A Randomized, Double-Blind, Placebo-Controlled Trial of Long-Acting Risperidone in Cocaine-Dependent Men

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Objective: There is no approved pharmacotherapy for cocaine dependence. Risperidone is an atypical antipsychotic drug with combined dopamine-2/serotonin-2 (D_2/5-HT_2) antagonist activity that has been effective in reducing cocaine use in some animal studies. We tested the efficacy of a long-acting, injectable preparation of risperidone on cocaine use in active cocaine users.

Method: Thirty-one cocaine-dependent men who met DSM-IV diagnostic criteria for current cocaine dependence entered a 12-week, randomized, double-blind, placebo-controlled trial of intramuscular risperidone, 25 mg every other week. The primary outcome measure was cocaine use as measured by urinary concentration of cocaine metabolites. Secondary outcomes were self-report of cocaine use and craving, depressive symptoms as measured by the Hamilton Rating Scale for Depression (HAM-D), and adverse events. Participants were recruited during a 12-month period from October 2005 to September 2006.

Results: Both groups reduced their cocaine use during the study. There were no between-group differences in the primary measure of cocaine use (urinary metabolites [$F = 0.7$, $p = .41$]) or on craving measures. Those assigned to risperidone reported significantly worsened depressive symptoms (mean ± SD HAM-D change scores: +7.4 ± 8.8 vs. –2.3 ± 5.8, respectively, $F = 7.5$, $p = .018$) and gained significantly more weight (mean weight change: +6.3 ± 9.4 lb vs. –4.0 ± 8.9 lb, respectively, $F = 4.65$, $p = .044$) than those assigned to placebo.

Conclusion: Treatment with long-acting injectable risperidone in active cocaine users was not associated with reduction in cocaine use or craving and was associated with worsening of depressive symptoms and weight gain.

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In 2003, an estimated 2.3 million persons in the United States were current cocaine users, while an estimated 1.5 million met criteria for cocaine abuse or dependence.[1] Cocaine use is a risk factor for cardiovascular and cerebrovascular events. In 2005, cocaine was associated with nearly 449,000 emergency department visits in the United States, more than any other illicit drug, and was involved in over half of illicit drug–related suicide attempts.[2] Currently, there are no U.S. Food and Drug Administration–approved pharmacotherapies for treatment of cocaine dependence. Because of the high prevalence, associated morbidity and mortality, and cost to society, identification of an effective treatment for cocaine dependence is a public health priority. While dopamine D_2 receptor antagonists have shown efficacy at reducing cocaine use in animal models, studies of the efficacy of D_2 antagonists such as risperidone for reducing cocaine use in humans have been mixed.

Cocaine exerts its euphoric effects by blocking the dopamine transporter, thus elevating dopamine concentration in the striatum, as demonstrated by Volkow et al.[3] The mesolimbic dopaminergic system, extending from the ventral tegmental area to the nucleus accumbens, is the critical shared neuroanatomical substrate in the reinforcing effect of all classes of substances of abuse, including ethanol, nicotine, and cocaine, and of natural rewards—water, food, sex, and nurture. Multiple lines of evidence from animal studies indicate that D_2 activation is central

to the effects of cocaine and that D_2 blockade may block cocaine effects and reduce its use. Self et al.[4] showed, in an animal model of cocaine dependence, that D_2 activation by its agonist, 7-OH-DPAT, reinitiated cocaine-seeking behavior after extinction and enhanced cocaine-primed cocaine-seeking behavior in rats. In another model, Weissenborn et al.[5] showed that the D_2 antagonist, raclopride, blocked responding for cocaine-associated cues. Khroyan at al.[6] replicated these findings in squirrel monkeys with D_1 and D_2 antagonists that attenuated cocaine-seeking behavior following cocaine priming or D_2 agonist activation.

Risperidone, an atypical antipsychotic, blocks D_2 and 5-HT_2 receptors and has been shown to block many effects of cocaine in animals and to reduce euphoria from cocaine and cocaine craving in humans. When Tsibulsky et al.[7] coadministered risperidone with cocaine in rats, risperidone blocked acute, cocaine-induced dopamine and serotonin release in nucleus accumbens, as measured by in vivo microvoltammetry, blocked cocaine-induced increase in locomotion, and antagonized cocaine facilitation of self-stimulation behavior. Results from a study by Broderick et al.[8] of subacute risperidone and cocaine coadministration suggest that risperidone may block both the acute effects of cocaine that are mediated by a monoamine surge and also the withdrawal effects from cocaine that are thought to be mediated by striatal dopamine depletion.

