EFFECTS OF SLEEP DISRUPTION AND QUETIAPINE ON COCAINE ABUSE: THE PATH TO DEVELOPMENT OF A MONKEY MODEL OF PTSD

BY

ROBERT E. BRUTCHER

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Approved By:

Michael A. Nader, Ph.D., Advisor

Examining Committee:

Jay R. Kaplan, Ph.D., Chairperson

Matthew L. Banks, PharmD, Ph.D.

Paul W. Czoty, Ph.D.

Anthony Liguori, Ph.D.

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LIST OF ABBREVIATIONS

5-HT	serotonin
5-HT_{1A}	serotonin 1A receptor subtype
5-HT_2	serotonin 2 receptor
5-HT_{2A}	serotonin 2A receptor subtype
α_1	alpha 1 adrenergic receptor
α_2	alpha 2 adrenergic receptor
Abs	abstinence
ANOVA	analysis of variance
APA	American Psychiatric Association
b.i.d.	*bis in die* or twice a day
BL	baseline
CANTAB	Cambridge Neuropsychological Test Automated Battery
CDC	Centers for Disease Control and Prevention
COC	cocaine
CPP	conditioned place preference
D	distractor image
D1	dopamine D1-like receptor superfamily
D_1	dopamine D_1 receptor subtype
D2	dopamine D2-like receptor superfamily
D_2	dopamine D_2 receptor subtype
D_3	dopamine D_3 receptor subtype
D_4	dopamine D_4 receptor subtype
D_5	dopamine D_5 receptor subtype
DA	dopamine
DAT	dopamine transporter
DEA	Drug Enforcement Agency
DMS	delayed-match-to-sample
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders (4^{th} ed.)
EEG	electroencephalogram
e.g.	*exempli gratia* or for example
EtOH	ethanol
FDA	Food and Drug Administration
FR	fixed-ration
H	histamine
H_1	histamine 1 receptor
i.e.	*id est* or that is
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
kg	killogram
MDMA	3,4-methylenedioxy-methamphetamine
mg	milligram
ml	milliliter

mRNA	messenger RNA
NE	norepinephrine
NHP	nonhuman primate
NIDA	National Institute on Drug Abuse
NIH	National Institutes of Health
NINDS	National Institute of Neurological Disorders and Stroke
NSDUH	National Survey on Drug Use and Health
NSF	National Sleep Foundation
P	preffered cocaine dose
PCP	phencyclidine
PET	positron emission tomography
PSG	polysomnography
PTSD	post-traumatic stress disorder
QTP	quetiapine
REB	Robert E Brutcher
REM	rapid eye movement
Sal	saline
SAMHSA	Substance Abuse and Mental Health Services Administration
SD	standard deviation (Chapter II, Figure 1 only); sleep disruption
SEM	standard error of the mean
SERT	serotonin transporter
SSRI	selective serotonin reuptake inhibitor
U	units
US	United States
VTA	ventral tegmental area

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ABSTRACT

Brutcher, Robert E.

EFFECTS OF SLEEP DISRUPTION AND QUETIAPINE ON COCAINE ABUSE: THE PATH TO DEVELOPMENT OF A MONKEY MODEL OF PTSD

Dissertation under the direction of Micahel A. Nader, Ph.D.,
Professor of Physiology and Pharmacology

The goal of the current research is to systematically evaluate several components needed to develop a monkey model of post-traumatic stress disorder (PTSD). For this dissertation, the aspects of PTSD investigated included sleep disturbance, cognitive disruptions and drug abuse. These studies used Old World macaques, rhesus monkeys, because of their close phylogeny to humans, their similar sleep-wake patterns and their cognitive abilities.

Sleep disturbances are a consequence of cocaine use and have been suggested to perpetuate the drug use cycle. In Chapter II, cocaine self-administration resulted in observable sleep disturbances, which were quantifiable using actigraphy. Results from Chapter III showed that quetiapine significantly improved sleep efficiency in cocaine self-administering monkeys, although it had no direct effect on cocaine use. Taken together, these results support the concept that treating an individuals sleep disturbances remains a potential adjunct treatment option for cocaine dependence, and quetiapine was able to effectively do so in our model of cocaine abuse.

A potential concern with using quetiapine to treat symptoms of cocaine addiction is its own abuse liability. In Chapter IV, the reinforcing effect of quetiapine was examined by self-administration studies. Quetiapine did not function as a reinforcer even during chronic oral treatment. Interestingly, in a majority of the monkeys studied, a

combination of quetiapine and cocaine exhibited a greater reinforcing strength than cocaine alone, supporting the possibility of co-abuse of quetiapine with cocaine.

Cognitive deficits are another consequence of cocaine use and may subsequently make abstinence more difficult, thus treating these deficits should be a goal of treatment. In Chapter V, the effect of sleep disruption or quetiapine treatment on cognitive performance using a delayed-match-to-sample (DMS) task was examined. Sleep disruption adversely affected cognition, as did quetiapine administration; tolerance did not develop to the effects of quetiapine over 10 days of treatment.

In conclusion, the research in this dissertation demonstrated that several symptoms of PTSD could effectively be measured in rhesus monkeys. Further, although quetiapine was able to effectively reduce cocaine induced sleep disturbances, the results of cognitive disruption and increased reinforcing strength would suggest using caution when determining the suitability of this treatment option.

CHAPTER I

INTRODUCTION: PRECLINICAL MODELS OF, RECEPTOR INVOLVEMENT IN, AND PHYSIOLOGICAL CONSEQUENCES OF COCAINE ABUSE: STEPS TO TREATMENT DEVELOPMENT

COCAINE ABUSE

Drug addiction is an economically taxing brain disease, costing approximately $593 billion annually, which currently has limited treatment options (Harwood 2000; National Drug Threat Assessment 2010; NIDA 2010; CDC 2011). There are an estimated 22.1 million people in the U.S. that met DSM-IV criteria for substance abuse or dependence in 2010, of which 1.5 million had cocaine dependence or abuse (NSDUH 2010). Further, recent reports indicate that of all admissions for treatement of substance abuse, 12.9% were for cocaine abuse (SAMHSA, 2011). Although those numbers have remained stable, or slightly declined, over the past few years, cocaine abuse/dependence represents an important area of concern to healthcare professionals and scientists alike.

Despite promising preclinical and clinical studies, it has been reported that no medication has demonstrated efficacy in promoting abstinence from psychostimulants (Jupp and Lawrence, 2010). More specifically, at present there are no medically approved treatments for cocaine addiction (Vocci et al., 2005), although several novel pharmacological avenues are being considered (O'Brien 2005; Elkashef et al., 2007; Heidbreder and Newman, 2010), and cocaine abuse/addiction represents an ongoing health concern. A fundamental problem encountered with studies examining treatment of cocaine dependence is that without a currently available therapeutic agent that effectively treats cocaine dependence there is not a compound that could serve as a comparison in the search for an ideal therapy. Although this presents a limitation to cocaine addiction research, it by no means indicates that we should not continue to pursue and evaluate compounds for their potential to treat cocaine dependence. An integral component in determining an appropriate treatment strategy is that we must first seek to understand the

physiological and neurobiological consequences of cocaine use, and this pursuit of an ideal treatment agent for cocaine addiction relies on several key principles, such as finding a suitable model of the human condition of cocaine abuse and the identification of key targets (i.e. specific receptors and physiological consequences of cocaine use).

It has been suggested that the first step in treating drug abuse is to identify and target those behaviors that produce outcomes that cause significant harm to the individual or to other people. The target behavior to be changed is self-administration of the abused drug and the desired outcome is abstinence (Poling et al., 2000). In a thorough and comprehensive review discussing schedules of drug self-administration, it was postulated that there are two main purposes of such drug self-administration procedures: 1) abuse liability testing of psychoactive compounds for potential scheduling of controlled substances by the Drug Enforcement Agency (DEA); and 2) understanding the pharmacological, environmental and biological determinants of drug-taking behavior as a model of drug addiction (Banks and Negus, 2012). Studies that directly assess drug self-administration have been suggested to provide a better measure of the relative abuse liability of drugs (Foltin and Fischman, 1991). Thus, an effective model of cocaine self-administration is crucial for examining therapeutic treatment options, which may have potential for treating cocaine dependence. *Although there are numerous behavioral models available to evaluate the potential effectiveness of treatment strategies aimed at cocaine addiction (e.g., drug discrimination, conditioned place preference, locomotor activity), all of the studies that will be discussed in this Chapter utilize a model of cocaine self-administration to examine key physiological consequences of cocaine use and, subsequently, to evaluate potential treatment strategies.*

Early in behavioral pharmacology, Schuster and Thompson (1969) observed and reported a correlation between drugs that function as reinforcers in laboratory animals and those that are abused by humans. Further, it has been well-established that animals will self-administer most drugs that are abused by humans, with similarities in patterns of intake and by similar routes of administration (Griffiths et al., 1980; and Brady and Lukas, 1984). Thus, these animal models can serve as useful tools for the evaluation of potential pharmacotherapeutic agents to treat dependence (Mello, 1992). In regard to cocaine specifically, it is widely accepted that preclinical evaluation of compounds and their potential to treat cocaine dependence relies heavily on two procedures: 1) measuring the ability to modify the discriminative stimulus effects of cocaine, and 2) measuring a similar ability to modify the reinforcing stimulus effects of cocaine (Winger, 1998).

When examining potential treatment therapies for cocaine abuse, it is also important to include measures that examine the non-specific behavioral effects of that compound. An ideal compound would target drug-taking behavior directly by decreasing it, and produce no negative non-specific effects on other behaviors. There are reports of compounds that have been shown to decrease cocaine self-administration; however, they also non-specifically decreased other behaviors. For example, dopamine (DA) agonists (cocaine, mazindol, and d-amphetamine) have been shown to decrease cocaine self-administration in rhesus monkeys, but doses that decreased cocaine self-administration also decreased food-maintained responding (Mansbach and Balster, 1993). Thus, although effective at reducing cocaine self-administration, this would not be a good therapy because compliance issues would need to be addressed. Another important characteristic to examine when searching for a compound to treat cocaine addiction

would be the abuse liability of the compound itself. GBR 12909, a dopamine reuptake blocker, was shown to produce results similar to cocaine in its ability to decrease cocaine self-administration (Skjoldager et al., 1993), although these effects were attributed to the rate disrupting effects of the drugs rather than a reduction of the reinforcing efficacy of cocaine. However, GBR 12909 has also been shown to exhibit reinforcing effects in rhesus (Skjoldager et al., 1993) and squirrel (Bergman et al., 1989) monkeys limiting the positive results observed on cocaine self-administration. Although these effects are similar to using methadone to treat opioid addicted patients, they do not represent what would traditionally be considered an "ideal" pharmacotherapy since the compound also has potential for abuse. Vocci (2007) suggests that since drug abuse typically occurs in environments that also include other commodities; a main goal of substance abuse treatment should seek not only to reduce drug-taking behavior but also to promote reallocation of behavior to activities maintained by more adaptive reinforcers. Further, the transition to drug addiction has been characterized by a progression toward compulsive drug use to the detriment of other socially valued behavioral choices (i.e. food, family, work) (O'Brien et al., 2006; Saunders, 2006; Martin et al., 2008). The studies described in this dissertation utilize conditions that compare cocaine self-administration in a context with other non-drug reinforcers available.

CHOICE STUDIES

In an effort to find suitable treatment options for cocaine addiction, we continue to pursue more translational animal models to study the abuse pattern. Preclinical assays of drug self-administration provide a valuable experimental tool, which can be used to

assess potential pharmacotherapies for the treatment of drug abuse (Mello and Negus, 1996). Studies of intravenous (i.v.) drug self-administration traditionally use simple schedules of reinforcement, such as fixed-ratio schedules. In such a procedure, subjects learn that obtaining the desired outcome is contingent upon responding when a specific discriminative stimulus is presented. The primary dependent variable collected and analyzed using this type of simple schedule procedure has historically been the response rate. Although we have obtained an immense amount of clinically relevant pharmacological and neurobiological information via this technique, it is not devoid of one striking disadvantage that was acknowledged early in the history of behavioral pharmacology. As early as 1976 it was reported that it was well established that rates of drug self-administration may be influenced by factors other than the reinforcing effects of the self-administered drug, and as a result, rate measures are not optimal for evaluating drug reinforcement (Kelleher, 1976). Therefore, drug self-administration procedures have evolved, and the process of model development has continued to remain dynamic, in pursuit of greater translatability to the human condition.

That ground-breaking concept proposed by Kelleher in 1976 has lead behavioral pharmacologists, in their pursuit of a translatable model, to continue to evaluate and refine more traditional models used to study the addiction process. Based on those evaluations, we have learned that when using simple schedules of reinforcement, the measures of self-administration response rate can be influenced by both the reinforcing effect of the self-administered drug and also by other direct effects of the self-administered drug that can either increase or decrease response rates (Zernig et al., 2004). Those other effects of the self-administered drug, have been referred to as

"reinforcement-independent rate-altering effects", and it has been established that the goal of more recently developed procedures is to dissociate the reinforcing drug effects from reinforcement-independent rate-altering effects (Woolverton and Nader, 1990; Banks et al., 2011; Banks and Negus, 2012). A recent review of therapeutic agents to treat substance abuse provided confirmation that, although many therapeutic agents have shown promise in preclinical models, they fail to translate into the human condition (Jupp and Lawrence, 2010). They suggest that this failure in translation can be attributed to the fact that the majority of animal studies do not provide access to alternative non-drug rewards in their experimental design and therefore potentially only model abusers that are at the highest risk for developing addiction. Thus, when deciding which animal model of drug abuse to use when evaluating potential new treatments, it is important to use validated animal models that more closely represent human addiction (Koob et al., 2009). *Further, it has been reported that when determining the abuse liability of drugs, a critical factor to consider is the direct effects of the reinforcing drug on other behaviors (Banks et al., 2008) and that medication effects on drug self-administration can be influenced by variables that include the schedule of reinforcement under which drug self-administration is maintained (Arnold and Roberts, 1997; Negus and Banks, 2011). This concept of examining the effect of the abused drugs on other behaviors will be examined in Chapter II by determining the effect that cocaine self-administration has on sleep, a critical component of good health. Subsequently, we will examine the effects of disrupting sleep on the relative reinforcing strength of cocaine, as sleep disturbances have been a predictor of relapse to drug taking.*

To address concerns over the disconnect between preclinical models of drug abuse and the human condition, a new form of drug self-administration procedures was developed utilizing concurrent schedules. Under this schedule of reinforcement, responding is maintained on two or more manipulanda by two or more motivationally relevant consequent stimuli (Griffiths et al., 1975, 1981; Aigner and Balster, 1978; Banks and Negus, 2012). This concurrent schedule has generally been referred to as a "choice" procedure because subjects must allocate their behavior, or "choose," between available consequent stimuli. Simply stated, choice procedures introduce alternative reinforcers as options to available drugs. Thus, we can derive the relative reinforcing effects of drug in comparison to an alternative reinforcer from measures of behavioral allocation (or "drug choice") rather than behavioral rate (Woolverton and Nader, 1990; Banks and Negus, 2012). Drug addiction has been classically defined as a disorder of choice and behavioral allocation (Hernstein and Prelec, 1992; Heyman, 2009) with addiction implying excessive drug choice at the expense of more adaptive behaviors (Banks and Negus, 2012). Thus, when the alternative reinforcer to a drug injection is a non-drug stimulus, such as food, the procedure more closely resembles the clinical abuse condition (Katz, 1990), such that choosing continued use of a drug results in forfeiture of other reinforcers (i.e. food, money, family) encountered in daily functioning.

In regard to viewing addiction as a disorder of choice, choice procedures have emerged as the standard approach in clinical studies of drug reinforcement (Comer et al., 2008; Haney and Spealman, 2008). Ultimately, these procedures generate distinct measures of behavioral allocation and behavioral rate that permit dissociation of reinforcing effects from reinforcement-independent rate-altering effects of drugs (Banks

and Negus, 2012). The primary dependent measure, of choice procedures, is response allocation that has been described to be independent of the rate-decreasing effects of the self-administered drug (Woolverton and Nader, 1990) allowing a more translatable analysis. This concept was further reinforced with reports that under concurrent-access conditions the effects of drugs on response rate are independent of the reinforcer strength (Banks et al., 2008). In terms of treatment development, choice procedures permit the assessment of the degree to which candidate medications can promote reallocation of drug-taking behavior (Banks et al., 2011), which is integral to successful development.

When applying drug choice procedures to experimental design, there are several drug choice models that can be employed: 1) drug vs. itself; 2) drug vs. other drug; and 3) drug vs. non-drug reinforcer (Banks and Negus, 2012). Clinical and preclinical studies have reported that the introduction of an alternative reinforcer has in turn decreased cocaine self-administration (Carroll et al., 1989; Nader and Woolverton, 1991; Hart et al., 2000; Vosburg et al., 2010) and nonhuman primates have been the predominant research subject for preclinical drug choice studies, with the rhesus monkey being the most commonly used species (Banks and Negus, 2012). Studies examining choice between cocaine and food have shown that manipulations that alter cocaine choice often produce a reciprocal and opposing change in food choice (Nader and Woolverton, 1991, 1992; Negus, 2003). Importantly, when studied under food-drug choice conditions, cocaine (Negus, 2003; Czoty et al., 2005; Banks et al., 2011, 2013) and MDMA (Banks et al., 2008) produce dose-dependent increases in drug choice resulting in approximately 100% drug choice at the higher doses. *In regard to dose selection, a study examining cocaine choice in socially housed cynomolgus monkeys indicated that individual differences in*

measures of reinforcement are most prominent at lower drug doses (Czoty et al., 2005). This finding would suggest that we are more apt to observe an effect at lower drug doses and therefore it is important when choosing a cocaine dose that we are aware of the location of where our dose is on the cocaine choice curve. Therefore, in Chapters II and III baseline cocaine choice curves were determined prior to any manipulations (pharmacological, environmental, and behavioral) and when comparing between subjects, it is location on the cocaine dose-response curve, not the actual dose that is most relevant.

The choice procedure has also served as a suitable model to examine pharmacological treatments aimed at reducing cocaine self-administration. Studies have also been conducted in rats that have indicated that acute diazepam (Augier et al., 2012) and aripiprazole (Thomsen et al., 2008) administration leads to decreases in cocaine choice. However, in the aripiprazole study, tolerance developed to the effect on cocaine choice with repeated treatment. Pharmacological treatment has also been shown to reduce cocaine choice in nonhuman primates (Negus, 2003). In another study, continued maintenance on a monoamine releaser, up to doses that produce nonselective behavioral disruption, was able to reduce the reinforcing effects of cocaine, although they were not able to eliminate those effects (Banks et al., 2011) and therefore, per current accepted standard, would be construed as a negative result although it can be argued that reducing the reinforcing effect of cocaine at any level should be considered a success. Further, a study conducted in socially housed cynomolgus monkeys showed that, when administered acutely, aripiprazole (an low-efficacy D2/D3 agonist) increased the choice of low cocaine doses, but when administered repeatedly, aripiprazole decreased cocaine

choice in dominant monkeys when self-administration occurred on only days 1 and 5 of treatment (Czoty and Nader, 2013). *The results of this study further suggest the importance of experimental design and reinforcement schedules when measuring the effects of pharmacological manipulation on the reinforcing effects of cocaine. The effect of quetiapine treatment (acute and continuous) on the reinforcing strength of cocaine will be examined in Chapter III. Interestingly, quetiapine is in the same class of drugs as aripiprazole, although their mechanisms differ.* Finally, and importantly, it has also been documented that pharmacological manipulations can significantly decrease cocaine choice and increase choice of an alternative reinforcer (Banks et al., 2013) providing support for choice procedures serving as valuable tools for studying therapeutic options for cocaine addiction.

