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Effects of escitalopram on attentional bias to cocaine-related stimuli and inhibitory control in cocaine-dependent subjects

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Abstract

Key characteristics of cocaine dependence include attentional bias to cocaine cues and impaired inhibitory control. Studies suggest that serotonin modulates both cocaine cue reactivity and inhibitory control. We investigated effects of the selective serotonin reuptake inhibitor escitalopram on cocaine cue reactivity and inhibitory processes in cocaine-dependent subjects. In a double-blind placebo-controlled design, cocaine-dependent subjects received placebo (*n*=12) or escitalopram (*n*=11; 10 mg on days 1–3, 20 mg on days 4–24 and 10 mg on days 25–28) orally, once daily for 4 weeks. The cocaine Stroop and immediate memory task (IMT) were administered at baseline, days 1, 4, 11, 18 and 25 after placebo or escitalopram initiation. There were no significant between-group differences in baseline performance on the cocaine Stroop task or the IMT. On day 1 (acute phase), escitalopram produced a significantly greater decrease from baseline than placebo in attentional bias measured by cocaine Stroop task 5 hours post-dose. No significant changes from baseline in attentional bias were observed on subsequent test days (chronic phase). Inhibitory control as measured by IMT commission error rate was not significantly different between two groups in either the acute or chronic phase. Consistent with preclinical data, serotonin-modulating drugs like escitalopram may have acute effects on cocaine cue reactivity in human cocaine users.

Keywords

Escitalopram; attentional bias; cocaine Stroop task; inhibitory control; cocaine dependence

Introduction

Difficulty directing attention away from cocaine-related stimuli (attentional bias) is thought to be related to cue reactivity and craving, which are key factors involved in relapse in

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cocaine-dependent subjects (Field and Cox, 2008; Garavan and Hester, 2007). The cocaine Stroop task has been used to measure attentional bias to stimuli associated with cocaine use (drug-related words or pictures) in cocaine-dependent subjects. In this task, participants focus on the color of the words or the edge color of pictures while inhibiting their response to the distracting salient (drug-related) feature of the word or picture (Cox et al., 2006; Williams et al., 1996). Several studies have demonstrated that cocaine-dependent subjects' reaction time to respond to cocaine-related words is significantly slower than to respond to neutral words (Hester et al., 2006; Liu et al., 2011; Vadhan et al., 2007); control subjects do not show this reaction time difference (Hester et al., 2006; Liu et al., 2011). These studies suggest that cocaine-related stimuli acquire incentive properties that selectively attract the attention of cocaine users and contribute to drug seeking and relapse. In an addiction treatment study, attentional bias to cocaine-related stimuli was associated with worse treatment outcome (Carpenter et al., 2006). Attentional bias was also associated with cocaine craving severity ratings (Copersino et al., 2004; Field et al., 2009).Therefore, it is important to investigate mechanisms of attentional bias to cocaine cues in cocaine-dependent subjects.

Another important factor involved in high relapse rate of cocaine use is impaired inhibitory control. Several behavioral tasks such as the Continuous Performance Test (CPT), the Go/NoGo task, the Stop Signal task and the Stroop task have been used to measure inhibitory control (Verdejo-Garcia et al., 2008). We previously reported that cocaine-dependent subjects had higher commission error rates than control subjects on a variant of the CPT, the Immediate Memory task (IMT), indicating a deficit in inhibitory control in cocaine-dependent subjects (Liu et al., 2011; Moeller et al, 2004, 2005). This deficit in inhibitory control was significantly associated with attentional bias to cocaine-related words in cocaine-dependent subjects but not in control subjects (Liu et al., 2011). We also found that cocaine-dependent subjects performed worse than controls on a Go/NoGo task measuring inhibitory control (Lane et al., 2007). Other studies using the Stop Signal task found that cocaine-dependent subjects showed a deficit in inhibitory control expressed as increased Stop Signal Reaction Time compared with control subjects (Fillmore and Rush, 2002; Li et al., 2006). Impaired inhibitory control in addiction has also been reported in imaging studies (see reviews by Goldstein and Volkow, 2002; Lubman et al., 2004). Inhibitory control measured by the classic Stroop task was associated with treatment retention in cocaine-dependent subjects (Brewer et al., 2008; Streeter et al., 2008). Therefore, improving inhibitory control may be an important strategy in the treatment of cocaine dependence.

