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ORIGINAL ARTICLE

Guanfacine extended-release for cannabis use disorder: a pilot feasibility trial

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ABSTRACT

Background: Currently, there are no established pharmacotherapies for cannabis use disorders (CUDs). As a long-acting alpha-2-adrenergic receptor agonist, guanfacine extended-release (G-XR) could be useful in the treatment of CUDs by mitigating withdrawal and improving behavioral control.

Objectives: To evaluate the feasibility and tolerability of G-XR as a treatment for CUDs.

Methods: In an eight-week open-label outpatient pilot trial, we evaluated the safety and tolerability of G-XR in 22 cannabis dependent individuals. Using 2 different titration schedules, G-XR was gradually titrated to a dose of 4 mg or the highest dose tolerated. All participants received standard medication management.

Results: Retention at week eight was 41%. Average daily amount of cannabis use (in grams: $F_{1,86} = 8.74$, $p = .004$; in dollars: $F_{1,86} = 16.67$, $p < .0001$) and cannabis using days ($F_{1,86} = 7.67$, $p = .007$) significantly reduced over the course of study participation. There were no significant differences between the titration schedules on emergence of side effects (Fisher exact test, $p = .378$) or retention (Log-Rank Test $X^2_1 = 0.021$, $p = .886$). A total of 3 participants achieved 3 weeks or greater of total abstinence.

Conclusions: G-XR is a feasible treatment for CUDs, and should be evaluated further in an efficacy trial.

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Cannabis use disorder; guanfacine

Introduction

Though cannabis is the most widely used illicit drug internationally (1), cannabis use disorders (CUDs) have been the subject of little treatment research, and no FDA-approved pharmacotherapy treatments are currently available (2). Two potential targets of pharmacotherapy for CUDs are withdrawal symptoms and difficulties with behavioral regulation (e.g., impulsivity). Alpha-2-adrenergic (α2A) receptor agonists represent a promising pharmacotherapy for substance use disorders, and for CUDs in particular, due to their preclinical effects on these vulnerabilities. Given their sympatholytic activity, α2A agonists have demonstrated effects on withdrawal symptoms in cannabis and opioid use disorders (3,4); withdrawal from cannabis as well as opioids may involve increased noradrenergic activity (5). In addition, the effect of α2A agonists on noradrenergic tone in the prefrontal cortex is postulated to enhance regulation of limbic structures, thereby improving behavior, cognition, and impulsivity (6). α2A agonists such as clonidine and guanfacine have therefore been approved for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD) (7). They may also impact on comparable deficits in substance use disorders, with preliminary data indicating an effect on stress- and cue-induced craving in cocaine dependent individuals (8). Prior research has shown α2A agonists, such as lofexidine, to be promising in decreasing symptoms of withdrawal and relapse in opioid use disorders (9). Lofexidine has also shown promise in a laboratory study assessing cannabis withdrawal severity (10), although limitations from the thrice daily dosing regimen may limit compliance and treatment retention.

Guanfacine, a selective α2A agonist currently FDA-approved for the treatment of ADHD and hypertension (11), can be dosed once daily and provides a more practical pharmacotherapy option than does lofexidine. The goal of this study was to determine the safety and feasibility of administering guanfacine extended-release (G-XR) to promote use reduction in cannabis dependent individuals.

Methods and materials

Twenty-two treatment-seeking cannabis dependent individuals between the ages of 18–60 who met the DSM-IV criteria for current cannabis dependence were enrolled in this trial. Participants responded to newspapers, radio and public service announcements, and reported at least 20 days of use in the past 30 days.

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Participants were not taking psychotropic medication, and were in good psychiatric and medical health, as assessed via medical history, Mini International Neuropsychiatric Interview (MINI) (12), physical examination, electrocardiogram, and serum and urine laboratory testing.

After providing consent, all participants were assigned to G-XR treatment under open-label conditions. Two methods of titration were tested to optimize tolerance and feasibility. For the first 12 participants, G-XR was titrated up over the course of 2 weeks to the target dose (4 mg) or the highest tolerated dose. A higher-than-expected incidence of adverse effects with the rapid titration protocol led us to revise the titration protocol for the remainder of the trial. For the latter 10 participants, G-XR was titrated up more gradually, over the course of 8 weeks, to the target dose or the highest tolerated dose. Dose reductions for tolerability were made by the research psychiatrist in coordination with the research pharmacy. Medication was taken once daily and dispensed in child resistant bottles containing a one-week supply of medication. In order to feasibly promote study medication adherence, participants were provided medication management by a physician once weekly, and other efforts were taken to facilitate and ascertain adherence. A structured calendar-based interview, based on the Timeline Follow-Back (TLFB) procedure, covered the time period since the last visit and accounted for every scheduled dose of medication (13). We also used a calendar-based structured pill count interview (timeline followback) to measure medication adherence with a weekly financial incentive for medication bottle return. This procedure provided a modest monetary incentive ($10) for returning the prior week's pill bottle. In cases where a participant was non-adherent to the prescribed study medication regimen, the research psychiatrist explored the reasons for non-compliance, and considered dose reductions if side effects were contributory.