Therefore, utilizing a choice procedure, we will examine the treatment effect of a potential therapeutic agent on cocaine choice, with food serving as the alternative reinforcer, in Chapter III. Further, with the choice procedure appearing to be a suitable model to study cocaine self-administration, the next logical step in medication development is determination of the mechanisms involved with cocaine's reinforcing effects. Stimulation of both serotonergic and dopaminergic systems have been implicated in substance abuse (Monnelly et al., 2004; Weisnam, 2003; Sattar et al., 2004) and would therefore serve as potential pharmacological targets. Quetiapine is an atypical antipsychotic, which functions as an antagonist at both the DA and 5-HT receptors, and the effects of quetiapine administration on a monkey model of cocaine abuse were examined in Chapter III. These two neurotransmitter systems are briefly reviewed next.

DOPAMINE

The involvement of the dopamine (DA) pathway in the initiation and maintenance of cocaine abuse has been well established (Steketee, 2005) and the behavioral-stimulant and reinforcing effects of cocaine have been linked to its ability to enhance dopaminergic neurotransmission by inhibiting DA uptake via transporter blockade (Ritz et al., 1987). Studies have also suggested a link between these neuropharmacological actions of cocaine and its discriminative stimulus effects in laboratory animals (Cline et al., 1992). Specifically, DA transporter (DAT) blockade results in elevated extracellular levels of DA, which subsequently acts downstream by binding to DA D1- and DA D2-like receptors (Sibley et al., 1993).

The DA receptors are broken down into two superfamilies and are classified as D1 (consisting of D_1 and D_5 receptors) or D2 (consisting of D_2, D_3, and D_4 receptors) based on their location and pharmacological profile (Schwartz et al., 1992; Sibley et al., 1993). Initial findings in clinical literature have reported results based on the two superfamilies of receptors. The role of DA in cocaine self-administration has been non-specifically identified by evidence that shows DA receptor agonists and antagonists can modulate or disrupt self-administration behavior (Koob et al., 1987; Corrigall and Coen, 1991; Hubner and Moreton, 1991). On a more specific level, it has been postulated that an important component in the reinforcing effects of cocaine and other drugs of abuse is the DA D2-like receptor (Roug-Pont et al., 2002). Adding evidence to this hypothesis are data showing that, under certain conditions, D2 agonists, but not D1 agonists, produce cocaine-like behavioral effects in animals trained to discriminate cocaine or to self-administer cocaine (Greech et al., 1996; Self et al., 1996; Caine et al., 1999, 2000a,b).

Thus, the D2 receptor has received a large amount of focus in cocaine self-administration studies.

Further evidence is provided by imaging studies conducted in humans and nonhuman primates utilizing positron emission tomography (PET) to provide an indirect measure of available DA receptors. [^{18}F]*N*-methylspiroperidol has been used with PET to determine if chronic cocaine use leads to up- or down-regulation of postsynaptic D2 receptors. A study in humans showed that non-detoxified cocaine abusers have lower than normal uptake of [^{18}F]*N*-methylspiroperidol in the striatum. This decreased uptake could represent either a decrease in postsynaptic D2 receptors, a decrease in receptor affinity secondary to chronic cocaine use, or increased extracellular DA competing for the receptor. From that study, the authors concluded that the decreased level of binding was due to a decrease in the availability of D2 receptors, suggesting that the striatal dopaminergic system compensates for the DA overstimulation induced by cocaine by decreasing the number of postsynaptic receptors. Of note in this study was the finding that detoxified subjects, having abstained from cocaine use for 4-5 weeks before PET, did not show a lower uptake of [^{18}F]*N*-methylspiroperidol suggesting the decreased receptor availability may be temporary and linked to the last administration of cocaine (Volkow et al., 1990). The initial results provided for detoxified, or abstinent, cocaine abusers was negated when the authors reported results from a subsequent study showing that cocaine users showed decreased D2 receptor availability after abstinence periods of 1 and 4 months (Volkow et al., 1993). Results from these imaging studies, and others, have provided evidence that cocaine addicts exhibit a small but very persistent decrease in

dorsal striatal dopamine D2 receptors (Volkow et al., 1993, 1996a, 2004; Martinez et al., 2004).

Expanding on those findings, it was further determined that DA D2 receptor availability was significantly correlated with the years of cocaine use, but not with the doses of cocaine that were being used (Volkow et al., 1993). Volkow and colleagues (1999a) also have reported that the levels of DA D2 receptor availability was more dependent on the duration of cocaine use, rather than on the amount of drug used prior to the imaging study. Adding support to the involvement of the D2 receptors in cocaine abuse, these findings were replicated in imaging studies conducted in nonhuman primates where there are similar decreases in D2 receptors following cocaine self-administration (Nader and Czoty, 2005; Nader et al., 2006). Also using PET imaging in nonhuman primates, binge access to cocaine resulted in significant reductions in D2 receptor availability at all time points (Nader et al., 2008) and strikingly, this decrease was detectable within one week of initiating cocaine self-administration (Nader et al., 2006). Taken together these results suggest that the reduction observed in DA D2 receptor availability may be a direct outcome of "drug seeking" behavior.

Further evidence of decreased D2 receptor availability following cocaine self-administration has been provided from studies utilizing rodents where binding assays or *in vitro* receptor autoradiography are employed to measure DA neurotransmission. In a study using rats, it was reported that extended (6 hr/day), but not limited (1 hr/day), access to cocaine self-administration for three weeks produced a persistent decrease in both D2 receptor mRNA expression and D2 protein levels in the medical prefrontal cortex, and of D2 mRNA in the orbitofrontal cortex out to 33 days post self-

administration (Briand et al., 2008a). Complementary to this study, a separate study in rats showed a decrease in D2 receptor protein in both the nucleus accumbens core and shell after discontinuing cocaine self-administration, relative to saline controls (Conrad et al., 2010). However, contrary to these findings, studies using D_2 receptor knockout mice (that still express D_3 and D_4 receptors) have shown that these mice, self-administering cocaine under fixed ratio (FR) 1 schedule of reinforcement, self-administer cocaine identically to wild-type controls on the ascending limb and the peak of the dose effect curve and self-administer higher cocaine doses at a greater rate when compared to wild-type littermates (Caine et al., 2002). The authors conclude that the D_2 receptor subtype is not necessary for the reinforcing effects of cocaine (Caine et al., 2002), which, combined with results obtained in studies done in humans and nonhuman primates would suggest involvement of the D_3 and/or D_4 receptor. In the same set of studies utilizing D_2 knockout mice the D2 agonist, quinelarone, was not self-administered and suggests that the D_2 receptor was necessary for quinelarone self-administration. Interestingly a D2 antagonist failed to modify cocaine self-administration behavior in D_2 knockout mice, which still express D_3 and D_4 receptors. In wild-type mice, pretreatment with a D_2 antagonist increased rates of high dose cocaine (situated on the descending limb of the cocaine dose-response curve) self-administration, while D_3 and D_4 antagonists were shown to be ineffective (Caine et al., 2002). These latter results lead the authors to conclude that the dopamine D_3 and D_4 receptors do not play critical roles in self-administration behavior. However, information obtained from the monkeys that served as subjects throughout the experiments contained in this dissertation, provide evidence for that not to be true. Specifically, monkeys showed a differential sensitivity to D_3 compounds (Hamilton et al.,

2010, 2011) although no differences in D2 receptor availability were noted (Hamilton et al., 2010). Further, the monkeys that demonstrated the greatest effects to D_3 compounds were exposed to cocaine *in utero, suggesting this history was involved, either directly or indirectly, in this increased sensitivity*. Based on the contrasting results obtained when using the dopamine D_2 receptor knockout mice it appears that we see different effects in genetic mutations of the D_2 receptor and pharmacological manipulations of the D_2 receptor. *Collectively these results suggest that there may be non-dopaminergic mechanisms partially responsible for cocaine self-administration, which will be discussed shortly.*

The D2 receptor exists in two inter-convertible affinity states for its endogenous agonist dopamine. It is either in a high-affinity state, or a low-affinity state, and receptors can rapidly change between these two states. DA binds primarily to the high-affinity state of the D2 receptor (referred to as $D2^{High}$), making this form of receptor the most functionally relevant state (Seeman et al., 2005). Relative to drug-naïve controls, rats that had 3 weeks of either limited (1 h/day) or extended (6 h/day) access to cocaine had approximately a 150% increase in dorsal striatal $D2^{High}$ receptors, and this effect persisted out to 30 days after discontinuation of cocaine self-administration. This increase in D_2 receptors would appear to conflict with what was presented earlier, where D_2 receptor availability decreased following extended access to cocaine (Briand et al., 2008a). However, in this study, there was no effect on overall number of D2 receptors, suggesting that a proportionate decrease in DA receptors in the low-affinity state occurs (Briand et al., 2008b). These results were consistent with a study that also showed no observed significant differences in levels of D2-like receptor binding densities in the striatum of

cocaine-exposed and control animals after 30 and 90 days of abstinence (Beveridge et al., 2009) although, these results could be a reflection of recovery due to abstinence.

The differing results from the research, discussed thus far, showing decreased D2 receptor availability associated with cocaine use may be a consequence of several mechanisms. The contrasting results could be due to species differences, different analytical techniques, or differences in the results may also be explained by different patterns and duration of cocaine use. Evidence is available that there are documented differences between nonhuman primate and rodent dopaminergic systems (Berger et al., 1991; Joel and Weiner, 2001) including differences in DA affinity at D1 and D2 receptors (Weed et al., 1998). The studies utilizing rats were conducted *ex vivo,* whereas the human and nonhuman primate studies were performed *in vivo* and the results could be a product of increased endogenous DA release leading to increased competition for the D2 receptor and displacement of the ligand rather than a decrease in receptor number. It could also be a direct result of human and nonhuman primate imaging studies only measuring the low-affinity state of the D2 receptor, or from an overall lack of discrimination between low- and high-affinity states. Further complicating the interpretation is the concept that there may be a more rapid recovery of D2 receptors to control levels following abstinence from cocaine use. Finally, and most interestingly, it could also be related to an initial low level of D2 receptors, since it has been suggested that lower D2 receptor basal levels in healthy humans predict an increased reinforcing efficacy of stimulants (Volkow et al., 1999b) and similarly low baseline levels in monkeys predicted the propensity to self-administer cocaine (Morgan et al., 2002; Nader

et al., 2006). This leads to the question of what came first - low levels of dopamine D2 receptors or reductions due to cocaine self-administration.

Monkeys with low D2 receptor levels self-administer cocaine at higher rates when compared with monkeys with higher D2 receptor availability (Nader et al., 2006). Parallel to this work, a study done in rats reported that DA D2 receptor adenoviral upregulation was associated with a significant decrease in cocaine self-administration for up to 6 days post administration and a 75% decrease in the number of cocaine infusions (Thanos et al., 2008). These results suggest that low D2 receptor availability makes an individual more vulnerable to cocaine reinforcement and continued exposure to cocaine further decreases those levels (Nader et al., 2002, 2006). Interestingly, Caine and colleagues reported that the D_2 receptor is not necessary for cocaine self-administration, but is involved in mechanisms limiting self-administration rates of high-doses of cocaine. Thus, they suggest that levels of the D_2 receptor may be a neurobiological variable responsible, in part, in modulating the vulnerability of individuals to drug abuse (Caine et al., 2002) and not directly involved in self-administration behavior. Expanding on those results (knockout mice self-administered cocaine, at higher rates than wild-type mice) would suggest there are other mechanisms and receptors involved in the reinforcing effects of cocaine. *Before addressing some of those other possible mechanisms (i.e. modulation via the D1 receptor) it is important to note the effects of D2 antagonism, as Chapter III will examine the effects of quetiapine, which functions as a D2 antagonist.* Of interest are reports that selective D2 antagonists have increased self-administration of cocaine in nonhuman primates (Woolverton, 1986) and rats (Britton et al., 2001; Corrigal and Coen, 1991) under a fixed-ratio schedule of drug delivery, which would suggest an

increase in the reinforcing strength of cocaine. Interestingly, when the selective D2 antagonist, spiperone, was administered as a pretreatment prior to cocaine self-administration under a progressive-ratio schedule, it was reported to produce dose-dependent decreases in the highest ratio completed in rats (Hubner and Moreton, 1991) suggesting that D2 antagonists decrease the reinforcing strength of cocaine. Further, both D1 and D2 antagonists have been shown to cause dose-related decreases in responding for both food and cocaine in rhesus monkeys performing in a 3 component multiple schedule of reinforcement (Woolverton and Virus, 1989). Taken together, these results suggest differential effects based on schedule of reinforcement. *Of note for the experiments planned in Chapter III, the typical antipsychotics chlorpromazine and haloperidol resulted in increases in the frequency of cocaine choice when administered at low and intermediate doses, while high doses completely suppressed responding for both reinforcers (Woolverton and Balster, 1981). Quetiapine, a new generation atypical antipsychotic, will be administered in Chapter III to examine its effects on cocaine choice. Interestingly, quetiapine functions as an antagonist at both D_1 and D_2 receptors, although it is reported to rapidly dissociate from the D_2 receptor (Kapur et al., 2000; Morin, 2007).*

There have also been studies that suggest that the D1 receptor is implicated in cocaine self-administration. Concentrations of DA D1 receptors were significantly higher throughout the striatum of monkeys that self-administered cocaine for 100 sessions, followed by a 30 day period of abstinence, when compared to food-maintained controls (Beveridge et al., 2009). These findings were consistent with those from another study, which also showed increased D1 receptor binding densities following cocaine self-

administration (Nader et al., 2002). While concentrations of D1 receptors remained elevated relative to controls after 30 days of abstinence, autoradiographic imaging studies conducted after 90 days of abstinence revealed a recovery of D1 receptors and there was no significant difference between cocaine-exposed animals and controls (Beveridge et al., 2009). Evidence has also been provided for increases in D1 receptors, with subsequent recovery, by studies using western blot analysis of dopamine receptors in crosslinked tissues in rats that showed that after cocaine self-administration, D_1 receptor surface expression was increased in the nucleus accumbens shell after 1 day of abstinence but normalized by day 45 of post self-administration (Conrad et al., 2010).

Interestingly, Caine et al. (2007) reported that D_1 receptor knockout mice do not reliably self-administer cocaine while their wild-type littermates do. They also found that the D1 agonist , SKF 82958, or the D2 agonist, quinelorane, failed to function as a positive reinforcer in D_1 knockout mice while acting as a positive reinforcer in wild-type controls (Caine et al., 2007). When taken together, these data would suggest that the D1 receptor is also critical for the reinforcing effects of cocaine and other DA agonists. However, an increase in D1 receptors seems contrary to what would be expected from an overstimulation of receptors with DA. Following chronic stimulation, we would anticipate that the numbers of D1 receptors would decrease; similar to what has been shown with the D2 receptor. With both receptor types being G-protein coupled, we would expect a downregulation following chronic stimulation and not an increase in one receptor and a decrease in another. It is possible that the explanation of these opposing effects could be a function of dose, time, or brain region differences.

Finally, it should be noted that the effects on the D2 receptor are not just specific to cocaine, but have also been induced by other drugs of abuse. Briefly, imaging studies conducted in humans have shown a decrease in D2 receptor availability that is associated with a population of patients who are alcoholics and heroin abusers (Volkow et al, 1996b; Wang et al., 1997) and there is also evidence from PET imaging that methamphetamine abusers (Volkow et al., 2001) and obese individuals (Wang et al., 2001) also show a decreased level of D2 receptor availability. Taken together these results indicate that reductions in D2 receptor availability are associated with several drugs of abuse and indicate that this receptor could serve as a target for pharmacological treatment.

In summary, decreased D2 receptor availability associated with chronic cocaine use may reflect receptor down regulation from increased extracellular concentration or competition of endogenous ligand (Dewey et al., 1991; Logan et al., 1991) or it could be a result of receptor dysregulation (Volkow et al., 1993). Evidence for the latter was provided by a postmortem study of human cocaine users that found a trend towards decreased D2 receptor levels in the nucleus accumbens using immunoblotting (Worley et al., 2000), which suggests that the PET data showing decreased D2 receptors is just that, and it is not due to elevated dopamine levels. Data were also presented that may imply that decreased D2 receptor availability in the striatum may be a predisposing neurobiological trait and not only a consequence of chronic cocaine exposure (Dalley et al., 2007). *Although further research is warranted, the evidence provided implies that targeting some aspect of the dopamine system may be beneficial in treating substance abuse. In Chapter III we will examine the effect of a potential treatment medication,*

quetiapine, which possesses antagonistic properties at both the D1 and D2 receptors, on cocaine self-administration using a choice procedure.

SEROTONIN

Although DA has long been implicated in modulating the behavioral effects of cocaine, published data has also described the involvement of other neurotransmitters as well. For example, over three decades ago, research showed that cocaine influences the serotonin (5-HT) system (Koe 1976) and research has later suggested a modulatory role of 5-HT in the discriminative stimulus effects of cocaine (Cunningham and Callahan, 1994). Further, it was reported in a review examining the therapeutics of drug abuse that 5-HT is strongly implicated in mediating the subjective effects of psychostimulants and significant changes in the serotonergic system, particularly hypofunction, are associated with withdrawl and chronic use of these drugs (Jupp and Lawrence, 2010). A majority of the difficulty in fully understanding the role of 5-HT on the behavioral effects of cocaine can be attributed to the large number of receptor subtypes. Continued research has led to the discovery and characterization of new receptor subtypes but has, at the same time, opened new avenues for examining serotonin's role in the behavioral effects of cocaine. In the efforts of discovering a treatment for cocaine addiction it is important to identify the key targets (systems and receptors), thus accumulating evidence has shown that the serotonin system and its numerous receptor subtypes should not go unnoticed.

There are several interactions between DA and 5-HT systems that have been identified, providing evidence that 5-HT is involved in modulating cocaine's behavioral effects. Cocaine blocks reuptake of 5-HT by binding to the 5-HT transporter (SERT),

resulting in increases in 5-HT neurotransmission (Koe 1976; Li et al., 1996). Further, early evidence revealed that midbrain DA cell bodies and DA terminals in the striatum and nucleus accumbens, key areas associated with the reward process, receive serotonergic innervations from the dorsal raphe nucleus (Dray et al., 1976; Giambalvo and Snodgrass, 1978; Kelland et al., 1990) where it appears 5-HT modulates DA's activity. Complimentary to this evidence are electrophysiological studies that indicate 5-HT exerts an inhibitory influence on the firing rate of dopaminergic neurons (Dray et al., 1976; Fibiger and Miller, 1977) in these areas. Based on some of these initial findings and other key literature available, Howell, Czoty and colleagues proposed that a possible mechanism to explain 5-HT's role in the behavioral effects of cocaine is that 5-HT activity on cell bodies decreases the firing rate of DA neurons or it may function at nerve terminals to decrease DA release (Czoty et al., 2002). Thus, the ability of 5-HT to attenuate the behavioral effects of cocaine could result from an attenuation of cocaine-induced elevation of extracellular DA. Alternatively, 5-HT may act postsynaptically on DA neurons, attenuating the effects of cocaine-induced increases of extracellular DA on a down-stream component of the pathway (Czoty et al., 2002). Previous studies have been conducted where researchers manipulated and targeted the 5-HT system (e.g., Kleven and Woolverton, 1993; Howell and Byrd, 1995; Czoty et al., 2002), which provides further information on the non-specific role that 5-HT has on cocaine behavior.

