Evaluation of the Reinforcing Effect of Quetiapine, Alone and in Combination with Cocaine, in Rhesus Monkeys

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ABSTRACT

There are several case reports of nonmedicinal quetiapine abuse, yet there are very limited preclinical studies investigating quetiapine self-administration. The goal of this study was to investigate the reinforcing effects of quetiapine alone and in combination with intravenous cocaine in monkeys. In experiment 1, cocaine-experienced female monkeys ($N = 4$) responded under a fixed-ratio (FR) 30 schedule of food reinforcement (1.0-g banana-flavored pellets), and when responding was stable, quetiapine (0.003–0.1 mg/kg per injection) or saline was substituted for a minimum of five sessions; there was a return to food-maintained responding between doses. Next, monkeys were treated with quetiapine (25 mg, by mouth, twice a day) for approximately 30 days, and then the quetiapine self-administration dose-response curve was redetermined. In experiment 2, male monkeys ($N = 6$) self-administered cocaine

under a concurrent FR schedule with food reinforcement (three food pellets) as the alternative to cocaine (0.003–0.3 mg/kg per injection) presentation. Once choice responding was stable, the effects of adding quetiapine (0.03 or 0.1 mg/kg per injection) to the cocaine solution were examined. In experiment 1, quetiapine did not function as a reinforcer, and chronic quetiapine treatment did not alter these effects. In experiment 2, cocaine choice increased in a dose-dependent fashion. The addition of quetiapine to cocaine resulted in increases in low-dose cocaine choice and number of cocaine injections in four monkeys, while not affecting high-dose cocaine preference. Thus, although quetiapine alone does not have abuse potential, there was evidence of enhancement of the reinforcing potency of cocaine. These results suggest that the use of quetiapine in cocaine-addicted patients should be monitored.

Introduction

Quetiapine is an atypical, or second-generation, antipsychotic which has approved labeling from the Food and Drug Administration for the treatment of schizophrenia, acute manic or mixed episodes associated with bipolar I disorder (as monotherapy or in combination with lithium or divalproex), acute depressive episodes associated with bipolar disorder, and as an adjunctive treatment of major depression (Borison et al., 1996; Sajatovic et al., 2002; Pisu et al., 2010; Prieto et al., 2010; see Lexicomp Online, “Quetiapine use: labeled indications and mechanism of action,” 2013, http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7598). Quetiapine has also been used off label to treat anxiety and insomnia (Murphy et al., 2008) with demonstrated efficacy (Cohrs et al., 2004; Ravindran et al., 2010). Quetiapine has a multifunctional pharmacological mechanism of action, acting at serotonin (5-hydroxytryptamine; 5-HT) receptors as a 5-HT_{1A} and 5-HT_{2A} antagonist, as an antagonist at both dopamine (DA) D₁ and D₂ receptors, histamine H₁, and adrenergic α_1 and α_2 receptors (Lexicomp Online, “Quetiapine use: labeled indications and mechanism of action,” 2013, <http://online.lexi.com/lco/action/doc/retrieve/>

[docid/patch_f/7598](http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/7598); Goldstein, 1999; Reeves and Brister, 2007; Riedel et al., 2007).

Although this profile of effects, antipsychotic/antidepressant with 5-HT and dopamine (DA) receptor antagonism, would not suggest abuse potential of quetiapine, there are multiple case reports of quetiapine abuse via multiple routes of administration (e.g., Morin, 2007; Erdoğan, 2010). For example, oral abuse of quetiapine has been documented in three separate case reports (Reeves and Brister, 2007). There are also multiple reports of quetiapine abuse among prison inmates. In one such case, an inmate was reported to be abusing quetiapine via intranasal administration, specifically by crushing the tablets and snorting them (Pierre et al., 2004). In a case report, Hussain and colleagues (2005) reported that a female prisoner would dissolve two tablets in water and subsequently inject herself. It was also reported that this patient had a history of substance abuse, depressive episodes, and borderline personality disorder. Quetiapine has been described as having a calming effect and has been referred to as “quell” or “baby heroin” among the prison population (Waters and Joshi, 2007). Recently, Klein-Schwartz et al. (2014) conducted a retrospective review of cases of quetiapine abuse from data reported to the American Association of Poison Control Centers National Poison Data System, and reported nearly 2000 cases between 2005 and 2011.