Study visits occurred twice weekly. At each visit, quantitative carboxy-tetrahydrocannabinol (THC) urine testing was conducted and information collected about cannabis consumption (using the TLFB) (13), marijuana withdrawal (using the MWC-10) (14) and side effects (SAFTEE) (15). A research psychiatrist performed study assessments and monitored medication effects once weekly. Medication management was provided, without therapy or behavioral treatment, as in previous research (16). At the end of the eight-week trial, participants returned for follow-up visits with the research psychiatrist for two weeks. Participants were offered a month of free continued treatment with G-XR. Those who chose to discontinue underwent a 12-day taper. Weekly follow-up visits allowed for monitoring effects of the medication taper or continued treatment. Appropriate clinical referrals were arranged for all participants.

Statistical analyses

Baseline demographics, frequency of side effects and adverse events were tabulated and summarized using means, standard deviations and percentages where appropriate. Differences in retention by titration regimens were examined using Kaplan-Meier survival curves and log-rank tests. Differences in side effects were examined using Fisher's exact tests.

Efficacy outcomes, i.e., average daily cannabis use in grams and in dollars; number of cannabis use days per study week; and withdrawal, were analyzed on the intent-to-treat sample 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. Mixed effect models assume missing data is missing at random and do not require complete measurement data, but rather uses all available information to estimate the outcome. PROC GLIMMIX in SAS® 9.4 was used to conduct all analyses. All statistical tests were two-sided on level of significance of 5%.

Results

Sample description

Table 1 shows the participant demographic and morbidity information. A total of 22 individuals were enrolled (14 males; mean age 37.0 years [standard deviation (SD) = 11.1]; 8 females; mean age 34.4 [SD = 9.1]). Of the participants, 22.7% identified as Black, 22.7% as Caucasian, 18.2% as Native American or Alaskan Native, 9.1% as Hispanic, and 27.3% identified as other.

Table 2 shows the retention and adverse effect incidence by titration schedule. The mean study retention was 5.9 weeks (SD = 3.9), with 40.9% (9/22) of participants completing all 8 weeks of the trial. Nine individuals achieved the target dose (4 mg). More than half of participants (63.6%, 14/22) noted experiencing side effects throughout the trial, though this did not appear to affect medication adherence in participants who remained in the trial, with a majority taking the prescribed amount as ascertained by pill-count. The most commonly reported side effects were fatigue (22.7%), dry mouth (22.7%), and

Table 1. Participant demographic and morbidity information (n = 22).

Characteristic	Mean (SD) or n (%)
Age, years	36.1 (10.3)
Race/Ethnicity	
African American	5 (22.7%)
Caucasian	5 (22.7%)
Hispanic	2 (9.1%)
Native American or Alaskan Native	4 (18.2%)
Other	6 (27.3%)
Male	14 (63.6%)
Education (>12 years H.S. equivalent)	22 (100%)
Baseline cannabis use days/week	5.5 (0.6)
Baseline cannabis amount/week, $	20.82 (16.67)

Abbreviation: H.S. = high school

insomnia (22.7%). There were no significant adverse events reported. No significant differences between the titration regimens on emergence of side effects (Fisher exact test, p = .378) or retention (Log-Rank Test $X^2_{DF=1}$ = 0.021, p = .886) were found.

Average daily cannabis use

The observed average daily cannabis use in grams at week 1 was 0.66 grams and at week 8, decreased to 0.46 grams (see Figure 1a). The average daily cannabis use in grams decreased significantly with each week in the trial ($F_{1,86}$ = 8.74, p = .004), while adjusting for baseline ($F_{1,86}$ = 9.66, p = .003).

The observed average daily cannabis use in dollars at week 1 was $9.00 and at week 8, decreased to $5.49 (see Figure 1b). The average daily cannabis use in dollars decreased significantly with each week in the trial ($F_{1,86}$ = 16.67, p < .0001) while adjusting for baseline use ($F_{1,86}$ = 2.00, p = .161). A total of three participants achieved 3 weeks or greater of total abstinence, as confirmed by urine toxicology. Quantitative THC levels were stable for other participants, without a significant reduction, as is expected when reductions in reported use are modest (17).