The interpretation of 5-HT on the behavioral effects of cocaine is complicated by the fact that non-specific alterations of 5-HT levels have been shown to produce conflicting behavioral effects. For instance, acute 5-HT depletion in humans reduces self-reports of craving elicited by cocaine-associated cues (Satel et al., 1995), but the

reinforcing efficacy of cocaine can be enhanced by chemical lesions of brain 5-HT systems in rats (Roberts et al., 1994). Although the differences in effects may be a result of species differences, it draws focus to 5-HT's non-specific affects. Further, non-specific manipulations that decrease 5-HT neurotransmission have been reported to attenuate cue-elicited reinstatement of cocaine-seeking behavior, but enhance cocaine-primed reinstatement of cocaine seeking behavior (Tran-Nguyen et al., 1999, 2001). There is also evidence that cocaine self-administration can be affected by treatments that alter 5-HT function. For example, research has shown that dietary supplementation with 5-HT precursors (L-tryptophan) can attenuate cocaine self-administration in rats (Carroll et al., 1990b), suggesting 5-HT involvement in modulating cocaine self-administration.

Non-specific pharmacological modulation of 5-HT activity has also been shown to alter the behavioral effects of cocaine (Howell and Byrd, 1995). The administration of fluoxetine (5 and 10 mg/kg), a selective 5-HT reuptake inhibitor (SSRI), resulted in a reduction in cocaine infusions (0.2 mg/kg) in rats by at least 50% on all treatment days (Carroll et al., 1990a). This effect was also evident in monkeys where SSRI's were also shown to decrease cocaine self-administration (Kleven and Woolverton, 1993). Taken together these data complement the results of Carroll and colleagues where administration of L-tryptophan attenuated cocaine self-adminstration in rats (Carroll et al., 1990b). However, evidence has also been provided that discounts the impact of 5-HT uptake inhibition on the behavioral effects of cocaine. Particularly of interest were conclusions that direct comparisons between the effects of cocaine and SSRI's and direct agonists on schedule-controlled behavior in squirrel monkeys, which suggested that the behavioral-stimulant and reinforcing effects of cocaine did not depend on inhibition of 5-

HT uptake (Howell and Byrd, 1995). Since publication of that earlier study, more recent experiments have demonstrated that inhibition of 5-HT uptake does seem to impact the reinforcing effects of cocaine. Specifically, the 5-HT uptake inhibitor alaproclate and the 5-HT direct agonist quipazine decreased response rates for cocaine self-administration, suggesting that enhancing 5-HT activity decreases the reinforcing effects of cocaine (Czoty et al., 2002). Complimenting this body of evidence was data obtained that showed alaproclate and quipazine attenuated cocaine-induced increases in extracellular DA in the caudate nucleus, the location of the axon terminals of midbrain DA neurons that supports the authors' hypothesis that 5-HT acts presynaptically with respect to terminals of these DA neurons to modulate the behavioral effects of cocaine (Czoty et al., 2002). The combined results were corroborated with microdialysis studies that suggested that the serotonergic modulation involves presynaptic mechanisms with respect to DA neurons, which decrease the ability of cocaine to elevate extracellular DA (Czoty et al., 2002).

Through non-specific manipulation of the 5-HT system it can be concluded that 5-HT does play some role in the modulation of cocaine-maintained behavior. Thus, examination of the different receptor subtypes can provide more specific targets underlying 5-HT's behavioral effects of cocaine. There is extensive literature available examining the role of different 5-HT receptor subtypes in cocaine behavior, some of which will be briefly discussed. Due to the complexity of the specific interactions and numerous subtypes, the following sections will only address the specific receptor subtypes that are targeted by quetiapine and the effect of quetiapine on the behavioral effects of cocaine will be examined in Chapter III.

One receptor that has been pharmacologically manipulated to examine the role of 5-HT on cocaine's behavioral effects is the 5-HT_{1A} receptor. 5-HT_{1A} receptors are widely distributed throughout the CNS. In the raphé nuclei, they are somatodendritic and act as autoreceptors to inhibit cell firing, while postsynaptic 5-HT_{1A} receptors are present in a number of limbic structures, particularly the hippocampus (Hoyer et al., 2002). It was suggested that intravenous administration of the specific $5HT_{1A}$ receptor agonist (8-OH-DPAT) resulted in excitation of the majority of ventral tegmental area (VTA) DA neurons indirectly, since microiontophoretic application of 8-OH-DPAT into the VTA did not affect the basal firing rate of DA neurons (Prisco et al., 1994). On the basis of those findings, the authors concluded that it appeared that DA neurons in the VTA are under a tonic inhibitory influence by 5-HT terminals that originate in the raphe nuclei (Prisco et al. 1994). To further examine the previous results, other researchers have utilized an antagonist approach to produce the opposite effect. An early study showed that the use of the $5HT_{1A}$-selective antagonist, NAN-190, produced a downward displacement of the cocaine-dose effect curve (Howell and Byrd, 1995), which would be consistent with the findings of Prisco and colleagues. Instrumental in the characterization of the $5HT_{1A}$ receptor's behavioral effects on cocaine were studies showing the differential effects on reinstatement. These studies showed that the $5HT_{1A}$ receptor antagonist, WAY 100635, attenuates cocaine-primed reinstatement (Schenk, 2000; Burmeister et al., 2004) but produced no effect on cue-induced reinstatement of cocaine-seeking behavior (Cervo et al., 2003; Burmeister et al., 2004). The findings presented would suggest the role of the 5-HT_{1A} receptor in regulating cocaine-primed reinstatement, and thus the 5-HT_{1A} receptor would be an interesting target for a treatment agent for

cocaine abuse. *This strategy will be examined in Chapter III when the effects of quetiapine, which functions as an antagonist at the 5-HT_{1A} receptor. Based on the results discussed in this section, the ability of quetiapine to block this receptor would suggest that this agent has potential to be useful in treating cocaine addiction.*

The 5-HT_2 receptor family, which is comprised of the 5-HT_{2A}, 5-HT_{2B} and 5-HT_{2C} receptors (Hoyer et al., 2002) has also been extensively studied in different models examining cocaine-related behaviors. Non-specific blockade of 5-HT_2 receptors with the 5-HT_2-selective antagonist, ritanserin, resulted in increased response rates for intravenous self-administration of cocaine over a range of cocaine doses (Howell and Byrd, 1995). Further, pretreatment with behaviorally inactive doses of two 5-HT_2-selective antagonists, ritanserin and ketanserin, or a nonselective 5-HT antagonist with high affinity for 5-HT_2 binding sites, mianserin, enhanced the rate-increasing effects of low and intermediate doses of cocaine (Howell and Byrd, 1995). In opposition, research from a different group showed that the administration of the 5-HT_2 receptor antagonist, ketanserin, resulted in an attenuation of cue induced reinstatement of cocaine-seeking behavior (Burmeister et al., 2004). The results from the non-specific blockade of the 5-HT_2 receptor demonstrate that this receptor may play a prominent role in the serotonergic systems modulation of the behavioral effects of cocaine. Further research has been completed that teases out the differential effects of the different subtypes of the 5-HT_2 receptor and their impact on cocaine behavior. *Of importance to the experiments that are presented, is the 5-HT_{2A} receptor, which is blocked by quetiapine and will be examined in Chapter III. There are also studies implicating the involvement of the 5-HT_{2C} receptor in modulating cocaine taking* behavior *(Di Giovanni et al, 1999; Di Matteo et al., 1999,*

2000; Grottick et al., 2000; Fletcher et al., 2002; Pentkowski et al, 2010). However, due to the specificity of quetiapine at the 5-HT$_{2A}$ receptor, these effects will not be discussed.

Briefly, a review of the literature involving the 5-HT$_{2A}$ receptor shows that this receptor is also involved in modulating the effect of 5-HT on the behavioral effects of cocaine. Preclinical studies utilizing 5-HT$_{2A}$ receptor antagonists have suggested that they reduce relapse to cocaine-seeking and conditioned place preference (CPP; Nomikos and Spyraki, 1988; Fletcher et al., 2002). Specifically, in one study, the selective 5-HT$_{2A}$ receptor antagonist (M100,907) was administered to male Sprague-Dawley rats and while it did not alter cocaine self-administration at any of the doses tested, it did produce an attenuation of cocaine-primed reinstatement (Fletcher et al., 2002). These limited results presented further suggest that different 5-HT receptor subtypes have varying influences of aspects of cocaine behavior. Fletcher and colleagues concluded that 5-HT$_{2A}$ receptor blockade has a differential impact on motor versus reinforcement or reward-related behaviors. *The conclusions drawn from Fletcher et al. (2002) that 5-HT$_{2A}$ receptor stimulation may contribute to the expression of the locomotor-stimulant effect of cocaine but not the reinforcing effect of cocaine leads to another potential target of interest in treating cocaine abuse disorders. Taken together with the results that 5-HT$_{1A}$ receptor antagonism has been shown to attenuate cocaine-primed reinstatement (Schenk, 2000; Burmeister et al., 2004) it would appear that pharmacological manipulation of both receptor subtypes may be a beneficial treatment strategy. Pharmacological manipulation via an atypical antipsychotic (quetiapine) possessing both 5-HT$_{2A}$ and 5-HT$_{1A}$ antagonistic properties will be examined in Chapter III.*

OTHER NEUROTRANSMITTER INVOLVEMENT

Although DA and 5-HT have traditionally been the key neurotransmitter systems implicated in cocaine taking behavior, evidence of the influence of other neurotransmitters, specifically norepinephrine (NE) and histamine (H), has been reported that further complicates determination of the exact mechanism behind what is responsible for the discriminative stimulus effects of cocaine. Noradrenergic involvement in the discriminative stimulus effects of cocaine has been discussed. Observations are that psychostimulants also exert their action through inhibition of norepinephrine (NE) uptake in the brain and that chronic use is associated with alteration in the function of this neurotransmitter system (Horne et al., 2008). A review examining new therapeutic strategies to treat substance abuse provides further support of noradrenergic involvement. In that review, the authors suggest additional evidence is provided by the fact that many of the symptoms associated with psychostimulant withdrawl (e.g., anxiety, heart palpitations) are mediated by the sympathetic nervous system (Jupp and Lawrence, 2010). Preclinical evidence is available to support this involvement of the noradrenergic system in cocaine behavior. Specifically, pretreatment of squirrel monkeys with an $alpha_1$ antagonist (prazosin) was shown to attenuate the discriminative stimulus effects of cocaine, under both high- and low-dose training conditions (Spealman, 1995). Finally, it has been suggested that the histaminergic system may modify the discriminative stimulus effects of cocaine as well. In a study by Mori and colleagues, they showed that administration of a histamine precursor (L-histidine) enhanced the discriminative stimulus effects of cocaine and this enhancement was attenuated by pyrilamine, a histamine 1 (H_1)-receptor antagonist (Mori et al., 2002). *Combining the limited results*

discussed briefly in this section, with the more thorough discussion of DA and 5-HT involvement in the behavioral effects of cocaine, one might hypothesize that a treatment agent targeting all of these systems might prove an effective treatment strategy. Based on this hypothesis, and limited literature suggesting a positive outcome, we will examine the use of quetiapine, a pharmacological agent that targets all of the specific receptors addressed, and the findings will be reported in Chapter III.

COCAINE, SLEEP, AND COGNITION

Sleep has been described as a dynamic activity that is as essential to good health as diet and exercise, and is as necessary for survival as food and water (NSF, 2006). Supporting this description are reports that rats deprived of REM sleep only live for about 5 weeks, while those deprived of all sleep live about 3 weeks (Rechtschaffen, 1998); rats typically live two to three years (NIH, 2012). At least 40 million Americans each year suffer from chronic, long-term sleep disorders with an additional 20 million experiencing occasional sleep problems (NIH, 2012). Due to several contributing factors (e.g. treatment, lost productivity, and accidents) sleep disorders are estimated to cost Americans over $100 billion annually (Stoller, 1994).

Drug addiction has been defined in literature as a chronically relapsing disorder involving repeated bouts of compulsive drug seeking and use despite potential adverse consequences associated with this behavior (Koob and LeMoal, 1997; Witkiewitz and Marlatt, 2004). Reports indicate that relapse rates for addicted humans range from 40-90%, even after a prolonged period of abstinence (DeJong 1994; McLellan et al., 2000; Paparrigopoulos et al., 2011). The wide range in reported relapse rates can be partially

explained by differences in the definition of relapse, which substance of abuse is being reported, and the length of treatment or abstinence period. It is known that most drugs can affect sleep patterns, usually adversely, impacting both the duration and frequency of sleep stages (Barkoukis and Avidan, 2007) and literature suggests cocaine abusers encounter a vicious cycle between relapse and sleep dysregulation when trying to abstain from the drug. Thus, it is possible that sleep disturbances may contribute to cocaine addiction and not just be a consequence of the illness. It has been reported in humans that current cocaine use is associated with prolonged wakefulness and hypersomnia is present during early withdrawl (Morgan et al., 2008). Research has shown that with sustained abstinence from cocaine, cocaine abusers exhibit decreased sleep, impaired vigilance and sleep-dependent procedural learning, and spectral activity suggestive of chronic insomnia (Morgan et al., 2006). These sleep disturbances may persist for months to years following abstinence (Gillin et al., 1994; Clark et al., 1998; Drummond et al., 1998; Landolt and Gillin, 2001) making these sleep disturbances a continuing problem for abstinent cocaine users. Another key concept integral to finding appropriate treatment strategies is a better understanding of the physiological consequences of cocaine use and the implications of those consequences.

DA-enhancing drugs have been shown to increase wakefulness (Boutrel and Koob, 2004) and the dopaminergic system has been identified as modulating sleep (Tufik et al., 2009), further supporting the idea of a relationship between cocaine and sleep with measures of poor sleep quality being shown to be predictors of relapse (Gillin et al., 1994; Clark et al., 1998; Foster and Peters, 1999; Brower, 2001) to drug taking. It has also been shown that abstinence-associated sleep-dependent learning deficits are related

to changes in sleep architecture supporting the concept that treatments directed at improving/aiding sleep could be beneficial in offsetting physiological consequences of cocaine abstinence (Morgan et al., 2008). It has been shown in both humans and animal models that cocaine use leads to disruptions in sleep. Specifically, a study in humans revealed that REM sleep was found to be shortest on nights following cocaine use (Morgan et al., 2008), while a complimentary study in rats reported that, following an acute intraperitoneal (i.p.) cocaine injection, the time spent in wakefulness increased and slow wave sleep decreased in a dose-dependent manner compared to controls (Knapp et al., 2007). DAT inhibitors have previously also been shown to affect the sleep-wake cycle of nonhuman primates (Andersen et al., 2010). A follow-up study also confirmed this relationship with reports that, during chronic treatment with the dopamine transporter (DAT) inhibitor RTI-336, rhesus monkeys showed significant increases in evening activity, sleep latency and sleep fragmentation, while sleep efficiency was decreased (Andersen et al., 2012). The psychostimulant methamphetamine has also been shown to disrupt the sleep process. A recent study in monkeys reported that methamphetamine self-administration increased sleep latency and decreased sleep efficiency (Andersen et al. 2013) similar to results seen with DAT inhibitors. *Chapter II will examine if these findings will extend to cocaine self-administration. Using a choice procedure, Chapter II will examine the effects of cocaine self-administration on several sleep measures, recorded using a minimally invasive technique, that have been recently reported to be disrupted by methamphetamine and the DAT inhibitor RTI-336.*

Further supporting a relationship between cocaine use and sleep problems, clinical literature has suggested that sleep deprivation is a factor that can induce patients

to relapse to drug taking. Previously, acute sleep deprivation was shown to increase the rate that rats' self-administered cocaine (Puhl et al., 2009). There is also evidence to support a relationship between the effects of sleep deprivation and cocaine self-administration. For example, Volkow and colleagues showed that one night of sleep deprivation in humans caused decreases in DA D2 receptor availability in the striatum and thalamus but did not affect DAT availability (Volkow et al., 2008). Subsequent studies by this group involved administering methylphenidate to sleep-deprived and rested-waking state individuals and found that the ability to elevate DA was not influenced by sleep deprivation, suggesting D2 receptor downregulation, rather than elevated DA concentrations as the mechanism mediating the effects of methylphenidate on sleep (Volkow et al., 2012). *There is also evidence of an inverse relationship between DA D2 receptor availability and cocaine reinforcement (Volkow et al., 1999b; Morgan et al., 2002; Nader et al., 2006; Dalley et al., 2007) and cocaine decreases DA D2 receptor availability (Volkow et al., 1999; Martinez et al., 2004; Nader et al., 2006). Therefore, a second goal of Chapter II was to examine how sleep disruption affects cocaine self-administration in our monkey model and determine if sleep disruption increases the reinforcing strength of cocaine.*

There are several methods in that sleep can be assessed (e.g., telemetry, EEG, actigraphy). Actigraphy measures have been used to assess sleep-wake patterns in rhesus macaques (Barrett et al., 2009) and in humans (Sadeh et al., 1995; Kushida et al., 2001; Sadeh and Acebo 2002; Ancoli-Israel et al., 2003) and are considered a valid index of human sleep (Sadeh et al,. 1995; Kushida et al., 2001). Further, a recent review indicated that pharmacological and non-pharmacological changes in sleep measures could be

detected using actigraphy (Sadeh 2011). *Thus, Actigraphy is a non-invasive technique that affords the opportunity to reliably examine activity and determine several sleep measures. Rhesus monkeys are the most extensively studied diurnal nonhuman primates and have features, such as consolidated nighttime sleep, that are similar to humans (Balzamo et al., 1977; Masuda and Zhadanova 2010). Similarities in sleep architecture between rhesus monkeys and humans make them an excellent model for studying human sleep (Daley et al., 2006). Thus, when studying sleep in Chapter II and III, actigraphy was used to monitor activity and calculate sleep parameters.*

In conclusion, substance abuse and insomnia are two major health concerns in the U.S. and elucidating the relationship between these two disorders may help in the search for effective treatment strategies aimed at both conditions. While research continues to examine potential treatment strategies, there is limited research examining the relationship between cocaine abuse and sleep. Elucidating this relationship would increase the number of potential treatment strategies to be examined if a relationship is determined. It is also important to determine other consequences of cocaine use as well in our quest for a suitable treatment for cocaine addiction.