Preclinical studies indicate that serotonin-modulating drugs such as selective serotonin reuptake inhibitors (SSRI) (Burmeister et al., 2003) diminish cocaine cue-induced drug-seeking behaviors during abstinence in rats trained to self-administer cocaine. Collectively, several more recent preclinical studies strongly suggest that selective 5-HT_{2C} receptor agonists are effective in attenuating cue-induced reinstatement of drug responding to cocaine and methamphetamine (Burbassi and Cervo, 2008; Graves and Napier, 2012; Manvich et al., 2012; Neisewander and Acosta, 2007; Pentkowski et al., 2010). Consequently, it is hypothesized that 5-HT_{2C} receptors in the medial prefrontal cortex (PFC) modulate control over the motivational salience of cocaine cues, whereas 5-HT_{2C} deficits exacerbate reactivity to drug cues, and enhancement of 5-HT_{2C} attenuates cue reactivity (Cunningham

et al., 2010). In human studies, acute depletion of tryptophan (a precursor for serotonin synthesis) in subjects with a family history of alcoholism increased commission error rates on a Go/NoGo task (LeMarquand et al., 1999) and increased Stop Signal Reaction Time on a Stop Signal task (Crean et al., 2002). Tryptophan depletion in healthy human subjects also increased commission error rate in the IMT continuous performance test (Dougherty et al., 2007). These studies suggest that manipulation of serotonin levels affects both drug-cue reactivity and inhibitory control.

The use of SSRIs for the treatment of cocaine dependence have produced mixed results (Batki et al., 1996; Grabowski et al., 1995; Moeller et al., 2007; Oliveto et al., 1995; Pani et al., 2011; Schmitz et al., 2001; Winstanley et al., 2011). It should be noted that binding affinities and mechanisms of action vary substantially across SSRIs, and these differences may have accentuated variability across studies. Notably, there has been recent interest in medications to improve cocaine-related cognitive impairment, including attentional bias to cocaine cues and impaired inhibitory control (Sofuoglu, 2010). Newer and more selective serotonergic compounds may prove critical in elucidating the effects of the serotonin system on drug-relevant measures such as cue reactivity. Accordingly, the present study tested the hypothesis that escitalopram, a serotonin reuptake inhibitor with high affinity for the 5-HT transporter and 5-HT_{2C} receptors (Owens et al., 2001), would (a) decrease attentional bias to cocaine-related words on the cocaine Stroop task and (b) improve inhibitory control measured by commission error rate on the IMT in cocaine-dependent subjects.

Methods

Subjects

Non-treatment-seeking cocaine-dependent subjects were recruited through newspaper, online advertisements and word of mouth referrals. All subjects signed a general screening consent form and were screened for psychiatric disorders using the Structured Clinical Interview for DSM-IV (SCID-I) (First et al., 1996) and a medical history and physical examination. Twenty-three current cocaine-dependent subjects passed the general screening and signed a consent form for this study after being fully informed of the study. All subjects reported no current or past history of neurological or psychiatric disorders. Subjects who met current dependence DSM-IV criteria for other abused drugs besides cocaine or marijuana were excluded. All subjects were tested for urine marijuana, opiates, cocaine (benzoylecgonine), amphetamine and benzodiazepines using integrated E-Z split key cup II (Innovacon Company, San Diego, CA, USA) and reported their cocaine craving intensity on a visual analogue scale ranging from 0 (no desire at all) to 7 (unable to resist) on each visit. All subjects were free of alcohol at the time of testing as determined by an Intoximeter Alcosensor III breathalyzer (Intoximeters, Inc., St. Louis, Mo., USA). Of the 23 subjects, 22 smoked cigarettes. Number of cigarettes smoked daily was not significantly different between the escitalopram and placebo groups. We required subjects not to smoke cigarettes for 1 h before computer task performance to control for acute effects of cigarette smoking on task performance. This study was approved by the Committee for the Protection of Human Subjects of the University of Texas Health Science Center at Houston and was performed in accordance with the Declaration of Helsinki.

