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The effects of dronabinol during detoxification and the initiation of treatment with extended release naltrexone

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ABSTRACT

Background: Evidence suggests that the cannabinoid system is involved in the maintenance of opioid dependence. We examined whether dronabinol, a cannabinoid receptor type 1 partial agonist, reduces opioid withdrawal and increases retention in treatment with extended release naltrexone (XR-naltrexone).

Methods: Opioid dependent participants were randomized to receive dronabinol 30 mg/d ($n = 40$) or placebo ($n = 20$), under double-blind conditions, while they underwent inpatient detoxification and naltrexone induction. Before discharge all participants received an injection of XR-naltrexone, with an additional dose given four weeks later. Dronabinol or placebo was given while inpatient and for 5 weeks afterwards. The primary outcomes were the severity of opioid withdrawal, measured with the Subjective Opioid Withdrawal Scale, and retention in treatment at the end of the inpatient phase and at the end of the 8-week trial.

Results: The severity of opioid withdrawal during inpatient phase was lower in the dronabinol group relative to placebo group ($p = 0.006$). Rates of successful induction onto XR-naltrexone (dronabinol 66%, placebo 55%) and completion of treatment (dronabinol 35%, placebo 35%) were not significantly different. Post hoc analysis showed that the 32% of participants who smoked marijuana regularly during the outpatient phase had significantly lower ratings of insomnia and anxiety and were more likely to complete the 8-week trial.

Conclusion: Dronabinol reduced the severity of opiate withdrawal during acute detoxification but had no effect on rates of XR-naltrexone treatment induction and retention. Participants who elected to smoke marijuana during the trial were more likely to complete treatment regardless of treatment group assignment.

1. Introduction

Rates of prescription opioid and heroin use and related morbidity and mortality continue to grow at an alarming rate (SAMHSA, 2013) with a parallel increase in unintentional overdose deaths (CDC, 2012). Treatment with opioid agonists, methadone and buprenorphine is a time-honored and effective approach to manage opioid dependence, however, agonists are not effective for all patients. Approximately 50% of individuals continue using opioids or other drugs, or drop out during the first 6 months of treatment (Mattick et al., 2008; Soyka et al., 2008). Treatment with the opioid receptor antagonist is an alternative treatment approach that has the potential to address some of the limitations of agonists and attract and retain more patients in stable long-term recovery (SAMHSA, 2012). In patients who are able to initiate treatment with extended-release naltrexone, the overall effectiveness of treatment is comparable with agonists with regard to treatment retention (50–70%) with lower rates of ongoing opioid use (Bisaga et al., 2014; Brooks et al., 2010; Comer et al., 2006; Krupitsky et al., 2011).

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Initiation of naltrexone treatment is best accomplished while the patient is completing residential treatment. For patients who are opioid dependent, initiation of naltrexone during detoxification is associated with significant withdrawal symptoms. An alternative approach, to wait for 7–10 days post-detoxification before administering naltrexone, results in high rates of relapse. Strategies for easing the rapid transition from agonist to antagonist generally involve a brief course of buprenorphine, followed by use of non-opioid medications to attenuate withdrawal symptoms (Sigmon et al., 2012). Nonetheless withdrawal symptoms can still be substantial, reducing success rates of naltrexone induction. Further, patients who start naltrexone frequently experience protracted withdrawal symptoms that persist for 2–3 weeks and may further limit naltrexone's acceptability and adherence. Approximately 30–40% of individuals who start detoxification leave treatment prior to receiving the first injection of XR-naltrexone and another 30–40% will drop out during the first 2 months of outpatient treatment (Bisaga et al., 2014; Comer et al., 2006; Nunes et al., 2006).

Ascertaining an adjunctive medication to alleviate acute and protracted withdrawal symptoms could have a significant impact on improving effectiveness of naltrexone and help with its widespread implementation. Observational data from several independent studies, and clinical experience, suggest that patients who use marijuana following induction onto naltrexone have better retention in treatment as compared to individuals who do not use marijuana (Church et al., 2001; Raby et al., 2009). This finding suggests marijuana may help alleviate withdrawal symptoms early in the course of naltrexone treatment and points to the role of the endocannabinoid system in preventing opioid dependence relapse.

The endocannabinoid system is involved in the maintenance of drug addiction, and targeting this system has been proposed as an approach to treatment (Panlilio et al., 2013; Scavone et al., 2013a; Serrano and Parsons, 2011). The cross-regulation between cannabinoid and opioidergic pathways has been well documented in preclinical studies (Robledo et al., 2008). Chronic exposure to opioids produces profound changes in the endocannabinoid system (Lopez-Moreno et al., 2008; Parolaro et al., 2010), possibly contributing to behavioral abnormalities emerging during early abstinence. Preclinical studies show that cannabinoid agonists reduce the severity of precipitated opioid withdrawal (Frederickson et al., 1976; Lichtman et al., 2001; Vela et al., 1995; Yamaguchi et al., 2001) possibly by modulating opioid signaling in noradrenergic cells of coeruleo-cortical pathways (Scavone et al., 2013a). Therefore, targeting cannabinoid systems may be a viable therapeutic strategy in opioid dependence.