Cannabis using days

The observed average cannabis using days is displayed in Figure 1c. During week 1, the average number of using days was 4.13 days, and at week 8, decreased to 3.10 days. The days of cannabis use per week decreased significantly ($F_{1,86}$ = 7.67, p = .007) with each week in the trial, adjusted for the number of using days in the 4 weeks prior to beginning the study ($F_{1,86}$ = 0.40, p = .530).

Withdrawal symptoms

The observed weekly average withdrawal symptom severity scores is displayed in Figure 2. There was no significant change in withdrawal symptom severity over treatment participation ($F_{1,146}$ = 1.02, p = .314) while adjusting for baseline withdrawal ($F_{1,146}$ = 1.29, p = .258).

Discussion

As expected, guanfacine demonstrated feasibility as a treatment for cannabis use disorder. Study retention was comparable to that of participants in substance use trials more generally (18) and there were no unusual or unexpected side effects. Cannabis use appeared to decrease in the sample as well, though this observation is highly preliminary,

Table 2. Retention and adverse effect incidence by titration schedule.

	Titration Schedule					
	2-Weeks (n = 12)		8-Weeks (n = 10)		Overall (N = 22)	
	n	%	n	%	n	%
Side Effects						
Reported at least 1 side effect throughout the trial	9	75.0%	5	50.0%	14	63.6%
Reported at least once:						
Constipation	2	16.7%	0	0.0%	2	9.1%
Drowsiness	2	16.7%	1	10.0%	3	13.6%
Dry mouth	4	33.3%	1	10.0%	5	22.7%
Fatigue	4	33.3%	1	10.0%	5	22.7%
Headache	1	8.3%	0	0.0%	1	4.5%
Hypotension	2	16.7%	1	10.0%	3	13.6%
Increased urination	0	0.0%	1	10.0%	1	4.5%
Insomnia	4	33.3%	1	10.0%	5	22.7%
Lightheadedness	3	25.0%	1	10.0%	4	18.2%
Nausea	2	16.7%	1	10.0%	3	13.6%
Dosage*						
Achieved 4 mg	6	60.0%	3	42.9%	9	52.9%
	Mean	**SD**	**Mean**	**SD**	**Mean**	**SD**
	Median	**IQR**	**Median**	**IQR**	**Median**	**IQR**
Maximum dose achieved (mg)	3.2	1.1	2.7	1.4	3.0	1.2
	4.0	2.0–4.0	3.0	1.0–4.0	4.0	2.0–4.0
Retention (weeks)	5.7	4.0	6.2	3.9	5.9	3.9
	6.0	1.5–10.0	8.0	2.0–10.0	7.5	2.0–10.0

*2-weeks schedule (n = 10), 2 subjects (ID 9, 11) are missing dose information; 8-weeks schedule (n = 7), 3 subjects. (ID 14, 19, 21) are missing dose information.

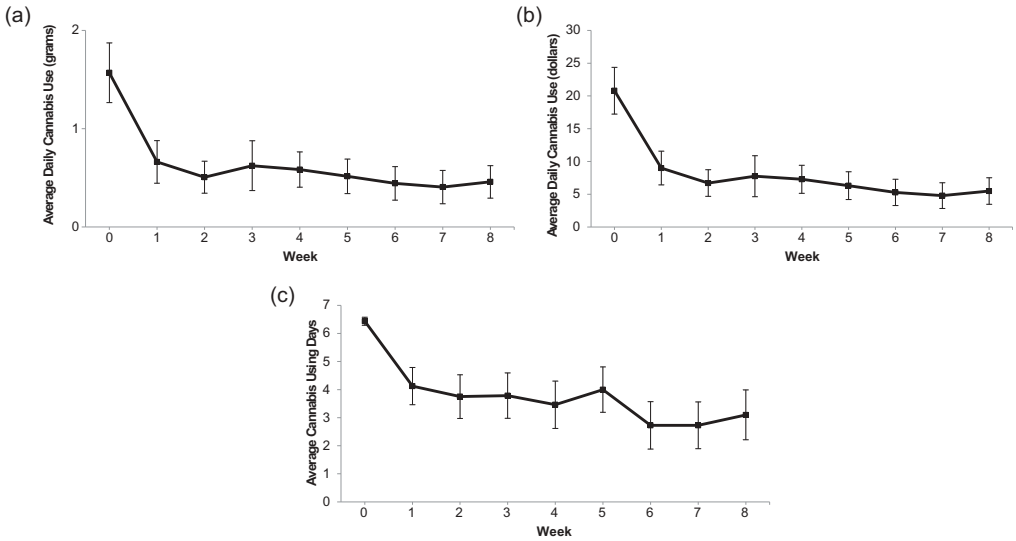

Figure 1. Observed means and corresponding standard errors of cannabis use (daily amount in (a) grams and (b) dollars; (c) use days per week).

ascertained through self-report, and limited by an open-label, non-controlled design. Thus, though any benefits observed could not be attributed to guanfacine with any certainty, this trial suggests that G-XR is a feasible option for treating CUDs, and deserves further evaluation in an efficacy trial.