Design

This was a 5-week double-blind placebo-controlled randomized study. Each week subjects had two visits, which were on either Monday/Thursday or Tuesday/Friday. In week 1, subjects signed the consent form and completed the Beck Depression Inventory-II (BDI-II) (Beck et al., 1996) during the first visit (Monday or Tuesday) and performed the baseline behavioral tasks during the second visit (Thursday or Friday). In week 2, subjects were randomly assigned to the escitalopram or placebo group. Experimenters were blind to the group assignment. Subjects in the escitalopram group received 10 mg (days 1–3, 26–28) or 20 mg (days 4–25) once daily at 9:00 AM based on its half-life of 27–32 hours at the dose range of 10–30 mg/day and its suggested dose for depression (Forest Pharmaceuticals, 2008). Escitalopram from Forest Pharmaceuticals was encapsulated in a single blue capsule filled with cornstarch. Subjects in the placebo group received a matching blue capsule containing only cornstarch once daily at 9:00 AM. Since escitalopram reaches peak blood level 5 hours after oral administration (Forest Pharmaceuticals, 2008), in week 2, test day 1 (acute phase), subjects performed the behavioral tasks 5 hours after administration of 10 mg escitalopram or placebo. On days 4, 11, 18, and 25 (chronic phase), subjects performed the behavioral tasks 30 min after administration of escitalopram or placebo. On days 8, 15, and 22, subjects simply received a refill of capsules. At the end of week 5, the dose of escitalopram was tapered to 10 mg for 3 days prior to discontinuation. Subjects had a follow-up evaluation and release 4 days later. In summary, subjects performed the behavioral tasks a total of six times: baseline session, session 1 (acute) on day 1 and sessions 2–5 (chronic) on days 4, 11, 18, and 25. One subject in the escitalopram group complained of elevated blood pressure and withdrew from the study after session 3. One subject in each group stopped showing up without notice and could not be recontacted after session 3.

Medication compliance was documented using Medication Event Monitoring System bottles (MEMS, AARDEX Ltd / APREX, Union City, CA, USA), which electronically recorded bottle opening times. The MEMS bottles were given to subjects on the second visit of week 2. Contingency management was used to improve medication compliance. Subjects were awarded $10 at the first visit based on compliance, and an additional $10 for each visit in which the MEMS bottle showed subjects' compliance with the medication protocol. The MEMS system showed that all subjects opened the MEMS bottles at least once a day as requested.

Behavioral tasks

The cocaine Stroop task was used to measure attentional bias to cocaine-related stimuli (Hester et al., 2006; Liu et al., 2011; Vadhan et al., 2007). Each session of this task included 60 practice trials and 240 test trials. The practice stimuli were colored repeated single letters of a different length matched to the length of the cocaine-related words (e.g. XXX, MMMMM). The stimuli in test trials included 10 cocaine-related words: "COCAINE", "CRACK", "ROCKS", "HIGH", "DEALER", "HIT", "SMOKE", "PUFF", "PIPE", "FREEBASE"; 10 household-related words such as "SOFA", "OVEN"; 10 environment-related words such as "CAR", "SIDEWALK"; and 10 non-drug reward words such as "MONEY" and "VACATION". In each trial, the stimulus of different colors (red, blue, or green) was presented against a black background. Subjects were asked to press keyboard

buttons covered by colored stickers (letter “B”: blue; letter “N”: green; letter “M”: red) to indicate the color of the stimulus as quickly and as accurately as possible while ignoring the meaning of the stimulus. A short beep sounded if the subject made an incorrect response. The stimulus stayed on the screen until the subject responded to the color or until 3000 ms had elapsed. The inter-trial interval was 500 ms. The test trials included two blocks of trials with cocaine-related words, two blocks of trials with household-related words, two blocks of trials with environment-related words and two blocks of trials with non-drug reward words. Each block included 30 trials, in which each word was randomly presented three times in the three different colors: red, green and blue. The four block types were counterbalanced randomly across subjects. The difference in mean reaction times between trials with cocaine-related words and all other word types was calculated as a measure of attentional bias to the cocaine-related words because the reaction times for household-related, environment-related, and non-drug reward words were not significantly different.

The IMT was used to measure inhibitory control. The IMT is a continuous performance test in which subjects were presented a series of 5-digit numbers via a computer monitor (Dougherty et al., 1998). Subjects were told to press the mouse button if the current number was identical to the preceding number and to withhold the response if the number was not identical to the preceding number. The trial types were as follows: identical (33% of the total trials), differed by 1 digit (33% of the total trials), and differed by more than 1 digit from the previous number (34% of total trials). The three types of trials were randomly distributed within each test session. The number stayed on the screen for 500 ms, with a 500 ms blank screen between numbers. For trials with a number identical to the preceding number, pressing the mouse button within 1000 ms was counted as a correct response. A commission error was defined as a response made when the number differed by 1 digit from the preceding number (when it should have been withheld). The commission error rate was used to measure inhibitory control: the ability to withhold an inappropriate behavioral response (see reviews by de Wit 2009; Moeller et al., 2001; Perry and Carroll, 2008).

