Galantamine and Computerized Cognitive Behavioral Therapy for Cocaine Dependence:
A Randomized Clinical Trial

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ABSTRACT

Objective: To examine whether galantamine, a cognitive-enhancing medication that is both acetylcholinesterase inhibitor and agonist at nicotinic acetylcholine receptors, is effective at improving cocaine use outcomes and cognitive functioning, alone and in combination with computerized cognitive behavioral therapy (CBT).

Method: A 12-week, randomized 2 × 2, factorial trial was conducted to evaluate galantamine versus placebo (double-blind) and computerized CBT plus standard methadone treatment versus standard methadone treatment alone in a community-based methadone maintenance program (September 2009–April 2015). One hundred twenty individuals diagnosed with *DSM-IV* cocaine use disorder were randomly assigned to the following conditions: (1) galantamine (8 mg/d) plus standard methadone maintenance treatment (treatment as usual [TAU]), (2) placebo plus TAU, (3) galantamine plus computerized CBT plus TAU, or (4) placebo plus computerized CBT plus TAU; medication administration was supervised at the time of daily methadone dosing. The primary cocaine use outcome was change in percent days of abstinence over time. Number of cocaine-negative urine toxicology screens submitted and cognitive function were secondary outcomes.

Results: Random effect regression analysis indicated significant reductions in frequency of cocaine use over time, with significant treatment-by-time effects for both galantamine over placebo ($F = 5.3$, $P = .02$, $d = 0.34$) and computerized CBT over standard methadone treatment ($F = 4.2$, $P = .04$, $d = 0.30$) but no evidence of significant benefit of the combination over either treatment alone. Pretreatment to posttreatment comparisons of multiple indices of cognitive functioning, including sustained attention, indicated no benefit of galantamine over placebo.

Conclusions: Findings suggest benefits of galantamine and computerized CBT for reducing cocaine use in this sample. Although galantamine did not improve measures of cognitive function in this sample, multiple measures of cognitive function were associated with cocaine use outcomes, underlining the significance of cognitive function in cocaine treatment outcomes.

Trial Registration: ClinicalTrials.gov identifier: NCT00809835

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Cocaine use within methadone maintenance programs remains an intractable problem associated with significantly poorer outcomes.[1–3] While there are no approved pharmacotherapies for cocaine use disorder, behavioral approaches such as contingency management and cognitive behavioral therapy (CBT) have been demonstrated to reduce cocaine use in this population.[4,5] Computerized CBT also demonstrated efficacy in reducing cocaine use relative to standard methadone maintenance-based counseling,[6] but there remains substantial room for improvement in outcomes.

CBT is comparatively cognitively demanding, as its emphasis on learning and applying complex concepts calls upon attention, memory, and decision-making skills. Cognitive impairment is associated with poorer outcome and higher dropout in CBT among cocaine users.[7–9] Potential strategies for improving responses to cognitively demanding therapies such as CBT include simplifying treatment for patients with cognitive impairment and targeting impairment directly via cognitive training exercises[10]; both strategies have yielded mixed results to date.[11–14] A novel strategy is use of cognitive-enhancing agents (eg, cholinesterase inhibitors) to improve attention and concentration as a means of addressing both cognitive function and substance use.[10,15,16]

The cholinergic system plays an important role in multiple brain functions including attention, working memory, reward, and motivation.[17–19] Evidence from preclinical studies suggests that down-regulation of the cholinergic system is a critical part of the neuroadaptations to chronic cocaine use.[20] Galantamine, a reversible and competitive inhibitor of acetylcholinesterase, elevates synaptic concentrations of acetylcholine, which leads to increased stimulation of both nicotinic and muscarinic receptors. Galantamine also directly stimulates the nicotinic alpha7 and alpha4-beta2 receptors, as an allosteric positive modulator. This results in dopamine release in the mesolimbic/mesocortical dopaminergic pathway,[21] providing an additional mechanism by which galantamine may enhance cognitive function and reduce stimulant use.[18,20,22]

Few studies have evaluated galantamine, either in terms of direct effects on substance use or as a strategy to improve cognitive impairment: among 114 alcohol-dependent individuals, galantamine was associated with

Clinical Points

- There are as yet no approved medications for treating cocaine use disorder among methadone-maintained patients.
- This study suggested the potential of galantamine in this challenging clinical population.

significant reductions in cigarette smoking compared with placebo.[23] A trial evaluating effects of galantamine in 149 recently detoxified alcohol-dependent patients reported no significant effects on relapse but some evidence of reduced drinking among those who relapsed.[24] In a randomized placebo-controlled pilot study with 14 cocaine-dependent methadone-maintained individuals, galantamine 16 mg/d was associated with fewer cocaine-positive urine specimens (45% vs 95%, $P = .15$), as well as a higher proportion of days of abstinence from cocaine (80% vs 60%, $P = .06$) relative to placebo, with participants reporting moderate nausea and fatigue.[25] Differential effects on cognitive functioning were not seen. In a 10-day proof-of-concept trial with 34 abstinent cocaine users, 8 mg/d of galantamine was associated with significant improvement in the Rapid Visual Information Processing task (RVP) of the Cambridge Neuropsychological Test Automated Battery (CANTAB) compared with placebo.[26] These 2 pilot studies by our group suggested that evaluation of the effects of galantamine on cocaine use and cognitive functioning was warranted in a full randomized clinical trial.

