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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 which 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.

Methods—Twelve-week, randomized 2X2, factorial trial evaluating galantamine versus placebo (double blind), and computerized cognitive behavioral therapy plus standard methadone treatment versus standard methadone treatment alone in a community based methadone maintenance program (September 2009–April 2015). 120 individuals diagnosed with DSM-IV cocaine use disorder were randomized to either extended-release galantamine (8 mg/day) or matched placebo, 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=.34) and computerized cognitive behavioral therapy over standard methadone treatment (F=4.2, p=.04, d=.30, but no evidence of significant benefit of the combination over either treatment alone. Pre- 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 cognitive behavioral therapy for cocaine use in this sample. While galantamine did not improve measures of cognitive

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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.

Introduction

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[10] or targeting impairment directly via cognitive training exercises[11]; both strategies have yielded mixed results to date[12–15]. A novel strategy is use of cognitive-enhancing agents (e.g., cholinesterase inhibitors) to improve attention and concentration as a means of addressing both cognitive function and substance use[11, 16, 17].

The cholinergic system plays an important role in multiple brain functions including attention, working memory, reward and motivation[18–20]. Evidence from preclinical studies suggest that downregulation of the cholinergic system is a critical part of the neuroadaptations to chronic cocaine use[21]. 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[22], providing an additional mechanism by which galantamine may enhance cognitive function and reduce stimulant use[19, 21, 23].

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 significant reductions in cigarette smoking compared with placebo[24].. 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[25]. In a randomized placebo controlled pilot study with 14 cocaine-dependent methadone-maintained individuals, 16 mg/day galantamine was associated with fewer cocaine positive urine specimens, (45% versus 95%, P=.15) as well as a higher proportion of days of abstinence from cocaine 80% versus 60%, P=.06) relative to placebo, with participants reporting moderate nausea and fatigue[26]. Differential effects on cognitive functioning were not seen. In a 10-day proof-of-concept trial with 34 abstinent cocaine users, 8/mg/day of galantamine was associated with significant improvement in the

Rapid Visual Information Processing task (RVP) of the CANTAB (Cambridge Neurologic Test Battery) compared with placebo[27]. These two pilot studies by our group suggested evaluation of galantamine on cocaine use and cognitive functioning was warranted in an a full randomized clinical tiral.

Herein we describe outcomes of a 2X2 randomized factorial trial in 120 methadone maintained individuals with cocaine use disorder who were randomized 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 to 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 #NCT0080935. Individuals were included as participants if they were 18 years or older and met DSM-IV-R criteria for current cocaine dependence, as assessed by the Structured Clinical Interview for DSM-IV-R (SCID)[28] and provided at least one cocaine-positive urine test during screening. Individuals were excluded if they (1) were currently dependent on another illicit drug or whose principal drug use was not 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[29] (e.g. 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 (EKG, urinalysis and blood work), (4) had a screening liver function test greater than 3 times normal (n=5) (5) used medications including beta-blockers and NSAIDS 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 IRB and were randomized. A masked, computerized urn randomization program used in previous trials[30–33] was used to produce equivalent group size and balance groups with respect to baseline level of cocaine use (more or less than 11 days per month), gender, ethnicity (ethnic minority/non-minority), age (over/under 40), and baseline Shipley[34] 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 limited tolerability of the 16 mg/day dose in our pilot study[27]. Galantamine or matched placebo capsules were dispensed daily at the time of methadone dosing and 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[35] that makes extensive use of video examples to each cognitive and behavioral control skills in 7 modules, each requiring about 30–40 minutes to complete. As described earlier[36], the CBT4CBT program 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; participants received a gift card worth $10 for each completed assessment), and at the 12-week treatment termination point. In cases where a randomized participant did not initiate (n=3), was withdrawn from treatment (n=3; one for elevated blood pressure, one for suicidal ideation, one for deliberately breaking the medication blind), or dropped out of treatment (n=25), he or she was interviewed at the 12-week point in order 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[37].

The Timeline Follow Back[38] 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 5 with adulterant checks, Branan Medical Corporation) obtained twice weekly. Of 1911 urine specimens collected, 1601 (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%) were positive for cocaine in cases where the participant denied use in the past 3 days. This rate is consistent with that reported for previous studies of cocaine-dependent samples evaluating the accuracy of self-report data[39, 40].