Although the abuse of quetiapine is pharmacologically perplexing, a survey of buyers and sellers of black-market

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ABBREVIATIONS: DA, dopamine; FR, fixed ratio; 5-HT, 5-hydroxytryptamine or serotonin.

drugs revealed that quetiapine (25-mg dose) sells for \$3.00–\$8.00, which is comparable to the amount charged for benzodiazepines (Tarasoff and Osti, 2007). Although lacking a definitive explanation, several hypotheses have been postulated as to why quetiapine is abused. One hypothesis is related to quetiapine's sedative and anxiolytic properties (Pierre et al., 2004; Pinta and Taylor, 2007), perhaps as a form of self-medication for anxiety and insomnia (Pierre et al., 2004; Reeves and Brister, 2007). Further, Hanley and Kenna (2008) suggest that antipsychotics, as well as other psychotropic drugs, are used for their sedative and anxiolytic properties in place of benzodiazepines and barbiturates, which are more difficult to obtain due to their already-known abuse liability and scheduling regulations. Interestingly, outside of the prison population, there is a case report of a patient who injected himself with a mixture of cocaine and quetiapine, referred to as “Q-ball,” so he could experience hallucinogenic effects (Waters and Joshi, 2007).

Despite these reports, there is little research in either humans or animal models examining the abuse potential of quetiapine. Cha et al. (2013), using rat models of drug abuse, reported that quetiapine (i.p.) administration did not produce a conditioned place preference, but quetiapine (i.v.) did maintain modest self-administration. It has been reported that quetiapine has come to dominate the atypical antipsychotic market, primarily through its “off-label” use (Murphy et al., 2008). Thus, the abuse potential of quetiapine has become more intriguing and clinically relevant. In a letter to the editor, two clinicians suggest their experience indicates the need for additional studies exploring the addiction potential of quetiapine (Pinta and Taylor, 2007). The goal of experiment 1 was to investigate the reinforcing effects of quetiapine in rhesus monkeys. To determine if chronic quetiapine treatment would increase the reinforcing effects of quetiapine, perhaps due to tolerance to aversive effects, the quetiapine self-administration dose-response curve was determined after 4 weeks of daily quetiapine treatment. The goal of experiment 2 was to examine the reinforcing effect of combinations of i.v. cocaine and quetiapine in a separate group of monkeys responding under a food-cocaine choice schedule of reinforcement.

Methods and Materials

Subjects. Ten (four females used in experiment 1 and six males used in experiment 2) individually housed adult (ages 16–18) rhesus monkeys (*Macaca mulatta*) with extensive experimental histories, including >5 years of cocaine self-administration (Hamilton et al., 2010, 2011; Brucher and Nader, 2013), served as subjects. Monkeys were weighed weekly, and body weights were maintained at approximately 98% of free-feeding weights by food earned during experimental sessions and by supplemental feeding of LabDiet Monkey Chow (LabDiet, St. Louis, MO) and fresh fruit no sooner than 30 minutes after the session; water was available ad libitum while in the home cage. Except during experimental sessions, monkeys had physical and visual contact with conspecifics. All monkeys were fitted with an aluminum collar (model B008; Primate Products, Redwood City, CA) and trained to sit calmly in a standard primate chair (Primate Products). All manipulations were performed in accordance with the 2011 National Research Council Guidelines for the Care and Use of Mammals in Neuroscience and Behavioral Research, and were approved by the Wake Forest University Institutional Animal Care and Use Committee. Environmental enrichment is provided as outlined in the Animal Care and Use Committee of Wake Forest University Nonhuman Primate Environmental Enrichment Plan.