Herein we describe outcomes of a 2 × 2 randomized factorial trial in 120 methadone-maintained individuals with cocaine use disorder who were randomly assigned to one of the following conditions: galantamine plus standard methadone maintenance treatment (treatment as usual [TAU]), placebo plus TAU, galantamine plus computerized CBT (computer-based training in CBT, or CBT4CBT) plus TAU, or placebo plus CBT4CBT + TAU. We hypothesized a main effect of both galantamine and CBT4CBT on reduction in cocaine use compared with their respective controls and a third hypothesis contrasting the combination of galantamine and CBT4CBT to each condition delivered singly (galantamine plus TAU or placebo plus CBT4CBT). We also hypothesized that galantamine would be more effective in improving cognitive functioning (memory and sustained attention) compared with placebo and explored relationships of cognitive function to cocaine use outcomes.

METHODS

Participants

Participants were recruited from individuals stabilized on methadone maintenance at Recovery Network of Programs, a community-based program in Bridgeport, Connecticut, between September 2009 and April 2015 (ClinicalTrials.gov identifier NCT00809835). Individuals were included as participants if they were 18 years or older and met *DSM-IV-TR* criteria for current cocaine dependence, as assessed by the Structured Clinical Interview for *DSM-IV-TR* (SCID),[27] and provided at least 1 cocaine-positive urine test during screening. Individuals were excluded if they (1) were currently dependent on another illicit drug or principally used a drug other than cocaine (n = 1); (2) met lifetime *DSM-IV-R* criteria for a non–substance-induced psychotic or bipolar disorder (n = 1); (3) had a current medical condition contraindicating galantamine[28] (eg, asthma, chronic obstructive lung disease, history of or current gastrointestinal ulcer, hepatic or renal impairment, cardiac rhythm disturbance, or pregnancy) (n = 3), as assessed by baseline physical examination (electrocardiogram, urinalysis, and blood work); (4) had a screening liver function test result greater than 3 times normal (n = 5); (5) used medications, including β-blockers and nonsteroidal anti-inflammatory drugs, that are contraindicated with galantamine (n = 1); or (6) were not sufficiently stable for outpatient treatment (n = 2). Two individuals were incarcerated prior to randomization, and 16 did not complete the screening process (Figure 1).

One hundred twenty of the 150 individuals screened were determined to be eligible, provided written informed consent approved by the Yale School of Medicine Institutional Review Board, and were randomly allocated. A masked, computerized urn randomization program used in previous trials[29–32] was used to produce equivalent group size and balance groups with respect to baseline level of cocaine use (more or fewer than 11 days per month), gender, ethnicity (ethnic minority/nonminority), age (older or younger than 40 years), and baseline Shipley[33] estimated IQ score.