When Newton et al.[9] pretreated active cocaine users with oral risperidone 2 mg per day for 5 days, they experienced modest reduction in the euphoric effect of experimentally administered cocaine. De La Garza et al.[10] also showed that risperidone reduced craving for cocaine in those for whom a priming dose of cocaine causes cocaine craving. The evidence from these preliminary studies and from the animal models led Grabowski et al.[11] to conduct a 12-week, randomized, double-blind, placebo-controlled study of risperidone, 2, 4, and 8 mg per day, as an adjunct to weekly cognitive behavioral therapy in 125 patients with cocaine dependence. While risperidone treatment was not associated with reduced cocaine use, aspects of this study may have limited its ability to detect a treatment effect if there had been one. Use of a highly efficacious psychotherapeutic intervention of 1-hour weekly cognitive behavioral therapy may have augmented the placebo effect. Importantly, retention was poor: 23% for the risperidone 2 mg per day group, 8% for the 4 mg per day group, 0% for the 8 mg per day group, and 7% for the placebo group.

The availability of a long-acting, injectable preparation of risperidone presented an opportunity to conduct a study of the effect of risperidone on cocaine use in a design that would ensure adherence to study medication. Therefore, we conducted a 12-week, randomized, double-blind, placebo-controlled study to examine the effect of long-acting injectable risperidone monotherapy on cocaine use, cocaine craving, and adverse effects in active cocaine-dependent patients.

METHOD

The study was reviewed and approved by the Human Studies Committee of the Massachusetts General Hospital. Participants were recruited during a 12-month period from October 2005 to September 2006 via advertisement in local press and screened by telephone prior to study enrollment. Participants gave their informed consent to participate after the procedures and possible adverse events were fully explained by a study physician. Men, 18 to 60 years old, who met diagnostic criteria for current cocaine dependence in a Structured Clinical Interview for DSM-IV[12,13] and who were using cocaine by self-report at a minimum of once every other week, were eligible to participate. Because participants were asked to complete a functional magnetic resonance imaging craving paradigm in which a gender effect on activation patterns has been described,[14] enrollment was limited to men. Potential participants who met diagnostic criteria for schizophrenia, bipolar disorder, or current severe major depressive disorder, or who had HIV infection, head trauma with loss of consciousness, corrected QT interval (QTc) greater than 450 milliseconds, or an unstable medical condition were excluded. Participants who completed the in-person screening and provided at least 2 urine samples that tested positive on a qualitative test for cocaine (Medimpex United Inc., Bensalem, Pa.) were randomly assigned to receive 12 weeks of risperidone or placebo treatment.

Interventions

After baseline evaluation, participants began treatment with oral risperidone at a dose of 1 mg per day for the first week and 2 mg per day for the next 3 weeks. Electrocardiograms were repeated after 1 and 2 weeks of risperidone use. Participants with QTc prolongation greater than 470 milliseconds at either of these occasions were excluded. After 1 week of oral risperidone treatment, those who tolerated oral dosing and had no serious adverse effects began intramuscular injections of long-acting risperidone at a dose of 25 mg every other week. Participants received both oral and intramuscular risperidone for 3 weeks per prescribing recommendations. Follow-up assessments were done 1, 2, 3, 5, 7, 9, and 11 weeks after randomization. Janssen Pharmaceutica LLC (Titusville, N.J.) provided oral and parenteral study medication and identical placebos. Participants received weekly blister cards. Pill counts were performed weekly to assess compliance. Intramuscular injections were given alternating between the gluteus muscles every other week. After 3 weeks of injectable risperidone treatment, oral medication was discontinued.