Multiple cognitive tasks, drawn from the CANTAB[41] 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 (Rapid Visual Information Processing, RVP A`: target sensitivity with higher scores indicating better attention[28, 42]), and potential effects of CBT4CBT on cognitive flexibility (Intra-Extra Dimensional Set Shifting (IED) total adjusted errors: number of intra- or extradimensional errors, adjusted for trials completed, where lower errors shows faster learning of changing contingencies[43, 44]). Response inhibition (Stop Signal Reaction Time (SSRT) where lower SSRT indicates better ability to inhibit a pre-potent motor response[45, 46]) and visual memory (Pattern Recognition Memory, PRM percent correct[47]) were also evaluated. Working memory was evaluated using Digit Span (longest backward span)[48].

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[49] to evaluate change across time, in monthly intervals, with the following contrasts: medication condition (galantamine versus placebo), behavioral condition (CBT4CBT versus TAU), and the combination of galantamine and CBT4CBT versus each intervention delivered singly (galantamine plus CBT4CBT versus 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[50] due to the likelihood of over-estimation of instances of cocaine use when obtained twice weekly due to carry-over effects [5051]. Repeated measures ANOVAs were used to evaluate changes in cognitive measures over time.

Power calculations utilizing estimates of effect sizes for galantamine (d=.4) and CBT4CBT (d=.5) on cocaine use outcomes based on previous trials[6, 27, 36] indicated 35 participants per cell would provide sufficient power (>80%, two-sided). This effect size would be sufficient to detect a large effect (.50 or more) for the interaction of galantamine plus CBT4CBT, as well as for the effect of galantamine on CANTAB RVP A' [27]. 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, 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 they used cocaine an average 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, 36].

Primary and secondary cocaine outcomes

Random effects regression for effects of study treatments on the primary outcome, days of self-reported cocaine use by month, are presented in Table 3 and illustrated in Figure 2. For the model which 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 which 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 (F1,286)=.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 twelve weeks, by baseline severity are shown in Supplemental Table e1.

Effects of study treatments on cognitive tasks over time

Data from the cognitive task battery are presented in Supplemental Table e2. 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 % correct, IED total adjusted errors, and Digit Span backwards), also indicated no 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=.25, P=0.01),

RVP A' (r=.20, P=.04), PRM % correct (r=.19, P=.05) and digits backward (r=.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 versus placebo, X^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 two. Contrary to our hypothesis, there was no effect of galantamine relative to placebo over time for the 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[26]. The potential for galantamine to have some benefit in treating cocaine use disorder is notable, and consistent with work suggesting a role for the cholinergic system in treating stimulant disorders[19, 21]. An ongoing RCT is evaluating galantamine versus placebo in a non-methadone sample of individuals with a primary cocaine use disorder (Clinicaltrials.gov #NCT01531153).

While evaluating galantamine in a methadone-maintained sample of cocaine users conferred several advantages from a methodologic 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 study medications at the time of daily methadone dosing, also permitting 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[52, 53] and include broad impairment in domains encompassing attention, memory, cognitive

impulsivity and cognitive flexibility in the methadone group[54]. 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[55]. In addition, cognitive functions may fluctuate depending on recency of methadone dose[56], 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. It 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.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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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.

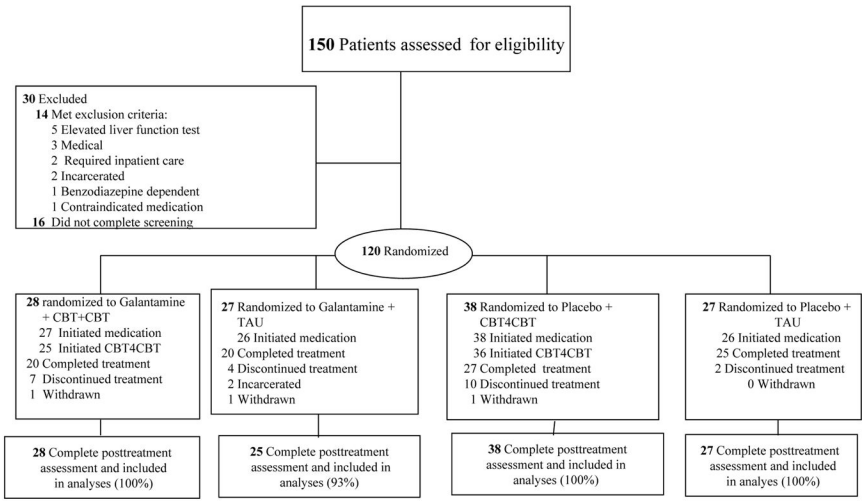

Figure 1.

CONSORT Flow Diagram of Participants through the Trial

Note : Completing treatment defined as taking at least 1 day of study medication in week 12 .