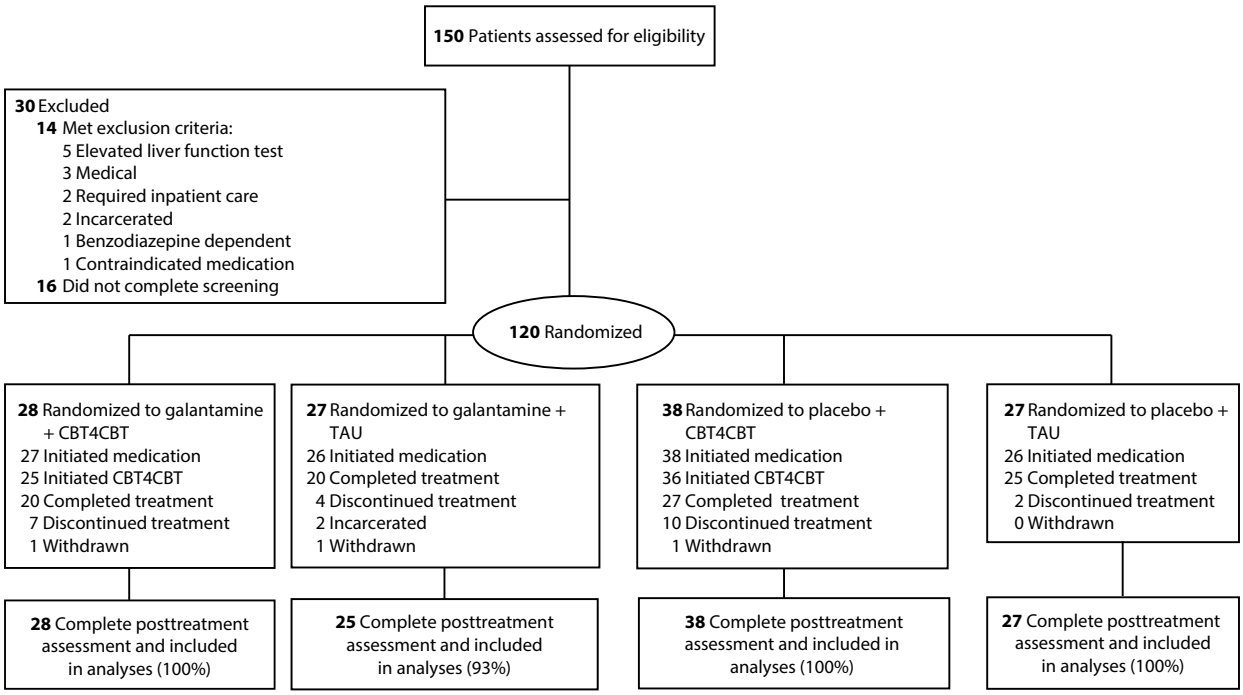
Treatments

All participants received standard methadone treatment, consisting of daily methadone and weekly individual or group counseling, with access to other program services. Participants met twice weekly with research staff blind to medication condition who collected urine and breath samples and monitored other clinical symptoms. Adverse events and blood pressure were monitored weekly.

Galantamine. Participants assigned to galantamine were prescribed a maximum dose of 8 mg galantamine extended release (ER), given the limited tolerability of the 16-mg/d dose seen in our pilot study.[26] Daily dispensing of galantamine or matched placebo capsules occurred at the time of methadone dosing and was observed by program nurses. To evaluate the medication blind, participants and the project nurse were asked to guess medication assignment at the end of the trial. Among the 117 participants who initiated medication, 69 (61%) guessed their medication condition correctly. The project nurse guessed no better than chance (56%).

Computerized Cognitive Behavioral Therapy (CBT4CBT). CBT4CBT is a direct-to-patient computer based version of a CBT manual[34] that makes extensive use of video examples to teach cognitive and behavioral control skills in 7 modules, each requiring about 30 to 40 minutes to complete. As described earlier,[35] the CBT4CBT program

Figure 1. CONSORT Flow Diagram of Participants Through the Trial[a]



[a]Completing treatment defined as taking at least 1 day of study medication in week 12.
Abbreviations: CBT4CBT = computerized cognitive behavioral therapy, TAU = standard methadone treatment as usual.

uses video vignettes, quizzes, and interactive exercises to model effective use of skills and strategies. The vignettes present connected scenes of engaging characters, portrayed by professional actors, who first experience a common risky situation or problem and then, after the skill is taught, demonstrate using the targeted skill to successfully negotiate that situation without resorting to drug use. Participants assigned to CBT4CBT worked with the program in a private area at the clinic on a weekly basis, usually at the time they completed study assessments.

Assessments

Participants were assessed before treatment, weekly during treatment (urine and breath samples were collected twice weekly, and participants received a gift card worth $10 for each completed assessment), and at the 12-week treatment termination point. In cases in which a randomly assigned participant did not initiate (n = 3), was withdrawn from treatment (n = 3; 1 for elevated blood pressure, 1 for suicidal ideation, 1 for deliberately breaking the medication blind), or dropped out of treatment (n = 25), he or she was interviewed at the 12-week point to collect data from the intent-to-treat sample, regardless of level of treatment involvement. Thus, complete 12-week self-report data were available for 118 of 120 (98.3%) of the randomized sample, permitting sensitivity analyses by including or excluding data points that were collected after a participant dropped out of treatment.[36]

The Timeline Follow Back[37] method was used to collect detailed day-by-day self-reports of substance use throughout the 84-day treatment period. Self-reports of cocaine were verified through onsite urine toxicology screens (ToxCup Drug Screen Cup 5Panel with adulterant checks, Branan Medical Corporation, Irvine, California) obtained twice weekly. Of 1,911 urine specimens collected, 1,601 (83.8%) were consistent with the participants' self-reports, 52 (2.7%) tested negative for cocaine although the participant reported recent cocaine use, and 258 (13.5%) tested positive for cocaine although the participant denied use in the past 3 days. These rates are consistent with those reported for previous studies of cocaine-dependent samples evaluating the accuracy of self-report data.[38,39]

