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Open-label pilot study of injectable naltrexone for cannabis dependence

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Abstract

Background—There are no FDA-approved pharmacotherapies for cannabis use disorders (CUD), despite the evaluation of numerous medications. Notably, chronic dosing of oral naltrexone decreases self-administration of cannabis in human laboratory studies.

Objectives—To test the feasibility of long-acting injectable naltrexone for the treatment of CUD, while obtaining preliminary safety and efficacy data.

Methods—Twelve adult participants (seven male) meeting DSM-IV-TR criteria for cannabis dependence enrolled into an 8-week, open-label pilot study conducted at an academic treatment research clinic. They received 380 mg intramuscular injections of long-acting naltrexone on study day 1 and at the start of study week 5. Outcome measures included percentages of study completers and participants who received the second injection, frequency of adverse events (AEs), and cannabis consumption measured by average daily grams, dollars, and using days per week as measured by timeline follow-back and urine oral delta-9-tetrahydrocannabinol (THC) concentrations.

Results—Of the 12 participants enrolled in the study, 9 completed the study and 6 received the second injection. There were no severe AEs but an unexpected AE led to the addition of supportive medications to the protocol. Number of cannabis use days per week significantly decreased over the course of the study ($p = .001$). Creatinine-corrected urine THC concentrations and average daily cannabis use per study week in grams and in dollars did not decrease over the course of the study.

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Declaration of Interest

Dr. Notzon, Dr. Kelly, Ms. Choi, Dr. Pavlicova, Dr. Mariani, Amy Mahony and Daniel Brooks have no disclosures. Dr. Levin served as a consultant to GW Pharmaceuticals and to Eli Lilly, and served on an advisory board to Shire in 2005–2007.

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Conclusions—Long-acting injectable naltrexone is a feasible intervention for CUD worthy of further study in a placebo-controlled, double-blinded randomized clinical trial.

Keywords

Cannabis; marijuana; medication; treatment; pilot

Introduction

Though cannabis remains the most commonly used illicit drug in the United States, with approximately 36 million individuals reporting use within the past year (1), treatment options for cannabis dependence are limited and include no FDA-approved pharmacotherapies. The primary evidence-based clinical strategies for treating cannabis use disorders (CUD) are psychosocial and behavioral interventions, with limited evidence that patients are likely to achieve abstinence or meaningful reductions in use(2). The development of a safe and effective pharmacotherapy for CUD would help address a largely unmet public health need.

In searching for promising medication targets for this disorder, the endogenous opioid and cannabinoid systems have been shown to have cross-modulating effects in preclinical studies(3,4) and in some human laboratory studies(5–7), though not in others(8–10). In animal studies, opioid antagonists have been shown to modulate analgesic(11) and anticonvulsant(12) effects mediated by the CB1 receptor; to diminish measures of physiological dependence and behavior that reinforces dependence on cannabis(13,14); and to decrease self-administration of CB1 agonists(15–17). In a human study of opioid-dependent patients, regular cannabis use was associated with increased adherence to the opioid antagonist naltrexone(18). In a placebo-controlled trial of opioid dependent patients receiving dronabinol (oral delta-9-tetrahydrocannabinol, or THC), cannabis use diminished withdrawal symptoms in both the dronabinol and placebo groups(19). The opioid and cannabinoid system appear to have cross-modulating effects, suggesting that mu-opioid antagonists such as naltrexone, an FDA-approved treatment for alcohol and opioid use disorders, could have a role in the treatment of CUD.

Initial human laboratory studies of naltrexone and its effects on the subjective, physiological and behavioral effects of THC found that a small, single dose of naltrexone blunted THC intoxication in cannabis smokers, while in non-cannabis smokers, naltrexone was associated with enhanced THC intoxication(6). Pleasurable effects from THC in regular cannabis users were shown to be increased with a single dose of naltrexone in a later study, however(5). In a subsequent study, chronic laboratory administration of naltrexone in humans was associated with decreased cannabis self-administration, decreased subjective effects of cannabis and partial blocking of the reinforcing effects of cannabis use in non-treatment-seekers (20). These effects of naltrexone are linked to both blockade of mu-opioid receptors and modulation of the dopaminergic reward system of the midbrain and striatum(21).