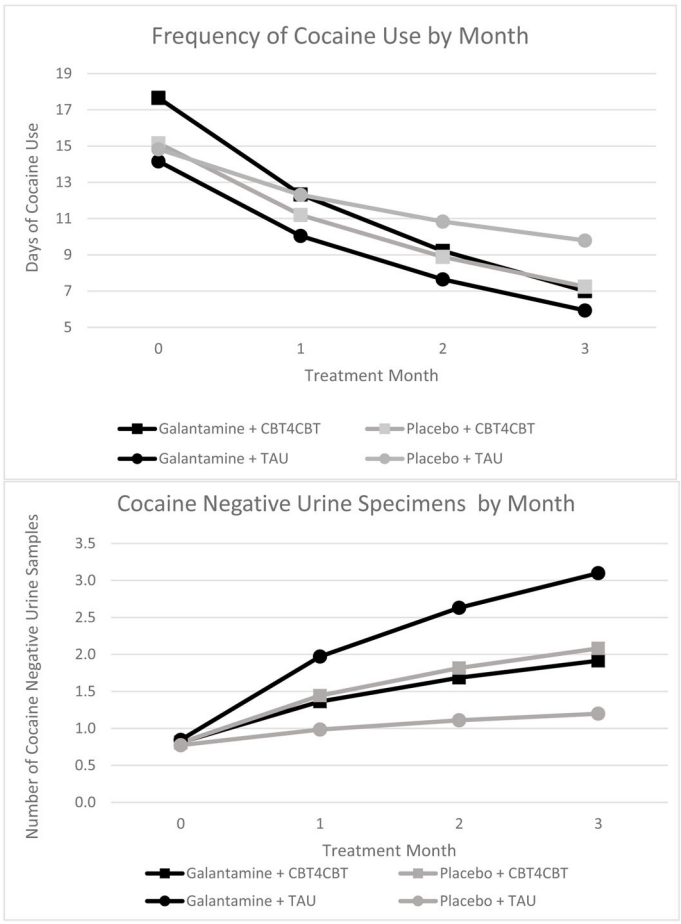

Figure 2.

Primary and Secondary Cocaine Use Outcomes by Group over Time, time, estimates from random effects regression models

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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 X2*	*p-value*
Female, No. (%)	12 (43%)	11 (41)	10 (26)	7 (26)	3.32	.35
Race and ethnicity, No. (%)						
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, No. (%)	17 61)	19 (70)	29 (77)	21 (78)	2.58	.46
Unemployed, No. (%)	20 (71)	21 (78)	27 (71)	19 (70)	0.50	.92
On public assistance, No. (%)	23 (83)	21 (78)	23 (61)	18 (67)	4.55	.21
Major depression -lifetime[a], No. (%)	1 (4)	3 (11)	2 (5)	4 (15)	3.06	.38
Anxiety disorder -lifetime, No. (%)	3 (11)	5 (19)	2 (5)	5 (19)	3.69	.30
Antisocial personality dis., No. (%)	3 (11)	3 (11)	5 (13)	5 (19)	0.91	.82
Alcohol use dis.-lifetime, No. (%)	15 (54)	14 (52)	21 (55)	16 (59)	0.33	.95
Age, mean (SD)	38.0 (8.7)	38.7 (10.8)	39.8 (9.0)	36.3 (9.4)	0.75	.52
Days marijuana use, past 28, mean (SD)	4.9 (8.9)	3.3 (7.8)	2.0 (5.5)	3.3 (7.4)	0.80	.50
Days cocaine use, past 28, mean (SD)	17.2 (8.3)	12.4 (8.1)	13.6 (8.5)	13.4 (7.9)	1.80	.15
Days cigarette use, past 28, mean (SD)	27.1 (4.9)	25.4 (7.8)	27.3 (4.5)	25.3 (7.9)	0.81	.49
Days alcohol use, past 28, mean (SD)	2.9 (5.3)	4.6 (7.8)	1.7 (4.9)	1.7 (3.1)	1.79	.15
Days opiate use, past 28, mean (SD)	1.6 (2.5)	3.3 (4.4)	4.3 (7.9)	1.5 (2.6)	2.15	.10
Days benzodiazepine use, past 28, mean (SD)	0.5 (1.9)	0.3 (0.7)	0.3 (0.8)	0.3 (1.0)	0.20	.90
Age of first cocaine use, mean (SD)	18.1 (3.5)	20.2 (6.1)	20.6 (6.6)	20.2 (5.0)	1.27	.29
Years of regular cocaine use, mean (SD)	10.2 (8.7)	12.6 (10.3)	8.5 (7.1)	8.5 (8.1)	1.53	.21
Lifetime number of arrests, mean (SD)	6.6 (7.3)	7.2 (10.9)	8.9 (14.7)	5.8 (6.6)	0.50	.69
Number of prior outpt drug treatments, mean (SD)	3.5 (4.6)	2.3 (2.7)	2.4 (2.6)	2.5 (2.2)	0.97	.41
Number of prior inpt drug treatments, mean (SD)	2.6 (2.5)	3.7 (6.8)	3.4 (5.7)	2.4 (3.9)	0.46	.71
Estimated IQ from Shipley, mean (SD)	98.4 (11.7)	101.6 (12.2)	101.4 (11.4)	100.5 (11.9)	0.45	.72
Methadone dose, mg/day, mean (SD)	77.3 (35.7)	65.3 (25.3)	72.4 (26.4)	65.3 (25.6)	1.15	.33