Statistical analysis

Demographic and baseline (pretreatment) differences between placebo and escitalopram-treated groups were analyzed using Student’s *t*-test for continuous variables and Fisher’s exact test for categorical variables. In order to assess effects of escitalopram on attentional bias and inhibitory control, the repeated measures analysis of variance (ANOVA) in a mixed model was used to analyze the main effects of treatment (placebo vs. escitalopram), time (sessions 1–5) and their interaction (treatment × time). Due to well-documented preclinical neurobiological and behavioral differences following acute versus chronic SSRI administration (Bosker et al., 2001; Czachura and Rasmussen, 2000; Robbins and Crockett, 2010), acute (5 hours) and chronic (weekly) effects were analyzed separately. For significant interactions, post-hoc Tukey–Kramer tests were used to compare the difference between two groups at each time point and between different time points in the same group. All analyses were performed in SAS 9.2 (SAS, Cary NC).

Results

Demographic and baseline data

There were no significant between-group differences for age ($t = 0.92$, $p = 0.37$;), gender (Fisher's exact $p = 1.00$), race (Fisher's exact $p = 0.48$;), educational level ($t = 0.40$, $p = 0.69$), baseline drug use history (days of cocaine use in the last 30 days ($t = 0.15$, $p = 0.56$) and years of cocaine use ($t = 1.33$, $p = 0.20$)), BDI-II scores ($t = 0.73$, $p = 0.48$) or baseline drug screen results (Fisher's exact $p = 1.00$ for cocaine urine screens and $p = 0.41$ for marijuana urine screens) (Table 1).

Attentional bias on the cocaine Stroop task

Cocaine-dependent subjects took significantly longer time to respond to the color of cocaine-related words than to the color of non-cocaine-related words (paired *t*-test, $t = 2.80$, $p = 0.01$, data not shown), indicating an attentional bias to cocaine-related words. There was no significant between-group difference in baseline attentional bias to cocaine-related words (45.92±31.54 ms in placebo group vs. 90.25±32.51 ms in escitalopram group, $t = 0.92$, $p = 0.37$). For the acute effects of escitalopram, the ANOVA showed a significant treatment × time interaction ($F_{1,21} = 5.164$, $p = 0.034$, $\text{Eta}^2 = 0.05$, Cohen's $f = 0.023$, small-medium effect size) for attentional bias. The post-hoc analysis showed that attentional bias on session 1 was significantly less than that on baseline in the escitalopram group ($p < 0.01$) but not in the placebo group. For the chronic effects of escitalopram, there was no significant treatment × time interaction ($F_{4,21} = 0.45$, $p = 0.773$, $\text{Eta}^2 = 0.03$, Cohen's $f = 0.019$, small effect size). Results are presented graphically in Figure 1.

Inhibitory control on the Immediate Memory Task

There was no significant difference in baseline commission error rates between the escitalopram and placebo groups (13.48±12.59 in placebo group vs. 20.72±15.92 in escitalopram group, $t = 0.75$, $p = 0.46$). The interaction of treatment × time was not significant for either the acute or chronic effects of escitalopram on commission error rate (data now shown). In summary, we did not observe improved inhibitory control in either the acute (session1) or chronic (session 2–5) phases as a function of escitalopram treatment.

ANOVA did not reveal any significant differences in reported cocaine craving intensity or percent positive urine cocaine screens.

Discussion

This study showed that compared with placebo, escitalopram acutely produced a significant decrease in attentional bias to cocaine-related words on day 1 at 5 hours post-dose. No significant decreases were found on later test days during the chronic administration phase. Escitalopram did not significantly alter commission error rates on the IMT compared with placebo after either acute or chronic administration.