We investigated the feasibility of recruitment, retention, and implementation of long-acting, injectable naltrexone for the treatment of cannabis dependence over an 8-week open-label trial. We used long-acting injectable naltrexone to maximize adherence during the course of

the study and because numerous studies have shown it to be well tolerated(22). In addition, we obtained preliminary data on safety and changes in cannabis use patterns, toward a goal of conducting a double-blinded study testing whether injectable naltrexone would decrease the quantity and frequency of cannabis use compared to placebo.

Materials and methods

Subjects

This trial was conducted at the Substance Treatment and Research Service (STARS), a research clinic at Columbia University Medical Center and the New York State Psychiatric Institute in New York, NY. Participant recruitment began in October 2014 and concluded in January 2016, with data collection completed in March 2016. All potential participants received a comprehensive medical and psychiatric evaluation including a physical exam, laboratory testing including serum transaminases, pregnancy testing for women, urine testing for toxicology, an electrocardiogram, the Mini-International Neuropsychiatric Interview (MINI) for DSM-IV(23), the Hamilton Depression Rating Scale(24), and other self-report measures. Cannabis use for the 28 days before entry in the study was measured using the timeline follow-back method, adapted for cannabis use. Participants were recruited by internal and external clinical referrals, and to the research clinic in general by local advertising across a variety of media outlets and locations (radio, print, television, internet and subway).

Participants ranged from ages 18–60, met DSM-IV criteria for current cannabis dependence, were seeking treatment for cannabis dependence, reported using cannabis an average of 5 days per week or more over the past 28 days, and were judged capable of giving informed consent and complying with study procedures. Participants were excluded if they had a lifetime history of the DSM-IV diagnosis of schizophrenia, schizoaffective disorder, or bipolar disorder; had another DSM-IV disorder that was unstable or felt likely to require intervention over the course of the study; were prescribed or taking opioids for analgesia; had a known history of allergy, intolerance or hypersensitivity to naltrexone; were pregnant or lactating; had unstable medical conditions, such as poorly controlled liver disease, which might make participation hazardous; had chronic pain conditions; had evidence of liver dysfunction by laboratory assessment; had a current DSM-IV diagnosis of substance dependence other than cannabis or nicotine dependence; were legally mandated to participate in a substance use disorder treatment program; or were assessed to be a risk for suicide. The study protocol was reviewed and approved by the Institutional Review Board of the New York State Psychiatric Institute, and all participants provided written informed consent.

Treatment

All participants were assigned to treatment with injectable naltrexone under open-label conditions accompanied by weekly medication management sessions with a study physician. Injectable naltrexone was administered as a 380 mg intramuscular (IM) depot into alternating gluteal muscles according to package instructions, and utilizing safe injection techniques by physician or nurse practitioner clinicians with prior experience with IM

injections. To receive the injection participants had to show multiple opioid negative urines from initial assessment through the start of the protocol, as well as stable transaminases and negative pregnancy tests for female patients. The first injection was given on study day 1, and was offered a second time between study days 28–30 after repeat of serum transaminases and urine pregnancy testing during study week 4. The second injection could be given up to 1 week beyond the scheduled date in the event of delays. Due to unanticipated symptoms that occurred in two early participants after their initial injections, a protocol amendment was submitted to the IRB to allow the dispensation of adjunct medication to help treat symptoms of nausea, vomiting, anxiety, insomnia, restlessness or irritability for up to 2 weeks after an injection.