Surgery. Each monkey was prepared with a chronic indwelling venous catheter and subcutaneous vascular port (Access Technologies, Skokie, IL) using aseptic surgical procedures. Anesthesia was induced with dexmedetomidine (0.04 mg/kg, i.m.) and ketamine (5 mg/kg, i.m.) then maintained with ketamine (5 mg/kg, i.m.) as needed. Vital signs were monitored for the duration of the surgery. In brief, a catheter was inserted into a peripheral vein to the level of the vena cava. The distal end of the catheter was passed subcutaneously to a point slightly off the midline of the back, where an incision was made and the catheter was attached to the vascular access port and placed in a pocket formed by blunt dissection. Anesthesia was reversed using atipamezole (0.2 mg/kg, i.m.).

Apparatus. The apparatus for operant responding consisted of a ventilated, sound-attenuating chamber (1.5 × 0.74 × 0.76 m; Med Associates, East Fairfield, VT) designed to accommodate a primate chair. Two photo-optic finger-poke apertures (model 117-1007; Stewart Ergonomics, Furlong, PA) were located on one side of the chamber with a horizontal row of three stimulus lights 14 cm above each aperture and a food receptacle between them. The receptacle was connected with Tygon tubing to a pellet dispenser (Gerbarands Corp., Arlington, MA) located on the top of the chamber for delivery of 1-g banana-flavored food pellets (P. J. Noyes Co., Lancaster, NH). An infusion pump (Cole-Parmer Inc., Chicago, IL) was located on the top of the chamber.

Experiment 1: Evaluation of the reinforcing effects of quetiapine. Prior to each self-administration session, the back of the animal was cleaned with 10% Povidone-iodine USP (CareFusion, Vernon Hills, IL) and 70% isopropyl alcohol, and the port was connected to the infusion pump located outside the chamber via a 22-gauge Huber Point Needle (Access Technologies). Prior to the experimental session, the pump was operated for approximately 3 seconds to fill the port and catheter with the concentration of drug or saline available for the session. Experimental sessions were conducted daily (Monday to Friday) at approximately 9:00 AM, with each session lasting until 30 reinforcers were earned or 60 minutes had elapsed. Initially, all monkeys responded under a fixed-ratio (FR) 30 schedule of food reinforcement (1.0-g banana-flavored pellets), with a 30-second time-out following each reinforcer. Once responding was stable (average response rate ± 20% for three consecutive sessions with a minimum of five sessions), saline was substituted for food for a minimum of five sessions and until response rates declined by at least 80% and were deemed stable. Following a return to food reinforcement, cocaine (0.03 mg/kg per injection) and various doses of quetiapine (0.003–0.1 mg/kg per injection) were substituted for food for at least the same number of sessions as was required for stable saline-contingent responding. Quetiapine doses were chosen based on pilot studies examining the effects of intravenous quetiapine on home cage activity (unpublished data). Doses were tested in random order, with a return to food-reinforced responding for at least three sessions prior to another substitution. Following each experimental session, the port and catheter were filled with heparinized saline solution (100 U/ml) to prolong patency.

After completion of the quetiapine dose-response curve, each monkey was treated chronically with quetiapine (25 mg by mouth, twice a day). The first treatment occurred at approximately 0730 (90 minutes prior to the experimental session) and the second treatment at approximately 1700. This quetiapine dose was chosen as the minimally disruptive dose in male monkeys (Brucher and Nader, 2015). During the first 4 weeks of treatment, only food-maintained responding was examined, after which saline and the quetiapine dose-response curve was redetermined as described earlier; oral quetiapine treatment continued throughout the redetermination of the self-administration dose-response curve.

Experiment 2: Examination of the Combination of Quetiapine and Cocaine on Self-Administration. Each morning (~0730), Monday to Friday, another group of monkeys ($N = 6$) self-administered cocaine under conditions in which food reinforcement was concurrently available (i.e., choice procedure). For these studies, food reinforcement (three 1.0-g banana-flavored pellets) was contingent upon completing 30 consecutive responses on one finger-poke aperture (i.e., FR 30), whereas a dose of cocaine (0.003–0.1 mg/kg per injection) was contingent on 30 consecutive responses on the other; a 30-second