9 participants were able to achieve the target dose of 4 mg, with roughly double achieving that dose in the rapid titration protocol than in the slower protocol. The slower and more gentle protocol, with participants remaining at the dose that is well-tolerated, appeared to change the risk profile of G-XR. For the 10 participants who underwent the second titration procedure, 50% reported experiencing no side effects at all, while for the 12 participants who underwent the first titration procedure, only 25% (3 out of 12) did not report any side effects. These findings, although preliminary and not statistically significant, suggest a novel titration method for G-XR that may work to increase tolerability in CUD individuals.

The open-label design also limited us from ascertaining the effect of G-XR on withdrawal severity, and so any observation pertaining to withdrawal during the trial should be tempered accordingly. Nonetheless, an interesting finding is that withdrawal severity did not significantly change over the course of study participation. This is in contrast to other trials testing alpha-2 agonists in cannabis users in both clinical and laboratory settings (10,13). One conjecture for this finding is that only a few participants attempted and achieved abstinence, with most participants opting to reduce use. Thus, only a few participants may have incurred withdrawal.

It is worthwhile considering the most advantageous treatment model for utilizing G-XR, and for testing its efficacy in future research. Given its putative effect on withdrawal severity, the best model for G-XR may be to enforce abstinence, as with a short hospitalization, and to assess post-detoxification discomfort as well as time to first use or relapse. It is therefore possible that a relapse prevention framework may be a better approach for optimizing

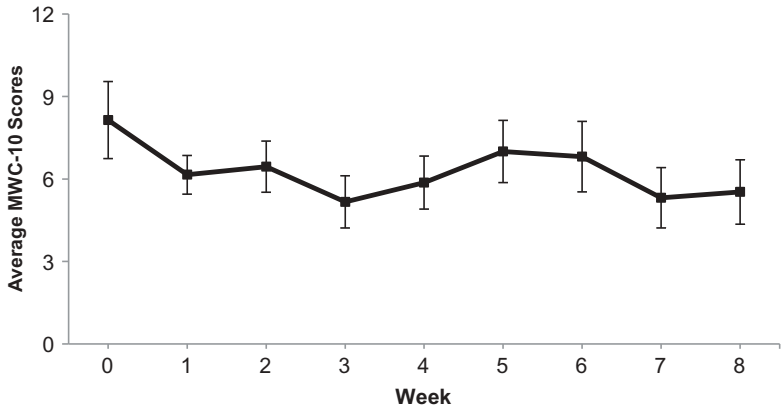

Figure 2. Observed means and corresponding standard errors of withdrawal (MWC-10).

the efficacy of G-XR and for testing its benefits more fully than is the abstinence initiation (or use reduction) model applied in this preliminary study. Similarly, because some of the side effects of guanfacine resemble the effects of cannabis (e.g., fatigue), it is likely that providing G-XR to individuals still using cannabis may work to potentiate some of its side effects. A relapse prevention framework for G-XR administration may additionally work to improve tolerability and retention.

This trial has several limitations consistent with its open-label nature, in addition to being brief. Most importantly, it is not possible to determine whether the reductions in cannabis use were due to G-XR, or whether they were related to other study procedures, such as meeting with staff for medication management, or to time. An additional limitation is that the trial was not adequately powered to detect differences between the two titration regimens, and the observation that the more gradual titration regimen may be more tolerable and feasible should be qualified accordingly.

Notwithstanding these limitations, our findings introduce the possibility that G-XR, when titrated gradually and with sensitivity to potential side effects, may benefit CUDs. Though G-XR was feasible in this use reduction or abstinence initiation setting, it may also be useful in participants who have already initiated abstinence and seek pharmacotherapy for managing withdrawal and other vulnerabilities, such as behavioral reactivity, that might contribute to relapse. Future research directed at testing the efficacy of G-XR at promoting abstinence or reducing relapse using the appropriate clinical trial design will undoubtedly be helpful in better understanding the role G-XR can play in managing CUDs.

Disclosures

The authors have no conflicts of interest to report.

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