These medications included prochlorperazine for nausea, zolpidem or trazodone for insomnia, clonidine for restlessness, and clonazepam for anxiety. Dosing was flexible based on persistence and severity of symptoms, but included maximum dosing on controlled substances. During the study, all participants also received a standardized medication management treatment, where they met weekly with a study psychiatrist to perform study assessments and monitor for both adverse events (AEs) and medication effects, while meeting twice weekly with research staff to perform further assessments. Grounds for early discontinuation of participation included worsening of psychiatric symptoms or substance use to an extent that placed the participant at risk for self-destructive behavior or other harm, pregnancy, elevation of liver enzymes to greater than 3 times the upper limit of normal, development of a pain condition requiring ongoing treatment with opioid analgesics, or other AEs deemed to place the subject at increased risk with continued treatment. Participants could refuse the second injection and continue to participate with study procedures for the duration of the protocol.

At each visit participants received \$5 for travel expenses as well as cash incentive payments starting at \$2.50 and increasing by \$2.50 for every consecutive made study visit along a protocol, up to \$25 per visit. During weeks 4 and 8, participants received a \$25 payment for completing study procedures whether or not they received the second injection. The maximum compensation was \$417.50 for completing all procedures and visits.

Measures

Retention in the study was measured by two end-points: the number of participants who completed all study assessments through the end of the protocol, and the number of participants who received the second injection. AEs during the study were assessed weekly with a version of the SAFTEE(25) by a study physician, recording both the number and type of AE. Cannabis use was assessed by self-report confirmed by urine toxicology. Using the timeline follow-back method(26), self-report of cannabis use and other substance use was obtained for each day of the study period. Urine was collected twice weekly and measured for both THC and creatinine concentrations to obtain creatinine-corrected quantitative tetrahydrocannabinol-9-carboxylic acid levels (CN-THCCOOH), by dividing the concentration of urine THC in ng/mL by the concentration of urine creatinine in mg/dL, and multiplying by 100 to yield a value in ng THC/mg creatinine.

Statistical analysis

Baseline demographics and non-efficacy outcomes, including retention, frequency of AEs, and receipt of the second injection of naltrexone were tabulated and summarized for this open-label treatment group using means, standard deviations and percentages where appropriate. Efficacy outcomes, i.e., average daily cannabis use in grams and in dollars during the 7-day study week, number of cannabis use days per study week, and mean creatinine-normalized THC urine concentrations, were analyzed using longitudinal linear mixed effects models with a main effect of time, adjusted by the corresponding efficacy outcome measured at baseline. A random intercept was used to account for the between subject variances and an autoregressive (AR1) covariance structure was used to account for the correlation of the repeated observations within subjects over time. PROC GLIMMIX in SAS® 9.4 was used to conduct all analyses. All statistical tests were two-sided with a level of significance of 5%. Post hoc, alcohol measures (average number of drinking days per study week, total drinks per week, and average drinks per day) were incorporated to model the effect of alcohol use on cannabis use over the course of the study.

Qualitative analysis

Participant trajectories during the study were described to characterize patterns of study participation, side effects, and cannabis use outcomes.

Results

Sample description

During the study, 15 adults were assessed for eligibility, and a total of 12 participants enrolled in the trial. Demographic characteristics are summarized in Table 1. Six participants (50%) received the second injection of long-acting naltrexone. Three subjects dropped out of the study: 2 occurred shortly before the scheduled 2nd injection, and the other dropout occurred near the end of the study.

Adverse events

On average, participants reported 2.8 AEs over the course of the 8-week trial (SD = 2.5; range: 0–8). Type, frequency and duration of AEs are tabulated in Table 2, with insomnia and nausea as the most common events (50%), followed by appetite change (33.3%). The unexpected AE reported to the IRB was for one participant with anxiety, temporary severe nausea and anorexia, but was not judged to be severe overall, or to warrant discontinuation from the study.

Cannabis using days

The observed average cannabis using days is displayed in Figure 1 and listed in Table 3. The days of cannabis use per week decreased significantly ($F_{1,76} = 11.50$, Beta estimate = -0.24 , $p = .001$) with each week in the trial, adjusted for the number of using days in the 4 weeks prior to beginning the study ($F_{1,76} = 1.97$, $p = .17$). A contrast was performed with the mean level of baseline cannabis use set to 27.4 days (during past 4 weeks prior to study entry) to compare the change in cannabis using days from week 1 to week 8. At week 1, the estimated

average cannabis using days per week for participants was 5.3 days ($SD = 0.69$) compared to 3.6 days ($SD = 0.73$) at week 8. By the end of the 8-week trial participants significantly decreased by approximately 1.70 ($SD = 0.51$) cannabis using days per week.

