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Short communication

Poor response to sertraline in methamphetamine dependence is associated with sustained craving for methamphetamine

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ABSTRACT

Background: Depression is common among individuals with methamphetamine (MA) use disorders. As agents that enhance serotonergic function are frequently used to treat depression, one might predict that they would be useful medications for MA dependence. However, clinical trials of serotonergic agents for MA addiction have been unsuccessful.
Objective: To identify factors that distinguish MA-dependent research participants who increased MA self-administration while receiving treatment with the selective serotonin reuptake inhibitor (SSRI) sertraline from other groups of participants.
Method: Using a dataset from a 12-week randomized, placebo-controlled trial of sertraline (100 mg daily) for MA addiction, we identified participants who had completed at least 8 weeks of the trial ($n = 61$ sertraline, $n = 68$ placebo). We compared the proportions of MA-positive urine tests for weeks 8–12 of the trial for these subjects to their pre-randomization baseline, and identified those subjects who increased MA use during treatment. Using classification trees, we then assessed all data collected during the study to identify factors associated with increasing MA use during treatment with sertraline, compared to placebo.
Results: More subjects in the sertraline condition increased MA use during treatment ($n = 13$) than in the placebo condition ($n = 5$; $p = 0.03$). Classification trees identified multiple factors from both pre-treatment and in-treatment data that were associated with increased MA use during treatment. Only elevated in-treatment craving for MA specifically characterized subjects in the sertraline group who increased their MA use.
Conclusions: Some MA-abusing individuals treated with SSRIs have sustained craving with an increased propensity to relapse during treatment despite psychosocial treatment interventions.
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1. Introduction

Methamphetamine (MA) is an abused psychostimulant that imposes a large global public health burden (UNODC, 2009). Currently there are no medications known to be effective in treating MA addiction (Karila et al., 2010).

Depressive symptoms are common among individuals with MA dependence (London et al., 2004) and in MA withdrawal (McGregor et al., 2005; Zorick et al., 2010), and psychosocial treatments are only partially effective (Glasner-Edwards et al., 2009). Taken together with preclinical data demonstrating that selective serotonin reuptake inhibitors (SSRIs) decrease the discriminative stimulus (Munzar et al., 1999) and locomotor effects of MA in rodents (Takamatsu et al., 2006), these observations have provided justification for testing serotonergic agents as treatments for MA dependence and withdrawal syndromes (reviewed in Shoptaw et al., 2009; Karila et al., 2010). Indeed, serotonergic antidepressants are commonly prescribed to individuals with active methamphetamine abuse (Darke and Ross, 2000).

However, the results of controlled clinical trials have been uniformly negative (Karila et al., 2010). In placebo-controlled, randomized trials, no effect of treatment on MA use was demonstrated for fluoxetine (Batki et al., 2000), paroxetine (both SSRIs; Piasecki et al., 2002) or odansetron (a 5-HT_3 receptor antagonist; Johnson et al., 2008), and no effect on MA withdrawal symptoms

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was demonstrated for mirtazepine (a 5-HT_2 receptor antagonist; Cruickshank et al., 2008). In the largest such placebo-controlled trial published to date, the group taking the SSRI sertraline (100 mg daily) showed poorer retention and poorer response to treatment than the placebo group (Shoptaw et al., 2006). The authors of this study concluded: *These data . . . suggest sertraline is contraindicated for methamphetamine dependence* (Shoptaw et al., 2006).

In order to clarify how treatment with sertraline worsened the outcomes for MA-dependent participants, we performed a re-analysis of the data from Shoptaw et al. (2006). Our aim was to identify subject-level factors that differentiated those individuals on sertraline who had a worse outcome in terms of MA use from those on placebo who also had a negative outcome. We used classification trees (CT; Breiman et al., 1983), which have high utility as a data mining tool in biological sciences (Goldman et al., 1982; Dean et al., 2009; Ilgen et al., 2009), as our primary analytic technique.