time-out followed each reinforcer presentation. Sessions ended after 30 total reinforcers or 60 minutes. Each session began with a forced trial for each reinforcer; a 30-second time-out separated forced trials. Also, following five consecutive same-choice reinforcers, there was a forced trial on the opposing finger-poke aperture. The cocaine dose remained constant for at least five sessions and until choice responding was deemed stable (defined as choice within 20% of the mean responding for three consecutive sessions without trends) before combining quetiapine (0.03 or 0.1 mg/kg per injection) with the cocaine solution. Once responding for the quetiapine/cocaine combination met stability criteria, another cocaine-alone dose was examined prior to the addition of quetiapine. For this experiment, at least two cocaine doses were studied in combination with quetiapine, one on the ascending limb (i.e., <50% cocaine choice) and a preferred dose (i.e., >80% cocaine choice).

Data Analysis. In experiment 1, for quetiapine self-administration studies, the primary dependent variable was response rate (responses per second), which was analyzed using one-way repeated-measures analysis of variance with all dose conditions (saline, cocaine, three quetiapine doses before and during chronic treatment) followed by Bonferroni post-hoc tests for pairwise comparisons. Quetiapine was operationally defined as functioning as a reinforcer if response rates were significantly higher than rates observed when saline was available for self-administration. Food-maintained response rates (Table 1) were compared using two-tailed *t* tests. In experiment 2, the primary dependent variables were percent cocaine choice (defined as number of cocaine injections divided by total reinforcers $\times$ 100), total number of food presentations, cocaine injections, and total session intake. Individual-subject data are presented as the mean $\pm$ S.D. of the last three sessions. A one-way analysis of variance with three cocaine doses was used to confirm that cocaine choice varied as a function of dose. To compare a dose of cocaine alone with that dose plus quetiapine, repeated-measures *t* tests were performed. For all analyses, $P < 0.05$ was considered statistically significant.

Drugs. Cocaine HCl (National Institute on Drug Abuse, Bethesda, MD) was dissolved in sterile 0.9% saline up to a concentration of 100 mg/ml. Different doses were studied by changing the drug concentration delivered intravenously. Quetiapine (LKT Laboratories Inc., St. Paul, MN) was dissolved in a sterile 0.9% saline and 10% acetic acid solution (pH adjusted) to a concentration of 25 mg/ml. For oral tests, 25-mg capsules were placed inside treats and given to the monkey.

Results

Experiment 1: Evaluation of the Reinforcing Effects of Quetiapine. Under the baseline FR 30 schedule of reinforcement, monkeys earned 30 food reinforcers per session, with mean response rates ranging from 0.77 ± 0.08 to 2.72 ± 0.41 responses/s (Table 1). When saline was substituted for food reinforcement, response rates declined to below 20% baseline response rates, typically within five sessions (Fig. 1). The reinforcing effects of quetiapine were studied before and

TABLE 1
Mean ($\pm$ S.D.) response rate (responses per second) under the FR 30 schedule of food presentation before, during, and after chronic quetiapine (25 mg, by mouth, twice a day) in each monkey

Monkey	Baseline	During Treatment ^a	Following Treatment ^b	<i>P</i> Value
R-1553	0.86 (0.04)	0.21 (0.01) ^c	0.69 (0.32)	<0.001
R-1554	2.72 (0.41)	2.87 (0.59)	3.49 (0.12)	NS
R-1555	0.77 (0.08)	0.81 (0.05)	0.57 (0.16)	NS
R-1559	1.39 (0.33)	0.21 (0.32) ^c	1.44 (0.17)	<0.05

NS, not significant.

^aLast three sessions of treatment.

^bBetween 20 and 30 sessions post-treatment.

^cSignificantly different from baseline.

during chronic quetiapine treatment, and compared with responding when saline or cocaine (0.03 mg/kg per injection) was available. There was a main effect of dose [$F(7,21) = 6.83$, $P < 0.001$], with only cocaine-maintained responding significantly higher than saline-contingent responding (Fig. 1). As shown in Fig. 1, when quetiapine (0.003–0.1 mg/kg per injection) was substituted for food, no dose maintained response rates significantly higher than saline (Fig. 1, open circles). For monkey R-1554, when 0.03 mg/kg per injection of quetiapine was first tested, a mean of 29 injections (out of 30 possible) were received, and the mean response rate was 0.45 ± 0.16 responses/s. When this monkey was retested with this dose, a mean of 10 injections were received, and response rates were not different from saline (0.1 ± 0.03 responses/s).