Table 1. Baseline Characteristics of Cocaine-Dependent Men[a]

Characteristic	Risperidone (N = 16)	Placebo (N = 15)
Age, y	44.1 ± 5.9	42.4 ± 6.4
Years of education	13.0 ± 1.8	13.7 ± 2.2
Race, N (%)		
African American	10 (62)	9 (60)
White	6 (38)	6 (40)
Alcohol dependence, N (%)		
Lifetime	9 (56)	5 (33)
Current	4 (25)	5 (33)
Depressive disorder (lifetime), N (%)[b]	4 (25)	3 (20)
Anxiety disorder (lifetime), N (%)[b]	3 (19)	5 (33)
Age at onset of cocaine dependence, y	29.3 ± 9.4	29.0 ± 7.3
Duration of illness, y	14.8 ± 6.5	13.1 ± 7.5
Baseline UBE, ng/mL	11,223 ± 17,811	18,081 ± 19,953
No. of days of cocaine use in the preceding 30 days	14.9 ± 10.0	10.2 ± 7.0
Money spent on cocaine in the preceding 30 days, $	448 ± 369	431 ± 323
ASI drug composite score	0.23 ± 0.08[c]	0.17 ± 0.06
Withdrawal symptoms (CSSA)	25.9 ± 17.6	31.7 ± 21.3
HAM-D score	9.4 ± 8.3	8.5 ± 9.0
Weight, lb	188 ± 24	187 ± 25

[a]Values expressed as mean ± SD except where noted.
[b]Including substance-induced disorder.
[c]p = .038.
Abbreviations: ASI = Addiction Severity Index, CSSA = Cocaine Selective Severity Assessment, HAM-D = 31-item Hamilton Rating Scale for Depression, UBE = urine benzoylecgonine.

The behavioral intervention consisted of a 15-minute session at each study visit that focused on medication compliance and assessment of adverse events. This intervention was based on the medication management intervention developed by Pettinati et al.[15]

Assessments

Assessments of cocaine use, cocaine craving, withdrawal symptoms, vital signs, and adverse effects were performed at each study visit. Cocaine use was assessed by self-report and quantitative urine benzoylecgonine (UBE) measurement by liquid gas chromatography/mass spectrometry (NMS Labs, Willow Grove, Pa.). The University of Minnesota Cocaine Craving Scale, developed by Halikas et al.,[16] was performed to assess cocaine craving. The scale contains 1 continuous scale for intensity and 2 qualitative scales for frequency and duration of craving episodes that were adapted for this study by converting them from ordinal to continuous scales (i.e., a value of 8 minutes' duration was imputed for the category of craving duration of 6–10 minutes) to allow quantitative comparison by treatment group. The Cocaine Selective Severity Assessment, designed by Kampman et al.,[17] was performed to assess cocaine withdrawal signs and symptoms. Adverse events were assessed weekly with the Systematic Assessment for Treatment Emergent Events General Inquiry.[18] Other assessments were performed at baseline and endpoint and included the Addiction Severity Index (ASI)[19] drug composite score, the 31-item Hamilton Rating Scale for Depression (HAM-D),[20] and the Snaith-Hamilton Pleasure Scale.[21]

Data Analysis

The analysis was based on intention to treat of all randomly assigned participants. Baseline and demographic variables were compared using Student t test, Wilcoxon rank sum test, or Fisher exact test. The primary outcome measure was concentration of UBE at endpoint. Secondary outcome measures were number of days of cocaine use in the preceding 30 days, cocaine use and other drug use as measured by the ASI drug composite score, cocaine craving, depressive symptoms, and weight gain. For these variables, mixed model repeated-measures analyses of variance were performed using PROC MIXED in SAS, controlling for baseline variables. Secondary treatment outcomes were analyzed as follows: time to first abstinence was compared between treatment groups by survival analysis, in which initial abstinence was defined as the first study week in which a urine sample with no detectable UBE was submitted. Incidence of adverse effects was compared using Fisher exact tests. All analyses were performed using SAS, version 9 (SAS Institute, Inc., Cary, N.C.).