2. Method

2.1. Participants and study design

Details of the participant screening procedures and study design have been published previously (Shoptaw et al., 2006). All but two of the 229 randomized participants met criteria for MA dependence; the other two met criteria for MA abuse. Briefly, the study consisted of a 2-week pre-randomization and pre-treatment baseline phase, followed by a 12-week active treatment phase, with thrice weekly 90-min CBT relapse prevention groups and urine drug testing throughout. A week 13 post-treatment follow up visit to assess side effects was also included. Participants were also randomized to contingency management or treatment as usual, divided equally among medication treatment groups. Participants randomized to the sertraline group were initiated on a single 50 mg daily dose, which was increased to *b.i.d.* (100 mg total daily dosage) on day 8 of the study.

2.2. Included data

From the data collected at screening and the pre-randomization baseline phase of the study, we included all items and composite scores from the Addiction Severity Index (ASI; McLellan et al., 1980), Risk Assessment Battery (RAB; Metzger et al., 1993), Beck Depression Inventory (BDI-I; Beck et al., 1996), University of Rhode Island Change Assessment scale (URICA; DiClemente and Hughes, 1990), Symptom Checklist-90 (SCL-90; Derogatis and Melisaratos, 1983), Clinical Global Impression (CGI; Guy, 1976), Structured Clinical Inventory for DSM-IV (SCID-I and –II), and Visual Analogue Scales (VAS; craving measure, with a 0–10 range; Folstein and Luria, 1973) for alcohol, cocaine, heroin, marijuana, and methamphetamine.

From data collected in- and post-treatment, we included all items from weekly repeated-measures of craving (VAS) and BDI, CGI, SCL-90, and RAB at 4, 8, and 13 weeks of study, and ASI at 13 weeks of study. Much of these data were not reported in the original publication (Shoptaw et al., 2006).

2.3. Data analysis

Classification trees (CT) were implemented with the rpart function (v. 3.1–46) in the R statistical software package (v. 2.9.0; Vienna, Austria; R Development Core Team, 2010), designed to follow Breiman et al. (1983). Demographic variables were analyzed by one-way analysis of variance (ANOVA) comparisons (continuous variables) or Pearson's Chi-square (categorical variables). Data for continuous variables are reported as mean ± standard deviation. Data for categorical variables are reported as *n* (%). In order to smooth the weekly cyclical component of the urine drug screen and MA craving data (possibly related to heavier MA use on weekends; see Fig. 2 in Shoptaw et al., 2006), we utilized a 3-week moving average of both variables for illustrative purposes (Fig. 1; Moran and Solomon, 2007) (note that we report values for weeks 1 and 12, averaging across only 2 weeks' worth of data for completeness). Repeated measures of MA craving were analyzed using linear mixed effects models; group comparisons used ANCOVA analyses with *post hoc* Bonferroni correction, using baseline MA craving as a covariate to adjust for potential bias. All statistical analyses (except CT) were performed using SPSS software (v. 17.0; Chicago, IL).

3. Results

3.1. More participants assigned to sertraline than placebo had >15% increased MA use during the last month of treatment

Of the 129 participants in the study who completed at least 8 weeks of the trial, 61 were in the sertraline group, and 68 in the placebo group. For all 129 participants, we compared their fraction of MA-positive urines during the pre-randomization baseline period to the fraction of MA-positive urines during weeks 8 through 12 of treatment to categorize those individuals who had increased their MA use during the last month of treatment. Based upon a histogram of these results, natural breakpoints at + and −15% change in MA use with treatment were observed (data not shown).