Multiple cognitive tasks, drawn from the CANTAB,[40] were administered at baseline and end of treatment to evaluate effects of study treatments on indicators of cognitive function. These included potential effects of galantamine on sustained attention (RVP A′: target sensitivity with higher scores indicating better attention[27,41]) and potential effects of CBT4CBT on cognitive flexibility (Intra-Extra Dimensional Set Shifting [IED] total adjusted errors: number of intradimensional or extradimensional errors, adjusted for trials completed, where fewer errors shows faster learning of changing contingencies[42,43]). Response inhibition (Stop Signal Reaction Time [SSRT] where lower SSRT indicates better ability to inhibit a prepotent motor response[44,45]) and visual memory (pattern recognition memory [PRM]

Table 1. Baseline Characteristics by Treatment Group

Characteristic	Galantamine + CBT4CBT (n = 28)	Galantamine + TAU[b] (n = 27)	Placebo + CBT4CBT (n = 38)	Placebo + TAU (n = 27)	*F* or χ^2	*P* Value
	n (%)	n (%)	n (%)	n (%)		
Female	12 (43)	11 (41)	10 (26)	7 (26)	3.32	.35
Race and ethnicity						
Caucasian	12 (42)	15 (56)	19 (50)	16 (60)	5.34	.80
African American	7 (25)	6 (22)	9 (24)	3 (11)		
Hispanic	9 (32)	6 (22)	9 (24)	8 (30)		
Multiracial/other	0	0	1 (3)	0		
Completed high school	17 (61)	19 (70)	29 (77)	21 (78)	2.58	.46
Unemployed	20 (71)	21 (78)	27 (71)	19 (70)	0.50	.92
On public assistance	23 (83)	21 (78)	23 (61)	18 (67)	4.55	.21
Major depression—lifetime[a]	1 (4)	3 (11)	2 (5)	4 (15)	3.06	.38
Anxiety disorder—lifetime	3 (11)	5 (19)	2 (5)	5 (19)	3.69	.30
Antisocial personality disorder	3 (11)	3 (11)	5 (13)	5 (19)	0.91	.82
Alcohol use disorder—lifetime	15 (54)	14 (52)	21 (55)	16 (59)	0.33	.95
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)		
Age, y	38.0 (8.7)	38.7 (10.8)	39.8 (9.0)	36.3 (9.4)	0.75	.52
Days marijuana use, past 28	4.9 (8.9)	3.3 (7.8)	2.0 (5.5)	3.3 (7.4)	0.80	.50
Days cocaine use, past 28	17.2 (8.3)	12.4 (8.1)	13.6 (8.5)	13.4 (7.9)	1.80	.15
Days cigarette use, past 28	27.1 (4.9)	25.4 (7.8)	27.3 (4.5)	25.3 (7.9)	0.81	.49
Days alcohol use, past 28	2.9 (5.3)	4.6 (7.8)	1.7 (4.9)	1.7 (3.1)	1.79	.15
Days opiate use, past 28	1.6 (2.5)	3.3 (4.4)	4.3 (7.9)	1.5 (2.6)	2.15	.10
Days benzodiazepine use, past 28	0.5 (1.9)	0.3 (0.7)	0.3 (0.8)	0.3 (1.0)	0.20	.90
Age of first cocaine use	18.1 (3.5)	20.2 (6.1)	20.6 (6.6)	20.2 (5.0)	1.27	.29
Years of regular cocaine use	10.2 (8.7)	12.6 (10.3)	8.5 (7.1)	8.5 (8.1)	1.53	.21
Lifetime number of arrests	6.6 (7.3)	7.2 (10.9)	8.9 (14.7)	5.8 (6.6)	0.50	.69
No. of prior outpatient drug treatments	3.5 (4.6)	2.3 (2.7)	2.4 (2.6)	2.5 (2.2)	0.97	.41
No. of prior inpatient drug treatments	2.6 (2.5)	3.7 (6.8)	3.4 (5.7)	2.4 (3.9)	0.46	.71
Estimated IQ from Shipley	98.4 (11.7)	101.6 (12.2)	101.4 (11.4)	100.5 (11.9)	0.45	.72
Methadone dose, mg/d	77.3 (35.7)	65.3 (25.3)	72.4 (26.4)	65.3 (25.6)	1.15	.33

[a]All psychiatric diagnoses made from SCID interviews for *DSM-IV-TR*.
Abbreviations: CBT4CBT = computerized cognitive behavioral therapy, TAU = standard methadone treatment as usual.

percent correct[46]) were also evaluated. Working memory was evaluated using digit span (longest backward span).[47]

Data Analyses

The primary outcome measure was self-reported cocaine use (operationalized as percent days of abstinence from cocaine per month), using random effect regression models[48] to evaluate change across time, in monthly intervals, with the following contrasts: medication condition (galantamine vs placebo), behavioral condition (CBT4CBT vs TAU), and the combination of galantamine and CBT4CBT versus each intervention delivered singly (galantamine plus CBT4CBT vs galantamine plus TAU or CBT4CBT plus placebo). A logarithmic transformation of time was used to accommodate more rapid change occurring earlier in treatment. Number of cocaine-negative urine toxicology screens by month was included a secondary measure[49] due to the likelihood of overestimation of instances of cocaine use when obtained twice weekly due to carryover effects.[49,50] Repeated measure analyses of variance were used to evaluate changes in cognitive measures over time.