Following twice-daily oral quetiapine treatment, food-maintained responding was significantly decreased in two of the four monkeys (Table 1). During quetiapine treatment, saline extinction rates were not different from those under baseline conditions, requiring approximately five sessions for response rates to decrease by at least 80% of food-reinforced rates (see Fig. 1). When the quetiapine dose-response curve (0.01–0.1 mg/kg per injection) was redetermined, response rates were not significantly higher than saline at any dose (Fig. 1, closed circles). Following termination of twice-daily quetiapine treatment, food-maintained responding was not significantly different from baseline in any monkey (Table 1).

Experiment 2: Examination of the Combination of Quetiapine and Cocaine on Self-Administration. Dose-dependent increases in cocaine choice [$F(2,10) = 40.87$, $P < 0.001$] occurred under the concurrent cocaine-food reinforcement schedule (Fig. 2). Figure 2 shows individual-subject variability in sensitivity to cocaine when studied under a concurrent schedule of reinforcement, with the lowest preferred dose (i.e., lowest dose resulting in $\geq 80\%$ cocaine choice) being 0.01 ($n = 3$), 0.03 ($n = 2$), and 0.1 ($n = 1$) mg/kg per injection (Fig. 2, closed symbols). When quetiapine (0.03 or 0.1 mg/kg per injection) was added to the cocaine concentrations at cocaine doses that were preferred (i.e., >80% cocaine choice), preference was not significantly decreased (Fig. 2, open symbols). When quetiapine was added to lower cocaine doses, preference increased in four of six monkeys (Fig. 2, open symbols). The number of cocaine injections varied as a function of dose [$F(2,10) = 7.27$, $P < 0.05$] and was characterized as an inverted U-shaped function (Fig. 3, closed symbols). The addition of quetiapine to doses of cocaine on the descending limb of the curve based on number of injections (corresponding to >80% cocaine choice) did not affect the number of injections in four monkeys, but increased cocaine injections in two monkeys (Fig. 3). The addition of quetiapine to doses of cocaine on the ascending limb of the curve based on the number of injections (corresponding to <50% cocaine choice) increased the number of cocaine injections in the same four monkeys (R-1563, R-1568, R-1662, and R-1663) that showed an enhanced preference for low-dose cocaine. Thus, in five of six monkeys, adding quetiapine to at least one cocaine dose resulted in increases in the number of cocaine injections (Fig. 3). Table 2 shows that at low, nonpreferred cocaine doses, the addition of quetiapine decreased the number of food reinforcers earned in four of the six monkeys; one animal showed no effects and the other had increases in total food reinforcers (R-1570). There was no apparent effect of adding quetiapine to high

Fig. 1. Response rates (responses per second) when saline, 0.03 mg/kg per injection of cocaine (Coc; filled squares), and 0.003–0.1 mg/kg per injection of quetiapine (QTP) were substituted for food presentation under an FR 30 schedule of reinforcement before (open circles) and during (filled circles) chronic quetiapine treatment (Tx). Each point represents the mean ($\pm$ S.D.) for the last three sessions of availability.

cocaine doses on the number of food reinforcers delivered (Table 2).

Discussion

The present study investigated the abuse potential of quetiapine under several conditions in adult rhesus monkeys. When substituted for food, quetiapine did not function as a

reinforcer. Chronic oral treatment did not increase the reinforcing effects of quetiapine. In contrast to these negative results, when quetiapine was coadministered with cocaine, it enhanced the reinforcing effects of cocaine. Thus, although there appears to be no abuse liability for quetiapine alone, it may augment the reinforcing effects of cocaine.

To our knowledge, this is the first study to characterize the reinforcing effects of quetiapine in rhesus monkeys. Cha et al.