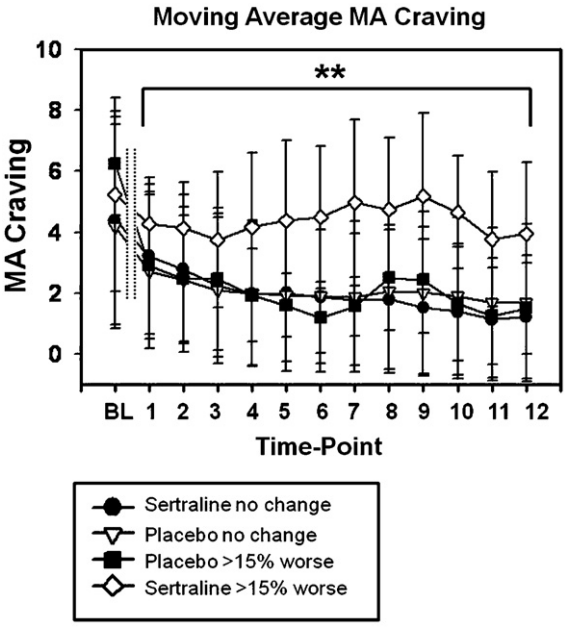

Fig. 1. Subjects who had >15% increased MA use with treatment taking sertraline had higher levels of craving for MA than other groups of subjects. BL: baseline pre-randomization average. Numbers 1–12 represent week of study. Graph depicts the smoothed 3-week moving average of craving for MA (scale of 0–10) among subjects in different treatment groups. **: $p < 0.001$ for sertraline >15% increased MA group vs. all other groups from weeks 1–12 of treatment, via linear mixed effect modeling.

We performed a 3 × 2 Chi-square analyses of the number of subjects in each study condition who either: had a >15% increase in MA use with treatment (sertraline 13(21%), placebo 5(7%)), had a >15% decrease in MA use with treatment (sertraline 24(39%), placebo 24(35%)), or whose MA use changed less than 15% with treatment (sertraline 24(39%), placebo 38(57%); overall $X^2(2) = 6.77$, $p = 0.034$). These results demonstrated that there was no difference between groups on the number of subjects who decreased MA use with treatment, but that the sertraline group had fewer subjects who remained unchanged during treatment, and more subjects who increased MA use during treatment than the placebo condition (Table 1).

3.2. Characteristics of participants who had >15% increase in MA use during the last month of treatment

Of the 18 participants in both groups (13 sertraline, 5 placebo) who had a >15% increase in MA use in the last month of treatment, there were no group differences in age, gender, ethnicity, length of lifetime MA use, assignment to contingency management, or baseline fraction of MA-positive urines (Table 1). Average baseline craving for MA for these subjects did not differ across treatment groups: sertraline group 5.2(3.2); placebo group 6.3(1.7); ($F(3) = 0.78$, $p = 0.51$).

3.3. Classification trees

CT identified multiple factors from both the baseline/pre-randomization phase and in-treatment phase which were asso-

Table 1
Characterics of subjects >15% increased MA use with treatment.

	Sertraline	Placebo	*p*-Value
Demographics			
>15% increased MA use *n*(%)	13(21)	5(7)	**0.03**
Age	37.6(9.5)	32.1(9.9)	0.3
Gender			
Male *n*(%)	8(61)	2(40)	0.72
Ethnicity			
White *n* (%)	11(85)	3(60)	0.53
Lifetime MA Use (years)	13.1(7.8)	13.2(11.8)	0.98
Fraction of MA-positive urine in baseline	0.30(0.26)	0.20(0.36)	0.94
Assigned to contingency management	7(54)	2(40)	0.84
RP factors			
Baseline SCID global assessment of functioning	48.2(8.2)	53.0(9.2)	0.29
Baseline ASI drug composite score	0.17(0.04)	0.16(0.04)	0.66
Week 13 Clinical global impression	5.7(0.7)	5.5(0.6)	0.61
Average MA craving weeks 8–13	4.6(1.7)	2.4(1.8)	**0.04**
SCL-90 positive symptoms total scale week 8	7.5(14.8)	13.8(11.1)	0.45

RP Factors: factors identified as contributing to >15% Increased MA use with treatment by recursive partitioning categorical variables (gender, ethnicity, >15% increased MA use, # of times detox, contingency management assignment) were analyzed by Chi-square test. Continuous Variables (all others) were analyzed by ANOVA, numbers tabled are means (s.d.). Factors showing significant group difference ($p < 0.05$) highlighted in bold.

ciated with a >15% increase in MA use during treatment (both groups; Table 1). The baseline/pre-randomization phase data identified were the SCID Global Assessment of Functioning and ASI Drug Composite Score (Table 1). The in-treatment data identified were the average craving for MA over weeks 8–13, the week 13 Clinical Global Impression, and SCL-90 Positive Symptoms Total scale (Table 1).