Interestingly, a study determining the association of navigational spatial learning and memory with circadian activity in elderly rhesus monkeys found that poor performance was associated with disruptions in circadian rhythms (Haley et al., 2009). This introduces another significant consequence of cocaine addition, which is that chronic cocaine use results in disruptions of executive funciton. Executive function includes all of the processes involved in learning, monitoring and adapting to stimuli to produce complex, goal-oriented behaviors. It has been proposed that, from a

psychological and neurological perspective, addiction is a disorder of altered cognition with addiction occuring in two distinct stages (Gould, 2010). The first stage occurs as an individual's drug use goes from occasional to chronic and uncontrolled and the second stage is marked by the development of clinical features that include a vulnerability to relapse, and alterations in cognitive processes, among others. Interestingly, several drugs of abuse, such as amphetamine, nicotine, and cocaine have been shown to acutely enhance learning and/or attention (Mattay, 1996; Del et al., 2007; Kenney and Gould, 2008). However, chronic drug users, irrespective of whether it is opiates or psychostimulants, share some deficits in memory, cognitive flexibility and decision making (Ornstein et al., 2000; Bechara, 2005; Verdejo-Garcia and Perez-Garcia, 2007; Fu et al., 2008; Fernandez-Serrano et al., 2010). Compared to control groups, chronic cocaine users show impaired cognitive performance across multiple cognitive domains, and it is suggested that these effects extend into abstinence and influence both treatment outcomes and predicting vulnerability to relapse. It has been hypothesized that attending to drug-induced cognitive deficits will enhance treatment outcomes (Sofuoglu, 2010; Sofuoglu et al., 2013). *In summary, cocaine use results in deficits in cognitive flexibility (Kelley et al., 2005) making abstinence more difficult. Further, the deficits associated with cocaine use may perpetuate the cycle of drugs use and increase relapse (cf. Rogers and Robbins 2001) and therefore it is possible that tending to an individuals cognitive disruptions may in part decrease relapse. A potential cognitive promoting medication will be examined in Chapter V.*

To assess executive functioning, working memory tasks have been traditionally used, and cocaine use has been shown to produce poorer performance on these tasks

(Verdejo-Garcia et al., 2006; Tomasi et al., 2007). Importantly, research has shown that nonhuman primates can be trained to perform tasks probing specific cognitive domains that are known to be imparied in human cocaine users. In terms of developmental and aging processes, neurotransmitter distribution, and complex social and cognitive behavioral repertoires macaques are reported to have a close homology to humans (Weerts et al., 2007). Cognitive performance has been shown to be significantly disrupted in rhesus monkeys with a history of cocaine self-administration (Gould et al., 2012, 2013). Examining working memory in animal models can be accomplished using visual or spatial cues. One task that has been traditionally used is the delayed-match-to-sample test (DMS). In this test, a visual stimulus is presented to the animal that must be retained across a variable delay interval. Following a predetermined delay, the animal must select the previously presented stimulus from an array of stimuli. If the animal chooses the correct stimulus, a reinforcer is earned. Increasing the cognitive demand can be accomplished by either increasing the delay value or increasing the number of distracter images presented. *To assess working memory in Chapter V, the Cambridge Neuropsychological Test Automated Battery (CANTAB) was utilized. CANTAB is comprised of a series of visual and spatial tasks designed to probe regional brain function by challenging specific cognitive components (Weed et al., 1999) and has been shown to be a valid model for examining working memory in rhesus monkeys.*

Adding to the relationship between cocaine use, sleep disruptions, and cognitive deficits is evidence that sleep deprivation is also responsible for causing cognitive disruptions and may further perpetuate the drug use cycle. Sleep deprivation has been described as having five major effects: 1) cognitive slowing; 2) optimum response shifts;

3) lapsing; 4) memory decrements; and 5) vigilance decrements (Dinges and Kribbs, 1991). It has been reported that sleep deprivation negatively affects levels of alertness and cognitive performance in both humans and animal models (Thomas et al., 2000; Drummond and Brown, 2001; Drummond et al., 2001; Chee and Choo, 2004; Habeck et al., 2004; Habeck et al., 2005; Choo et al., 2005) that may be due, in part, to sleep deprivation being reported to cause subjects to lapse and miss the deadline for responding during the probe phase of memory trials (Habeck et al. 2004). Further, it has been suggested that an absence of sufficient sleep may be as important to learning deficits in chronic cocaine users as it is to sleep-dependent learning in healthy subjects (Morgan et al., 2006). The effects of sleep deprivation on cognition has been extensively studied in the rhesus monkey and the DMS task using multiple delays and stimulus images and effectively measures cognitive deficits produced by sleep deprivation (Hampson et al., 2004, 2009; Porrino et al., 2005; Deadwyler et al., 2007). These studies all used a method of complete sleep deprivation that consisted of 30-36 hours of continued sleep prevention. While the DMS task has effectively measured cognitive disruption induced by sleep deprivation, it has also proven useful to examine the ability of medications to effectively block or attenuate those deficits (Porrino et al., 2005; Deadwyler et al., 2007; Hampson et al., 2009). *Chapter V will also examine the effect of sleep disruption, not total sleep deprivation, has on working memory in rhesus monkeys. Cocaine use has been associated with sleep disturbances in humans (Morgan et al., 2008) and therefore it doesn't appear that total sleep deprivation occurs as a consequence of chronic cocaine use. Thus, based on literature reviewed, it could be hypothesized that chronic cocaine*

users present with disrupted sleep and an effective monkey model of sleep disruption would function as a better model of the human condition.

In pursuit of an effective treatment for cocaine addiction, the information presented thus far would suggest a compound that targets multiple receptor systems focusing on specific receptor subtypes and modulates several physiological consequences of cocaine use. Literature has begun to link the prognostic importance of cognitive performance for treatment retention (Aharonovich et al., 2003) and outcome (Teichner et al., 2001, 2002) and it has been reported that some of the most promising candidate pharmacotherapies for cocaine addiction either promote sleep or daytime wakefulness (Morgan et al., 2006). Thus, an agent with a broad pharmacological profile that has the ability to promote sleep, and may also function as a cognitive enhancer, would appear to have the potential to have a positive influence on cocaine abuse.

QUETIAPINE: AS A TREATMENT OPTION

Quetiapine is an atypical, or second generation, antipsychotic that has approved labeling from the Food and Drug Administration (FDA) for the treatment of the following affective disorders: schizophrenia; acute manic or mixed episodes associated with bipolar I disorder (as monotherapy or in combination with lithium or divalproex); maintenance treatment of bipolar I disorder (in combination with lithium or divalproex); acute depressive episodes associated with bipolar disorder; and adjunctive treatment of major depressive disorder (Lexi-Comp Online, 2013). It has been proposed that quetiapine exerts its activity primarily through a combination of DA D2 and 5-HT_2 antagonism. However, the pharmacological mechanism of action of quetiapine is

multifunctional with it acting as an antagonist at serotonin 5-HT_{1A} and 5-HT_{2A}, dopamine D1 and D2, histamine H_1, and adrenergic α_1 and α_2 receptors (Goldstein, 1999; Reeves and Brister, 2007; Riedel et al., 2007; Lexicomp 2013).

Although quetiapine is FDA approved to treat a number of disorders, it has become increasingly utilized for off-label uses (Murphy et al., 2008). A group of authors examined patterns of quetiapine use in their institution and found that only 28.5% of the patients were receiving quetiapine for an approved indication, with the most common uses being to treat agitation, anxiety, or insomnia mostly in patients with depressive or substance use disorders (Phillip et al., 2008). Thus, besides showing efficacy in its approved indications, quetiapine has been used off-label to treat anxiety and insomnia (Murphy et al., 2008; Philip et al., 2008; Wine et al., 2009; Dolder and McKinsey, 2010) with demonstrated efficacy being reported (Cohrs et al., 2004; Wiegand et al., 2008; Ravindran et al., 2010). Subsequently, quetiapine has been characterized in recent literature as an antipsychotic, anxiolytic and antidepressant (Borison et al., 1996; Pisu et al, 2010; Prieto et al., 2010; Sajatovic et al., 2002). In addition to its supposed efficacy in sleep disturbances and other off-label indications, clinical literature has shown promise for quetiapine as a treatment for cocaine abuse (Brown et al., 2002, 2003; Kennedy et al., 2008). The potential use of quetiapine for the treatment of cocaine addiction is intriguing since quetiapine only temporarily binds postsynaptic D2 receptors and dissociates rapidly, which contributes to a favorable side effect profile (Kapur et al., 2000; Morin, 2007).

Treatment guidelines have recommend the use of antipsychotics in patients with concomitant psychiatric disorders and insomnia (NIH 2005; Schutte-Rodin et al., 2008)

and the lifetime prevalence rates of substance abuse in patients with bipolar disorder are as high as 60% (Regier et al., 1990; Strakowski and DelBello, 2000). It was previously reported that after administering antipsychotic medications to control psychotic symptoms, the observed quantity of substance use decreased (Volkow et al., 2002). More specifically, quetiapine was examined as add-on therapy in a group of outpatients with bipolar disorder and cocaine dependence. It was reported that quetiapine administration significantly decreased drug cravings and the amount of money spent on cocaine, with a trend toward a reduction on days of cocaine use (Brown et al., 2002). To complement this study, quetiapine efficacy was also investigated for the treatment of cocaine dependence in individuals who lacked psychotic symptoms. Results showed quetiapine significantly decreased craving for cocaine, with a downward trend in the money spent on cocaine and a decrease of 22% in positive urine drug screens (Kennedy et al., 2008). A retrospective chart review examining the potential benefits of quetiapine in substance dependence disorders revealed a mean decrease in Likert score (a measure of craving) with negative breathalyzer and urine test results (Sattar et al., 2004). In a study examining cocaine and amphetamine use in patients with psychiatric disorders, it was reported that patients placed on quetiapine showed a reduction in the Cocaine Craving Questionaire (~54% decrease) with a significant change from baseline noted when compared to a group receiving a typical antipsychotic (Brown et al., 2003). In that study, quetiapine was reported as being superior to haloperidol in treating both mood symptoms and drug cravings. Although quetiapine has shown promise as a treatment option for cocaine abuse, other atypical antipsychotics were proven ineffective. Specifically, the 5-HT_{2A}/D2 like antagonists, risperidone and olanzapine, have been reported as being ineffective for

reducing cocaine use and craving (Sattar and Bhatia, 2003; Smelson et al., 2004; Reid et al., 2005; Loebl et al., 2008). *The effect of quetiapine on cocaine self-administration will be examined in a rhesus monkey model of cocaine abuse in Chapter III. To examine quetiapine as a potential treatment, cocaine choice will be examined during both acute and chronic oral treatment with quetiapine.*

Positive results for quetiapine as a treatment for substance abuse have also been documented for abuse of opioids, methamphetamine, and alcohol, further suggesting the potential role of quetiapine in treating addiction. Pinkofsky et al. (2005) reported that 74% of patients believed quetiapine helped reduce cravings for opioids and 49% reported that quetiapine helped reduce anxiety symptoms associated with opioid withdrawal. In a study comparing risperidone and quetiapine (both atypical antipsychotic medications), administration of either drug resulted in decreases in cocaine and methamphetamine craving with those reductions predicting less frequent drug use (Nejtek et al., 2008). Finally, quetiapine, given as a monotherapy, was also shown to decrease alcohol consumption, craving for alcohol and psychiatric symptom intensity in patients with comorbid Bipolar Disorder and alcohol dependence (Martinotti et al., 2008). *However, all of these studies carried potential limitations such as psychiatric comorbidities, polypharmacy, placebo effects, and concomitant substance use disorders. Further, many of the studies examining the efficacy of quetiapine in substance abuse have a similar limitation in that they lack a placebo control group, so it is difficult to rule out a "placebo-effect" when interpreting their results. Finally, many of the studies have strict inclusion/exclusion criteria limiting the sample size and most were accompanied by high attrition rates for various and obvious reasons. Thus, examination of the effect of*

quetiapine treatment on cocaine self-administration in rhesus monkeys (Chapter III) will provide a critical piece of information and the results will be reflective of a model of cocaine abuse that is devoid of some of the above mentioned limitations.

As stated earlier, quetiapine has also been reported to be prescribed off-label for the treatment of sleep withdrawl (Robert et al., 2005; Rowe, 2007; Philip et al., 2008) and insomnia (Wine et al., 2009; Dolder and McKinsey, 2010). However, there are only a limited number of studies that have examined the efficacy of quetiapine as a sleep-promoting agent. In one such study, conducted at a Thailand teaching hospital, quetiapine administration tended to increase sleep time and reduce sleep latency, although these measures did not reach statistical significance (Tassniyom et al., 2010) likely due to a low number of participants. Although these results were positive, similar results were reported from patients receiving placebo, so the possibility of a "placebo-effect" cannot be ruled out. In another study, quetiapine was shown to significantly improve objective (total sleep time and sleep efficiency) and subjective (Pittsburgh Sleep Quality Index and sleep diaries) measures from baseline in a group of patients diagnosed with primary insomnia (Wiegand et al., 2008). *Although these limited studies suggest quetiapine may be beneficial at promoting sleep, a recent meta-analysis reported inconclusive evidence regarding the efficacy of quetiapine for treating insomnia (Maher et al., 2011) indicating that more research is needed to make any conclusions. Also important, would be to examine the effect quetiapine treatment has on sleep measures in the presence of cocaine self-administration. These effects will be examined in Chapter III.*

Finally, quetiapine could potentially provide a beneficial effect in cocaine addicts by promoting cognitive function or by blocking the cognitive deficits induced by chronic

cocaine use. Although this relationship has not been directly assessed herein, literature is available that would support this strategy. In an open-label trial examining the effect of quetiapine in patients with comorbid schizophrenia and substance use disorders the investigators reported significant improvements in substance abuse measures, psychiatric symptoms, and cognition (Potvin et al., 2006). Adding evidence to the cognitive-promoting capabilities of quetiapine another study showed that quetiapine improved executive functioning in patients with borderline personality disorder (Van den Eynde et al., 2009) and partially improved cognitive functions in schizophrenic patients (Zhang Y et al., 2009). Further, it has been reported that quetiapine improved self-rated cognitive dysfunction and subjects' performance on neurocognitive tasks (Voruganti et al., 2007). The authors of this study suggested that the cognitive benefits of quetiapine may be attributable to its loose binding to and fast dissociation from DA receptors, which was proposed in this paper as a beneficial effect of quetiapine. Lastly, it was reported that repeated quetiapine administration was able to ameliorate phencyclidine (PCP)-induced cognitive deficits in mice (Tanibuchi et al., 2009). To complement that study, cognitive inflexibility in rats, induced by ketamine administration, was reversed by quetiapine and quetiapine promoted set shifting in cognitively unimpaired controls (Nikiforuk and Popik, 2012).

While several studies support the cognitive promoting effects of quetiapine, there is also literature suggesting that quetiapine is ineffective with regard to cognitive measures. Contrary to the study by Tanibuchi et al. (2009), it was reported in rats that chronic quetiapine did not attenuate PCP-induced cognitive disruptions, and further, at the highest dose tested, quetiapine disrupted performance in the 5-choice serial reation

time task in the absence of PCP treatment (Amitai and Markou, 2009). A study examining the effects of quetiapine on cognition in a group of first-episode antipsychotic-naïve patients concluded that there was very little evidence of the efficacy of quetiapine on cognition (Anderson et al., 2011) and further, results from another study reported no efficacy of quetiapine on cognitive improvement in a sample of adolescents with psychosis (Robles et al., 2011). Finally, the combination of quetiapine with an SSRI resulted in no effect on cognitive functioning although the authors proposed that the failure may be caused by attention difficulties owing to somnolence (de Geus et al., 2007). However, another study combining quetiapine with an SSRI showed that the combination resulted in no worsening, and some improvement, of cognitive performance (Olver et al., 2008). *Thus, from the literature available we cannot draw conclusions to the efficacy of quetiapine to promote cognitive function or attenuate deficits in functioning. To partially address this concept, the effect of quetiapine on cognitive performance was examined in Chapter V.*

QUETIAPINE: AS A DRUG OF ABUSE

While quetiapine appears to have potential to be a treatment option for cocaine addiction, there has recently been a growing concern over the abuse potential of quetiapine. A group of researchers examined quetiapine misuse among clients enrolled in a methadone maintenance program and found that 75% of individuals who were prescribed quetiapine had engaged in at least one form of misuse with the participants who reported misuse being significantly younger than those who did not (McLarnon et al., 2012). Although limited reports of quetiapine abuse are available, those reports have

indicated that quetiapine abuse occurs via multiple different routes of administration. Oral abuse of quetiapine has been documented and was detailed 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). It has been noted elsewhere, although not specifically supported by evidence in the literature, that intranasal use would produce effects more rapidly than oral use (Morin, 2007). Intravenous administration of quetiapine has been another reported route for its abuse. In a case report by Hussain and colleagues, it was reported that a female prisoner dissolved two tablets in water and subsequently injected herself (Hussain et al., 2005). The patient described in that report also had a history of substance abuse, depressive episodes, and borderline personality disorder. *Among the cases of quetiapine abuse reported, a common feature is that the individuals had a prior history of a substance use disorder. Therefore, the extensive cocaine self-administration of the rhesus monkeys examined in this study proves to be valuable for studies examining quetiapine abuse. The reinforcing effect of quetiapine will be examined in Chapter IV in four adult female rhesus monkeys possessing an extensive cocaine self-administration history (Hamilton et al., 2010, 2011).*

It was reported that a history of substance abuse was common among inmates who report malingered psychotic symptoms in order to obtain quetiapine (Pierre et al., 2004). Research suggests individuals with an extensive substance use history are at increased risk for misusing sedative and anxiolytic medications (McLarnon, 2011), which may increase risk for abusing quetiapine (Fischer et al., 2010; Sansone et al., 2010).

Confirming these earlier findings, it was recently reported that individuals with a history of anxiolytic/sedative misuse were more than 8 times more likely to report quetiapine misuse (McLarnon et al., 2012). Quetiapine has been described, by those abusing the medication, as having a calming effect and is sometimes referred to as "quell" or "baby heroin" among the prison population (Waters and Joshi, 2007). While many of the initial reports of quetiapine abuse have mainly involved incarcerated individuals, it should not discount the possibility that it would be abused by non-incarcerated individuals. *Of note, outside of the prison population, it was reported that a patient injected himself with mixture of cocaine and quetiapine so he could experience hallucinogenic effects (Waters and Joshi, 2007). Thus, quetiapine may not only be abused individually, but there is the possibility that it may be co-abused with other substances of abuse in a manner similar to "speedballing" (combining cocaine and heroin). Combination i.v. cocaine and quetiapine self-administration will also be examined in Chapter IV to determine the reinforcing effect.*

While the abuse of quetiapine is pharmacologically perplexing, and without a clear explanation, a survey of buyers and sellers of black-market drugs revealed that quetiapine (25 mg dose) sells for $3-8, which is comparable to the amount charged for benzodiazepines (e.g., alprazoloam or Xanax®, Tarasoff and Osti, 2007) indicating a black market demand for the drug. Thus, although lacking a definitive explanation, several hypotheses have been postulated as to why quetiapine is abused. Literature suggests that the abuse of quetiapine is most likely related to the drug's sedative and anxiolytic properties (Pierre et al., 2004; Pinta and Taylor, 2007) with the motivation appearing to be self-medication for anxiety and insomnia (Pierre et al., 2004; Reeves and

Brister, 2007; Kaya et al., 2009). Further, in an article by Hanely and Kenna (2008), the authors suggest that antipsychotics, as well as other psychotropic drugs, are used for their sedative and anxiolytic properties in place of benzodiazepines and barbiturates that are more difficult to obtain due to their already known abuse liability. Finally, the calming and sedating effects of quetiapine appear to be helpful in patients experiencing anxiety, restlessness, and insomnia associated with withdrawl and craving for central nervous system stimulants (Morin, 2007). This latter observation could help explain the use by prison inmates with limited access to more typical drugs of abuse.

More specifically, it has been suggested that a likely explanation for the abuse potential of quetiapine is related to its antihistaminic effects (Fischer and Boggs, 2009) with reports that quetiapine has a high antagonistic affinity for the histamine H1 receptor, especially in relationship to its affinity at D2 receptors (Kroeze et al., 2003). A lower affinity for the D2 receptor would also support a possible abuse potential due to a reduced extrapyramidal side effect profile (Kapur et al., 2000; Tauscher et al., 2004; Farah, 2005; Morin, 2007) and therefore is not likely to produce euphoria or enhance dysphoria associated with drug withdrawl (Morin, 2007). There are multiple reports in humans that show antihistamines are misused (Halpert et al., 2002; Bailey and Davies, 2008; Thomas et al., 2009). Individuals with a history of abusing sedatives have ranked antihistamines significantly higher on "liking" versus placebo (Preston et al., 1992) and not significantly different from the benzodiazepine lorazepam (Mumford et al., 1996). Data are available from clinical studies demonstrating diphenhydramine, an antihistamine, functions as a positive reinforcer (Preston et al., 1992; Mumford et al., 1996). The abuse potential of antihistamines has also been documented in pre-clinical

studies. In nonhuman primates and rodents, antihistamines demonstrate behavioral properties similar to cocaine (McKearney, 1982; Bergman and Spealman 1986, 1988; Bergman, 1990; Jun et al. 2004). Like cocaine, diphenhydramine, an antihistamine, has been shown to increase extracellular DA levels in similar brain areas (Tanda et al., 2008). Behavioral studies in nonhuman primates have found that antihistamines can maintain responses in cocaine-conditioned animals (Bergman and Spealman, 1986; Sannerud et al., 1995) and lead to motor excitation (Evans and Johanson, 1989). Although these effects in nonhuman primates contrast the calming and sedating effect of antihistamines in humans, they support antihistamines functioning as reinforcers.