Average daily cannabis use per study week

The means and standard deviations of the average daily cannabis use in grams and dollars at each week in the trial are listed in Table 3. By contrast, the average daily cannabis use in grams did not significantly change with each week in the trial ($F_{1,76} = 1.59, p = .21$) or with baseline use ($F_{1,76} = 2.80, p = .098$). Similarly, the average daily cannabis use in dollars did not significantly change with each week in the trial ($F_{1,60} = 1.06, p = .31$) or with baseline use ($F_{1,60} = 0.22, p = .64$).

Creatinine-corrected urine THC concentrations

The means and standard deviations of the creatinine-corrected urine THC concentrations at each week in the trial are listed in Table 3. The mean corrected urine THC concentration did not change significantly with each week in the study ($F_{1,121} = 0.37, p = .54$).

Alcohol use outcomes

There were no significant associations between any alcohol use measures with cannabis use outcomes over the course of the study.

Qualitative summary of participant courses

Given the significant variability between subjects in the study, the trajectory of individual study participation, side effects, and cannabis use patterns for all 12 participants were examined. Six participants completed the study and all procedures. Two participants refused the second injection due to a presumed lack of efficacy of the study medication; one of these participants dropped out. Another two participants refused the second injection due to developing induration at the initial injection site; one of these participants dropped out as well. Only one participant who left the study did so citing the severity of systemic side effects, also refusing the 2nd injection. The other participant to refuse the 2nd injection, however, did so because they had already ceased cannabis use and did not perceive a need for a 2nd injection.

All three participants with a urine THC concentration of zero at the end of the study had relatively more side effects relative to the whole study population, though four participants with more side effects did not decrease their use. One participant had few side effects relative to the whole study population and evidence of reduced use at the end of the study; four participants also had few side effects, but no evidence of reduced use.

Discussion

Our results suggest that long-acting injectable naltrexone is a feasible intervention for the treatment of cannabis dependence, and worthy of further study. 75% of those enrolled completed the study. While a small sample (and an open-label study), these rates are comparable to larger medication trials in cannabis dependence (27–29). There were no severe

AEs over the 12 participants, no early terminations by staff, and only one participant dropped out of the study citing systemic side effects (compared to two citing induration at the injection site). Side effects, however, were greater and quicker to emerge than anticipated, leading to a protocol amendment to allow participants to receive supplemental medications as mentioned beforehand; it should again be noted that many appeared to be related to variables involving the injection of naltrexone (such as induration at the injection site) rather than drug effects of naltrexone itself (see Table 2). While only 50% of participants received the second injection of naltrexone, the cause of this low percentage is multi-factorial, as one of the participants refused the second injection because they had already ceased their marijuana use and saw no need for another dose.

Our preliminary, uncontrolled findings as to the study medication's efficacy for cannabis dependence showed a reduction in the average number of days per week of marijuana use, but no reduction in the mean creatinine-corrected urine THC concentration, and no reduction in the average reported grams or cash value of marijuana used, suggesting decreased frequency of use but no significant decrease in quantity of use. This pattern differs from the reduction in THC-positive urines but not in cannabis using days seen in a randomized trial of N-acetylcysteine for cannabis dependent adolescents(27). In a small, open-label study such as ours, there is less ability to detect statistical differences, but given the time it takes for frequent, heavy marijuana users to clear THC from their urine, it may have been difficult over an 8 week period of study to detect reduction of their marijuana use, and standard deviations for our cannabis outcomes were relatively large with our small sample size. Gray et al., however, showed lower odds of THC-positive urines over the same duration of treatment with N-acetylcysteine in a controlled study(27), though in that study of adolescents both groups received cessation counseling, participants with shorter use histories were shown to be more likely to test negative, and some participants had negative urines at the start of the trial (a subgroup who were much more likely to have negative urines throughout that study). A later trial of N-acetylcysteine in a larger adult sample showed no difference in cannabis abstinence(30).