Power calculations utilizing estimates of effect sizes for galantamine ($d = 0.4$) and CBT4CBT ($d = 0.5$) on cocaine use outcomes based on previous trials[6,26,35] indicated that 35 participants per cell would provide sufficient power (> 80%, 2-sided). This effect size would be sufficient to detect a large effect (0.50 or more) for the interaction of galantamine plus CBT4CBT, as well as for the effect of galantamine on CANTAB RVP A′.[26] Recruitment fell short of this target (averaging 30 per condition), but high rates of data availability permitted analysis of the full intention-to-treat sample.

RESULTS

Sample Characteristics and Treatment Adherence

Sample characteristics by treatment condition are presented in Table 1; there were no statistically significant differences across groups on multiple demographic and baseline substance use variables. The sample was predominantly male; about half were white, 21% were African American, and 27% were Latino. Participants reported that they used cocaine a mean of 14 days of the 28 prior to baseline.

Table 2 indicates there were no differences across treatment group, medication condition, behavioral therapy condition, or their interaction in terms of days retained in the protocol, days receiving methadone, or percent days of compliance with study medication. Participants assigned to the CBT4CBT condition completed an average of about 5 of the 7 modules offered, consistent with prior trials.[6,35]

Primary and Secondary Cocaine Outcomes

Random effects regression for effects of study treatments on the primary outcome, days of self-reported cocaine

Table 2. Treatment Process and Adherence by Group[a]

Variable	Galantamine + CBT4CBT (n = 28)	Galantamine + TAU (n = 27)	Placebo + CBT4CBT (n = 38)	Placebo + TAU (n = 27)	Contrast 1 Galantamine + CBT4CBT vs Galantamine + TAU and Placebo + CBT4CBT		Contrast 2 Galantamine vs Placebo		Contrast 3 CBT4CBT vs TAU	
					F/χ^2	P	F/χ^2	P	F/χ^2	P
Days in treatment (of 84)	65.79 (31.06)	66.96 (30.11)	70.21 (25.77)	79.41 (17.6)	0.22	.64	2.95	.09	1.12	.29
Days took study medication	62.25 (30.89)	63.89 (29.55)	65.45 (26.11)	77.67 (17.34)	0.16	.69	3.01	.09	2.00	.16
Percent days medication adherent	89.85 (20.89)	91.73 (20.37)	92.69 (11.14)	94.22 (19.06)	0.34	.56	0.66	.42	0.27	.60
No. of CBT4CBT modules completed (of 7)	4.43 (2.87)		4.95 (2.31)				0.66	.42		
Total individual treatment sessions completed[b]	5.00 (2.33)	7.50 (4.29)	5.97 (4.98)	6.44 (3.65)	2.48	.12	0.00	.96	3.04	.09
Total group treatment sessions completed[b]	8.37 (20.66)	2.70 (4.21)	13.97 (40.50)	3.32 (7.84)	0.00	1.00	0.35	.56	2.41	.12

[a]Values expressed as mean (SD) unless otherwise noted.
[b]Includes only those participants who initiated treatment.
Abbreviations: CBT4CBT = computerized cognitive behavioral therapy, TAU = standard methadone treatment as usual.

use by month, are presented in Table 3 and illustrated in Figure 2. For the model that included all data collected (that is, including data collected after the point of attrition if the participant dropped out), there was a significant effect of time ($F_{1,351} = 152.0$, $P = .00$), medication by time ($F_{1,351} = 5.27$, $P = .02$), and behavioral therapy by time ($F_{1,351} = 4.22$, $P = .04$), but the third contrast evaluating the interaction effect was not statistically significant. Effects were similar when only those data collected while each participant was still actively enrolled in the treatment protocol were analyzed.

Analyses evaluating change in the number of urine specimens collected that were negative for cocaine by month are presented in Table 3; the effect for time was significant, indicating an increase in the frequency of negative urine specimens submitted across time ($F_{1,286} = 32.2$, $P < .001$); however, the effect for medication by time fell short of statistical significance ($F_{1,286} = 3.5$, $P = .06$), and the effect of behavioral therapy by time was not significant ($F_{1,286} = 0.11$, $P = .74$). Unlike the self-report data, the interaction of medication, behavioral therapy, and time was statistically significant ($F_{1,286} = 5.0$, $P = .03$). These effects are presented in Figure 2, which indicates greatest change (improvement) in the number of cocaine-negative urine specimens submitted for the group assigned to galantamine plus TAU, least change in the group assigned to placebo plus TAU, and an intermediate rate of change for those assigned to galantamine plus CBT4CBT or placebo plus CBT4CBT. Post hoc comparisons of the primary and secondary outcomes, summarized across the 12 weeks, by baseline severity, are shown in Supplementary eTable 1.