Interestingly, 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 a greater reinforcing strength than was predicted based on additivity alone (Wang and Woolverton, 2007). Finally, self-administered combinations of cocaine (0.03 mg/kg/injection) and diphenhydramine resulted in significant increases in response rates compared to cocaine alone in rhesus monkeys (Banks et al., 2009). Although diphenhydramine was previously shown to increase extracellular levels of DA (Tanda et al., 2008), Banks et al. (2009) noted that diphenhydramine did not signficantly increase extracellular levels of DA in the caudate nucleus, nor did the combination of diphenhydramine and cocaine enhance the increases in DA induced by cocaine alone. The authors concluded that their data supports the notion that combinations of an antihistamine and cocaine produce an enhanced reinforcing effect, although this enhancement does not appear to be through increased extracellular DA. *These data would suggest that it is possible that combinations of*

quetiapine and cocaine would be more reinforcing than cocaine alone, and this hypothesis was examined in Chapter IV.

Although reports of quetiapine abuse are available, there is little research (either in humans or animal models) examining the abuse potential of quetiapine. 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 especially with reports that quetiapine overdose has resulted in death (Fernandes and Marcil, 2002). 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). *Thus, the aim of Chapter IV will be to thoroughly investigate the reinforcing effect of quetiapine in adult female rhesus monkeys and also the reinforcing effect of a combination of i.v. cocaine and quetiapine in a separate group of adult male rhesus monkeys.*

Taken together, these studies highlight several novel variables with regard to cocaine abuse. The use of concurrent choice allows for the examination of response allocation – the goal is to find pharmacological variables that don't simply decrease cocaine use, but rather redistribute responding from cocaine to a non-drug alternative. The influence of sleep disruption also significantly impacts maintenance of cocaine abuse. Also, the use and abuse of quetiapine will be described, and the consequences of each of these variables (cocaine, sleep, quetiapine) on cognitive performance are examined in this dissertation.

The overarching goal of this dissertation research is to examine key physiological consequences of cocaine abuse using a nonhuman primate model of cocaine abuse, and subsequently, to investigate the potential for quetiapine as a treatment agent for cocaine addiction.

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Chapter II

THE RELATIONSHIP BETWEEN COCAINE SELF-ADMINISTRATION AND ACTIGRAPHY-BASED MEASURES OF SLEEP IN ADULT RHESUS MONKEYS

Robert E. Brutcher and Michael A. Nader

The following manuscript was accepted for publication in *Psychopharmacology* on March 31, 2013. Stylistic variations are due to the requirements of the journal. Robert E. Brutcher performed the experiments, analyzed the data and prepared the manuscript. Michael A. Nader acted in an advisory and editorial capacity.

Abstract

*Rationale***:** Clinical trials show that chronic cocaine users suffer from sleep disturbances and preclinical research has shown that acute sleep deprivation increases the rate of cocaine self-administration in rats. *Objective*: This study examined the effect of cocaine self-administration on behavioral indices of sleep, and alternatively the effect of sleep disruption on cocaine-maintained responding by rhesus monkeys. *Methods***:** Seven adult rhesus monkeys, fitted with Actical® activity monitors, were trained to respond under a concurrent choice paradigm with food (three 1.0-g pellets) and cocaine (0.003-0.3 mg/kg) or saline presentation. For each monkey the lowest preferred dose of cocaine (> 80% cocaine choice) was determined. Activity data were analyzed during lights out (2000-0600) to determine sleep efficiency, sleep latency and total activity counts. Subsequently, the monkeys' sleep was disrupted (every hour during lights-out period) the night prior to food-cocaine choice sessions. *Results***:** Self-administration of the preferred dose of cocaine resulted in a significant decrease in sleep efficiency, with a significant increase in total lights-out activity. Sleep disruption significantly altered behavioral indices of sleep, similar to those seen following cocaine self-administration. However, sleep disruption did not affect cocaine self-administration under concurrent choice conditions. *Conclusions***:** Based on these findings, cocaine self-administration does appear to disrupt behavioral indices of sleep, although it remains to be determined if treatments that improve sleep measures can affect future cocaine taking.

Key Words: cocaine, sleep, sleep disruption, monkeys

Introduction

Drug addiction is an economically taxing brain disease, costing approximately $593 billion annually, which currently has limited treatment options (Harwood 2000; National Drug Threat Assessment 2010; National Institute of Drug Abuse 2010; Centers for Disease Control and Prevention 2012). There were an estimated 22.1 million people in the USA that met DSM-IV criteria for substance abuse or dependence in 2010, of which 1.5 million had cocaine dependence or abuse (Substance Abuse and Mental Health Services Administration 2010). At present there are no medically approved treatments for cocaine addiction. Thus, treating cocaine addiction represents an important area of concern to healthcare professionals and scientists. Integral to finding appropriate treatment strategies is a better understanding of the physiological consequences of cocaine use.

It is known that most drugs can affect sleep patterns, usually adversely, impacting both the duration and frequency of sleep stages (Barkoukis and Avidan 2007) and literature suggests cocaine abusers encounter a vicious cycle between relapse and sleep dysregulation when trying to abstain from the drug (Morgan et al. 2006, 2008). Thus, it is possible that sleep disturbances may contribute to cocaine addiction and not just be a consequence of the illness. It has been reported that current cocaine use is associated with prolonged wakefulness and hypersomnia is present during early withdrawal (Morgan et al. 2008). Research has shown that with sustained abstinence from cocaine, cocaine abusers exhibit decreased sleep, impaired vigilance and sleep-dependent procedural learning, and spectral activity suggestive of chronic insomnia (Morgan et al. 2006). These sleep disturbances may persist for months to years following abstinence (Gillin et al.

1994; Clark et al. 1998; Drummond et al. 1998; Landolt and Gillin 2001) making these sleep disturbances a continuing problem for abstinent cocaine users. It has also been shown that abstinence-associated sleep-dependent learning deficits are related to changes in sleep architecture supporting the concept that treatments directed at improving sleep could be beneficial in offsetting physiological consequences of cocaine abstinence (Morgan et al. 2008). A recent study in monkeys reported that methamphetamine self-administration increased sleep latency and decreased sleep efficiency (Andersen et al. 2013). One goal of the present study was to extend these findings to cocaine self-administration.

Clinical literature suggests that sleep deprivation is a factor that can induce patients to relapse to drug-taking behavior. Consistent with this clinical observation, preclinical studies have shown that acute sleep deprivation increased the rate at which rats self-administered cocaine (Puhl et al. 2009). There is evidence to support a relationship between the effects of sleep deprivation and cocaine self-administration. For example, Volkow et al. (2008) showed that one night of sleep deprivation in humans caused decreases in dopamine (DA) D2-like receptor availability in the striatum and thalamus but did not affect dopamine transporter (DAT) availability. Subsequent studies by this group involved administering methylphenidate to sleep-deprived and rested-waking state individuals and found that the ability to elevate DA was not influenced by sleep deprivation, suggesting D2-like receptor downregulation, rather than elevated DA concentrations as the mechanism mediating the effects of methylphenidate on sleep (Volkow et al. 2012). Of relevance to the present study, there is evidence of an inverse relationship between DA D2-like receptor availability and cocaine reinforcement

(Volkow et al. 1999; Morgan et al. 2002; Nader et al. 2006; Dalley et al. 2007) and cocaine decreases DA D2-like receptor availability (Volkow et al. 1993; Martinez et al. 2004; Nader et al. 2006). Thus, so a second goal was to examine how sleep disruption affected cocaine self-administration in our monkey model.

In the present study, rhesus monkeys were trained to self-administer cocaine under a concurrent schedule of reinforcement with food pellets as the alternative reinforcer. Activity was monitored in the home cage using Actical® activity monitors, as described previously (Andersen et al. 2010, 2012, 2013). Actigraphy measures have been used to assess sleep-wake patterns in rhesus macaques (Barrett et al. 2009) and in humans (Ancoli-Israel et al. 2003; Kushida et al. 2001; Sadeh et al. 1995; Sadeh and Acebo 2002) and are considered a valid index of human sleep (Sadeh et al. 1995; Kushida et al. 2001). Furthermore, a recent review indicated that pharmacological and non-pharmacological changes in sleep measures could be detected using actigraphy (Sadeh 2011). Rhesus monkeys are the most extensively studied diurnal nonhuman primates and have features, such as consolidated nighttime sleep, that are similar to humans (Balzamo et al. 1977; Masuda and Zhadanova 2010). Similarities in sleep architecture between rhesus monkeys and humans make them an excellent model for studying human sleep (Daley et al. 2006). We hypothesized that cocaine self-administration would disrupt sleep measures and that sleep disruption would increase the reinforcing strength of cocaine.

Methods and Materials

Subjects: Seven individually housed adult (age 16-18) male rhesus monkeys (*Macaca mulatta*) currently trained to respond on a cocaine-food choice paradigm served

as subjects. All monkeys had an extensive (> 5 years) history of cocaine self-administration, as well as treatments with the D3/D2 receptor agonist quinpirole and the D1-like receptor agonist SKF 81297 (Hamilton et al. 2010, 2011). Monkeys were weighed weekly and body weights were maintained at approximately 95% of free-feeding weights by food earned during experimental sessions and by supplemental feeding of LabDiet Monkey Chow and fresh fruit no sooner than 30 minutes after the session; water was available ad libitum in the home cage. Each monkey was 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 experimental manipulations were performed in accordance with the 2003 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 was 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.) and maintained with ketamine (5 mg/kg, i.m.) as needed. Vital signs were monitored for the duration of the surgery. Briefly, 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. The end of the catheter was then 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.). Prior to each self-administration session, the back of the animal was cleaned with betadine and 95% EtOH, and the port was connected to the infusion pump located outside the chamber via a 22-gauge Huber Point Needle (Access Technologies). The pump was operated for approximately 3 s to fill the port and catheter with saline or cocaine prior to starting the session. Each port and catheter was filled with heparinized saline solution (100 U/ml) after every experimental session to prolong patency.

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 switches (5 cm wide) were located on one side of the chamber with a horizontal row of three stimulus lights 14 cm above each switch and a food receptacle between the switches. 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 (BioServ, Frenchtown, NJ). An infusion pump (Cole-Palmer, Inc., Chicago, IL) was located on the top of the chamber.

Activity and sleep measures: In order to quantify behavioral indices of sleep all monkeys were fitted with an Actical® (Phillips Respironics, Bend, OR) activity monitor, an omnidirectional accelerometer that measures the subject's physical activity, secured to the collar. Actigraphy is a non-invasive technique to examine activity and can be used to

determine several sleep measures. Of note, sleep measures obtained can only be inferred as a recorded lack of movement. Activity was recorded in 1-min epoch lengths (1440 epochs/day) and the period of activity during the lights-out cycle was quantified. Data were downloaded and analyzed using Actiware Sleep 3.4 (Mini-Matter Co. Inc., Bend, OR) software. The following behavioral indices of sleep were assessed: sleep efficiency (total sleep time as a percentage of the period of time with the lights out (600 min)); sleep latency (latency before the onset of sleep following lights out); and the total activity in the lights out period. For baseline measures we monitored activity for 1 week in the absence of any other behavioral testing (light-dark cycle, 0600-2000). Baseline measures occurred one week prior to the cocaine self-administration experiments.

Experiment 1. Effects of cocaine self-administration on nighttime activity. Initially, activity was monitored each night for 1 week when experimental sessions were not conducted in the mornings and served as "baseline". For self-administration studies, each morning (~0730), Monday-Friday, monkeys self-administered cocaine under conditions in which food reinforcement was concurrently available (i.e., choice procedure). For these studies, food reinforcement (three 1.0-gram banana-flavored pellets) was contingent upon completing a 30-response fixed-ratio (FR) on one switch, while cocaine (0.003-0.3 mg/kg per injection) or saline presentation was contingent on responding on the other switch under an FR 30 schedule of reinforcement. Reinforcement was contingent on 30 consecutive responses on a switch and sessions ended after 30 total reinforcers or 60 min. Each session began with a forced trial for each reinforcer. Also, following five consecutive same-reinforcer choices there was a forced trial on the

opposing switch. The cocaine dose remained constant for at least 5 sessions and until choice responding was deemed stable (choice was within 20% of the mean responding for three consecutive sessions without trends) before changing the dose. Doses were tested in random order for each monkey. Activity during "lights out" was recorded during this same time period for quantification of sleep measures. Following determination of a cocaine-choice dose-response curve **(**Fig. 1**)**, the lowest preferred dose (i.e., the lowest cocaine dose that engendered ≥ 80% choice on the cocaine-associated switch), based on 3-day means of stable performance, was determined for each monkey.

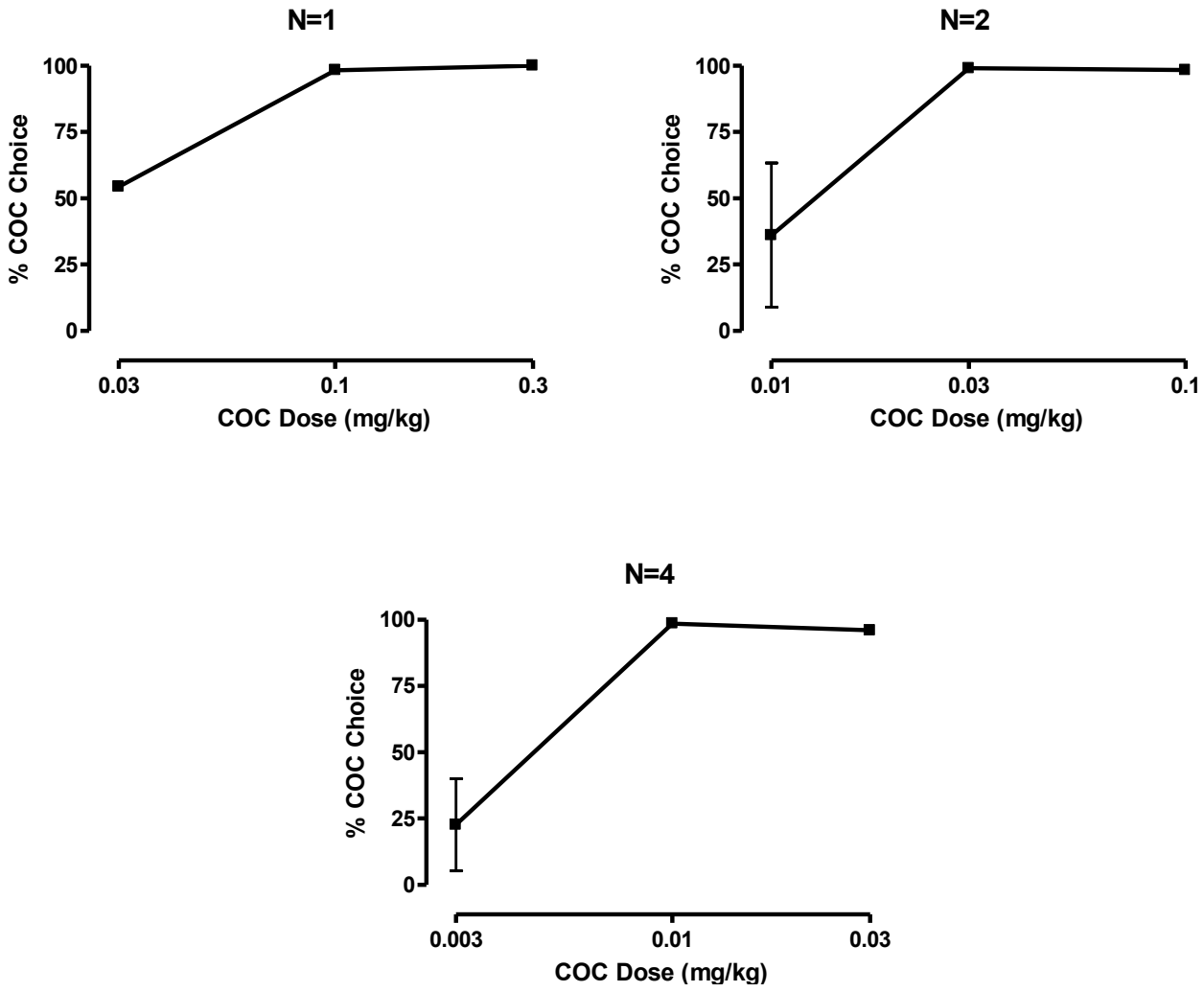

Fig. 1 Mean (± SD or SEM) cocaine-choice curves grouped according to the lowest preferred doses: 0.1 (left), 0.03 (right), and 0.01 mg/kg (bottom)

Experiment 2. Effects of sleep disruption on cocaine self-administration For these studies, the effect of sleep disruption on cocaine self-administration was examined using a half-log unit dose of cocaine below each individual monkey's preferred cocaine dose. Sleep disruption occurred while the monkey was in his home cage and was achieved by keeping the lights on during the typical lights-out period and by having an investigator (R.E.B.) enter the room hourly to awaken the monkeys by tapping on their

cage with a stick. This protocol was designed to disrupt sleep each hour, not to produce sleep deprivation by forcing the monkeys to stay awake all night. On the morning (0730) immediately following a night of sleep disruption, the monkeys were again studied in the cocaine-food choice paradigm and the percentage of cocaine choice was calculated.

Data Analysis: The primary dependent variables were behavioral indices of sleep (sleep efficiency, sleep latency, total lights out activity) and the percent of cocaine choice. Changes in sleep measures were analyzed using a one-way repeated measures ANOVA and the percentage of cocaine choice was analyzed using a paired *t* test. For all analyses, $p<0.05$ was considered statistically significant. All data were analyzed using seven subjects as one monkey lost catheter patency during the study.

Results

Experiment 1. Effects of cocaine self-administration on nighttime activity There was individual-subject variability in sensitivity to cocaine when studied under a concurrent schedule of reinforcement, with the lowest preferred dose being 0.01 (*n*=4), 0.03 (*n*=2) and 0.1 (*n*=1) mg/kg (Fig. 1). While a dose one-half log-units higher resulted in similar (i.e. >80%) cocaine preference, intake at the higher dose was significantly greater ($p<0.05$), with mean (± SEM) intakes of 0.83 (0.33) and 1.50 (0.56) mg/kg at the lowest preferred dose and one-half log-unit higher, respectively. Under baseline conditions (i.e. no morning experimental sessions), nighttime activity (beginning at 2000) averaged 2031.6 counts (range 890.3-4008.3), sleep efficiency was approximately 93% (range 88.5-96.7%) and the latency to sleep was approximately 19 min (range 1.5-32.5

min; see Table 1). There were no significant differences between baseline conditions and saline self-administration for activity, sleep efficiency and latency to sleep **(**Table 1**)**. During the nighttime following self-administration of the preferred dose of cocaine, there was a significant decrease in sleep efficiency ($p<0.05$) and a significant increase in total lights out activity ($p<0.01$); sleep latency modestly ($p=0.1$) increased **(**Fig. 2**)**. Sleep efficiency was not influenced by cocaine dose, while total activity was significantly ($p<0.05$) lower than following the lowest preferred dose, representing an inverted U-shaped function of cocaine dose **(**Fig. 2**)**.

