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Open-label pilot study of quetiapine treatment for cannabis dependence

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Abstract

Background—There are no efficacious pharmacotherapies for cannabis dependence. The effects of quetiapine are well matched to the symptoms of cannabis withdrawal and could be useful in the treatment of cannabis dependence.

Objectives—To evaluate quetiapine for the treatment of cannabis dependence and determine the optimal dosing.

Methods—In an eight-week open-label outpatient pilot trial, we evaluated the feasibility of quetiapine treatment for cannabis dependence in 15 outpatients. Quetiapine was gradually titrated to 600 mg or the maximum tolerated dose.

Results—The mean study retention was 6.5 weeks (± 2.3), with 67% of participants completing all eight weeks of the trial. The mean maximum dose achieved was 197 mg/day (range: 25–600 mg/day). Only two of the 15 participants were able to achieve the target dose of 600 mg daily. There were no serious adverse events and no participants were discontinued from the trial due to adverse effects. The most common reported adverse effects were fatigue (80% of participants) and somnolence (47%). From baseline to week 8, the modeled overall decrease in daily dollar value of marijuana was 76.3% (CI: 63.4%, 84.7%). Over the eight weeks of the study, there was a 46.9% (CI: 11%, 68.3%) decrease in urine tetrahydrocannabinol-9-carboxylic acid (THCOOH) levels.

Conclusions—These preliminary results are promising in that quetiapine treatment was tolerated by cannabis-dependent patients and associated with decreased cannabis use. The recommended maximum target dose for cannabis-dependent patients is 300 mg daily. These preliminary data support further evaluation of quetiapine as a treatment for cannabis dependence.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Keywords

Cannabis; dependence; pharmacotherapy; quetiapine; treatment

Introduction

Marijuana is the most widely-used illicit drug in the United States with approximately 17.4 million individuals reporting past-month use (1). The estimated past-year and lifetime prevalence of marijuana abuse is thought to be 1.1% and 7.2%, respectively, and past-year and lifetime marijuana dependence to be 0.3% and 1.3% (2,3). The use of abstinence-based voucher incentives combined with cognitive-behavioral therapy is associated with rates of abstinence of up to 40% (4,5), and cognitive behavioral therapy up to 27% (6–8). There have been a number of negative double-blind trials of putative cannabis dependence pharmacotherapy agents (9–12), and while some preliminary work with N-acetylcysteine (13) and gabapentin (14) is promising, there is still no clearly efficacious pharmacotherapy agent available for cannabis dependence.

The psychotropic effects of cannabis are produced mainly by delta-9-tetrahydrocannabinol (THC), although other cannabinoids may modify its effects (15). When a regular user of cannabis reduces or ceases use, the development of a withdrawal syndrome may occur. Cannabis withdrawal symptoms are common and clinically significant among regular users of cannabis (16), and include insomnia, irritability, anorexia, craving, restlessness, anxiety, and depression.

Quetiapine is an atypical antipsychotic effective for the treatment of schizophrenia, bipolar disorder and as an adjunctive treatment for major depressive disorder. Quetiapine is a dibenzothiazepine that acts as an antagonist at serotonin 5HT_{1A} and 5HT₂, dopamine D₁ and D₂, histamine H₁, and adrenergic α_1 and α_2 receptors (17). Its weak D₂ receptor binding (18,19) most likely accounts for the low incidence of extrapyramidal side effects associated with quetiapine as compared to other atypical antipsychotic agents. Post-marketing surveillance has demonstrated that quetiapine is generally safe and well-tolerated (20).

The known clinical effects of quetiapine – mood stabilization, anxiolysis, appetite stimulation, and sedation – are well matched for the symptoms of cannabis withdrawal, which include dysphoria, irritability, anxiety, and insomnia. We hypothesized that by reducing craving and other symptoms of cannabis withdrawal, quetiapine would reduce cannabis consumption and promote abstinence. Our goal was to titrate participants to the highest tolerable dose up to 600 mg daily in order to explore the feasibility of quetiapine treatment for cannabis dependence and determine the optimal dosing range.