Fig. 2. Percent cocaine choice as a function of cocaine dose for monkeys responding under a concurrent cocaine (0.003–0.3 mg/kg per injection) versus food (three pellets) reinforcement schedule under baseline (filled symbols) and when quetiapine (QTP; 0.03 mg/kg per injection: open squares; 0.1 mg/kg per injection: open triangles) was added to the cocaine solution. Each point represents the mean $\pm$ S.D. of the last three sessions of availability.

Fig. 3. Number of cocaine injections as a function of cocaine dose for monkeys responding under a concurrent cocaine (0.003–0.3 mg/kg per injection) versus food (three pellets) reinforcement schedule under baseline (filled symbols) and when quetiapine (QTP; 0.03 mg/kg per injection: open squares; 0.1 mg/kg per injection: open triangles) was added to the cocaine solution. Each point represents the mean $\pm$ S.D. of the last three sessions of availability.

(2013) reported quetiapine self-administration in rats responding under an FR 1 schedule, although the reinforcing effects were considered modest (maximum of seven injections over the course of a 2-hour session). An important advantage of the present study was the monkeys' cocaine history. Among the cases of quetiapine abuse reported, one of the common features was that the individuals abusing quetiapine all possessed a prior history of substance abuse. The monkeys in our study have all had an extensive history of cocaine self-administration, and therefore, we felt they would serve as suitable subjects to model this population. Although we did not observe quetiapine functioning as a reinforcer, it is possible that the patients who have reported abusing quetiapine have also had other psychiatric comorbidities and poly-substance abuse that contributed to their perceived reinforcing effects associated with quetiapine. Specifically, it has been reported that individuals with a history of anxiolytic/sedative misuse were more than 8 times as likely to report quetiapine misuse (McLarnon et al., 2012). Further, it has been suggested

that the misuse of quetiapine is motivated by self-medication for insomnia (Reeves and Brister, 2007), anxiety (Morin, 2007; Reeves and Brister, 2007; Chen et al., 2009), or depression (Chen et al., 2009). Thus, it is possible that, if we had introduced a stressor, this may have enhanced the reinforcing effects of quetiapine.

Another measure of the reinforcing effect of quetiapine involved combining the drug with cocaine in monkeys responding under a concurrent food-drug choice paradigm. Adding quetiapine to cocaine resulted in an increase in low-dose cocaine preference and in the number of injections earned in the majority of monkeys (5/6). Our results are similar to a documented case report of a patient injecting himself with a mixture of cocaine and quetiapine, referred to as "Q-ball," so he could experience hallucinogenic effects (Waters and Joshi, 2007). The present findings highlight the importance of using multiple behavioral assays to better characterize the abuse liability of drugs. Other studies document different interpretations when drugs are studied under simple schedules versus

TABLE 2
Number of food choices

Monkey	Baseline Low Dose	QTP 0.03	QTP 0.1	Baseline High Dose ^a	QTP 0.03	QTP 0.1
R-1563 ^b	28.7 $\pm$ 1.53	29.3 $\pm$ 1.15	1.30 $\pm$ 3.61	9.3 $\pm$ 0.58	10.3 $\pm$ 0.58	11.3 $\pm$ 1.15
R-1567 ^b	13.3 $\pm$ 1.53	15.0 $\pm$ 1.00	15.7 $\pm$ 4.62	0.0 $\pm$ 0.00	4.0 $\pm$ 2.65	2.3 $\pm$ 3.21
R-1568 ^c	14.7 $\pm$ 3.51	0.3 $\pm$ 0.58	N/A	2.7 $\pm$ 3.79	0.7 $\pm$ 1.15	0.0 $\pm$ 0.00
R-1570 ^b	14.3 $\pm$ 3.06	30 $\pm$ 0.00	28.0 $\pm$ 3.46	0.3 $\pm$ 0.58	0.0 $\pm$ 0.00	N/A
R-1662 ^c	13.3 $\pm$ 2.08	4.0 $\pm$ 2.65	N/A	0.0 $\pm$ 0.00	4.3 $\pm$ 4.04	6.7 $\pm$ 1.53
R-1663 ^c	25.7 $\pm$ 2.52	16.7 $\pm$ 3.51	N/A	2.3 $\pm$ 2.31	0.3 $\pm$ 0.58	N/A

N/A, not assessed.