The observed acute effect of escitalopram on attentional bias is consistent with preclinical studies by Burmeister et al. (2003, 2004) showing that acute administration of the SSRI fluoxetine or the serotonin releasing drug fenfluramine dose-dependently decreased cue-

induced cocaine-seeking behaviors in a rat cocaine self-administration model. Burmeister et al. (2004) also found that the 5-HT_{2C} receptor antagonist SB 242,084 reversed the d-fenfluramine-induced attenuation of cocaine cue-induced cocaine-seeking behaviors, while the 5-HT_{1A} receptor antagonist WAY100635 and the 5-HT_{2A} receptor antagonist ketanserin did not. Given that preclinical studies reported that the 5-HT_{2C} receptor agonists attenuated or blocked cocaine cue-induced behaviors (Cunningham et al., 2011; Fletcher et al., 2008), the effects of acute escitalopram administration on attentional bias are possibly related to activation of 5-HT_{2C} receptors via increased 5-HT induced by escitalopram (Bosker et al., 2001; Ceglia et al., 2004).

Wiers et al. (2006) reported that alcohol attention control training decreased attentional bias to alcohol-related stimuli in heavy alcohol users. Similarly, attention retraining in patients with generalized anxiety decreased the attentional bias to threat cues (Hazen et al., 2009). Attention retraining in combination with the acute effects of escitalopram might be a useful way to decrease attentional bias to cocaine cues in cocaine-dependent subjects.

We did not find significant effects of escitalopram on attentional bias to cocaine-related words in the chronic administration phase. Similarly, prior studies showed that fluoxetine did not decrease cocaine-positive urines or cocaine craving (Batki et al., 1996; Grabowski et al., 1995; Oliveto et al., 1995; Pani et al., 2011; Schmitz et al., 2001; Winstanley et al., 2011). It is possible that increase of serotonin in the synaptic cleft by chronic escitalopram administration (Ceglia et al., 2004) created adaptive changes in post-synaptic receptors such as 5-HT_{2C} (Pälvimäki et al., 2005) that may have had a subsequent influence on attentional bias. In addition, escitalopram-induced desensitization of autoinhibitory somatodendritic 5-HT_{1A} autoreceptors could increase serotonin levels (Ceglia et al., 2004) such that further increase of serotonin at higher doses of escitalopram (e.g. in the chronic phase of this study) would be mitigated. In either case, chronic administration was not effective in modulating behavior on the attentional bias or response inhibition tasks employed here.

Escitalopram did not affect the commission error rate in the IMT after acute or repeated exposure. This finding is inconsistent with previous reports showing that acute tryptophan depletion in subjects with family history of alcoholism or healthy controls impaired the inhibitory control on a Go/NoGo task (LeMarquand et al., 1999), Stop Signal task (Crean et al., 2002) or the IMT (Dougherty et al., 2007). However, Nandam et al. (2011) failed to observe a significant effect of the SSRI citalopram on inhibitory control in healthy control subjects performing the Stop Signal task. Clark et al. (2005) also found that inhibitory control assessed by the Stop Signal task was not altered by tryptophan depletion in control subjects. Methodological differences in subject selection, behavioral tasks, or pharmacological manipulation may account for the different findings across studies. In the present study, subjects reported an average of 15 years of cocaine use, making it possible that neuroadaptation in brain serotonin function (Seger, 2010) influenced performance of the behavioral task. In addition, the small sample size in our study resulted in considerable variability within and across subjects. Any effects on inhibitory control may be modest and require larger groups to observe a statistically significant outcome.

Ataya et al. (2012) reported that behavioral tasks measuring bias toward alcohol- and tobacco-related stimuli have poor internal reliability (Cronbach's alpha less than 0.7). They evaluated the visual probe tasks and modified Stroop tasks from seven independent studies for their internal reliability. The modified Stroop with block design showed the best internal reliability, although the Cronbach's alpha for these tasks was larger than 0.7 in only two of five studies. In the present dataset, we generally found acceptable Cronbach's alpha levels in the majority of test sessions with the block-design cocaine Stroop task. Cronbach's alpha was >0.7 for both groups at baseline. Cronbach's alpha was >0.7 for sessions 2–5 in the pacebo group, but alpha was >0.7 only in sessions 4 and 5 in the escitalopram group.

The computer tasks were performed at different times across the acute and chronic test phases: 5 hours post-administration in the acute phase, and 30 min post-administration in the chronic phase. We also used different doses across the study, starting at 10 mg once per day on days 1–3 and increasing to 20 mg once per day on day 4. We cannot exclude the possibility that different testing times or different doses influenced the outcome differences between the acute and chronic phases. However, escitalopram reaches its peak plasma levels 5 hours after oral administration with a half-life of 27–32 hours (Forest Pharmaceuticals, 2008). This pharmacokinetic profile suggests that escitalopram plasma levels during the chronic phase were about 1.1–2.7 times that of the peak level 5 hours after the first acute administration of escitalopram. Therefore, the failure to observe a statistically significant effect of escitalopram in the chronic administration phase (vs. the acute phase) was unlikely due to different plasma levels or testing times between the two phases. Failure to experimentally control for these factors leave this issue unresolved and in need of replication with a revised experimental design.