By contrast, Mason et al. showed decreases in grams per week of marijuana use, CN-THCCOOH ratios, and using days per week from roughly 5 to 1 in a placebo-controlled study of gabapentin for cannabis dependence, but both groups in that study received manual-guided, abstinence oriented individual counseling(29). Notable when looking at our results, however, is that 3 of the 12 enrolled were reporting abstinence from cannabis at the end of the study confirmed by urine markers, and an overall reduction in frequency of use if not quantity, without a structured psychotherapy intervention. This is clinically relevant given the paucity of treatment options for CUD, and is an argument for future study despite the apparently higher incidence of side effects compared to medications like gabapentin(29) or N-acetylcysteine(27).

Another indication for further study is the heterogeneity of our study results when looking at our sample qualitatively. The incidence of side effects and the amount of change in cannabis use varied considerably amongst participants, and it is notable that most of the participants who ceased or significantly moderated their cannabis use were the same who reported side effects like nausea, insomnia or changes in appetite. Those whose cannabis use did not

appear to change objectively reported few such side effects. This discrepancy brings several plausible speculations to mind, first, that there may be a heterogeneous level of bioactivity of naltrexone in cannabis users. Second, another possibility is that the side effects seen in our study were due to naltrexone alone, independent of cannabis use or withdrawal, and independent of naltrexone's impact on the brain circuitry related to cannabis using behavior. Third, the report of side effects could have been mediated by cannabis withdrawal that happened to emerge more quickly and more intensely in particular participants, independent of naltrexone exposure. Finally, the presence of side effects may have created an 'active placebo' or were aversive enough to deter those participants from using cannabis.

In the first case, there is little evidence from the literature that can confirm or deny that the bioactivity of naltrexone in cannabis users is heterogeneous. Data derived from clinical trials of naltrexone for alcohol use disorders have identified distinct groups of naltrexone responders and non-responders(31). Based on the preliminary showing here in our data, we wonder if cannabis users will demonstrate a similar stratification in a larger study, and whether this stratification would be due to relative bioactivity of naltrexone or to other factors. In the second case, if side effects were related to the effects of long-acting injectable naltrexone alone, it is notable that long-acting injectable naltrexone has a high peak blood level 1–2 days after injection but for most of its duration has a concentration well below that seen in studies of high-dose oral naltrexone where side effects were frequently noted(32). We were surprised by the prominence of side effects in our small sample size given this fact. It begs the question of whether side effect rates from naltrexone are comparable among cannabis users relative to other disorders.

In the third case, more severe substance withdrawal would not generally be associated with likelihood of abstinence, and would imply the existence of some other mediating factor for cessation of use. In the last case, many factors other than active placebos or aversive effects could mediate a true response to naltrexone therapy in cannabis users even if side effects emerge, including anti-craving effects, reduced hedonic response to cannabis, blunting of relief from withdrawal or withdrawal-like symptoms with cannabis use, or reduced prospective valuation of cannabis use. Post hoc, we looked at quantity and frequency of alcohol use over time as a predictor of cannabis use outcomes, but found no significant associations, arguing that alcohol use did not confound our study outcomes. Researchers attempting to more directly answer questions about a potential mechanism of action should keep in mind that injectable naltrexone may be prone to the development of an active placebo condition or aversive conditioning effects without rigorously designed controls or sham procedures.

Though these points of interest highlight the need for further study, there were several points to take away from this study that can help guide the design of future trials to test such hypothetical formulations with larger sample sizes, control groups and blinding interventions. First, though we are not equipped to make a definitive inference as to the safety of the study medication in this population, the fact that side effects were significant enough to warrant a protocol amendment allowing the prescribing of supportive medications was notable, and should be in place for future studies until more data are available. Whether an initial detoxification taper with gabapentin or a washout phase with long-acting, FDA-

approved cannabinoids like dronabinol or nabilone would help bridge participants to long-acting injectable naltrexone is intriguing given the initial side effects seen in some participants. Increasing the length of the study may increase the likelihood of detecting significant differences not just in self-reported cannabis use but also in corrected urinary THC concentrations.