3.4. Craving for MA characterizes subjects in the sertraline group with increased MA use during treatment

We compared each of the CT-identified factors by group (sertraline or placebo) in all subjects who had >15% increase in MA use during treatment by either ANOVA (continuous variables) or Pearson's Chi-square (categorical variables; see Table 1). Only average MA craving over weeks 8–13 was significantly higher in the sertraline group compared to placebo ($F(1,125) = 4.44$, $p = 0.037$; Table 1).

3.5. Craving for MA distinguished sertraline condition participants who had >15% increased MA use during treatment

In order to better assess the evolution of craving for MA over time, we divided the dataset into four groups: (1) sertraline, <15% increase in MA use with treatment ($n = 48$); (2) placebo, <15% increase in MA use with treatment ($n = 63$); (3) sertraline, >15% increase in MA use with treatment ($n = 13$); (4) placebo, >15% increase in MA use with treatment ($n = 5$; Fig. 1). We then compared these groups using a 3-week moving average MA craving and linear mixed effect modeling, using baseline MA craving as a covariate, across all 12 weeks of the study. This analysis demonstrated that those subjects in Group 3 (sertraline, >15% increase in MA use with treatment) were significantly different from all other groups in MA craving across the study versus all other groups ($p < 0.001$; Fig. 1); there was no effect of time in treatment for this group ($p = 0.35$). A linear mixed effect model using raw (non-smoothed) MA craving data also showed that Group 3 had greater MA craving than all other groups ($p < 0.001$), demonstrating that this result was not affected by smoothing.

4. Discussion

4.1. Classification trees to identify factors associated with poor response to sertraline in MA-dependence

SSRIs and other serotonergic agents have been frequently tried as potential therapeutic agents for addictive disorders, but the results have been mixed, despite the frequent co-morbidity of addiction and depressive symptoms (Nunes and Levin, 2004).

Differential responses to SSRI treatment have been observed among sub-types of patients with alcoholism, with certain sub-types of alcoholics demonstrating increased drinking behavior during treatment (Pettinati, 2001; Dundon et al., 2004). To date all such reports utilized already extant sub-typing methodologies (Babor et al., 1992). This report describes subject-level factors that specifically associate with increased substance use behavior among addicts during treatment using the SSRI sertraline, without *a priori* sub-typing.

4.2. Sustained craving in MA dependence is associated with propensity to relapse

Our finding that sustained craving for MA is associated with increased MA use among MA-dependent individuals treated with sertraline is consistent with the clinical literature regarding the association of craving for MA and propensity to relapse (Hartz et al., 2001; Galloway et al., 2009). In a study of 31 treatment-seeking MA-dependent individuals, individuals with a craving for MA that was rated as >20 (with 100 as the maximum), exhibited a 2.5-fold risk of relapse compared to those who reported craving of <20 (Hartz et al., 2001). In a larger study of 691 MA-dependent treatment-seekers, each increase of 1 (out of 100) in MA craving increased the relative risk of relapse within 1 week by 0.4%, and this effect was largely independent of recent MA use or time spent in psychosocial treatment (Galloway et al., 2009). Therefore, craving for MA is likely to be an independent predictor of propensity to relapse in MA-dependent individuals.

4.3. Limitations

The number of participants identified in this study which showed >15% increase in MA use with treatment was small ($n = 18$ total, out of 129 participants), which limits the statistical power to identify factors which are associated with increased MA use in treatment. The dataset was limited to a study of mostly MA-dependent individuals treated with sertraline or placebo, and therefore these results may not generalize to other serotonergic agents or populations with other substance use disorders. Similarly, the study group was screened to exclude individuals with comorbid medical, psychiatric, or addictive disorders, and therefore the current results may not be applicable to clinical populations.

4.4. Clinical implications

Our findings suggest that MA abusers taking SSRIs for comorbid depressive symptoms should be evaluated for continued craving for MA during treatment, as some of these individuals will likely have sustained craving despite abstinence and psychosocial treatment. These findings also suggest that clinicians treating MA-addicted individuals with SSRIs should be aware that some patients may exhibit increased MA use behavior despite psychosocial treatment, which may be influenced by medication treatment.

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Conflict of interest

The authors declare no conflicts of interest with the work described here.

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