Materials and methods

Subjects

The clinical trial was conducted at the Substance Treatment and Research Service (STARS) of Columbia University Medical Center/New York State Psychiatric Institute. Recruitment occurred from August of 2009 through May of 2010, and data collection completed in

August of 2010. During the screening period, a comprehensive psychiatric and medical evaluation including history, physical and laboratory examinations, and the Structured Clinical Interview (SCID) for DSM-IV Axis I disorders (21) interview were performed. Self-reported cannabis use for the prior 28 days was measured using the timeline followback method (22) adapted for marijuana (23). All participants were seeking outpatient treatment for problems related to marijuana use and were recruited by local advertising (internet, print, radio, television, and subway) or by clinical referrals in the New York City metropolitan area.

Treatment-seeking participants were 18–65 years old; met Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) criteria for cannabis dependence; and reported using cannabis at least an average of five days per week during the 28 days prior to study entry. Participants were excluded if they had: a DSM-IV-TR diagnosis of major depressive disorder, bipolar disorder, or schizophrenia; a DSM-IV-TR Axis I psychiatric disorder that was unstable or likely require treatment during the study period; physiological dependence on any substances (other than nicotine or cannabis) that would require medical intervention; were prescribed psychotropic medication; were at significant risk for suicide; coronary vascular disease as indicated by clinical history or electrocardiogram; unstable physical condition such as poorly controlled hypertension or acute hepatitis; diabetes, hyperglycemia, obesity or elevated lipids; history of an allergic reaction to quetiapine; were pregnant or lactating; or were compelled to receive treatment to avoid imprisonment or other penalties. This study was reviewed and approved by the Institutional Review Board of the New York State Psychiatric Institute, and all participants gave written informed consent.

Treatment

All participants were assigned to quetiapine treatment under open-label conditions. Quetiapine was administered in 25 and 100 mg tablets and was gradually titrated to 600 mg or the maximum tolerated dose (see Table 1) in twice-daily divided dosing. Study medication was dispensed weekly. Dosing was flexible, with reductions made for tolerability problems.

All participants received a manualized behavioral treatment, the “Brief Counseling for Marijuana Dependence: A Manual for Treating Adults,” (24) which combines the use of motivational enhancement therapy (MET) and cognitive behavior therapy (CBT). Study visits occurred twice weekly during the study period. One visit per week was with the research psychiatrist to perform study assessments and to monitor medication effects. The second visit each week was for manualized therapy sessions.

Measures

Cannabis use was assessed by self-report confirmed by urine toxicology. On a weekly basis, self-reported cannabis use data was collected using the timeline followback method for marijuana (23) for each day of the study period. Urine samples were collected two times per week and creatinine-corrected quantitative tetrahydrocannabinol-9-carboxylic acid (THCOOH) levels were determined.

We used a calendar-based structured pill count interview (timeline followback) to measure medication compliance 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. Participants were paid \$4 for each screening visit and \$5 for each study visit to cover transportation costs. Subjects earned an additional \$15 during Week 1, Week 4, and Week 8 upon completing additional assessment measures. The total compensation a patient may have earned for completion of the screening process and the entire study was \$276. The frequency of adverse events during the study period was assessed each week by a modified version of the SAFTEE (25). Female participants had serum pregnancy tests performed monthly.

Data analyses

All analyses were conducted on the intent-to-treat sample of all participants. All statistical tests were two-tailed and employed at a significance level of 5%, unless otherwise stated. The distributions of all continuous outcome variables (if not normal) were properly identified and correctly modeled in the analysis stage with corresponding link functions.

The primary outcome in this study was the mean highest tolerated dose of quetiapine achieved. Retention, adverse effect reports, and discontinuation of treatment due to adverse effects were measured to assess tolerability. The measures of marijuana use analyzed in this study were: (i) marijuana use; (ii) daily dollar value of marijuana used; (iii) number of non-using days; and (iv) creatinine-corrected quantitative urine. Except the variable 'number of non-using days per week', the variables were analyzed using longitudinal mixed effect model for negative binomial distribution with log link function. The weekly time correlations within subject were modeled using autoregressive function and subjects were modeled as random factors. The variable 'number of non-using days' were modeled with a linear spline procedure (26) with a "knot" at week 4 in order to appropriately model the changing trend of non-using days per week, which increases until week 4 and then stabilizes.