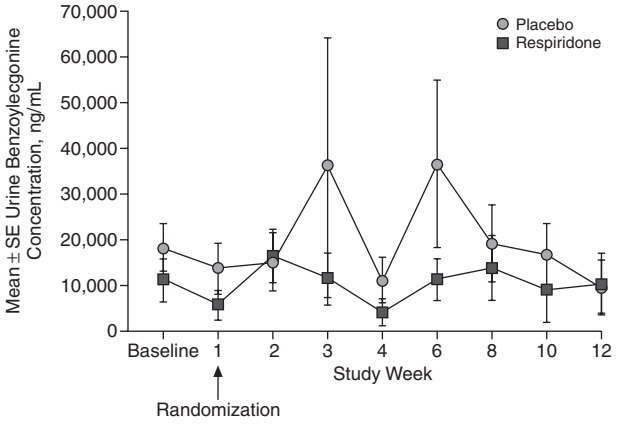
RESULTS

Eighty-nine adult men with cocaine dependence were screened for the study; 23 participants failed to complete screening, 3 withdrew consent, and 32 were not eligible. The most common reasons for ineligibility were infrequent cocaine use and medical conditions such as HIV infection and history of serious head trauma. Thirty-one participants were eligible to participate and were randomly assigned to treatment. Mean ± SD baseline frequency of cocaine use was 12.6 ± 8 days in the past 30 days. There were no between-group differences in age, education, race, lifetime prevalence of mood or anxiety disorders or alcohol dependence, current depressive symptoms, weight, age at onset of cocaine dependence, days of cocaine use, or money spent on cocaine in the past 30 days (Table 1). Because those randomly assigned to risperidone had a higher mean composite drug score on the ASI (0.23 vs. 0.17; z = –2.15, p = .03), all analyses were controlled for baseline ASI score.

Attrition

The groups did not differ significantly by weeks in study (8.06 weeks for risperidone vs. 6.70 weeks for placebo; p = .44) or completion rate (50% [N = 8] vs. 40% [N = 6]; Fisher exact test = 0.72; risperidone group vs. placebo, respectively).

Figure 1. Concentration of Urine Benzoylecgonine During the Study



Cocaine Use

The primary outcome measure was cocaine use, as assessed by UBE concentration. Neither a main effect of treatment ($F = 0.70$, $p = .41$) nor a treatment-by-time interaction ($F = 0.67$, $p = .65$) was observed for UBE concentration, indicating that the change in UBE concentration over time in the study was not different between the treatment groups (Figure 1). Two participants had UBE concentrations that were above the normal cutoff concentration of 50,000 ng/mL for the automated UBE assay, one at week 3 and the other at week 6. The UBE concentrations were measured manually for these 2 samples and included in the main analysis, above. The mixed model analysis of variance for an effect of treatment on UBE concentration was repeated excluding these outliers, and again, neither a main effect of treatment on UBE nor a treatment-by-time interaction was observed. Because participants were paid for providing a urine sample free of cocaine at study weeks 1 and 12 when they would be asked to complete a functional magnetic resonance imaging procedure for a related study, the analysis of the effect of treatment on UBE was repeated for an effect on UBE from weeks 2 through 10, controlling for baseline UBE, and the results were unchanged.

Although those assigned to risperidone had a higher mean number and percentage of visits at which they submitted urine samples with undetectable UBE (1.81 [25.9%], SD = 2.29 [32.67%] in the risperidone group and 0.87 [12.4%], SD = 1.8 [25.8%] in the placebo group), the differences were not significant: $t = 1.272$, $p = .21$ for both. Missing values in this analysis were imputed as positive for cocaine. Five participants in the risperidone group had 50% and more of their visits with no detectable UBE, while only 1 participant from the placebo group had more than 50% of his visits with no detectable UBE. This difference was not significant (Fisher exact test = 0.17). There was also no between-group difference in the survival curves of time to first urine with no detectable UBE, calculated by survival analysis from randomization to first visit with negative urine test, log rank = 1.37, $p = .24$.

Although the sample was small, we identified a subsample of 5 participants in the risperidone group who had urine samples in which UBE was undetectable at 50% or more of postrandomization visits. The other 11 participants from the risperidone group were abstinent at 28% or fewer of their visits. We conducted exploratory comparisons of these 2 subsamples of the risperidone group for age, years of education, age at first cocaine dependence, UBE concentration at baseline, days of cocaine use in the preceding month, baseline craving intensity and HAM-D score, race, and ability to achieve negative urine test on their randomization visit, reflecting ability to respond to a monetary incentive for abstinence. On average, the participants who responded to risperidone were older (mean age = 47.2 vs. 42.7 years), were more likely to be white rather than African American (60% [N = 3] vs. 27% [N = 3]), developed cocaine dependence at an older age (mean = 31.8 vs. 28.2 years), were more likely to achieve a negative urine test in response to a monetary incentive (60% [N = 3] vs. 36% [N = 4]), had fewer days of cocaine use in the preceding month (mean = 9.6 vs. 17.3), and had lower HAM-D scores at baseline (mean = 5.2 vs. 11.3) and end of treatment (mean = 10.8 vs. 24.0). None of these differences were significant.

