



Feasibility and effects of galantamine on cognition in humans with cannabis use disorder



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ABSTRACT

Background: As long-term use of medicinal and recreational cannabis becomes more common and concentrations of delta-9-tetrahydrocannabinol (THC) in cannabis increase, it is timely to identify strategies to counteract the cognitive effects of cannabinoids.

Objective: Galantamine is an acetylcholinesterase inhibitor approved for the treatment of Alzheimer's disease and other dementias. This study aimed to investigate the feasibility of galantamine administration to individuals with cannabis use disorder (CUD), and the effects of galantamine on cognition. We hypothesized galantamine would be well tolerated and would not have procognitive effects in the absence of acute cannabis intoxication.

Methods: Thirty individuals with CUD (73.5% male, 26.5% female) participated in a randomized, double-blind, parallel-group trial. Participants completed a baseline session followed by a 10-day outpatient treatment period, during which they received either 8 mg/day of galantamine orally or placebo. Cognitive assessments were conducted at three time points and self-reported measures that may impact cognitive performance (cannabis withdrawal, craving, and mood) were completed at six time points.

Results: There were no significant differences in demographic and baseline variables between groups (galantamine vs. placebo). There were no significant adverse effects from galantamine. Cannabis withdrawal and craving continuously decreased over the study. We saw evidence of a modest improvement in cognitive outcomes during the 10-day period, exemplified by a statistically significant increase in measures of response inhibition (increased median reaction time on the Stop Signal Task), and a trend for improvement in measures of attention (increased RVP A'), for both groups. Analyses did not show, however, a significant main effect for treatment or treatment-by-time interactions.

Conclusions: The findings of this pilot study support the feasibility of the administration of galantamine for individuals with CUD. Adequately powered, randomized, placebo-controlled trials are required to investigate the potential of galantamine to improve cognitive deficits associated with CUD.

1. Introduction

Cannabis is one of the most widely used substances in the United States. According to the 2017 National Survey on Drug Use and Health (NSDUH), 26 million individuals – 9.6% of Americans aged 12 years or older – used cannabis in the past month (Substance Abuse Mental Health Services Administration, 2018). Approximately 41 million individuals used in the past year, and 3 million used for the first time, which amounts to approximately 8300 new users each day (Substance Abuse Mental Health Services Administration, 2018). From 1992 until 2017, the proportion of Americans regularly using cannabis increased

by approximately 60% (Substance Abuse Mental Health Services Administration, 2018). Several factors may account for this increase, such as the significant momentum gained by changes in medicinal and recreational cannabis legislations, with several states moving toward legalization, and the increased perception of cannabis use as “benign” and socially acceptable (Blevins et al., 2018).

As long-term use of medicinal and recreational cannabis becomes more common and concentrations of delta-9-tetrahydrocannabinol (THC) in cannabis increase (ElSohly et al., 2016), it is timely to identify strategies to reduce the cognitive effects of cannabinoids. Cognitive effects of cannabinoids may be a particular challenge for treatment-