Table 1 Sleep measures for baseline and saline self-administration (expressed as the average ± SEM) with the ranges in parentheses

	Baseline	Saline
Sleep Efficiency (%)	92.92 ± 1.17 (88.5-96.7	94.54 ± 0.98 (89.2-96.8)
Sleep Latency (min)	19.15 ± 4.18 (1.5-32.5)	12.08 ± 2.56 (4-22.0)
Total lights-out Activity Counts	2031.55 ± 392.70 (890.3-4008.3)	1684.20 ± 375.72 (740.0-3736.5)

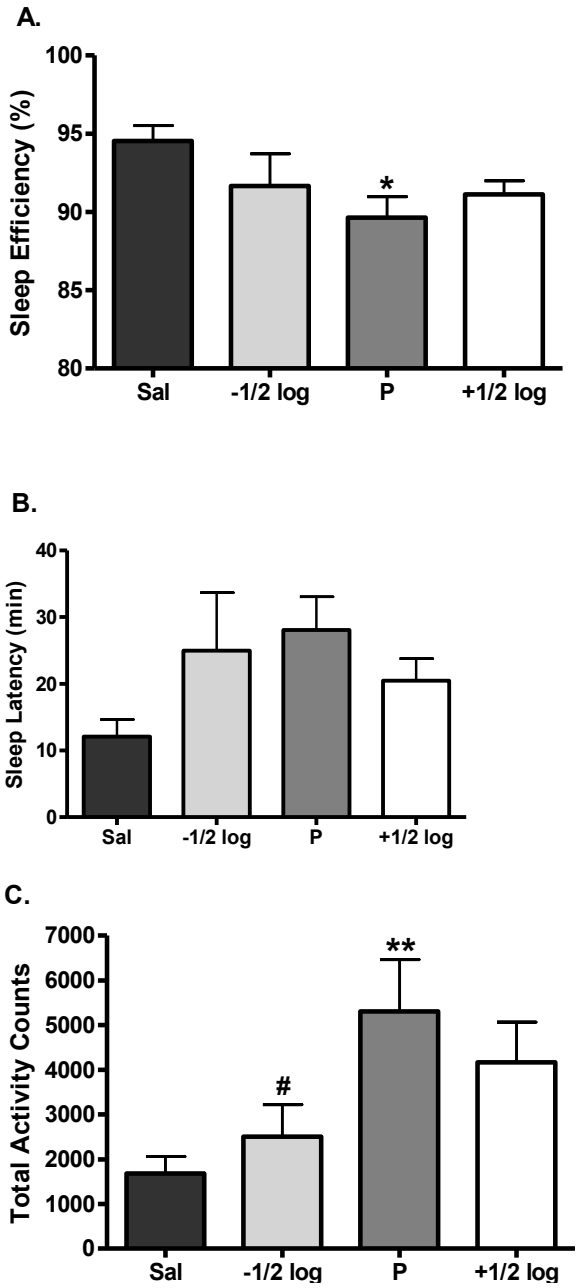

Fig. 2 Mean (± SEM) effect of self-administered saline (*dark gray bars*) and different cocaine doses on (A) sleep efficiency, (B) sleep latency, and (C) total lights-out activity. *p < 0.05 compared with saline, **p < 0.01 compared with saline; #p<0.05 compared with lowest preferred dose; n=7

Experiment 2. Effects of sleep disruption on cocaine self-administration

Leaving the lights on and entering the housing room each hour between 2000-0600 significantly affected behavior, as shown in a representative actogram (Fig. 3). Sleep disruption decreased sleep efficiency ($p<0.0001$), and significantly increased sleep latency ($p<0.001$), and total nighttime activity ($p<0.0001$) **(**Fig. 4**)**. The consequences of sleep disruption were examined on cocaine self-administration using a dose one-half log-unit below the lowest preferred dose. Following one night of sleep disruption, there were no observed differences ($p=0.331$) in cocaine preference, nor were the total number of trials significantly affected (Fig. 5).

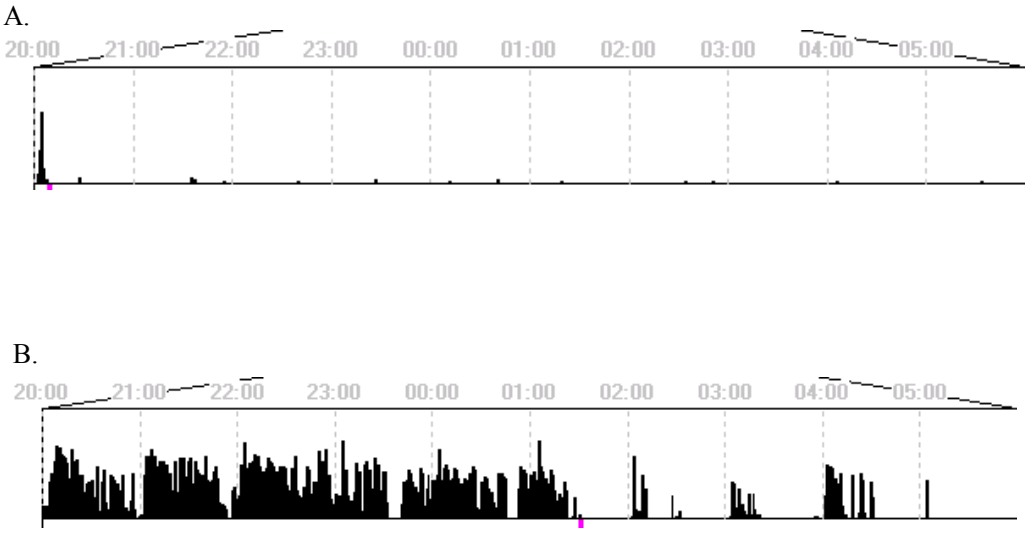

Fig. 3 Individual (R-1568) lights-out (2000-0600) actograms showing activity for low-dose cocaine baseline (A) and sleep disruption (B).

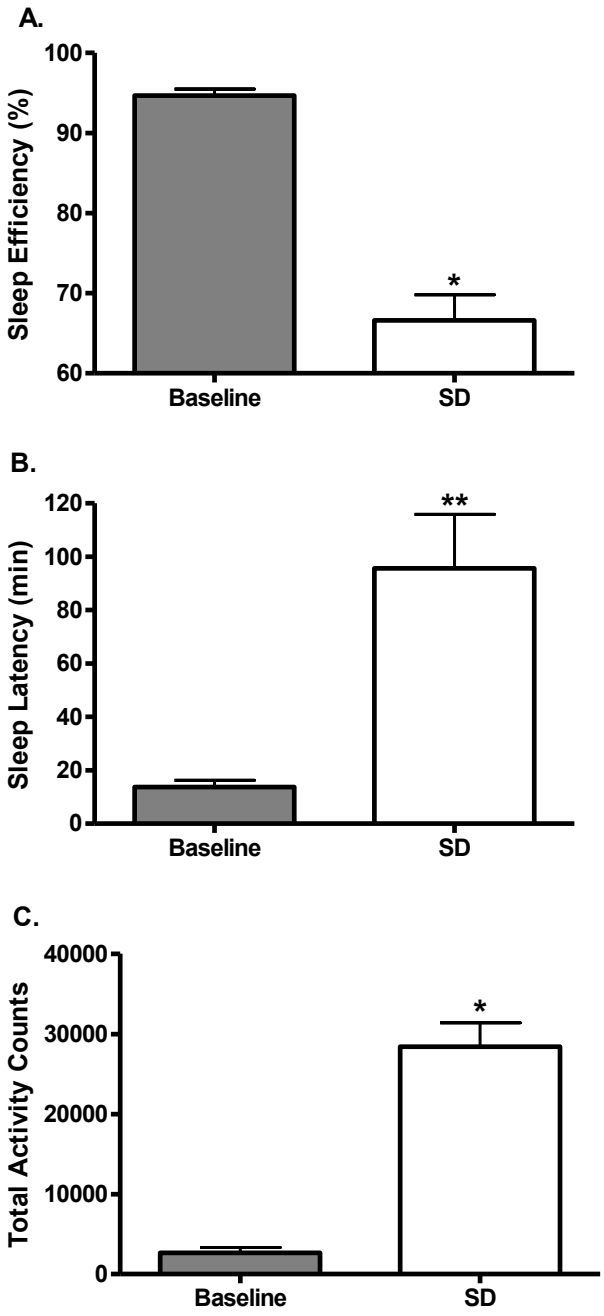

Fig. 4 Mean (± SEM) sleep measures during baseline cocaine conditions (*light gray bars*) and following one night of sleep disruption (*SD; white bars*)): (A) sleep efficiency; (B) sleep latency; and (C) total lights-out activity. *$p < 0.0001$, **$p < 0.01$; n=7

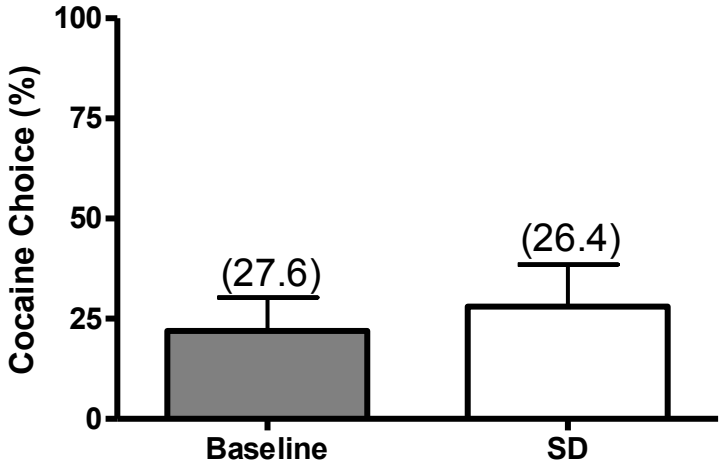

Fig. 5 Mean (± SEM) percent of cocaine choice for baseline conditions (*light gray bars*) and following one night of sleep disruption (*SD; white bars*) with the average total number of trials (out of 30 maximum) in parentheses; *n*=7

Discussion

The present study investigated the relationship between cocaine self-administration and sleep disturbances using actigraphy in adult rhesus monkeys. Behavioral indices of sleep did not differ between baseline conditions (1 week of uninterrupted home cage activity) and conditions where the monkeys chose between self-administered saline and food, indicating that the experimental procedure (i.e. removal from home cage, interaction with the investigator and food reinforcement) did not affect nighttime sleep measures. Following cocaine self-administration, monkeys had significantly lower sleep efficiencies while their latency to fall asleep and total lights out activity increased. For latency to sleep and activity, these measures varied as a function of dose in an inverted U-shaped fashion. Finally, when choosing between a low, non-preferred dose of cocaine and food, nighttime sleep disruption did not significantly increase cocaine choice. While these findings suggest that sensitivity to cocaine may not

be enhanced by single-night sleep disruption, it remains possible that treating the sleep disturbances following high-dose cocaine self-administration may provide a viable adjunct treatment strategy for cocaine addiction.

To our knowledge, these are the first studies to characterize the effects of cocaine self-administration on nighttime activity in a rhesus monkey model of cocaine abuse. Of particular importance was the observation that these effects were noted at the lowest preferred dose of cocaine and were apparent at least 12 h after cocaine self-administration. If the increases in activity and decreases in sleep efficiency were a direct pharmacological mechanism to cocaine reinforcement at 7:30 am, secondary sleep measures obtained following a dose one-half log-unit higher should have shown similar or greater effects relative to the lowest preferred dose**.** Despite significantly greater intakes at the highest cocaine dose, the effects on behavioral indices of sleep were not greater. This is in contrast to results from a study conducted in rhesus monkeys, in which a single, non-contingent, intramuscular dose of 1.0 mg/kg methamphetamine produced greater nighttime activity than lower methamphetamine doses and disrupted nighttime cooling that was observed out to 18 hours after injection (Crean et al. 2006). Additional research is necessary to elucidate the mechanism by which cocaine self-administration disrupts behavioral indices of sleep in a non dose-dependent manner.

Our results suggest that cocaine self-administration is responsible, either directly or indirectly, for causing some of the observed and reported sleep disturbances described by human cocaine users and are similar to a study conducted in humans where REM sleep was found to be shortest on nights following cocaine use (Morgan et al. 2008). These results are also similar to findings that, following an acute intraperitoneal (i.p.)

cocaine injection in rats, the time spent in wakefulness increased and slow-wave sleep decreased in a dose-dependent manner compared to controls (Knapp et al. 2007). The present results in monkeys are also supported by a vast literature showing that the use of stimulant medication is associated with sleep problems. For instance, modafinil, a dopamine transporter (DAT) inhibitor, has been shown to affect the sleep-wake cycle of nonhuman primates (Andersen et al. 2010). These investigators also examined several measures of sleep in rhesus monkeys during chronic treatment with the DAT inhibitor RTI-336 and found significant increases in evening activity, sleep latency and sleep fragmentation, while sleep efficiency was decreased (Andersen et al. 2012). While actigraphy has been shown to correlate significantly with polysomnography (PSG) (Weiss et al. 2010), it should be noted that these investigators also reported that the correlation between Actical and PSG-determined sleep efficiency was just below significance ($r = 0.35$, $p<0.0598$).

The present study also tested the hypothesis that sleep disruption would increase sensitivity to the reinforcing effects of cocaine, providing a potential environmental variable that influenced drug self-administration. To achieve significant disruptions in sleep measures, the lights in the animal housing room were left on all night and a person (R.E.B.) entered the room hourly to awaken the monkeys. This method of sleep disruption was not intended to provide complete sleep deprivation. Although we were able to produce significant disruption in several behavioral indices of sleep, as represented by increases in nighttime activity, no monkey showed increases in the percent of cocaine choice for a dose of cocaine that was one-half log-unit below the preferred dose, in contrast to our hypothesis. One possible explanation for the lack of an

effect on the percent of cocaine choice could be a result of the alternative reinforcer (food pellets) that was available. Clinical literature suggests that sleep loss will increase food intake (Brondel et al. 2010), enhance the drive to consume food (Benedict et al. 2012), and that the associated stress of sleep loss may lead to increased hunger and appetite (Pejovic et al. 2010). Thus, the effect of sleep disruption on cocaine choice with a food reinforcer as the competing stimulus may have negated any effect that we had hypothesized. While we examined sleep disruption on low-dose cocaine self-administration, it may be that the higher, reinforcing doses are more vulnerable to sleep disturbances. Thus, another limitation of the present choice paradigm is that intake for the lowest preferred dose could not be substantially increased if we had tested sleep disruption when that dose was available. Future studies will need to be conducted to more thoroughly examine the relationship between sleep disruption and the consequences on cocaine self-administration.

Sleep has been described as a dynamic activity that is as essential to good health as diet and exercise and as necessary for survival as food and water (National Sleep Foundation 2006). While there appears to be a clear link between sleep problems and substance abuse, there is limited research examining this relationship. It has been shown that one night of sleep loss led to increased impulsivity toward negative stimuli (Anderson and Platten 2011) and impulsiveness is a trait associated with an increased likelihood to self-administer drugs of abuse (Moeller et al. 2001; Perry et al. 2005). Furthermore, a study conducted in adolescents found that those who had more sleep problems were more likely to abuse drugs (Fakier and Wild 2011). Also, a study examining the associations between weekend-weekday shifts in sleep timing and the

neural response to monetary reward in healthy adolescents led the authors to hypothesize that the circadian misalignment associated with weekend shifts in sleep timing may contribute to reward-related problems, including substance abuse (Hasler et al. 2012). Since substance abuse and insomnia are two major health concerns, elucidating the relationship between these two disorders may help in the search for effective treatment strategies aimed at both conditions. While there is a disconnect between cocaine-induced effects on behavioral indices of sleep and the effects of sleep disruption on low-dose cocaine reinforcement, it remains to be determined if treating an individual's sleep disturbances following high doses of cocaine could be a potential treatment strategy for cocaine addiction.

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Chapter III

EFFECTS OF QUETIAPINE TREATMENT ON COCAINE SELF-ADMINISTRATION AND BEHAVIORAL INDICES OF SLEEP IN ADULT RHESUS MONKEYS

Robert E. Brutcher and Michael A. Nader

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Abstract

Clinical literature suggests a link between substance abuse and sleep disturbances although the direct relationship remains to be elucidated. Quetiapine, an atypical antipsychotic has shown efficacy in treating sleep disturbances and other off-label indications, with clinical studies showing promise for quetiapine as a treatment for cocaine abuse. The goal of this study was to examine the effects of quetiapine on cocaine self-administration and behavioral indices of sleep in monkeys. Seven adult male rhesus monkeys, fitted with Actical® activity monitors, were trained to respond under a choice paradigm of food (1.0-g pellets) and cocaine (0.003-0.3 mg/kg per injection) presentation. First, monkeys received acute pretreatment (45 min) with quetiapine (25-75 mg, p.o.) prior to choice sessions; three cocaine doses were studied in combination with quetiapine. Next, the effect of chronic (14-17 days) quetiapine treatment (25-250 mg, p.o., BID) was examined in combination with the lowest preferred cocaine dose (≥ 80% cocaine choice). Behavioral indices of sleep were recorded throughout the study. Acute quetiapine decreased cocaine choice in four of the seven monkeys. Chronic treatment at the lowest preferred cocaine dose resulted in initial decreases, but tolerance developed to these effects. Acute doses of quetiapine did not improve sleep efficiency the following night, while chronic quetiapine significantly improved sleep efficiency; this effect was lost after one day of quetiapine abstinence. These findings suggest that while quetiapine does not affect cocaine use, it may have utility as an adjunct therapy for treating cocaine-related sleep disturbances.

Key Words: quetiapine, cocaine, self-administration, actigraphy, sleep, monkeys

INTRODUCTION

Cocaine dependence represents an important area of concern to healthcare professionals and scientists. At present there are no medically approved treatments for cocaine addiction. Clinical literature suggests a link between substance abuse and sleep disturbances (e.g., Puhl et al., 2009; Morgan et al., 2006) although the direct relationship remains to be elucidated. Using positron emission tomography (PET), Volkow and colleagues have shown that sleep deprivation in humans results in reductions in dopamine D2/D3 receptor availability (Volkow et al., 2008, 2012), as does chronic cocaine abuse (Martinez et al., 2004; Volkow et al., 1993, 1996, 2004). These latter PET findings in human cocaine addicts have been replicated in imaging studies conducted in nonhuman primates (Nader et al., 2006). Taken together these results provide evidence of similarities between the neurobiological consequences of cocaine self-administration and sleep disturbances. Consistent with this literature, it has been hypothesized that treating an individual's sleep disturbances could be beneficial in attenuating physiological consequences of cocaine abstinence (Morgan et al., 2008) and therefore improve the duration of abstinence.

Quetiapine is an atypical, second generation, antipsychotic which has approved labeling from the Food and Drug Administration (FDA) for the treatment of several affective disorders including schizophrenia, acute manic or mixed episodes associated with bipolar I disorder and as an adjunctive treatment of major depression (Borison et al., 1996; Malhi and Berk, 2002; Emsley and Oosthuizen, 2003; Prieto et al., 2010; FDA, 2011; Lexicomp Online, 2013). It has been proposed that quetiapine exerts its activity primarily through a combination of DA D2/D3 and serotonin (5-HT) 2 (5-HT_2) receptor

antagonism. However, the pharmacological mechanism of action of quetiapine is multifunctional with it also acting as an antagonist at 5-HT_{1A} and 5-HT_{2A}, dopamine D1-like, histamine H_1, and adrenergic α_1 and α_2 receptors (Goldstein, 1999; Reeves and Brister, 2007; Riedel et al., 2007; Lexicomp Online, 2013). Although quetiapine is FDA approved to treat a number of disorders, it has become increasingly utilized off-label (Cohrs et al., 2004; Murphy et al., 2008; Philip et al., 2008; Wiegand et al., 2008; Wine et al., 2009; Dolder and McKinsey, 2010; Ravindran et al., 2010). A group of investigators examined patterns of quetiapine use by analyzing information obtained from the pharmacy database in their institution (Butler Hospital, Providence, RI) and found that only 28.5% of the patients were receiving quetiapine for an approved indication, with the most common use being to treat agitation, anxiety, or insomnia mostly in patients with depressive or substance use disorders (Phillip et al., 2008). In addition to its proposed efficacy in sleep disturbances and other off-label indications, results from clinical studies have shown promise for quetiapine as a treatment for cocaine abuse (Brown et al., 2002, 2003; Sattar et al., 2004; Kennedy et al., 2008). The potential use of quetiapine for the treatment of cocaine addiction is intriguing since quetiapine only temporarily binds postsynaptic D2/D3 receptors and dissociates rapidly which, although contributing to a favorable side-effect profile (Kapur et al., 2000; Morin, 2007), may lack sufficient D2/D3 receptor antagonism to decrease cocaine use.