Though medication management, the model of study care utilized in our study, is validated as an active treatment(33,34) incorporation of cognitive-behavioral and motivational enhancement interventions to help participants formalize goal-setting, help problem solve, clarify motivation for change and lower the potential for relapse, would be intriguing to study in combination as this would fit a model of the delivery of treatment for cannabis dependence more reflective of current treatment standards. Finally, quality control as to injection procedures is of paramount importance to the study of this treatment intervention as several participants refused the second injection due to discomfort related to their first study injection. While the quality of an injection procedure can never eliminate the risk of local induration or injection site reactions that may be random or determined by unknown individual biological factors, a focus on injection procedure quality control would appear prudent as in our case these side effects were reported somewhat more frequently than in larger studies of the study medication(35).

Limitations

Our study was open-label, uncontrolled and with a small sample size, and was not designed to test *a priori* hypotheses as to the safety, efficacy or effectiveness of our treatment intervention beyond its feasibility for further study. The addition of supportive medications to our study protocol midway through the study may have confounded some of our analyses, though only two participants completed their participation without the ability to receive adjunct medications. Descriptive analysis, while useful for a small sample intended to guide further research, could have been subject to confirmation bias.

Conclusions

Long-acting injectable naltrexone is a feasible intervention for further study in a placebo-controlled, double-blinded randomized clinical trial for the treatment of CUD.

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Figure 1.
Cannabis use days per week.

Table 1Demographics ($N = 12$).

	Mean	SD
Age (years)	35.42	9.73
Income (\$) *	51,500.00	22,000–150,000
	<i>N</i>	%
Male	7	58.33
Race/Ethnicity		
<i>African-American</i>	7	58.33
<i>Caucasian</i>	2	16.67
<i>Hispanic</i>	1	8.33
<i>Other</i>	2	16.67
Single/Unmarried	11	91.67
Education		
<i>HS diploma</i>	6	50.00
<i>Some college</i>	1	8.33
<i>Post-HS technical training</i>	1	8.33
<i>Bachelor's degree</i>	4	33.33

* Median and IQR reported for non-normally distributed data.

Table 2

Summary of reported adverse events.

Adverse event	Number of occurrences	Percent of participants (%)	Number rated moderate or severe?	Longest duration (days)
Insomnia	6	50.00	1	28
Nausea	6	50.00	2	14
Appetite change	4	33.33	2	7
Induration/irritation at injection site	4	33.33	1	28
Anxiety	3	25.00	1	21
Vomiting	2	16.67	1	4
Irritability	2	16.67		
Fatigue	1	8.33		
Headache	1	8.33		
Muscle pain or weakness	1	8.33		
Vivid dreams	1	8.33		
Diaphoresis	1	8.33	1	4
Light-headedness	1	8.33		
Chills	1	8.33	1	4
Dry Heaves	1	8.33		

Table 3

Means and standard deviations of cannabis use by study week.

Week	N	Daily cannabis use (grams)		Daily cannabis use (dollars)		Cannabis using days		Urine THC/ Creatinine ratio (ng THC/mg creatinine)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
1	22	1.70	2.54	15.14	15.09	5.33	2.31	280.59	177.27
2	17	1.35	1.73	14.17	19.41	4.75	2.73	259.77	233.90
3	18	1.30	1.68	13.35	12.66	5.50	2.50	287.66	190.83
4	18	1.06	0.96	12.91	12.63	5.08	2.71	326.97	284.98
5	19	1.05	1.41	15.05	17.68	3.67	3.06	223.21	174.54
6	16	0.92	1.16	11.67	15.32	4.10	3.21	235.65	231.89
7	17	0.98	1.50	10.67	13.51	4.30	2.98	349.93	298.58
8	18	0.43	0.56	6.14	8.37	3.56	2.96	296.96	294.92