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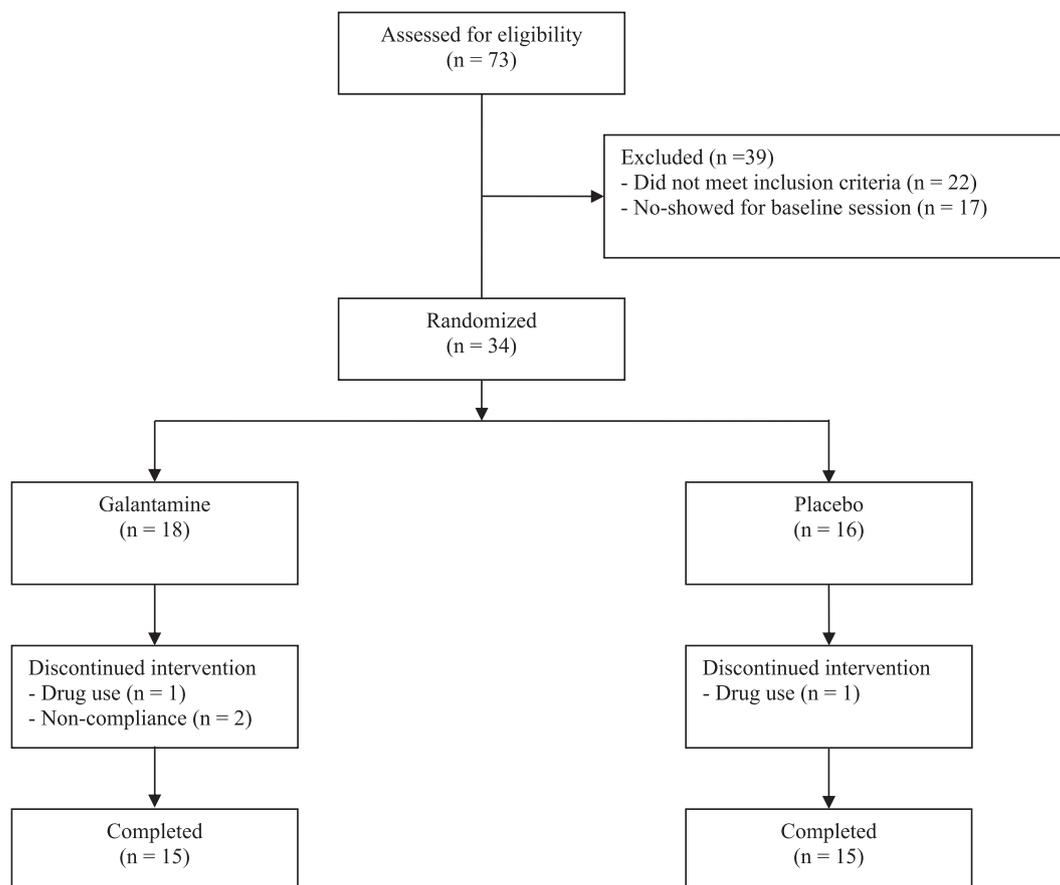


Fig. 1. CONSORT diagram.

seeking individuals with cannabis use disorder (CUD), as cognitive impairments may be a predictor of higher treatment dropout (Aharonovich et al., 2008). These findings are consistent with studies of individuals with other substance use disorders (e.g., alcohol and cocaine use disorders), which also found negative effects of cognitive impairments on treatment retention (Aharonovich et al., 2003; Aharonovich et al., 2006; Boggs et al., 2018). Among the cognitive domains impaired by cannabis are sustained attention, response inhibition, verbal learning, and memory (Bhattacharyya et al., 2012; Kucewicz et al., 2011). THC, the main psychoactive constituent of cannabis, is partial agonist at the cannabinoid receptors 1 (CB1-R), which is densely expressed in the hippocampus and the prefrontal cortex, neuroanatomical structures markedly implicated in cognitive processes such as sustained attention, response inhibition and verbal learning and memory (Bhattacharyya et al., 2012; Kucewicz et al., 2011). Preclinical studies indicate that CB1-R are particularly concentrated on presynaptic cholinergic terminals (Lichtman et al., 2002; Davies et al., 2002), which are involved in long-term potentiation (LTP), widely regarded as a neurophysiological substrate of learning and memory (Salavati et al., 2014; Hoffman et al., 2017). By binding at the presynaptic CB1-R located at the cholinergic nerve terminals, cannabinoids may cause inhibition of acetylcholine release, contributing to acute cognitive deficits (Heishman et al., 1990; Solowij et al., 2011; Solowij et al., 2002). This is also exemplified by reports of cognitive effects of cannabinoids as manifesting clinically akin to the cognitive impairment produced by cholinergic antagonists (Morley, 2011; Dawson and Iversen, 1993). Collectively, these data suggest cannabinoids act on the cholinergic system and raise the question whether increasing acetylcholine levels pharmacologically can counteract the cognitive effects of cannabinoids, via the administration of an acetylcholinesterase inhibitor (AChEI) (Verrico et al., 2003; Mishima et al.,

2002; Sofuoglu et al., 2010).

Galantamine is an AChEI used to treat major neurocognitive disorder associated with Alzheimer's disease and other disorders characterized by cognitive impairment (Farlow, 2002). AChEIs have also been shown to enhance cognitive functioning in healthy volunteers and individuals with mild neurocognitive disorder (Farlow, 2002; Freo et al., 2002; Marco-Contelles et al., 2006; Ochoa and Clark, 2006; Khateb et al., 2005; Sitaram et al., 1978; Davis et al., 1978; Goekoop et al., 2004). Further, evidence exists that populations with substance use disorders can derive procognitive effects from galantamine, as exemplified by findings of galantamine-induced increases in sustained attention among individuals with cocaine use disorder (Sofuoglu et al., 2011). On the other hand, other clinical studies suggest that galantamine's effects in reducing cocaine (Carroll et al., 2018) or tobacco use (MacLean et al., 2018) is not mediated by its procognitive effects. Preclinical studies suggest that by increasing ACh levels in basal ganglia, especially in the nucleus accumbens, galantamine may reduce the reinforcing effects of drugs of abuse (Jensen et al., 2018).