We conducted a double blind, placebo-controlled trial of dronabinol in combination with XR-naltrexone among opioid-dependent patients. Dronabinol is oral synthetic Δ^9tetrahydrocannabinol, the primary psychoactive cannabinoid in marijuana and a cannabinoid receptor type 1 partial agonist (Pertwee, 2009). We hypothesized that administering dronabinol during detoxification and the first weeks of treatment with XR-naltrexone would diminish the severity of opioid withdrawal and, as a result, improve treatment retention and reduce rates of opioid use as compared to treatment with placebo.

2. Methods

2.1. Participants

Opioid-dependent individuals seeking treatment were evaluated at an outpatient research clinic using the Structured Clinical Interview for DSM-IV (First et al., 1995) and a clinical interview assessing substance abuse severity. Medical evaluation included history, laboratory tests, electrocardiogram together with physical and psychiatric exam. The Institutional Review Board of the New York State Psychiatric Institute approved the study.

Eligible individuals were between 18 and 60 years old who met criteria for current opioid dependence and were able to give an informed consent to participate.

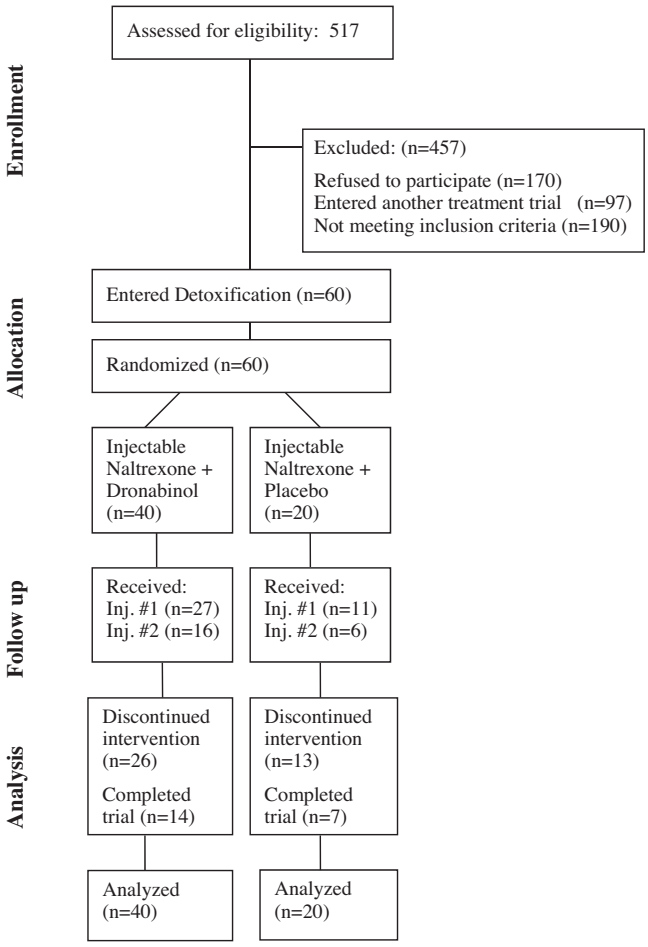

Fig. 1. CONSORT diagram of participants in a controlled study of dronabinol in combination with extended-release naltrexone as a relapse prevention strategy in opioid dependent individuals.

Individuals with unstable medical or psychiatric disorders were excluded. Other exclusion criteria included: (1) physiological dependence on alcohol or sedative-hypnotics; (2) history of recent opioid overdose; (3) treatment with opioids for chronic pain or regular use of methadone; and (4) treatment with psychotropic medications.

We only enrolled participants who had experience smoking marijuana, to avoid exposing participants naïve to THC effects. We excluded participants who were at risk for marijuana withdrawal during inpatient treatment (i.e., those smoking multiple times every day), and excluded participants with cannabis dependence in remission to minimize the risk of relapse.

We evaluated 517 individuals; of whom 170 declined to participate and 190 were not eligible to participate (84 had significant medical problems, 46 had significant psychiatric co-morbidities, 14 were taking other psychotropic medications, and 46 were not eligible for other reasons; see Fig. 1). In addition, 97 participants entered other naltrexone-based treatment studies conducted concurrently at the clinic. A total of 60 individuals provided informed consent and entered the study. Participants were stratified on baseline opioid use (high/low) and age (younger/older). Low use group included participants using five or fewer bags/d (200 mg of morphine equivalent or less) versus six or more bags/d for high use group. Younger group included participants 39 years old and younger versus 40 years and older in older group. There were 22 participants in older/high use stratum, 6 in older/low use stratum, 21 in younger/high use stratum and 11 in younger/low use stratum. Within each stratum participants were randomized to dronabinol 30 mg ($n = 40$) or placebo ($n = 20$) with uneven randomization to obtain additional clinical experience (dosing, safety) with dronabinol.

2.2. Study procedures

Enrolled participants were admitted to an inpatient research unit for an eight-day detoxification and XR-naltrexone induction (Study Day 1). Participants were stabilized on buprenorphine (4 mg bid, Day 2), followed by an opioid washout (Days 3 and 4), and then increasing daily doses of naltrexone (Day 5: 3.125 mg, Day 6: 6.25 mg, Day 7: 25 mg) followed by an injection of XR-naltrexone (Day 8: Vivitrol