^aHigh dose = 0.1 mg/kg cocaine, except monkey R-1570 = 0.03 mg/kg cocaine.

^bLow dose = 0.003 mg/kg cocaine.

^cLow dose = 0.01 mg/kg cocaine.

complex schedules. For example, the cocaine analog 2- β -propanoyl-3- β -(4-tolyl)-tropane (PTT) maintained low response rates when substituted for cocaine under simple schedules of reinforcement (Nader et al., 1997; Birmingham et al., 1998) but resulted in an approximately 50% drug choice when studied concurrently with cocaine (Lile et al., 2002). The results of the present study suggest that the effects of quetiapine on cocaine self-administration depend on which dose of cocaine is available for self-administration. When quetiapine was tested with nonpreferred cocaine doses, the reinforcing potency of cocaine was enhanced. Consistent with this observation, low and intermediate doses of chlorpromazine and haloperidol have been shown to increase the frequency of cocaine choice (Woolverton and Balster, 1981), as have other DA D2/D3 receptor antagonists (e.g., John et al., 2015). The reason a receptor antagonist would increase low-dose cocaine choice over food is not known.

The present findings replicate earlier results using cocaine-food choice (Brutcher and Nader, 2015), where oral quetiapine did not affect cocaine choice when preferred (i.e., >80% choice) cocaine doses were available for self-administration. These data appear in contrast to the findings in psychiatric patients in which quetiapine treatment decreased cocaine/amphetamine craving (Brown et al., 2003), although the latter findings required up to 5 weeks of treatment, and dollars spent on drugs (i.e., actual self-administration) were not affected by quetiapine treatment. When quetiapine was tested with non-preferred cocaine doses, the reinforcing potency of cocaine was enhanced.

Quetiapine binds to multiple receptors and affects several neurotransmitters. It is a DA D2-like receptor antagonist—although chlorpromazine and haloperidol (Seeman et al., 1976) have higher D2-like receptor affinity than quetiapine (Riedel et al., 2007). Further, quetiapine has high affinity at 5-HT_{2A} receptors (Riedel et al., 2007) and ritanserin, a 5-HT₂–selective antagonist, has been shown to increase cocaine self-administration across a range of cocaine doses (Howell and Byrd, 1995). Finally, it has been suggested that the abuse of quetiapine may be due to its high affinity for the histamine H₁ receptor (Fischer and Boggs, 2010), and there are reports of antihistamine abuse (Halpert et al., 2002; Bailey and Davies, 2008; Thomas et al., 2009) consistent with laboratory findings in humans (Preston et al., 1992; Mumford et al., 1996) and animals (McKearney, 1982; Bergman and Spealman, 1986, 1988; Bergman, 1990; Jun et al., 2004). When tested in combination with cocaine, antihistamines have been shown to enhance the discriminative stimulus effects of cocaine (Campbell et al., 2005), and a combination of diphenhydramine and cocaine in rhesus monkeys had greater reinforcing strength than was predicted based on additivity alone (Wang and Woolverton, 2007). Finally, self-administered combinations of cocaine (0.03 mg/kg per injection) and diphenhydramine significantly increased response rates compared with cocaine alone in rhesus monkeys (Banks et al., 2009).

In summary, quetiapine alone did not function as a reinforcer when substituted for food in cocaine-experienced monkeys, but increased the reinforcing potency of cocaine when studied under a concurrent schedule of reinforcement. With reports of off-label quetiapine use increasing (Murphy et al., 2008), the results of these experiments suggest caution to prescribers who are considering using quetiapine in cocaine-addicted patients.

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Authorship Contributions

Participated in research design: Brutcher, M. Nader.

Conducted experiments: Brutcher.

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Wrote or contributed to the writing of the manuscript: Brutcher, S. Nader, M. Nader.

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