dronabinol, a synthetic form of delta-9-tetrahydrocannabinol, a naturally occurring pharmacologically active component of marijuana, and lofexidine, an alpha-2 agonist, in treating cannabis dependence.
Methods: One hundred fifty six cannabis-dependent adults were enrolled and following a 1-week placebo lead-in phase 122 were randomized in a double-blind, placebo-controlled, 11-week trial. Participants were randomized to receive dronabinol 20 mg three times a day and lofexidine 0.6 mg three times a day or placebo. Medications were maintained until the end of week eight, were then tapered over two weeks and patients were monitored off medications during the last study week. All participants received weekly motivational enhancement and relapse prevention therapy. Marijuana use was assessed using the timeline follow-back method.
Results: There was no significant difference between treatment groups in the proportion of participants who achieved 3 weeks of abstinence during the maintenance phase of the trial (27.9% for the medication group and 29.5% for the placebo group), although both groups showed a reduction over time.
Conclusions: Based on this treatment study, the combined intervention did not show promise as a treatment for cannabis use disorder.

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1. Introduction

Marijuana use has progressively increased over the past decade, with approximately 19.8 million Americans over the age of 12 estimated to have used marijuana in the past month (SAMHSA, 2014). With the exception of alcohol, marijuana is the primary substance bringing Americans into their most recent substance abuse treatment episode (SAMHSA, 2014). Although there has been substantial work assessing various psychotherapeutic strategies for cannabis use disorders (Budney et al., 2011, 2006; Dennis et al., 2004; McRae et al., 2003) most patients with cannabis use disorder continue to use. Up until this time most of the medication development studies have consisted of laboratory studies (Cooper and Haney, 2010), although the outpatient treatment literature is growing. A recent review looked at 14 pharmacologic treatment studies targeting cannabis use disorder and concluded that there was inadequate evidence to support the utility of any specific medication, perhaps not surprising given the heterogeneity of medications studied, study quality, and variability in study outcomes (Marshall et al., 2014). One of its conclusions was that some agents, such as gabapentin and the glutamatergic modulator, *N*-acetylcysteine, or combination therapies warrant further investigation.

☆ Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:10.1016/j.drugalcdep.2015.11.025.

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http://dx.doi.org/10.1016/j.drugalcdep.2015.11.025
0376-8716/Published by Elsevier Ireland Ltd.

Dronabinol (delta-9-tetrahydrocannabinol, THC) is a cannabinoid receptor partial agonist, and has been a reasonable choice to test as a treatment for cannabis use disorders since other partial agonists have been found to be effective for other substance use disorders (i.e., buprenorphine for opiate use disorders and varenicline for nicotine use disorder). While dronabinol has shown benefit in reducing some withdrawal symptoms and subjective effects of marijuana (Haney et al., 2004; Hart et al., 2002), it has not been shown to alter smoked marijuana self-administration under laboratory conditions (Haney et al., 2008; Hart et al., 2002). Similarly, dronabinol has been shown to reduce withdrawal symptoms and improve retention in an outpatient treatment trial, but was not superior to placebo in reducing marijuana use or promoting abstinence (Levin et al., 2011).

Because emerging evidence suggests that dronabinol may not treat all aspects of cannabis use disorder, it was hypothesized that augmentation with an agent exhibiting complementary pharmacologic properties would provide added benefit. Lofexidine, an α_2 noradrenergic agonist, has been hypothesized to be helpful at dampening cannabis withdrawal and craving given its utility in treating opioid withdrawal and in reducing stress-induced and cue-induced opioid craving (Sinha et al., 2007). Indeed, Haney et al. (2008) found that the combination of lofexidine and dronabinol (Lofex–Dro) was superior to placebo in improving sleep and other cannabis withdrawal symptoms; the combination also outperformed either lofexidine or dronabinol alone in mitigating withdrawal symptoms. Thus, we carried out a double-blind placebo-controlled 11-week trial testing lofexidine and dronabinol for the treatment of cannabis use disorder. We hypothesized that lofexidine and dronabinol (Lofex–Dro) would be superior to placebo in reducing withdrawal and achieving abstinence.

2. Methods

2.1. Study participants

As described in our prior marijuana treatment studies (Levin et al., 2011, 2013; Mariani et al., 2011), all participants were seeking outpatient treatment for problems related to marijuana use and were recruited by local advertising. The medical screening included a history and physical examination, an electrocardiogram, and laboratory testing (Levin et al., 2011). The psychiatric evaluation included the Structured Clinical Interview (SCID) for Diagnostic and Statistical Manual of Mental Disorders—Axis I disorders DSM-IV (American Psychiatric Association, 1994; First et al., 1995). A Timeline Follow Back (TLFB; Sobell and Sobell, 1992) assessment was conducted for marijuana, nicotine, alcohol and other drugs for the past 30 days. Participants were treated at the Substance Treatment and Research Service (STARS) of Columbia University/New York State Psychiatric Institute (NYSPI). Study enrollment occurred from December, 2009 through May, 2014 with study completion in September, 2014.