Abbreviations: GAL=galantamine, PLA=placebo, CBT4CBT=computerized cognitive behavioral therapy, TAU=standard methadone treatment as usual

[a] All psychiatric diagnoses made from SCID interviews for DSM-IV-R

Table 2

Treatment Process and Adherence by Group

Variable	Galantamine + CBT4CBT (n=28)	Galantamine + TAU (n=27)	Placebo + CBT4CBT (n=38)	Placebo + TAU (n=27)	Contrast 1: GAL+CBT4CBT v GAL +TAU and PLA +CBT4CBT F/X2	Contrast 1 p	Contrast 2: GAL v PLA F/X2	Contrast 2 p	Contrast 3: CBT4CBT v TAU F/X2	Contrast 3 p
Days in treatment (of 84), mean (SD)	65.79 (31.06)	66.96 (30.11)	70.21 (25.77)	79.41 (17.6)	.22	.64	2.95	.09	1.12	.29
Days took study medication, mean (SD)	62.25 (30.89)	63.89 (29.55)	65.45 (26.11)	77.67 (17.34)	.16	.69	3.01	.09	2.00	.16
Percent days medication adherent, mean (SD)	89.85 (20.89)	91.73 (20.37)	92.69 (11.14)	94.22 (19.06)	.34	.56	.66	.42	.27	.60
Number CBT4CBT modules completed (of 7), mean (SD)	4.43 (2.87)		4.95 (2.31)				.66	.42		
Total individual tx sessions completed, mean (SD)[a]	5.00 (2.33)	7.50 (4.29)	5.97 (4.98)	6.44 (3.65)	2.48	.12	.00	.96	3.04	.09
Total group tx sessions completed, mean (SD)[a]	8.37 (20.66)	2.70 (4.21)	13.97 (40.50)	3.32 (7.84)	.00	1.00	.35	.56	2.41	.12

Abbreviations: GAL=Galantamine, PLA=Placebo, CBT4CBT=computerized cognitive behavioral therapy, TAU=standard methadone treatment as usual

[a]Includes only those participants who initiated treatment

Table 3

Primary outcomes by time and treatment condition: Random effects model estimates

Variable	N, obs.	−2RLL	Denominator. *df*	*F*	*p*	*Effect size, d*
Self-reported percent days abstinent by month						
Intercept	120, 475	3100.139	215.58	517.86	.00	
Medication Condition (GAL *vs* PLA)			215.58	.45	.50	
Behavioral Condition (CBT4CBT *vs* TAU)			215.58	1.98	.16	
Time			351.07	152.04	.00	
Contrast 1: Gal + CBT4CBT *vs* GAL+TAU and PLA+CBT4CBT by time			351.07	.03	.86	.03
Contrast 2: Galantamine *vs* placebo by time			351.07	5.27	.02	.34
Contrast 3: CBT4CBT *vs* TAU by time			351.07	4.22	.04	.30
Number of cocaine-negative urine specimens submitted by month						
Intercept	120, 367	1495.842	267.52	21.58	.00	
Medication Condition (GAL *vs* PLA)			267.52	.01	.91	
Behavioral Condition (CBT4CBT *vs* PLA)			267.52	.00	1.00	
Time			286.14	32.17	.00	
Contrast 1: Gal + CBT4CBT *vs* GAL+TAU and PLA+CBT4CBT by time			286.14	5.04	.03	.75
Contrast 2: Galantamine *vs* placebo by time			286.14	3.46	.06	.43
Contrast 3: CBT4CBT *vs* TAU by time			286.14	.11	.74	.03

Abbreviations: −2Rll=-2 restricted log likelihood. Gal=Galantamine, PLA=placebo, CBT4CBT=Computerized CBT, TAU=Treatment as Usual