This study had two goals: (1) to examine the feasibility of galantamine administration for individuals with CUD; and (2) to examine the effect of galantamine on cognition among individuals with CUD. We hypothesized that galantamine would be well-tolerated. Further, as previous studies with another AChEI, rivastigmine, have only shown procognitive effects in humans acutely intoxicated with cannabis (Theunissen et al., 2015; Giacobini, 2004), we hypothesized the effect of galantamine for counteracting the cognitive effects of cannabinoids would not be observed in the absence of acute cannabis intoxication.

2. Materials and methods

2.1. Participants

Participants were aged between 18 and 55. The inclusion criteria were: (a) a DSM-IV diagnosis of cannabis abuse or dependence (i.e., DSM-5 cannabis use disorder); (b) a history of cannabis use on the average of at least twice a week over a one-month period; (c) recent exposure to cannabis confirmed by positive urine toxicology for cannabinoids; (d) absence of current medical problems and a normal ECG. Exclusion criteria were: (a) current major psychiatric disorders (i.e., mood, psychotic, or anxiety disorders); (b) current alcohol or other substance use disorders (except cannabis and tobacco); (c) history of major medical illnesses; (d) use of other medications; (e) known allergy to galantamine, and (e) current pregnancy or breastfeeding. Participants were asked to refrain from using alcohol and drugs during study participation. Those who were non-compliant were discharged from the study. Although participants were asked to refrain from using cannabis, the extreme lipid solubility and long half-life of cannabinoid metabolites precludes accurate estimation of recent exposure. Urine toxicology tests for cannabinoids may be positive for as long as two months in chronic users. To minimize nicotine withdrawal effects on cognitive performance, participants who used nicotine were advised to continue smoking as usual.

Seventy-three individuals were screened to participate in the study. Thirty-four participants were randomized, and 30 completed all study visits (Fig. 1). Of the four participants that did not complete the study, two were discharged for drug use and two for non-compliance with study procedures (1 participant attended the day 1 visit and did not return, and 1 participant missed a dose of medication and was discharged). There were no differences between study completers and non-completers on any demographic variables, or by group assignment. All participants provided informed consent prior to study entry and were paid for participation. This study was approved by the VA Connecticut Healthcare System Human Subjects Subcommittee.

2.2. Design and procedures

This was a randomized, double-blind, parallel-group study. Participants were randomized to receive oral galantamine extended release (8 mg/day) or placebo treatment for 10 days. All participants had a baseline session (day 0), where they were familiarized with study procedures and baseline measures (e.g., cognitive performance and mood assessments) were collected. On day 1, participants received the first dose of the study medication in the clinic. Participants returned to the clinic for outpatient visits on days 2, 4, 7, and 9 or 10 to receive medication. Participants received take-home bottles to self-administer study medication for days 3, 5, 6, and 8. If participants completed their outpatient visit on day 10, they also received take-home medication for day 9. Pill counts were conducted to ensure adherence to study medication. Cognitive test sessions took place at baseline and days 4, 9 or 10.

2.3. Measures

2.3.1. Physiological measures

Blood pressure and heart rate were measured at each visit. Urine toxicology screening tests were performed before each visit to rule out exposure to drugs other than cannabis. Breath alcohol was measured prior to each visit to rule out acute alcohol intoxication.

2.3.2. Adverse effects

Adverse events were monitored using a locally developed comprehensive symptom checklist that included side effects of galantamine.

2.3.3. Cannabis use, withdrawal, craving, and mood

Cannabis use was collected from the medical interview screening

notes. The Marijuana Withdrawal Checklist (MWC) (Budney et al., 2003; Budney et al., 1999) was used to assess withdrawal symptoms in the last 24 h and the 12-item Marijuana Craving Questionnaire (MCQ) (Heishman et al., 2001); was used to assess cannabis craving. The 65-item Profile of Mood States (POMS), composed of six subscales – tension, depression, anger, vigor, fatigue, and confusion – was used to measure mood (McNair et al., 1971). Withdrawal, craving, and mood measures were collected as they can influence cognitive outcomes (Sofuoglu et al., 2011).