It was previously reported that after administering antipsychotic medications to control psychotic symptoms, substance use decreased (Volkow et al., 2002). Studies showing efficacy of quetiapine have a potential limitation of being evaluated in individuals with psychiatric comorbidities. Further, many of the studies examining the

efficacy of quetiapine in substance abuse have a similar limitation in that they lack a placebo control group. Previous preclinical studies involving monkeys and antipsychotics as potential pharmacotherapies for cocaine abuse have been uniformly negative in outcome (e.g., Woods et al., 1978; Woolverton and Balster, 1979; Nader et al., 1999). However, all those studies involved acute, intravenous drug administration. The present study examined acute and chronic quetiapine, administered via the oral route, in monkeys self-administering cocaine in the context of an alternative non-drug reinforcer. In addition, this self-administration paradigm has been shown to significantly affect sleep efficiency in monkeys (Brutcher and Nader, 2013), providing a baseline on which to assess the ability of quetiapine to influence several behavioral indices of sleep in monkeys. Similarities in sleep architecture between rhesus monkeys and humans make them an excellent model for studying human sleep (Daley et al., 2006).

METHODS

Subjects: Seven adult (age 16-18) male rhesus monkeys (*Macaca mulatta*) with an extensive behavioral history (Hamilton et al., 2010, 2011) including cocaine self-administration under a concurrent cocaine-food choice paradigm (Brutcher and Nader, 2013) served as subjects. Monkeys were weighed weekly and body weights maintained at approximately 95% of free-feeding weights by food earned during experimental sessions and by supplemental feeding of LabDiet Monkey Chow and fresh fruit no sooner than 30 minutes after the session; water was available *ad libitum* in the home cage. Each monkey was 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 experimental

manipulations were performed in accordance with the 2003 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 was 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.) and maintained with ketamine (5 mg/kg) as needed. Vital signs were monitored for the duration of the surgery. Briefly, 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. The end of the catheter was then 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.). Prior to each self-administration session, the back of the animal was cleaned with betadine and 95% EtOH, and the port was connected to the infusion pump located outside the chamber via a 20-gauge Huber Point Needle (Access Technologies). Prior to the start of the daily experiment, the pump was operated for approximately 3 s to fill the port and catheter with the concentration of cocaine (or saline) available during the session. Each port and catheter was filled with heparinized saline solution (100 U/ml) after every experimental session to prolong catheter patency.

***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 switches (5 cm wide) were located on one side of the chamber with a horizontal row of three stimulus lights 14 cm above each switch and a food receptacle between the switches. The food receptacle was connected with tygon tubing to a pellet dispenser (Gerbrands Corp., Arlington, MA) located on the top of the chamber for delivery of 1.0-g banana-flavored food pellets (Bio-Serv, Frenchtown, NJ). An infusion pump (Cole-Palmer, Inc., Chicago, IL) was located on the top of the chamber.

Experiment 1. Effects of quetiapine on cocaine self-administration. For these studies, food reinforcement (three 1.0-gram banana-flavored pellets) was contingent upon completing the response requirement on one switch, while cocaine (0.003-0.3 mg/kg per injection) was contingent on responding on the other manipulandum. For both reinforcers, a fixed-ratio (FR) 30 schedule of reinforcement was used; switching between manipulanda reset the FR value to 30. Sessions ended after 30 total reinforcers or 60 min. Each session began with a forced trial for each reinforcer. Also, following five consecutive same-reinforcer choices there was a forced trial on the opposing switch. The same cocaine dose or saline remained constant for at least 5 sessions and until choice was deemed stable (within 20% for 3 consecutive sessions without trends). Following completion of the entire cocaine dose-response curve, the lowest preferred dose (defined as the lowest cocaine dose that engendered ≥ 80% reinforcers being received on the cocaine-associated switch), based on 3-day means of stable performance, was identified for each monkey.

Once stable, quetiapine (25-75 mg) was given orally 45 minutes prior to the session. The doses of quetiapine tested began with 25 mg and increased if there were no observable effects on the monkey **(Table 1)**. If acute administration of quetiapine produced a reduction in number of cocaine reinforcers the monkey would return to baseline conditions and the effect of acute quetiapine treatment was redetermined before advancing to the next dose of cocaine. The effects of acute quetiapine administration were examined with three cocaine doses in each monkey. Following these experiments, the effects of twice-daily quetiapine treatment was examined in each monkey using the lowest preferred dose of cocaine. Monkeys self-administered their lowest preferred cocaine dose until responding was deemed stable prior to beginning the chronic treatment. Oral administration of quetiapine (25-250 mg, BID) began 45 min prior the session; the initial dose tested was the highest dose administered acutely. Cocaine choice sessions continued daily (Mon-Fri). If the quetiapine dose did not affect choice responding for 3 consecutive sessions, the dose was raised by 25 mg. The entire chronic treatment lasted 14-17 days.

Table 1. Doses of quetiapine for both acute and chronic treatment studies.

Monkey	Acute QTP Dose (mg)	Chronic QTP Dose (mg)
R-1563	**75**	**250**
R-1567	**25**	**25**
R-1568	**75**	**200**
R-1570	**25**	**100**
R-1661	**75**	**100**
R-1662	**50**	**100**
R-1663	**25**	**100**

Experiment 2. Effects of quetiapine on behavioral indices of sleep. In order to quantify sleep measures each monkey was fitted with an Actical® (Phillips Respironics, Bend, OR) activity monitor, an omnidirectional accelerometer that measures the subject's physical activity, secured to the collar. Actigraphy is a non-invasive technique which measures activity and provides a means to determine several sleep measures. Actigraphy measures have been used to assess sleep-wake patterns in rhesus macaques (Barrett et al., 2009) and in humans (Ancoli-Israel et al., 2003; Kushida et al., 2001; Sadeh et al., 1995; Sadeh and Acebo, 2002) and are considered a valid index of human sleep (Sadeh et al., 1995; Kushida et al., 2001). Further, recent review indicated pharmacological and non-pharmacological changes in sleep measures can be detected using actigraphy (Sadeh, 2011). Of note, sleep measures obtained can only be inferred as a recorded lack of movement that is quantified as sleep but could also be that the monkey is awake but not

moving. Activity was recorded in 30-sec epoch lengths (2880 epochs/day) and the period of activity during the lights-out cycle was quantified. For quantification of sleep measures data were downloaded and analyzed using Actiware Sleep 3.4 (Mini-Matter Co. Inc., Bend, OR) software. Sleep efficiency, defined as total sleep time as a percentage of the period of time with the lights out (600 min) was examined for both acute and chronic quetiapine treatment (see Brutcher and Nader, 2013 for more details).

Data Analysis: The primary dependent variables were the percent cocaine choice and sleep efficiency. A one-way ANOVA followed by Bonferroni post-hoc tests for pairwise comparisons was used to analyze the effect of acute quetiapine treatment on cocaine choice and to examine chronic quetiapine treatment on sleep efficiency. To examine the effect of chronic quetiapine on cocaine choice, a repeated measures t-test was used for each monkeys preferred dose. For all analyses, $p<0.05$ was considered statistically significant.

RESULTS

Experiment 1. Effects of quetiapine on cocaine self-administration. There was individual-subject variability in the sensitivity of cocaine preference over three 1.0-g food pellets (**Figure 1**). For four of the seven monkeys, the lowest preferred dose was 0.01 mg/kg cocaine, for one monkey it was 0.03 mg/kg and for two monkeys it was 0.1 mg/kg cocaine. Pretreatment with a single acute dose **(Table 1)** of quetiapine (average dose = 50 mg) resulted in significant ($p < 0.001$) decreases in the percentage of cocaine choice in four out of seven monkeys; the ability of quetiapine to reduce cocaine choice did not appear to be dependent on the potency of cocaine (i.e., the lowest preferred dose) **(Figure**

1). If quetiapine had an effect, it was most likely at the lowest preferred dose, except in R-1661. For two animals, increasing the cocaine dose did not attenuate the effects of acute quetiapine (R-1662, R-1567). Examination of the average number of reinforcers earned, for cocaine and food, at all three doses tested revealed no significant difference between baseline cocaine self-administration and following acute quetiapine treatment **(Figure 2)**.

FIGURE 1.

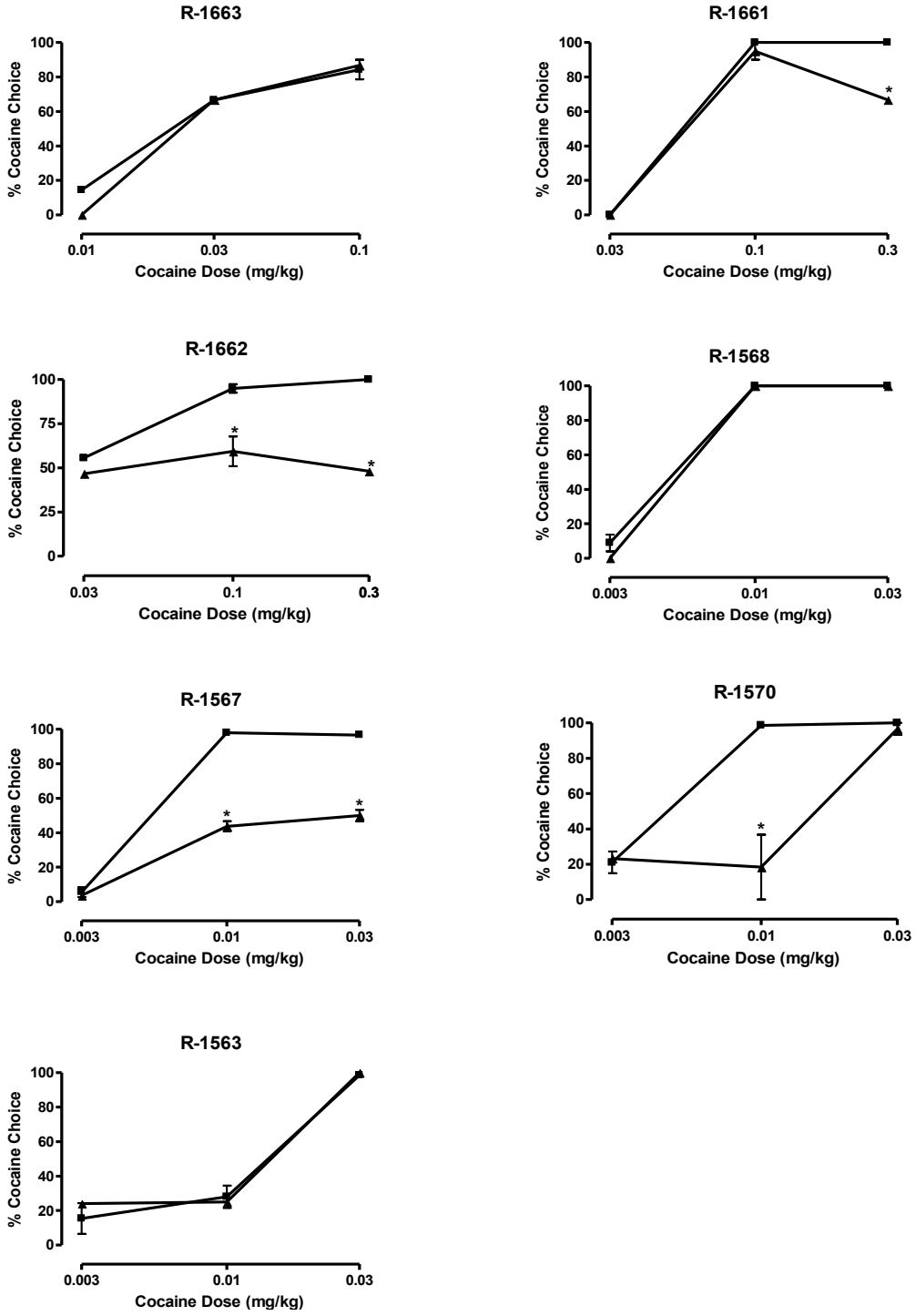

FIGURE 1. Effect of acute quetiapine treatement (filled triangles) on the percent of baseline cocaine choice (filled squares) for individual monkeys. *$p < 0.001$

FIGURE 2.

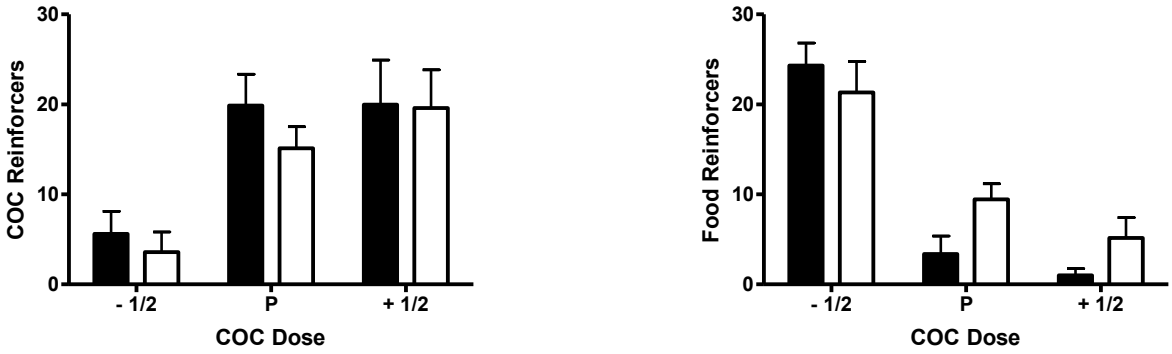

FIGURE 2. Mean number of cocaine (left panel) and food (right panel) reinforcers for baseline cocaine self-administration (black bar) and following acute quetiapine (open bar) pretreatment for the lowest preferred cocaine dose (P) and a half-log unit dose above and below that dose (+1/2 and -1/2, respectively). n=7

Chronic quetiapine treatment did show a downward trend in reducing the percent cocaine choice for the lowest preferred dose **(Figure 3)**, although significance was not achieved. Individual subject data show that chronic quetiapine treatment reduced cocaine choice in five monkeys although tolerance to those effects developed quickly in four of those monkeys **(Figure 4);** these quetiapine effects on cocaine choice are also consistent with the effects on the number of cocaine and food reinforcers **(Figure 5).**

FIGURE 3.

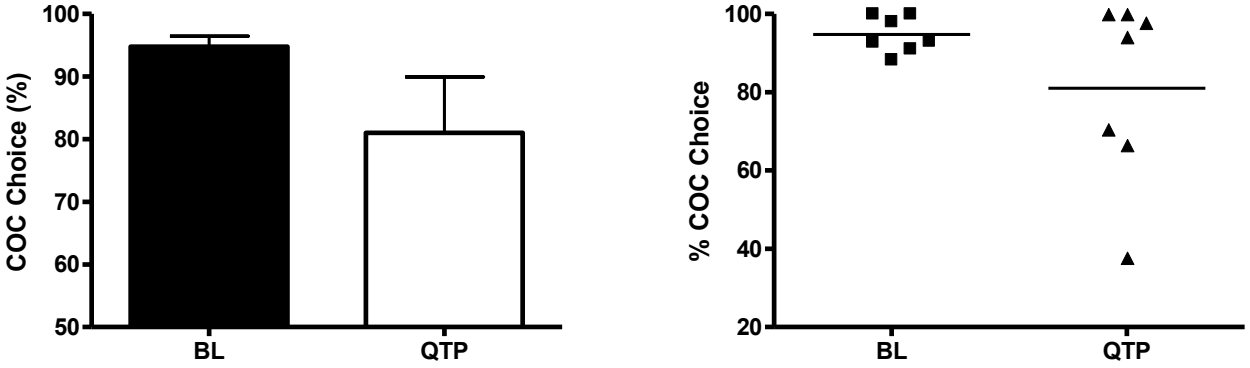

FIGURE 3. Effect of chronic quetiapine (open bar, filled triangles) on self-administration of the lowest preferred dose of cocaine (black bar, filled squares). n=7

FIGURE 4.

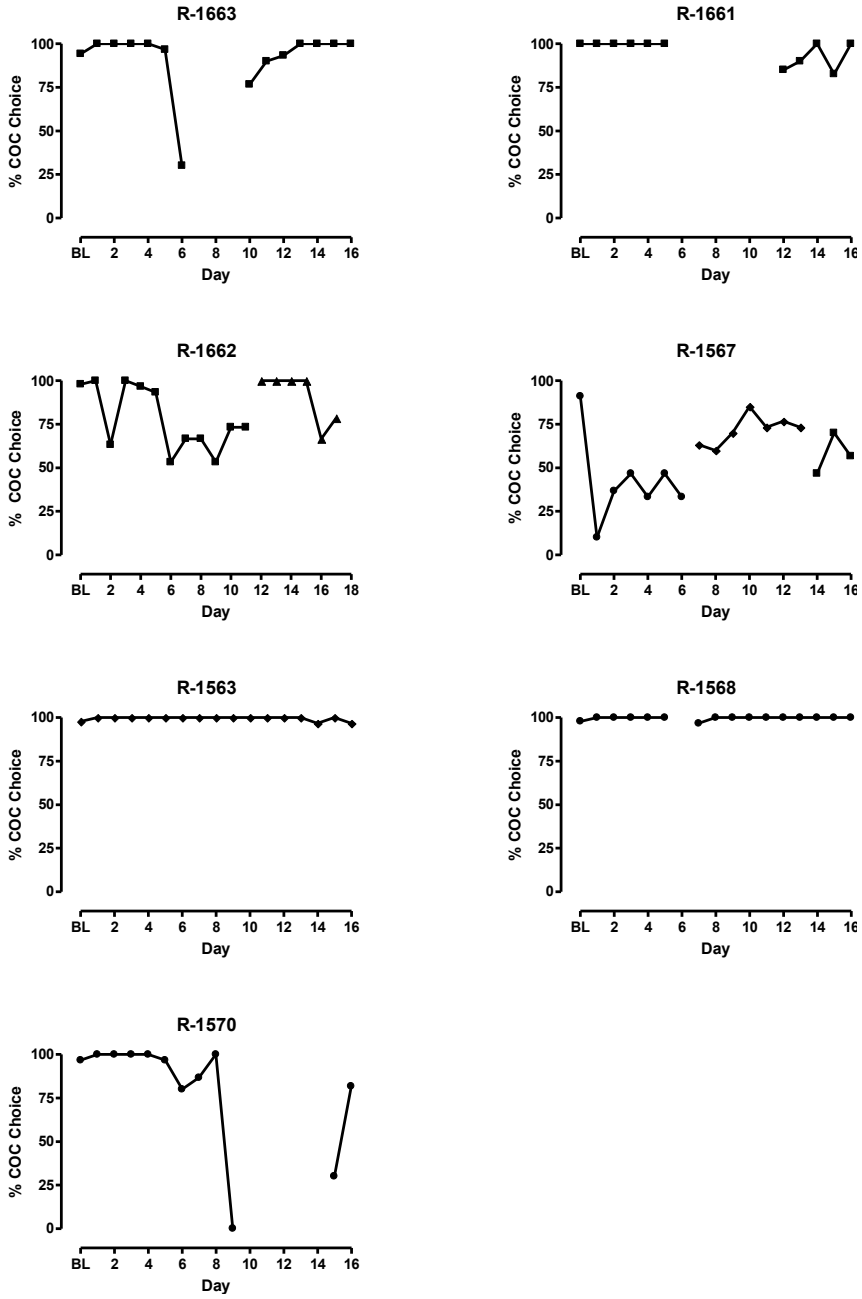

Figure 4. Effect of chronic quetiapine treatment on the percent of cocaine (0.01 mg/kg – filled circles; 0.03 mg/kg - filled diamonds; 0.1 mg/kg –filled squares; 0.3 mg/kg – filled triangles) choice for individual monkeys.