Longitudinal mixed effects models account for unobserved data and do not require the complete measurement data to estimate the outcome variable. The inferences from analyses with missing data are valid provided that they are MAR "missing at random" (i.e. the missing mechanism does not depend on the value of the unobserved outcome). This is untestable in most medical research and in our study as well.

Results

We enrolled 15 participants (11 males; mean age 28.2 years [± 8.1]; 46% black), who were daily marijuana smokers. The mean study retention was 6.5 weeks (± 2.3), with 87% of participants completing four weeks, and 67% of participants completing all eight weeks of the trial. The mean maximum dose achieved was 197 mg/day (range: 25–600 mg/day). Only two of the 15 participants were able to achieve the target dose of 600 mg daily. Participants who requested dose reductions generally preferred to reduce or eliminate the morning dose. Longitudinal outcome measures of marijuana use decreased significantly over the eight-week period (see Figures 1 and 2). The observed daily dollar value of marijuana used at

baseline was on average \$33.56 (SD = \$34.28) and at week 8 was on average \$7.98 (SD = \$6.74). The observed average number of abstinence days at baseline was 0 days, at week 1 was on average 1.13 days (SD = 2.07) and at week 8 was on average 3.44 days (SD = 2.60).

Using a mixed-effects model

The daily dollar value of marijuana used over a one-week period significantly decreased by 16.5% each week (CI: 11.8%, 20.9%, $p < 0.0001$); From baseline to week 8, the modeled overall decrease in daily dollar value was 76.3% (CI: 63.4%, 84.7%); Non-using days per week significantly increased by a 41.2% each week (CI: 18.4%, 68.4%, $p = 0.0002$) up to week 4, at which time the abstinent days per week were stabilized through week 8; From baseline to week 4, there was a 3.97 (CI: 1.97, 8.05) times increase in the rate of non-using days. Creatinine-corrected quantitative urine THCOOH levels per week were significantly decreased by 7.6% each week (CI: 1.4%, 13.4%, $p = 0.0170$). Overall, over the 8 weeks of the study, there was a 46.9% (CI: 11%, 68.3%) decrease in the THCOOH levels.

There were no serious adverse events and no patients were discontinued due to adverse effects. Participants who did not complete the trial were lost to follow-up. The most common reported adverse effects were fatigue (80% of participants) and somnolence (47%). Other adverse effects that were reported by more than one participant include appetite change (19%), constipation (13%), and dry mouth (31%). During the trial, 11 participants gained weight and four participants lost weight; the mean weight gain was 1.6 lbs (range: -5.0–11.5 lbs). However, no participants gained more than 7% of their baseline weight, developed a BMI greater than 30, developed persistently elevated glucose levels, or developed hypercholesterolemia or hypertriglyceridemia.

Discussion

The primary goals of the study were to determine the feasibility of quetiapine treatment for cannabis dependence and the optimal dosing range. The average tolerated quetiapine dose in this study was approximately 200 mg per day. However, the mean dose achieved was likely depressed by participant drop-out during the titration phase (six weeks) for reasons other than tolerability and future studies should exceed this dose. Only two of the 15 participants were able to achieve a dose of 600 mg daily, suggesting poor tolerability of this dose. We suggest a target dose of 300 mg daily for future studies of quetiapine treatment of marijuana dependence. Quetiapine dosing was twice daily in this pilot study. Participants who requested dose reductions generally preferred to reduce or eliminate the morning dose due to sedation. Based on this experience, we would recommend a single evening dose.

While this study was not designed to assess the efficacy of quetiapine treatment for cannabis dependence, these preliminary results seem promising in that quetiapine treatment was associated with reductions in marijuana use. Retention rates were similar to other cannabis dependence pharmacotherapy clinical trials (12).