In summary, the results showed that acute administration of escitalopram significantly decreased attentional bias to cocaine cues, while chronic administration of escitalopram did not. Effect sizes were small or small–medium in both phases. In addition, escitalopram did not significantly change inhibitory control measured by commission error rate in the IMT in either the acute or chronic phase. These results and several previous clinical trials (Batki et al., 1996; Grabowski et al., 1995; Oliveto et al., 1995; Schmitz et al., 2001; Winstanley et al., 2011) argue (in general) against use of SSRIs as a mainstay of treatment for cocaine dependence. However, the observed acute effects of escitalopram on attentional bias to cocaine cues is consistent with preclinical findings on the effects of 5-HT-modulating drugs on cocaine cue-induced responding – furthering our understanding of mechanisms in attentional bias to drug cues.

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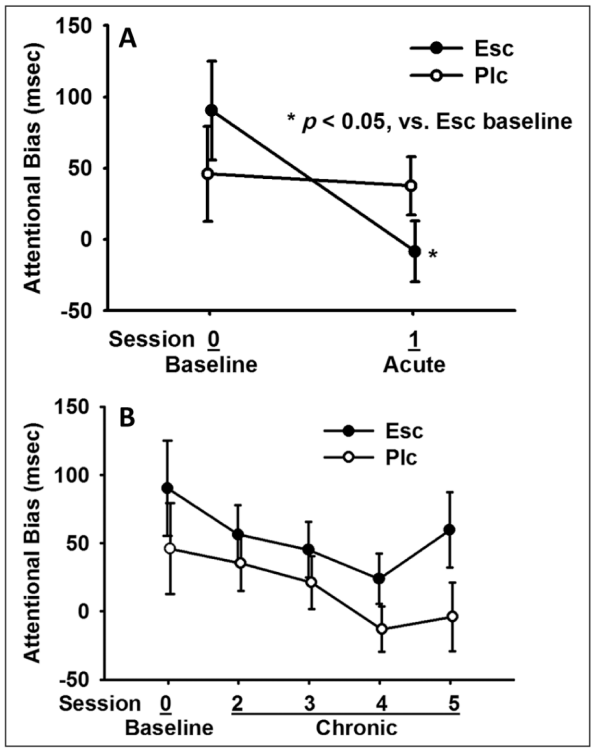

Figure 1.

Escitalopram decreased attentional bias acutely but not chronically. Attentional bias (mean ± SEM) was used to compare effects of escitalopram. The attentional bias was calculated as the difference of reaction times (cocaine-related words - non-cocaine-related words). A smaller number indicated less attentional bias to cocaine-related words. Dose of escitalopram: 10 mg daily for days 1–3, 20 mg daily for days 4–25; 10 mg daily for days 26–28. Computer tasks were performed on 4 days before first dose (baseline, session 0), day 1 (acute, session 1), days 4, 11, 28, 25(chronic, session 2–5). * $p < 0.05$, vs. baseline attentional bias of the escitalopram subjects. Plc: placebo; Esc: escitalopram. A. Acute effects of escitalopram; B. Chronic effects of escitalopram.

Table 1

Demographic and baseline data.

	Placebo	Escitalopram	*t*	*p*
Age	41.75 (6.65)	38.40 (7.88)	0.92	0.37
Gender (F/M)	11/1	10/1		1.00
Education(years)	12.83 (1.78)	13.09 (1.04)	0.40	0.69
Ethnicity	10 AA, 2 Cau	10 AA, 1 Oth		0.48
Days of cocaine use in last 30 days	14.54 (5.34)	14.09 (8.58)	0.15	0.56
Years of cocaine use	17.54 (7.12)	13.09 (8.48)	1.33	0.20
BDI scores	4.56 (5.64)	6.70 (6.99)	0.73	0.48
Baseline drug screen results (number of positive/number of negative)				
Cocaine	9/3	8/3		1.00
Marijuana	5/7	7/4		0.41

AA: African American; Cau: Caucasian; Oth: Other Ethnicity.

Student *t*-test was used for continuous variables (mean(SD)); Fisher's exact test was used for categorical data.