Effects of Study Treatments on Cognitive Tasks Over Time

Data from the cognitive task battery are presented in Supplementary eTable 2. In general, these showed little change across time, with no evidence of significant medication-by-time or behavioral therapy–by-time effects on any of these tasks. A composite score, computed by averaging the standardized scores for the 5 key cognitive tasks and corrected for direction so that higher scores indicate better performance (RVP A′, SSRT, PRM percent correct, IED total adjusted errors, and digit span backward), also indicated neither significant change over time nor any evidence of any treatment condition by time effects on the composite score.

While these cognitive indicators did not improve during treatment, they were nevertheless consistently associated with treatment outcome. For example, multiple cognitive measures at baseline were significantly positively correlated with percentage of urine specimens submitted that were negative for all drugs, including the composite score ($r = 0.25$, $P = .01$), RVP A′ ($r = 0.20$, $P = .04$), PRM percent correct ($r = 0.19$, $P = .05$), and digit span backward ($r = 0.26$, $P = .01$). Similar relationships were found for self-reported days of abstinence from cocaine, where better cognitive function was consistently associated with less frequent cocaine use.

Adverse Events

The most frequently reported adverse events were nausea/vomiting (reported at least once by 21% of participants), headache (17.7%), loss of appetite (15.9%), fatigue (15%), and diarrhea/constipation (13.3%), but none of these differed significantly by medication condition. Four participants reported significant weight loss; all were in the placebo condition (galantamine vs placebo, $\chi^2 = 3.54$, $P = .06$). Rates of serious adverse events occurred infrequently (8.3% of all those randomized, n = 10; 3 for medical reasons, 6 for substance use hospitalization, and 1 for psychiatric reasons) and did not differ by treatment condition.

DISCUSSION

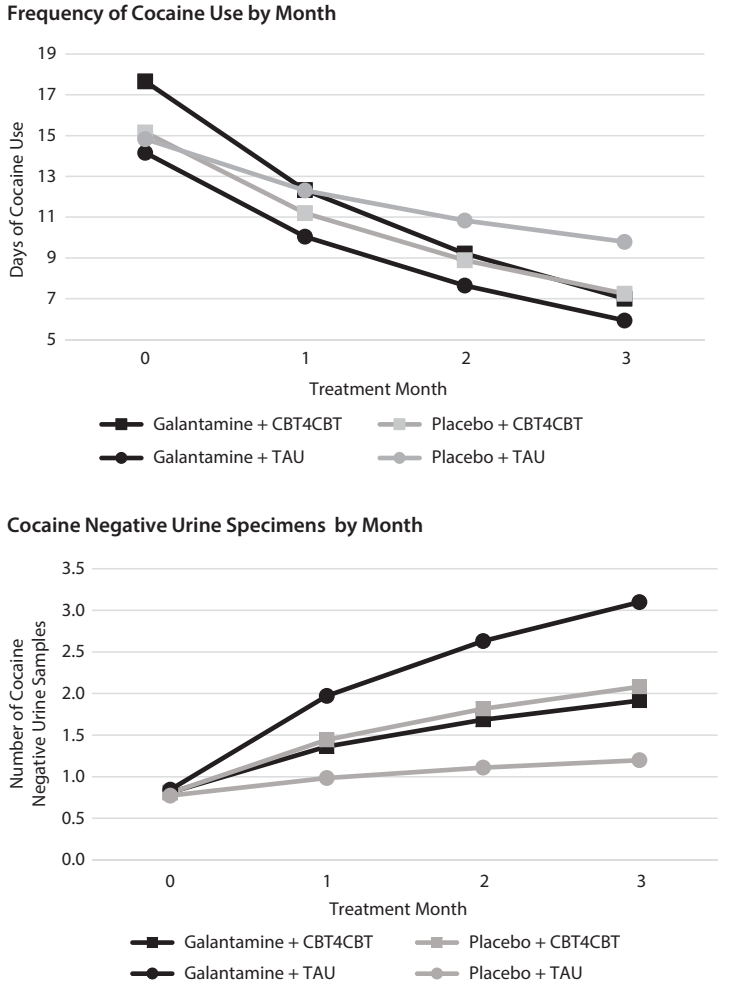
Analyses of primary outcomes in this randomized controlled trial of galantamine and computerized CBT4CBT supported the hypotheses of a main effect of each treatment over time on the primary cocaine use outcome, but there was no evidence of an additive or synergistic effect by combining the 2. Contrary to our hypothesis, there was no effect of galantamine relative to placebo over time for the

Table 3. Primary Outcomes by Time and Treatment Condition: Random Effects Model Estimates