2.3.4. Cognitive battery

The cognitive battery used in this study included the Hopkins Verbal Learning Test Revised (HVLT-R) (Benedict et al., 1998) and two modules from the Cambridge Neuropsychological Test Automated Battery (CANTAB) (Fray et al., 1996; Sahakian and Owen, 1992) the Rapid Visual Information Processing (RVIP) and the Stop Signal Task (SST). Practice effects were minimized by the use of alternate versions of the HVLT-R and parallel versions of the CANTAB modules across all testing sessions.

The HVLT-R is a brief verbal learning and memory test with six alternate forms. Aside from verbal memory and learning being one of the cognitive domains most affected by cannabinoids (Solowij et al., 2011), previous studies indicate that HVLT-R performance is sensitive to the effects of cannabinoids on verbal memory (Broyd et al., 2016). In this study, the HVLT-R outcomes were total recall, delayed recall, percent retention, and recognition discrimination index scores.

The RVIP is a measure of sustained attention with a working memory component and is also sensitive to the cognitive effects of cannabinoids (Broyd et al., 2016; Solowij and Battisti, 2008). The RVIP has three key outcome measures: 1) A' (target sensitivity, a measure of the ability to detect sequences); 2) B'' (response bias, a measure of the tendency to respond regardless of whether a target is present) and; 3) mean latency.

The SST is a test of response inhibition. Cannabis-using individuals have previously shown impairment in the SST (Broyd et al., 2016; Solowij and Battisti, 2008). The SST has four main outcome measures: 1) direction errors; 2) proportion of successful stops; 3) median correct response time on 'Go' trials and; 4) the stop signal delay, at which the subject is able to stop 50% of the time (SSD 50%).

2.4. Data analysis

Pearson chi-square and *t*-tests were used to compare groups on baseline characteristics. The primary outcomes were analyzed with repeated measures of variance. For these analyses, effects of treatment (galantamine or placebo) and time (baseline, test session 1, test session 2) and the interaction between treatment and time were included.

3. Results

3.1. Demographics and baseline assessments

Demographic information for all randomized participants is presented in Table 1. There were no statistically significant differences between groups on frequency of cannabis use or any of the demographic variables (*p*-values > 0.05). Moreover, there were also no significant group differences on any of the baseline physiological, self-report or cognitive measures (*p*-values > 0.05), presented in Table 2. At baseline, compared to normative cognitive performance, participants in this study showed evidence of cognitive deficits on measures of sustained attention (RVP A', *Z*-score = −0.6, and RVP B' *Z*-score = −0.51, or 73rd, and 70th percentiles, respectively). Further, participants demonstrated evidence of verbal memory deficits indexed by HVLT measures (total recall delayed recall, percent retention and recognition discrimination index), both compared to normative data (Norman et al., 2011) and also compared to previously conducted

Table 1
Demographic information for randomized sample.

	Galantamine (n = 18)	Placebo (n = 16)	Total Sample (N = 34)
N (%)			
Sex			
Male	15 (83.3)	10 (62.5)	25 (73.5)
Female	3 (16.7)	6 (37.5)	9 (26.5)
Race/Ethnicity			
White	3 (16.7)	3 (18.8)	6 (17.6)
Black	14 (77.8)	12 (75.0)	26 (76.5)
Hispanic	1 (5.6)	1 (6.3)	2 (5.9)
Current Smoker	11 (61.1)	11 (68.8)	22 (64.7)
Mean (SD)			
Age	30.2 (8.0)	29.8 (9.7)	30 (8.8)
Cannabis use (joints per day)^a	2.2 (1.3)	1.7 (1.0)	2.0 (1.2)
Years of cigarette smoking	9.3 (9.8)	7.4 (9.0)	8.4 (9.3)
Years of education completed	12.4 (1.0)	12.6 (1.1)	12.5 (1.0)

There were no significant differences between conditions on any of the demographic variables (p -values > 0.05).

^a Cannabis use data were missing for 2 participants in the placebo group.

Table 2
Baseline assessment data for randomized sample.