Self-Report of Cocaine Use

Participants reported a mean ± SD reduction of 31% ± 85% in the number of days in the past 30 days in which they used cocaine; Wilcoxon signed rank test $p = .013$. Those randomly assigned to risperidone had a mean ± SD reduction of 51% ± 45% in the days of cocaine use in the preceding 30 days, while those assigned to placebo had a mean ± SD reduction of 9% ± 117%; Wilcoxon rank sum test $z = 0.64$, $p = .52$.

Craving

Intensity. There was no effect of treatment on intensity of craving ($F = 0.03$, $p = .86$), nor was there a treatment-by-time interaction ($F = 1.69$, $p = .11$), controlling for baseline craving intensity.

Frequency. Baseline frequency of craving episodes predicted frequency of craving episodes during the trial ($F = 26.1$, $p < .0001$). There was no main effect of treatment on craving frequency and no treatment-by-time interaction.

Duration. The duration of craving episodes at baseline predicted duration of craving episodes during the trial ($F = 6.96$, $p = .013$). There was a trend for a main effect of treatment on duration of craving episodes, such that those assigned to risperidone had a smaller decrease in the

duration of craving episodes (56.6% reduction) than those assigned to placebo (65.7% reduction; F = 2.71, p = .11).

Cocaine Selective Severity Assessment

There was no main effect of treatment and no treatment-by-time interaction for endpoint Cocaine Selective Severity Assessment scores.

ASI Drug Composite Score

There was a significant mean ± SD reduction in ASI drug composite score for the group as a whole (34.2% ± 42.0%; Wilcoxon signed rank test p = .008). However, there was no effect of treatment on mean ± SD endpoint ASI drug composite score (0.09 ± 0.12 for risperidone vs. 0.06 ± 0.073 for placebo).

Depressive Symptoms

Mean ± SD HAM-D scores increased from baseline by 7.4 ± 8.8 in those randomly assigned to risperidone and decreased in those randomly assigned to placebo by –2.3 ± 5.8. This effect was significant before and after controlling for baseline HAM-D scores (F = 7.5, p = .018) and remained significant after controlling for change in days of cocaine use. No participants assigned to risperidone who completed the trial had an improvement in depressive symptoms; the range of change from baseline to endpoint in HAM-D score was 0 to 26. After splitting the scale into its cognitive and vegetative clusters, as described by Faustman et al.,[22] the differences between the placebo and the risperidone groups were significant only for the cognitive subscale (z = –2.164, p = .029).

Snaith-Hamilton Pleasure Scale

There was no effect of treatment on the Snaith-Hamilton Pleasure Scale scores.

Weight

Those assigned to risperidone gained a mean ± SD of 6.3 ± 9.4 lb during the trial and those assigned to placebo lost a mean ± SD of 4.0 ± 8.9 lb, such that there was a significant main effect of treatment on weight (F = 4.65, p = .044), controlling for baseline weight. There was no treatment effect on heart rate or blood pressure.

Adverse Events

There were no serious adverse events. Two participants discontinued study procedures due to adverse events. One discontinued treatment in week 6 due to self-reported muscle twitching. The second displayed signs of tardive dyskinesia in week 8, and study staff discontinued study medication. Both were randomly assigned to risperidone. Other adverse events included somnolence, dizziness, decreased libido, increased appetite, and muscle rigidity. Somnolence was reported more frequently in the active than in the placebo group ($\chi^2 = 0.069$). Study procedures were discontinued in a third participant in the third week after it was learned that he had a stable, untreated chronic psychotic disorder that he had denied at screening. This participant was referred for antipsychotic treatment. It was learned after completion of study procedures that a participant randomly assigned to placebo had concurrent treatment with quetiapine during the study that he had denied at screening. Data from this participant are included in the analysis.