Variable	N, No. of Observations	−2RLL	Denominator *df*	*F*	*P*	Effect Size, *d*
Self-reported percent days abstinent by month						
Intercept	120, 475	3,100.139	215.58	517.86	.00	
Medication condition (galantamine vs placebo)			215.58	0.45	.50	
Behavioral condition (CBT4CBT vs TAU)			215.58	1.98	.16	
Time			351.07	152.04	.00	
Contrast 1: galantamine + CBT4CBT vs galantamine + TAU and placebo + CBT4CBT by time			351.07	0.03	.86	0.03
Contrast 2: galantamine vs placebo by time			351.07	5.27	.02	0.34
Contrast 3: CBT4CBT vs TAU by time			351.07	4.22	.04	0.30
No. of cocaine-negative urine specimens submitted by month						
Intercept	120, 367	1,495,842	267.52	21.58	.00	
Medication condition (galantamine vs placebo)			267.52	0.01	.91	
Behavioral condition (CBT4CBT vs placebo)			267.52	0.00	1.00	
Time			286.14	32.17	.00	
Contrast 1: galantamine + CBT4CBT vs galantamine + TAU and placebo + CBT4CBT by time			286.14	5.04	.03	0.75
Contrast 2: galantamine vs placebo by time			286.14	3.46	.06	0.43
Contrast 3: CBT4CBT vs TAU by time			286.14	0.11	.74	0.03

Abbreviations: CBT4CBT = computerized cognitive behavioral therapy, TAU = treatment as usual, −2RLL = −2 restricted log likelihood.

Figure 2. Primary and Secondary Cocaine Use Outcomes by Group Across Time, Estimates From Random Effects Regression Models



Abbreviations: CBT4CBT = computerized cognitive behavioral therapy, TAU = standard methadone treatment as usual.

cognitive measures, including sustained attention (RVP A′); moreover, there were few indications of improvement over time for any of these cognitive indicators. Thus, galantamine and CBT4CBT each seemed to contribute to better self-reported cocaine use outcomes; however, as there was no evidence that galantamine improved cognitive functioning in this sample, it was unlikely to have improved response to CBT4CBT by improving participants' ability to learn CBT skills and strategies.

Galantamine, while not demonstrating efficacy on cognitive function in this sample, was associated with a significant effect on reducing cocaine use. These findings are consistent with our prior pilot study in a cocaine-dependent methadone-maintained sample, where galantamine appeared more effective than placebo in reducing cocaine use but did not demonstrate a significant effect on cognitive tasks, including RVP.[25] The potential for galantamine to have some benefit in treating cocaine use disorder is notable and is consistent with work suggesting a role for the cholinergic system in treating stimulant disorders.[18,20] An ongoing randomized controlled trial is evaluating galantamine versus placebo in a non–methadone treated sample of individuals with a primary cocaine use disorder (ClinicalTrials.gov identifier NCT01531153).

Although evaluating galantamine in a methadone-maintained sample of cocaine users conferred several advantages from a methodological point of view, it introduced limitations as well. A key advantage of studying a methadone-maintained sample is that retention and adherence were high via dispensing of study medications at the time of daily methadone dosing,

which also permitted close monitoring of adverse events. In terms of limitations, a sample of individuals maintained on methadone over a long period reduces generalizability and may not have been ideal to detect galantamine effects on cognitive function. Significant problems in cognitive function are well established in individuals maintained on methadone[51,52] and include broad impairment in domains encompassing attention, memory, cognitive impulsivity, and cognitive flexibility.[53] The level of impairment in this sample who had both cocaine and opioid use disorders may have overwhelmed galantamine's effects on cognitive enhancement, which tend to be modest, particularly at lower doses.[54] In addition, cognitive functions may fluctuate depending on recency of methadone dose,[55] which may have further undercut the ability to detect possible galantamine effects on cognitive function, particularly with the relatively low dose used here.

In summary, this randomized controlled trial included several important design features intended to enhance internal validity, including random assignment to treatment using an urn variable program, relatively high adherence across conditions, twice weekly collection of urine specimens in conjunction with monitored medication ingestion, a well-validated set of assessments to assess cognitive function (CANTAB), and a comparatively complete dataset with few missing data. Although galantamine did not appear to improve cognitive functioning or response to CBT4CBT in this sample, this trial provided evidence for galantamine as a potential therapy for cocaine use disorder, which also proved to be safe and well tolerated in this sample at the dose provided. The trial also provided confirmatory evidence for the efficacy of CBT4CBT in this challenging sample, which is significant given the relative lack of confirmatory trials of computerized therapies with appropriate control conditions.

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Potential conflicts of interest: **Dr Carroll** is a member in trust of CBT4CBT LLC, which makes CBT4CBT available to qualified clinical providers and organizations on a commercial basis, and she works with Yale University to manage any potential conflicts of interest. The other authors have no conflicts to disclose.

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Supplementary material: See accompanying pages.

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Supplementary material follows this article.