	Galantamine (n = 18)	Placebo (n = 16)	Total sample (N = 34)
Mean (SD)			
Physiological			
Systolic BP	132.3 (16.5)	133.0 (11.7)	132.6 (14.3)
Diastolic BP	73.4 (12.7)	76.1 (10.4)	74.7 (11.6)
Heart rate	70.3 (11.6)	73.3 (10.3)	71.7 (10.9)
Marijuana Craving Questionnaire			
Total score	45.2 (15.9)	44.3 (19.7)	44.8 (17.5)
Compulsivity subscale	8.7 (4.5)	8.8 (4.6)	8.8 (4.5)
Emotionality subscale	10.3 (4.9)	11.6 (5.8)	10.9 (5.3)
Expectancy subscale	13.5 (5.0)	11.9 (5.7)	12.7 (5.4)
Purposefulness subscale	12.7 (3.6)	11.9 (5.5)	12.3 (4.5)
Marijuana Withdrawal Checklist			
Total score	6.7 (5.5)	6.4 (5.6)	6.5 (5.5)
Profile of Mood States			
Tension subscale	14.7 (3.6)	16.2 (3.7)	15.4 (3.7)
Depression subscale	20.1 (4.5)	21.1 (6.8)	20.6 (5.6)
Anger subscale	15.9 (4.5)	16.1 (5.0)	16.0 (4.7)
Vigor subscale	21.7 (5.8)	24.9 (3.7)	23.2 (5.1)
Fatigue subscale	9.7 (3.3)	10.5 (4.1)	10.0 (3.7)
Confusion subscale	11.7 (3.4)	11.8 (2.5)	11.7 (2.9)
Cognition			
Rapid Visual Information Processing (RVIP)			
RVP A'	0.89 (0.06)	0.89 (0.06)	0.89 (0.06)
RVP B'	0.81 (0.31)	0.88 (0.19)	0.84 (0.26)
Mean latency	412.40 (112.3)	446.97 (132.40)	428.67 (121.53)
Stop Signal Task (SST)			
Direction errors	1.72 (1.78)	1.81 (2.37)	1.76 (2.05)
Proportion of successful stops	0.56 (0.14)	0.57 (0.12)	0.56 (0.13)
Median correct RT on Go trials	520.14 (161.75)	520.91 (178.78)	520.50 (167.35)
SSD (50%)	345.98 (173.93)	355.72 (152.76)	350.56 (161.91)
Hopkins Verbal Learning Test-Revised (HVLTR)			
Total recall	19.0 (5.7)	20.8 (6.2)	19.9 (5.9)
Delayed recall	6.7 (2.4)	7.2 (2.7)	6.9 (2.5)
Percent retention	86.3 (25.4)	82.5 (27.5)	84.5 (26.1)
Recognition discrimination index	9.8 (1.6)	9.8 (1.7)	9.8 (1.6)

There were no significant differences between conditions on any of the baseline assessment variables (p -values > 0.05). SSD 50%: Stop signal delay, at which the subject is able to stop 50% of the time. RT: Reaction time.

studies of healthy individuals and individuals with CUD (Rabin et al., 2017).

3.2. Adverse effects

There were no significant main effects and no significant group by time interactions for blood pressure and heart rate (p -values > 0.05). None of the participants reported adverse events during the study.

3.3. Cannabis withdrawal, craving, and mood

Though cannabis withdrawal total score decreased over time, we found no significant main effects and no significant group by time interactions for cannabis withdrawal scores (p -values > 0.05).

The total MCQ score [$F(5, 140) = 11.72$; $p < 0.001$] and total MWC score [$F(5, 135) = 6.31$; $p < 0.001$] decreased over time, though there were no significant interactions by group. Three of the POMS subscale scores also decreased over time (Tension-Anxiety: [$F(5, 135) = 6.61$; $p < 0.001$], Vigor-Activity: [$F(5, 135) = 4.78$; $p < 0.001$], and Confusion-Bewilderment: [$F(5, 135) = 3.64$; $p < 0.01$]), however there were no significant interactions by group.

3.4. Cognitive battery

Table 3 shows the cognitive performance test score means by group, across the three testing sessions. There were no significant main effects and no significant group by time interactions for any of the RVIP measures (p -values > 0.05), though we found a trend for improvement in measures of attention (increased RVP A') for both groups (Fig. 2). For the SST, median correct reaction time on Go trials increased over time [$F(2, 56) = 3.59$; $p < 0.05$], yet there was no significant interaction by group (Fig. 3). For the HVLTR, only delayed recall decreased over time [$F(2, 56) = 4.48$; $p < 0.05$], but did not differ by group.