The pharmacodynamic actions of quetiapine provide a theoretical rationale for why it may be beneficial in treating marijuana dependence. The low and transient level of dopamine D₂ receptor affinity of quetiapine (27) combined with 5-HT_{2A} antagonism (28), may be

beneficial for stabilizing dysregulation of the mesostriatal dopaminergic pathway “reward circuit.” Preclinical data suggests that quetiapine may attenuate reward through antagonism of dopamine and non-dopamine neurotransmission (29). An alternative proposed mechanism is the high affinity of quetiapine for noradrenergic alpha-1 receptors (29), since noradrenergic pathways may be critical to rewarding effects of substances of abuse (30). The clinical effects of quetiapine, including anxiolysis, mood stabilization, sedation, and appetite stimulation are potentially well matched to the symptoms of marijuana withdrawal. Most adults seeking treatment for marijuana dependence report experiencing marijuana withdrawal symptoms of moderate severity (31), including, depression, irritability, anxiety, insomnia and anorexia (32).

Quetiapine was well tolerated during the trial. There were no serious adverse events and no participants discontinued due to medication intolerability or development of metabolic abnormalities. Reports of sedation were very common, but these symptoms were not severe, and did not lead to study drop out and overall retention was similar to other pharmacotherapy trials for cannabis dependence. Weight gain, which is a known adverse effect due to quetiapine, was modest during the trial, with a mean weight gain over the entire study period of 1.6 lbs. This may be due to the relatively brief course of treatment or a finding related to treating patients potentially in cannabis withdrawal, which is associated with weight loss. Quetiapine is associated with metabolic, psychiatric, and neurological risks with chronic administration. A potential model for treating cannabis dependence is a short course of quetiapine to manage withdrawal symptoms and facilitate reductions or discontinuation of cannabis use. This approach could potentially maximize the benefit of the medication during the phase of cannabis dependence it would theoretically be most effective, while limiting exposure to the risks of ongoing quetiapine treatment.

While quetiapine did not induce prolonged abstinence in this small sample over an eight-week period, abstinence from cannabis use is difficult to achieve in daily smokers of marijuana. A medication that could help alleviate cannabis withdrawal symptoms and facilitated reductions in cannabis use, could be usefully clinically, particularly in combination with behavioral strategies. A human laboratory study of 14 non-treatment-seeking (i.e. not motivated to reduce or abstain from cannabis) marijuana smokers found that quetiapine improved sleep quality and appetite and reduced weight loss as compared to placebo (33). However, quetiapine increased marijuana craving and self-administration during a laboratory model of relapse, which is inconsistent with the results of this open-label trial. One possible explanation for these divergent results is that motivation and treatment goals are important determinants of outcome, and non-treatment-seeking laboratory participants may respond differently to pharmacotherapy than treatment seeking clinical trial participants.

A limitation of this study is the open label design. While conducting the trial under open label conditions facilitated tailoring a tolerable dosing schedule for each participant, the lack of a control group and the unblinded nature of the investigation limits the interpretation of the effect of quetiapine on cannabis use. While cannabis use declined among participants, this effect could be due entirely to the psychosocial intervention or other factors other than quetiapine administration. Another limitation of the study is that participants received an

active psychosocial treatment during the trial, which presumably affected cannabis use. However, this psychosocial approach in the context of a pharmacotherapy clinical trial for near-daily marijuana users has demonstrated only limited benefit (12), where only 15.6% of the placebo group achieved a two-week period of end-of-trial abstinence. Other limitations include a lack of objective medication compliance data and a small sample size.

The results of this open-label pilot study suggest that quetiapine is well-tolerated and is associated with decreased cannabis use in cannabis-dependent outpatients. The optimal target dose for cannabis-dependent patients appears to be approximately 300 mg daily in a single evening dose to minimize daytime sedation. These preliminary data support the further evaluation of quetiapine as a treatment for cannabis dependence.

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Figure 1.
Observed average daily dollar amount of marijuana per week.

Figure 2.
Observed average days of abstinence per week.

Table 1

Open-label quetiapine dosing.

Open-label quetiapine dosing										
Study week	1	1	1	2	2	3	3	4	5	6
Study day	1-2	3-4	5-7	8-10	11-14	15-17	18-21	22-28	29-35	36-42
Total daily dose quetiapine	25mg	50mg	75mg	100mg	150mg	200 mg	250mg	300mg	400mg	500mg
										600mg