Eligible participants were: (1) between the ages of 18–60, (2) meeting DSM-IV criteria for current marijuana dependence, (3) using marijuana ≥5 days/week and (4) providing a THC-positive urine on the day of study entry (as measured by a qualitative on-site dip test). Participants were excluded for the following: (1) severe mental illness (e.g., bipolar illness; schizophrenia); (2) unstable physical condition; (3) history of a seizure disorder; (4) current suicidal risk; (5) observed cognitive difficulties; (6) bradycardia (<50 beats/min), hypotension (sitting or standing BP < 90/50); (7) currently nursing, pregnant, or, if a women refusing to use an effective method of birth control; (8) physiologically dependent on any other drugs (excluding nicotine) that would require a medical intervention; (9) known sensitivity to dronabinol or lofexidine; (10) coronary vascular disease; (11) currently being treated with an alpha-2 agonist antihypertensive medication; (12) currently being prescribed a psychotropic medication (however, medication for depression, anxiety, and ADHD was allowed if stable for at least 1 month); (13) a job in which even mild marijuana intoxication would be hazardous; and (14) court-mandated to treatment. The study was approved by the Institutional Review Board of the NYSPI and all participants provided written informed consent. The study was registered with clinicaltrials.gov: Identifier NCT01020019.

2.2. Study design

The study was a randomized, double-blind, 11-week clinical trial comparing placebo to the combination of lofexidine and dronabinol (Lofex–Dro). The whole study included a one-week placebo lead-in phase, followed by randomization and a 2-week medication titration phase, a 6-week medication maintenance phase, a 2-week dose taper phase, followed by a one-week placebo lead-out phase. Participants were randomized at the end of the placebo lead-in phase using computer generated random blocks of sizes 4, 6, and 8, with a 1:1 allocation ratio stratified by joints used per week [<21 (n = 49) versus ≥21 (n = 73)]. A Ph.D. statistician at Columbia University independent of the research team conducted the randomization and maintained the allocation sequence. Participants, investigators and study staff were blind to allocation. A study timeline figure and a table detailing the scheduling of assessments and procedures have been included in Supplemental section (Fig. 1 and Table 1, respectively)[1].

2.2.1. Medication. Lofex–Dro or matching placebo (PBO) was prepared by the un-blinded pharmacy at the NYSPI, packaged in matching gelatin capsules with lactose filler and an equal amount of riboflavin (25 mg in each capsule) and was taken three times a day. The riboflavin marker procedure is a standard method to measure adherence to study medication in a clincal trial (Del Boca et al., 1996).

To minimize risks associated with study medication, we instructed patients to take the first dose of their assigned medication (week 1, day 1) 3–4 h prior to their study appointment. This allowed medical staff to evaluate side effects and vital sign changes. Because lofexidine can lower blood pressure, at each weekly visit, blood pressure was closely monitored. If there was a significant drop in blood pressure, medication dose was adjusted and if necessary, discontinued.

Lofex–Dro or matching PBO was given in a "fixed-flexible" dose schedule with the dose titrated to 1.8 (0.6 three times a day) and 60 mg (20 mg three times a day) per day or the maximum tolerated dose. Lofexidine was titrated in 0.2 mg increments and dronabinol was given in 10 mg increments until maximum or tolerated dose was reached. If the participant could not tolerate at least 10 mg/day of dronabinol and 0.2 mg/day lofexidine, the medication was discontinued.

Study medication was provided to participants on a weekly basis. Each week, participants were asked to return all bottles and unused medication. The placebo lead-in phase allowed us to randomize only those participants who demonstrated compliance with study procedures and to assess if some participants were able to abstain during the first week of the study without receiving active medication. Participants who reported marijuana use less than once a week during the placebo lead-in phase were considered placebo responders (n = 8) and were not randomized but

[1] Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:10.1016/j.drugalcdep.2015.11.025.

Please cite this article in press as: Levin, F.R., et al., Dronabinol and lofexidine for cannabis use disorder: A randomized, double-blind, placebo-controlled trial. Drug Alcohol Depend. (2015), http://dx.doi.org/10.1016/j.drugalcdep.2015.11.025