4. Discussion

The current study investigated the feasibility and the potential efficacy of the centrally acting AChEI galantamine to improve cognitive function among individuals with cannabis use disorder. As hypothesized, galantamine was well tolerated by participants, such that there were no differences in physiological measures or adverse effects for participants who received galantamine, compared to those who received placebo.

The results of this study show that individuals with CUD demonstrated evidence of mild cognitive deficits at baseline, in accordance with previous studies demonstrating cognitive deficits among individuals with CUD (Volkow et al., 2016; Meier et al., 2012). As expected, the cognitive performance of participants who received galantamine in the absence of cannabis intoxication did not differ from those who received placebo, on any of the measures of sustained attention, response inhibition and verbal memory and learning. AChEI have been previously found to enhance cognition in acutely cognitively impaired individuals intoxicated with cannabis (Theunissen et al., 2015). In this study, the procognitive effects of galantamine were not demonstrated, likely due to the fact that our sample was composed of young, healthy individuals who did not demonstrate substantial cognitive deficits and were not acutely intoxicated with cannabis, unlike in a previous human laboratory study that found procognitive effects of rivastigmine in acutely intoxicated cannabis users (Theunissen et al., 2015). Some participants experienced mood changes during the course of the study, possibly in the context of early, mild cannabis withdrawal. However, on the Marijuana Withdrawal Checklist we did not see a pattern of scores initially increasing and then decreasing over time, which might be expected if participants were abstaining from cannabis. Moreover, because all participants were able to continue with full, uninterrupted sessions of the cognitive tests, we estimate the impact of

Table 3
Cognitive testing scores for placebo vs. galantamine treatment.

	Baseline	Test session 1	Test session 2
	Mean (SD)		
<i>Rapid Visual Information Processing (RVIP)</i>			
<i>RVIP A'</i>			
PLA	0.89 (0.02)	0.92 (0.02)	0.92 (0.02)
GAL	0.90 (0.02)	0.92 (0.02)	0.92 (0.01)
<i>RVIP B'</i>			
PLA	0.85 (0.06)	0.87 (0.04)	0.72 (0.15)
GAL	0.88 (0.03)	0.89 (0.03)	0.94 (0.03)
<i>RVIP Mean Latency</i>			
PLA	449.15 (35.31)	428.25 (39.34)	436.26 (33.81)
GAL	405.63 (31.21)	398.37 (22.39)	383.86 (18.65)
<i>Stop Signal Task (SST)</i>			
<i>Direction errors</i>			
PLA	1.93 (0.62)	1.13 (0.63)	2.33 (1.09)
GAL	1.73 (0.49)	1.27 (0.49)	1.73 (0.61)
<i>Proportion of successful stops</i>			
PLA	0.58 (0.03)	0.57 (0.03)	0.53 (0.04)
GAL	0.56 (0.03)	0.54 (0.03)	0.57 (0.03)
<i>Median correct RT on Go trials</i>			
PLA	515.00 (47.36)	559.03 (60.99)	557.10 (69.41)
GAL	536.00 (44.58)	585.90 (50.55)	605.63 (61.38)
<i>SSD (50%)</i>			
PLA	353.69 (40.77)	369.40 (54.02)	392.98 (64.42)
GAL	359.18 (46.83)	411.81 (54.02)	441.02 (57.51)
<i>Hopkins Verbal Learning Test-Revised (HVLT-R)</i>			
<i>Total recall</i>			
PLA	21.33 (1.57)	21.67 (1.61)	21.13 (1.14)
GAL	19.80 (1.52)	23.27 (1.14)	21.07 (1.15)
<i>Delayed recall</i>			
PLA	7.27 (0.72)	6.80 (0.63)	6.07 (0.71)
GAL	6.73 (0.64)	7.73 (0.40)	6.13 (0.64)
<i>Percent retention</i>			
PLA	82.27 (7.36)	76.93 (4.99)	72.40 (7.13)
GAL	84.07 (5.51)	82.73 (3.43)	74.93 (6.60)
<i>Recognition Discrimination Index</i>			
PLA	9.73 (0.45)	9.27 (0.49)	9.87 (0.49)
GAL	9.67 (0.43)	9.67 (0.37)	10.47 (0.35)

Note: PLA = placebo; GAL = galantamine; $n = 30$ (15 PLA, 15 GAL). SSD 50%: Stop signal delay, at which the subject is able to stop 50% of the time. RT: Reaction time.

any withdrawal symptoms on the study results was limited.