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Supplementary Material

Article Title: Galantamine and Computerized Cognitive Behavioral Therapy for Cocaine Dependence: A Randomized Clinical Trial

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List of Supplementary Material for the article

1. **eTable 1** Exploratory Analyses, Primary and Secondary Outcomes by Baseline Severity of Cocaine Use

2. **eTable 2** Cognitive Function Indicators by Treatment Condition and Time

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary eTable 1: Exploratory analyses, primary and secondary outcomes by baseline severity of cocaine use

						Contrast 1		Contrast 2		Contrast 3							
						GAL+CBT4CBT v GAL + TAU v. CBT4CBT+PLA		Gal v. PLA		CBT4CBT v TAU		Severity of cocaine use		Contrast 1 by severity		Contrast 2 by severity	
Variable	Galantamine +CBT4CBT	Galantamine + Placebo	Placebo + CBT4CBT	Placebo + TAU	TOTAL	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*	*F*	*p*
Percent of days of cocaine abstinent, mean (SD)																	
Low Severity	80.7 (11.0)	77.5 (17.7)	80.2 (14.9)	73.5 (11.1)	77.8 (14.4)	2.84	.09	4.98	.03	1.16	.28	25.85	.00	1.19	.31	4.52	.01
Mod Severity	76.2 (13.8)	80.5 (14.3)	50.0 (28.1)	70 .0 (15.7)	63.2 (25.2)												
High Severity	55.1 (24.5)	43.4 (27.1)	56.8 (26.6)	27.0 (19.3)	47.9 (26.2)												
Percent of urine specimens negative for cocaine, mean (SD)																	
Low Severity	46.3 (42.9)	34.7 (35.2)	37.5 (33.9)	16.4 (17.9)	32.5 (33.1)	.933	.34	5.01	.03	.006	.94	9.65	.00	1.11	.33	3.55	.03
Mod Severity	26.0 (46.3)	52.2 (34.5)	7.9 (9.7)	24.4 (25.2)	22.4 (29.5)												
High Severity	11.2 (25.1)	4.7 (9.5)	7.0 (10.6)	6.1 (15.2)	8.2 (18.3)												

Abbreviations: GAL=Galantamine, PLA=Placebo, CBT4CBT=computerized cognitive behavioral therapy,

Baseline severity: low = 0 to 10 days, medium 11-20 days, high=21 or more days in the 28 days prior to baseline assessment

Supplementary eTable 2: Cognitive function indicators by treatment condition and time

	Galantamine + CBT4CBT			Galantamine + TAU			Placebo + CBT4CBT			Placebo + TAU			Contrast 1: GAL+CBT4CBT vs. GAL +TAU and PLA+CBT4CBT		Contrast 2: GAL vs PLA		Contrast3: CBT4CBT vs TAU	
Variable	***m***	*sd*	*n*	*m*	*sd*	*n*	*m*	*sd*	*n*	*m*	*sd*	*n*	*T*	*p*	*T*	*p*	*T*	*p*
CANTAB																		
Intra-Extradimensional Set Shifting (IED), Total Adjusted Errors, mean (SD)																		
Week 0	45.21	51.68	19	45.59	42.96	22	46.00	49.29	27	35.00	21.10	19	.11	.92	-.48	.63	.65	.52
Week 12	46.74	36.22		39.55	38.23		52.22	54.38		34.68	40.79							
Pattern Recognition Memory (PRM), % Correct																		
Week 0	81.14	13.84	19	88.26	87.88	22	85.42	83.33	28	82.50	81.67	20	-.02	.98	.17	.86	-.31	.76
Week 12	79.82	15.54		14.01	14.94		14.46	18.00		13.22	16.80							
Rapid Visual Processing (RVP), A'																		
Week 0	.89	.87	19	.88	.90	22	.89	.89	26	.89	.88	19	-1.71	.09	.14	.89	-.86	.39
Week 12	.05	.08		0.06	.05		.06	.06		.05	.06							
Stop Signal Task (SST), Stop Signal Reaction Time (SSRT)																		
Week 0	271.13	153.00	19	218.64	213.10	22	237.87	209.46	27	262.10	208.19	19	-.57	.57	.52	.60	-.15	.88
Week 12	229.82	70.00		81.97	41.39		156.70	100.28		127.93	77.01							
DIGIT SPAN																		
Longest Backwards Span																		
Week 0	5.36	2.38	22	6.80	2.78	25	5.85	2.87	33	5.91	2.28	23	1.43	.16	.50	.62	.92	.36
Week 12	6.18	3.53		6.64	2.87		6.24	2.53		6.57	2.73							

Abbreviations. GAL=Galantamine, PLA=Placebo, CBT4CBT=computerized cognitive behavioral therapy,
TAU=standard methadone treatment as usual; CANTAB:Cambridge Neuropsychological Test Automated Battery