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) as the alternative to cocaine (0.003–0.3 mg/kg per injection). 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; Psu 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-HT1A and 5-HT2A antagonist, as an antagonist at both dopamine (DA) D1 and D2 receptors, histamine H1, and adrenergic α1 and α2 receptors (Lexicomp Online, “Quetiapine use: labeled indications and mechanism of action,” 2013, http://online.lexi.com/lco/action/doc/retrieve/docid/patch_f/77598; 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

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 benzo-
diazepines (Tarasoff and Osti, 2007). Although lacking a
definitive explanation, several hypotheses have been postu-
lated 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-
médication 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 benzodi-
azepines and barbiturates, which are more difficult to obtain due
to their already-known abuse liability and scheduling regula-
tions. 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 rele-
vant. 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 deter-
mined after 4 weeks of daily quetiapine treatment. The goal of
experiment 2 was to examine the reinforcing effect of combina-
tions 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; Brutzer and Nader, 2013), served as subjects. Monkeys
were weighed weekly, and body weights were maintained at approx-
imately 98% of free-feeding weights by food earned during exper-
mental 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 out-
lined 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 experimen-
tal 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 (Brutzer 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 Queti-
pine 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

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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. Qetiapine 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 * 100), total number of food presentations, cocaine injections, and total injection intake. Individual-subject data are presented as the mean ± 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. Qetiapine (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 Qetiapine. 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 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 Qetiapine 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 ≥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 the 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

<table>
<thead>
<tr>
<th>Monkey</th>
<th>Baseline</th>
<th>During Treatment</th>
<th>Following Treatment</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-1553</td>
<td>0.86 (0.04)</td>
<td>0.21 (0.01)</td>
<td>0.69 (0.32)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>R-1554</td>
<td>2.72 (0.41)</td>
<td>2.87 (0.59)</td>
<td>3.49 (0.12)</td>
<td>NS</td>
</tr>
<tr>
<td>R-1555</td>
<td>0.77 (0.08)</td>
<td>0.81 (0.05)</td>
<td>0.57 (0.16)</td>
<td>NS</td>
</tr>
<tr>
<td>R-1559</td>
<td>1.39 (0.33)</td>
<td>0.21 (0.32)</td>
<td>1.44 (0.17)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

NS, not significant.

*Last three sessions of treatment.

†Between 20 and 30 sessions post-treatment.

‡Significantly different from baseline.
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.
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 polysubstance 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

<table>
<thead>
<tr>
<th>Monkey</th>
<th>Baseline Low Dose</th>
<th>QTP 0.03</th>
<th>QTP 0.1</th>
<th>Baseline High Dose¹</th>
<th>QTP 0.03</th>
<th>QTP 0.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>R-1563</td>
<td>26.7±1.53</td>
<td>29.3±1.15</td>
<td>1.30±3.61</td>
<td>9.3±0.58</td>
<td>10.3±0.58</td>
<td>11.3±1.15</td>
</tr>
<tr>
<td>R-1567</td>
<td>13.3±1.53</td>
<td>15.0±1.00</td>
<td>15.7±4.62</td>
<td>0.0±0.00</td>
<td>4.0±2.65</td>
<td>2.3±0.21</td>
</tr>
<tr>
<td>R-1568</td>
<td>14.7±3.51</td>
<td>0.3±0.58</td>
<td>N/A</td>
<td>2.7±3.79</td>
<td>0.7±1.15</td>
<td>0.0±0.00</td>
</tr>
<tr>
<td>R-1570</td>
<td>14.3±3.06</td>
<td>30.0±0.00</td>
<td>28.0±3.46</td>
<td>0.3±0.58</td>
<td>0.0±0.00</td>
<td>N/A</td>
</tr>
<tr>
<td>R-1662</td>
<td>13.3±2.08</td>
<td>4.0±2.65</td>
<td>N/A</td>
<td>0.0±0.00</td>
<td>4.3±4.04</td>
<td>6.7±1.53</td>
</tr>
<tr>
<td>R-1663</td>
<td>25.7±2.52</td>
<td>16.7±3.51</td>
<td>N/A</td>
<td>2.3±2.31</td>
<td>0.3±0.58</td>
<td>N/A</td>
</tr>
</tbody>
</table>

N/A, not assessed.
  ¹High dose = 0.1 mg/kg cocaine, except monkey R-1570 = 0.03 mg/kg cocaine.
  ²Low dose = 0.003 mg/kg cocaine.
  ³Low dose = 0.01 mg/kg cocaine.
complex schedules. For example, the cocaine analog 2-β-prop- 
-anoxy-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 quetia-
pine 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 obser-
-vation, low and intermediate doses of chlorpromazine and 
-haloperidol have been shown to increase the frequency of 
cocaine choice (Woolvert 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 
networktransmitters. 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-HT2A receptors (Riedel et al., 2007) and ritanserin, a 
5-HT2A-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 
anhistamine 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 Speelman, 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 
Woolvert, 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 re-
-inforcer 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.

Performed data analysis: Brutcher, S Nader.

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

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