The absence of main effects of galantamine on cognition among individuals with CUD in this study is aligned with the conflicting pre-clinical data regarding the involvement of the brain acetylcholine (ACh) system in the neurobiology of the cognitive effects of cannabinoids. Some studies in rats have shown reduced choline uptake in the hypothalamus, reduced synthesis of ACh after THC administration (Lindamood and Colasanti, 1980), and a reduction of cannabis-induced working memory deficits by AChEI (Braidia and Sala, 2000). In contrast, other studies have not confirmed the hypothesis that the cognitive effects of cannabinoids are explained by a reduction in ACh release. Nava et al. (2001) showed that the decrease in extracellular hippocampal ACh concentrations in rats was delayed in relation to the timing of the THC-induced cognitive deficits, thus not supporting a causal relationship between low ACh levels and cognitive deficits. Moreover, the AChEI physostigmine did not counteract THC-induced cognitive deficits in rats (Lichtman and Martin, 1996). Collectively, the preclinical human laboratory study and clinical trial data indicate the effects of AChEI on cognition may be time (i.e., may only be present during acute

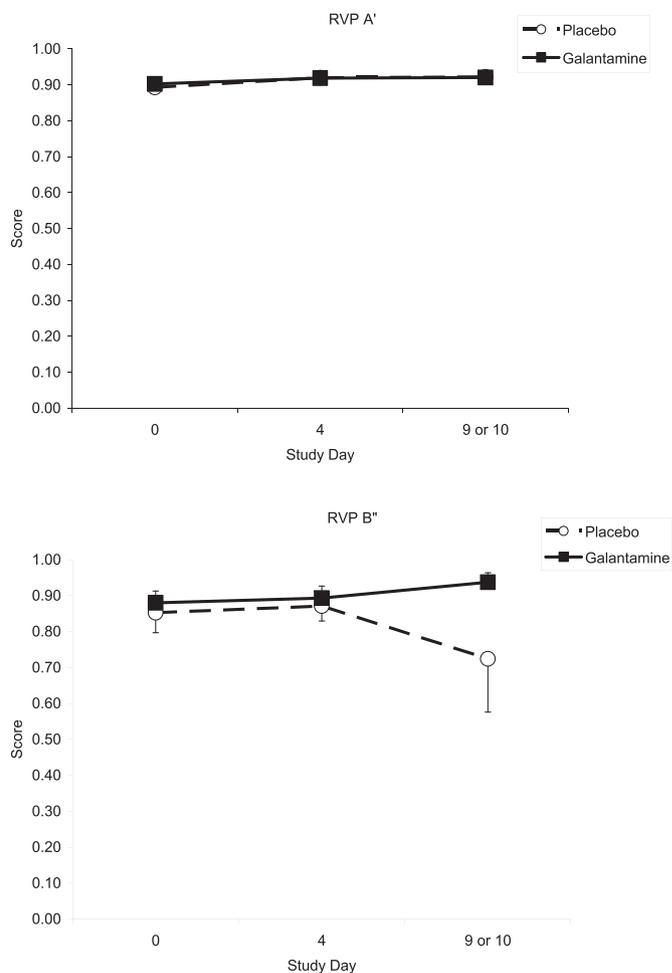


Fig. 2. Effects of galantamine and placebo on sustained attention, indexed by Rapid Visual Processing (RVP) A' and B' scores, over time.

cannabis intoxication) and dose-dependent (i.e., be contingent on the cannabinoid and AChEI dose exposure). In this study, marijuana craving decreased over time for both groups, with no significant interactions by group. Thus, we did not find evidence that galantamine reduced the reinforcing effect of the drug.

The current study has several limitations that need to be addressed in further studies. First, although all participants met criteria for CUD and there were no significant differences in cannabis use histories, the effects of cannabis on cognition may depend on other factors such as the THC/CBD ratio of cannabis, with higher concentrations of CBD inducing less cognitive deficits (De Aquino et al., 2018). Further, the chronic cognitive effects of cannabinoids are more complex and challenging to interpret their acute effects, appearing to be related not only to the dose of exposure (frequency, duration, amount) but also to the age of onset of use (Boggs et al., 2018; Englund et al., 2017). Some individuals with CUD may have blunted responses to the cognitive deficits induced by cannabis, and in these populations abstinence from cannabis may, in fact, be associated with cognitive impairment (McDonald et al., 2003). In addition, we were also unable to determine if individuals abstained from cannabis use during the study, due to the extended length of time that cannabis remains in the system. Future studies with a within-subject design may account for the potential confounding effects of individual differences in cannabis use histories.