DISCUSSION

In this study we replicated results from previous studies by Levin et al.[23] and by Grabowski et al.,[11,24] which showed that risperidone treatment is not associated with reduced cocaine use in adults with cocaine dependence. We extend and strengthen these findings by assuring medication compliance and steady-state drug levels with a long-acting, injectable preparation of risperidone. These data add to an accumulating body of evidence that dopamine antagonists, while having a promising rationale and positive results in animal models of drug use, are ineffective in reducing cocaine use in humans with cocaine dependence as previously described in a review by Gorelick et al.[25] While it is possible that a subgroup of patients will be responsive to a dopamine antagonist treatment approach, more sensitive tools will be required to assess this idea.

Importantly, we did not find evidence that risperidone treatment was associated with increased cocaine use. Although risperidone may block euphoric effects of cocaine, as described by Newton et al.,[9] this possibility did not appear to result in self-administration of higher or more frequent doses of cocaine in order to compensate for such blockade.

Consistent with a recent, double-blind, placebo-controlled study reported by Smelson et al.,[26] risperidone treatment was not associated with reduced craving for cocaine. Further, those assigned to placebo reported greater reduction in the duration of their cocaine craving episodes. This finding differs from findings in earlier studies by Smelson et al.[27,28] and De La Garza et al.[10] that found that risperidone had a significant effect in reducing cocaine craving. However, the present study employed a retrospective self-report of cocaine craving, while the above-mentioned studies assessed current craving, using cocaine-priming and cocaine-cue paradigms.

Risperidone treatment was associated with an increase in depressive symptoms, even after controlling for change in cocaine use. Chronic cocaine use is associated with down-regulation of striatal dopamine receptors. In a recent [C]Raclopride positron emission tomography (PET) study, Volkow et al.[29] demonstrated decreased striatal D_2 binding and decreased dopamine release and euphoria in response to methylphenidate challenge in recently

detoxified cocaine-dependent adults compared with controls. These physiologic changes may make those with cocaine dependence vulnerable to developing depressive symptoms with D_2 antagonist therapy. Our finding of significant worsening in the cognitive symptom cluster of the HAM-D replicates a finding by Krakowski et al.[30] in which dysphoric effects of haloperidol were correlated with extrapyramidal symptoms. Risperidone actions in the extrapyramidal system and its euphoria-blocking effects[9] may explain the more selective worsening in the cognitive cluster in this study. The worsening in depressive symptoms observed in participants receiving risperidone in this study is consistent with that explanation. In this study we also replicated the finding, reviewed by Nasrallah,[31] that risperidone is associated with weight gain.

There are several limitations to this study. Quantitative measurement of UBE is standard in cocaine studies, with reported high correlation between self-report and biochemically confirmed cocaine use. (For example, Ciraulo et al.[32] reported 75% correlation.) Jones[33] states that because of large intra- and inter-individual variability in UBE concentration due to multiple factors, samples for UBE assay are usually taken 2 to 3 times a week in cocaine studies. However, in this study of biweekly medication administration, urine samples were taken on the day of medication administration, i.e., every 1 to 2 weeks, therefore increasing variability and reducing the power to detect a treatment effect on UBE concentration. As is common in small, randomized trials, there was a significant between-group difference at baseline. Participants randomly assigned to risperidone had higher ASI drug composite scores than those assigned to placebo, such that the absence of a treatment effect could be interpreted in terms of more severe addiction at baseline, which can be associated with more severe and treatment refractory addiction. The high attrition rates further diminish the study power to detect an effect. Lastly, although the behavioral treatment was brief and focused on treatment adherence to minimize placebo effect, participation in the study had a significant effect in reducing self-reported cocaine use. The placebo effect is a common problem in clinical trials for cocaine dependence, as reviewed by Kiev.[34]

CONCLUSION

Long-acting, injectable risperidone, at a dose of 25 mg every other week, was not effective for reducing cocaine use in adult men with cocaine dependence. This is the third study to indicate that risperidone treatment is not associated with reduced cocaine use in humans. Further, data from this study suggest that risperidone use may carry the risk for worsening depressive symptoms and weight gain in this population.

Drug names: haloperidol (Haldol and others), risperidone (Risperdal).

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