Second, we only used one dose (8 mg/day) of galantamine in this study. Since this is the first study to assess galantamine on cognitive function in individuals with CUD, we established our dosage based on other studies of populations with substance use disorders – in

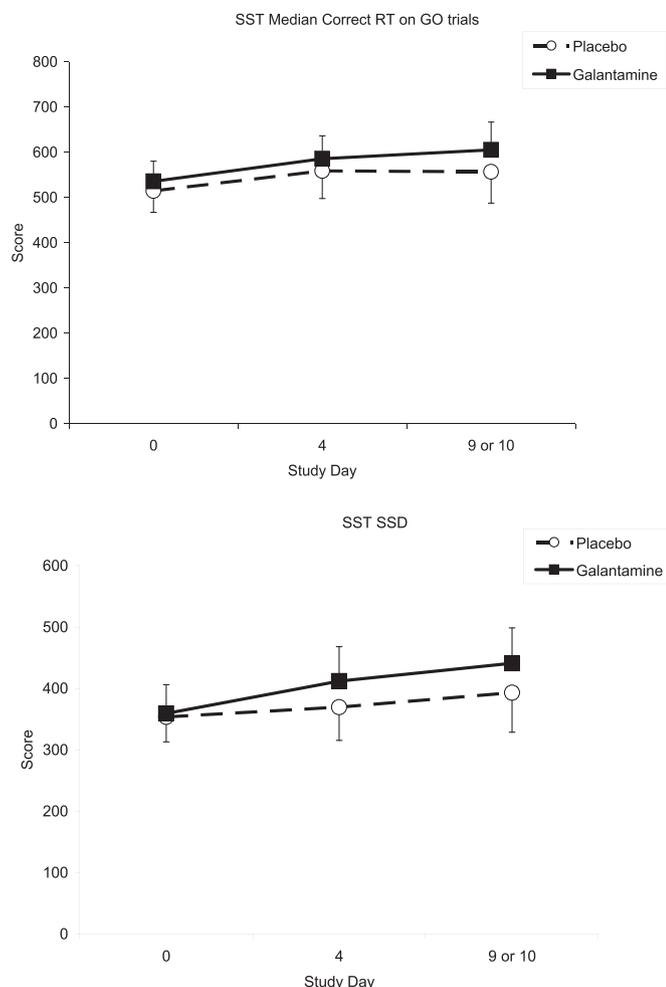


Fig. 3. Effects of galantamine and placebo on response inhibition performance over time. Response inhibition performance is indexed by stop signal delay, at which the subject is able to stop 50% of the time (SSD 50%), and reaction time (RT) scores.

particular, our previous study of the effects of galantamine on individuals with cocaine use disorder (Sofuoglu et al., 2011). As the recommended therapeutic target dose for galantamine for Alzheimer's disease ranges from 8 to 24 mg, it is possible that higher doses of galantamine may have produced cognitive effects in our sample. This is supported by the fact that eptastigmine, a more potent AChEI than physostigmine, was effective for reducing the cognitive effects of cannabinoids in preclinical studies (Braidia and Sala, 2000). Third, the short treatment duration and small sample size may not have been enough to capture procognitive effects of galantamine in individuals with CUD. A meta-analysis of neuropsychological studies found that only small magnitude effects are apparent in the first few weeks of abstinence from cannabis (of the order of $d = 0.25$ to 0.35), and these become smaller and non-significant with extended abstinence (to around $d = 0.15$) (Broyd et al., 2016; Pope et al., 2002). Future studies should test higher doses of galantamine for a longer period of time and with an adequately powered sample. Lastly, the small sample size prohibits us from examining differences in improvement between those with and without mild cognitive deficits. Larger studies with individuals of various levels of cognitive deficits are needed to help determine whether modulation of cholinergic neurotransmission with galantamine is a viable therapeutic strategy, especially for individuals with early onset CUD and severe CUD, who may have more substantial cognitive deficits.

In conclusion, this pilot study shows feasibility and tolerability of

galantamine, for individuals with cannabis use disorder. This study has broad methodological implications for the emerging field of development of cognitive enhancers for addiction treatment (Sofuoglu et al., 2013). More specifically, it has significance for the design of future studies investigating the potential of galantamine for counteracting the cognitive effects of cannabinoids, a potential target for the treatment of CUD.

Declaration of Competing Interest

The authors report no conflicts of interest.

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