FIGURE 5.

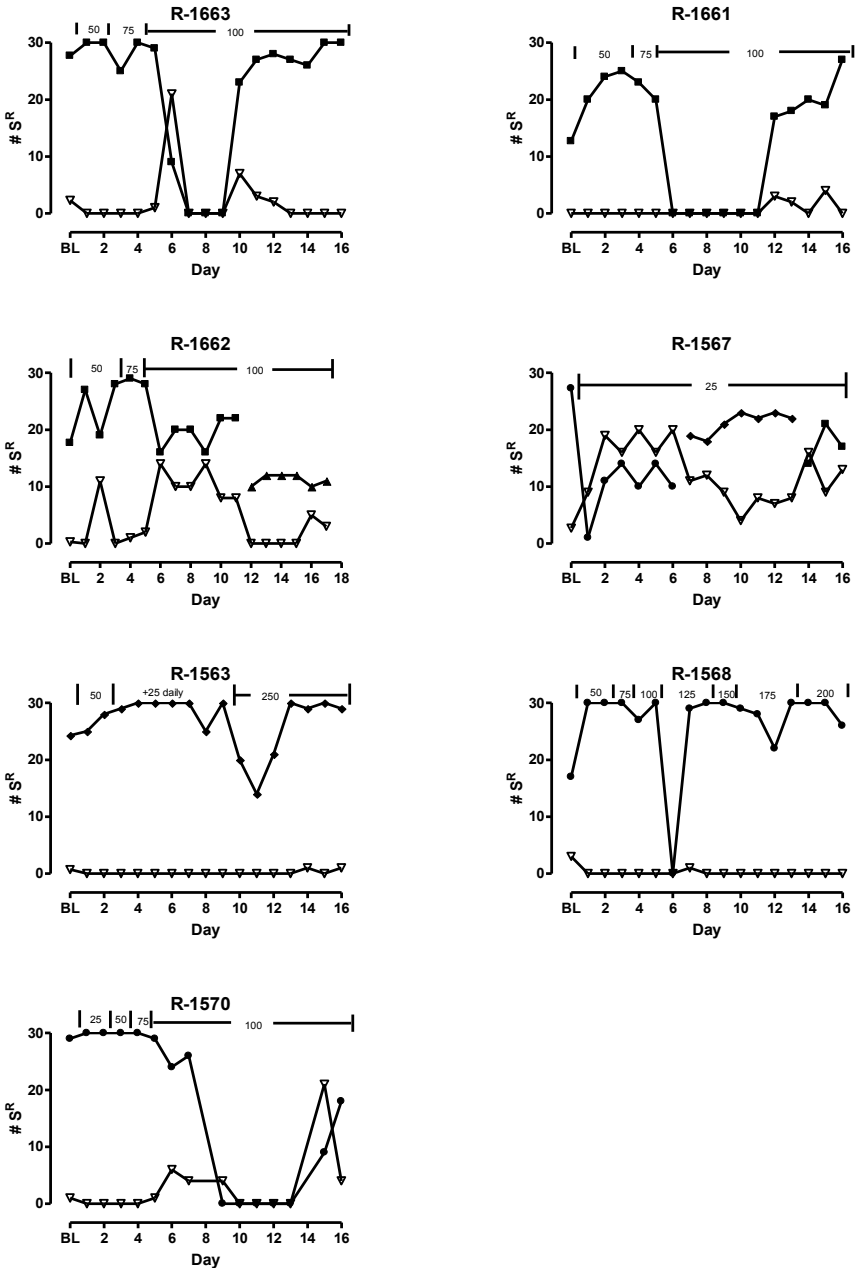

Figure 5. Effect of chronic quetiapine (doses annotated across top of each graph in mg) treatment on the number of food (open, inverted triangles) and cocaine (0.01 mg/kg – filled circles; 0.03 mg/kg - filled diamonds; 0.1 mg/kg –filled squares; 0.3 mg/kg – filled triangles) reinforcers earned for individual monkeys.

Experiment 2. Effects of quetiapine on behavioral indices of sleep. Sleep efficiency was disrupted across three cocaine doses (preferred dose and one-half log-unit above and below that dose) **(Table 2)**. Quetiapine, given as a single acute dose, did not affect the sleep efficiency the evening following treatment and cocaine self-administration **(Figure 6**). Individual variability was observed on the effects of quetiapine treatment on the sleep efficiency, although most monkeys showed improvement in sleep efficiency while undergoing chronic treatment **(Figure 7)**. Chronic twice-daily quetiapine treatment significantly ($p < 0.05$) improved the sleep efficiency following self-administration of the lowest preferred dose of cocaine. Following one day of withdrawal from treatment, sleep efficiency was significantly below that observed while on quetiapine treatment ($p<0.01$) **(Figure 8)**.

Table 2. Mean sleep efficiency (± SEM) for the preffered (P) dose of cocaine and doses one-half log-unit above (+1/2) and below (-1/2) that dose. n=7

Dose	Sleep Efficiency (%) ± SEM
-1/2	96.9 ± 0.8
P	96.8 ± 0.7
+1/2	97.0 ± 0.4

FIGURE 6.

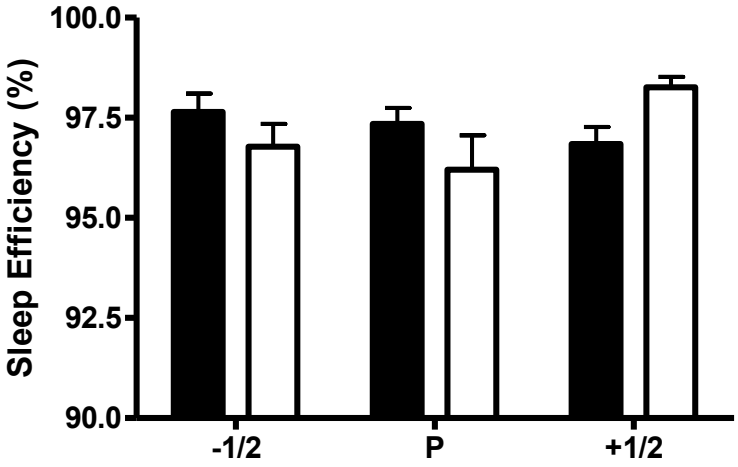

FIGURE 6. The effect of acute quetiapine (open bar) pretreatment on the percent of sleep efficiency the night following cocaine self-administration (black bar) of the lowest preferred cocaine dose (P) and a half-log unit dose above and below that dose (+1/2 and -1/2, respectively). n=6

FIGURE 7.

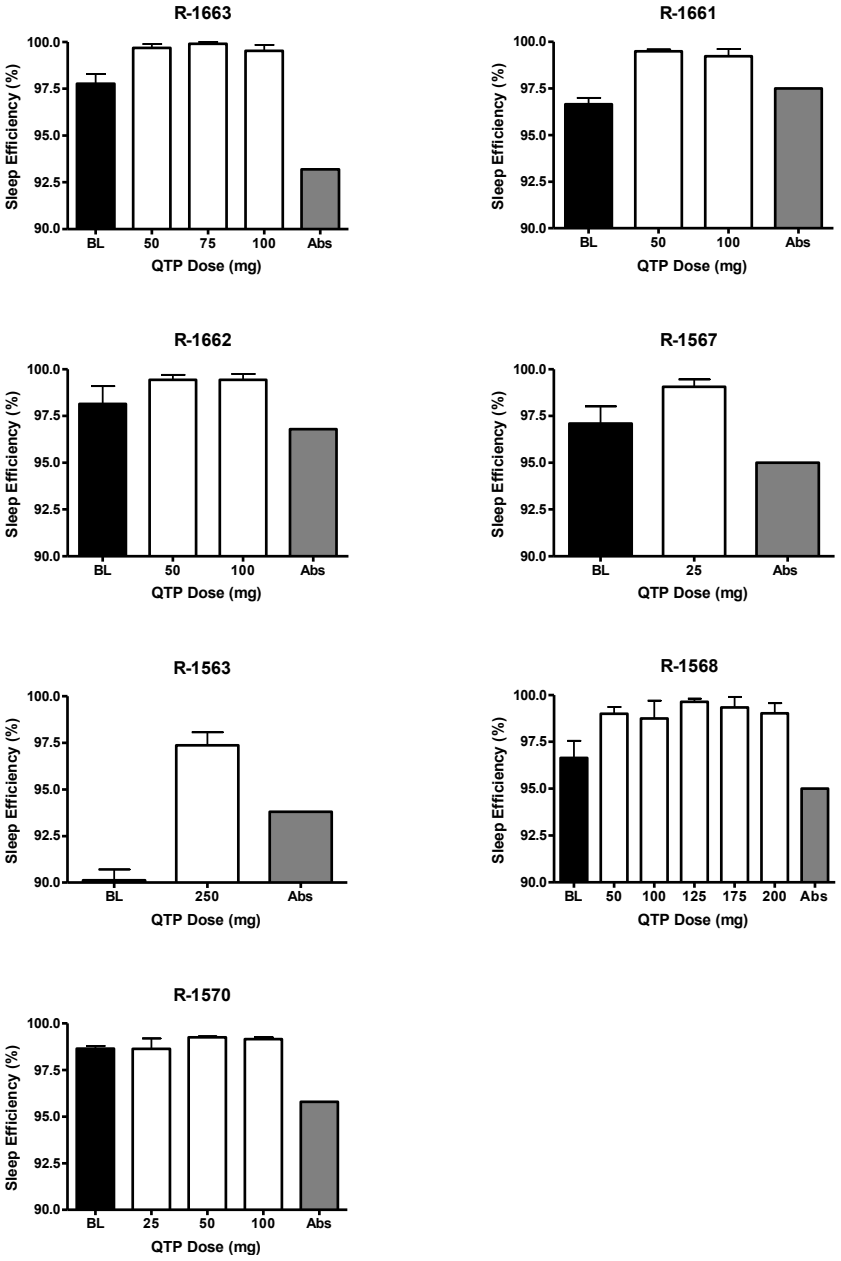

Figure 7. Individual effect of chronic quetiapine treatment (QTP, open bars) on baseline (BL, filled bar) sleep efficiency associated with self-administration of the lowest preferred cocaine dose, and one day after discontinuation of treatment (Abs, gray bars).

FIGURE 8.

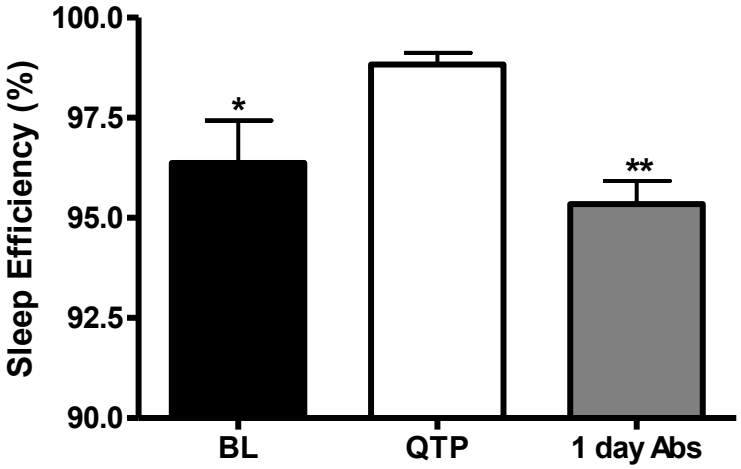

FIGURE 8. Effect of chronic quetiapine (open bar) and one day of abstinence from quetiapine (gray bar) on nighttime sleep efficiency following self-administration of the lowest preferred dose of cocaine (black bar). *$p < 0.05$, **$p < 0.01$, n=7

DISCUSSION

The present study investigated quetiapine, an atypical antipsychotic, as a potential treatment option for cocaine addiction using a monkey model of cocaine abuse. Acute oral administration of quetiapine resulted in decreases in cocaine choice in some, but not all the monkeys. When tested chronically (twice daily oral administration), quetiapine showed modest effects, but tolerance developed to the reductions in cocaine choice in most of the subjects. While single dose acute administration of quetiapine did not improve sleep efficiency the following night, chronic, twice-daily oral administration of quetiapine was able to significantly improve the sleep efficiency, even under conditions when there was no effect on cocaine self-administration. While these findings do not offer support the use of quetiapine as a monotherapy for treatment of cocaine abuse, they

suggest the potential of quetiapine treatment as an adjunct therapy to treat sleep disturbances associated with stimulant abuse.

To our knowledge, these are the first studies to examine the potential of quetiapine as a treatment option for cocaine addiction in a rhesus monkey model of cocaine abuse. While these results are inconsistent with reports showing positive results of quetiapine for reducing substance abuse (Brown et al., 2003; Sattar et al., 2004; Pinkofsky et al., 2005; Potvin et al., 2006), these findings do support the use of quetiapine for the treatment of some adverse consequences of cocaine abuse. One explanation for the divergent effects on cocaine use is that many of the studies showing positive results with using quetiapine to reduce substance abuse are in the presence of a comorbid psychiatric condition. The lifetime prevalence rates of substance abuse in patients with bipolar disorder are as high as 60% (Regier et al., 1990; Strakowski and DelBello, 2000). Decreases in the quantity of substance abuse have been noted following administration of antipsychotic medications to control psychotic symptoms (Volkow et al., 2002). These findings suggest that in the absence of a psychotic disorder quetiapine treatment may lack efficacy in treating cocaine abuse. To support this hypothesis, a recent study which included patients with comorbid bipolar disorder and alcohol dependence, revealed that quetiapine decreased alcohol consumption, craving for alcohol and psychiatric symptom intensity (Martinotti et al., 2008). Interestingly, in that study, quetiapine was used as a monotherapy and not given as adjunctive pharmacological treatment. Other studies report the efficacy of quetiapine as adjunctive therapy. A retrospective chart review examining the potential benefits of quetiapine in substance dependence disorders (alcohol, marijuana, amphetamine and cocaine) revealed a mean

decrease in Likert score (a measure of craving) with negative breathalyzer and urine test results (Sattar et al. 2004). Quetiapine was also examined as add-on therapy in a group of outpatients with bipolar disorder and cocaine dependence. It was reported that quetiapine administration significantly decreased drug cravings and the amount of money spent on cocaine, with a trend toward a reduction on days of cocaine use (Brown et al., 2002). However, contrary to the above hypothesis, quetiapine efficacy was also investigated for the treatment of cocaine dependence in individuals who lacked clinical symptoms of affective disorders and the results showed quetiapine significantly decreased craving for cocaine, with a downward trend in the money spent on cocaine (Kennedy et al., 2008). Additional studies using different preclinical models of cocaine abuse may be necessary to fully evaluate the efficacy of this treatment in deceasing cocaine self-administration.

It is possible that quetiapine may be beneficial in treating substance abuse by inhibiting the sleep disturbances which are a characteristic of drug addiction. Quetiapine is commonly used off-label for a variety of conditions, one of which is insomnia (Hartung et al., 2008; Philip et al., 2008; Wine et al., 2009; Dolder and McKinsey, 2010), although results from a meta-analysis described quetiapine efficacy as inconclusive (Maher et al., 2011). There are, however, several studies showing positive results of quetiapine for treating insomnia (Robert et al., 2005; Wiegand et al., 2008; Tassniyom et al., 2010; Endicott et al., 2012; Sheehan et al., 2012). Clinical treatment guidelines recommend use of antipsychotics in patients with concomitant psychiatric disorders and insomnia (NIH, 2005; Schutte-Rodin et al., 2008). Importantly, the present findings indicated that following discontinuation of chronic quetiapine administration the sleep efficiency declines to baseline self-administration percentages as early as one day. A

recent study showed that sedation associated with quetiapine administration was reported in 100% of the participants receiving quetiapine in the absence of psychatric symptoms, which decreased to 75% by the end of week 1 of treatment to 29% at the end of week 6 (Kennedy et al., 2008). In the present study, improvements in sleep disruption were still evident following two weeks of twice daily quetiapine administration. Supporting these findings, a study examining the efficacy of mirtazapine (a sleep-promoting agent) in patients with comorbid depression and cocaine dependence showed that mirtazapine was superior to placebo in improving sleep, however it was not more effective than placebo in reducing cocaine use (Afshar et al., 2012).

The present findings support earlier work (Brutcher and Nader, 2013) indicating that variables that affect cocaine-induced changes in sleep do not necessarily affect cocaine self-administration. One possible reason for the disconnect between cocaine-induced changes in sleep efficiency (12 hrs after the pharmacological challenge) and subsequent cocaine self-administration the next day is the use of a food-cocaine choice paradigm. While the choice paradigm provides an index of reinforcing strength that is sensitive to recent pharmacological manipulations (Banks and Negus, 2012), it may be a less sensitive baseline for studying interactions with other independent variables presented later in the day (like sleep disruption) than a simple schedule of reinforcement in which cocaine intake can more readily increase or decrease. For example, using an FR schedule of reinforcement, Andersen et al. (2013) reported significant correlations between methamphetamine intake and several behavioral measures of sleep. Nonetheless, the present data using a food-cocaine choice paradigm support the use of quetiapine to

treat cocaine-related disruptions in sleep, with the strategy of the use of another drug to treat cocaine addiction (Karila et al., 2011; Fox et al., 2012).

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Chapter IV

REINFORCING EFFECTS OF QUETIAPINE, ALONE AND IN COMBINATION WITH COCAINE, IN ADULT RHESUS MONKEYS

Robert E. Brutcher and Michael A. Nader

The following manuscript is in preparation to be submitted to *Journal of Pharmacology and Experimental Therapeutics* in April, 2013. Stylistic variations are due to the requirements of the journal. Robert E. Brutcher performed the experiments, analyzed the data and prepared the manuscript. Michael A. Nader acted in an advisory and editorial capacity.

Abstract

Rationale: There is a growing concern over the abuse potential of quetiapine, with multiple case reports of quetiapine abuse. *Objective*: To investigate the reinforcing effects of quetiapine alone and in combination with i.v. cocaine in adult rhesus monkeys.

Methods: Eleven (7 male and 4 female) adult rhesus monkeys were trained to respond under a fixed-ratio (FR) 30 schedule of reinforcement. For quetiapine self-administration, female monkeys responded under an FR 30 schedule for food reinforcement (1-g banana-flavored pellets) and quetiapine (0.01-0.1 mg/kg per injection) or saline was substituted for a minimum of 5 sessions. After the quetiapine dose-response curve was determined, monkeys were treated with quetiapine (25 mg, p.o., b.i.d.) for approximately 30 days and then the quetiapine dose-response curve was redetermined. For combination studies, cocaine self-administration occurred under a two-lever concurrent choice schedule with food reinforcement (three 1.0-gram banana-flavored pellets) as the alternative to cocaine (0.003-0.1 mg/kg per injection) presentation. Once cocaine-food choice responding was stable, the effects of adding quetiapine (0.03 or 0.1 mg/kg per injection) were examined.

Results: Quetiapine alone did not function as a reinforcer; chronic quetiapine treatment did not alter the lack of reinforcing effects. While the addition of quetiapine to cocaine did not affect cocaine choice, it did increase the number of injections earned and total cocaine intake in most monkeys compared to cocaine alone. **Conclusions:** Based on these findings, quetiapine alone does not have abuse potential. However, the addition of quetiapine enhanced the reinforcing effect of cocaine and suggests that the use of quetiapine in cocaine-addicted patients should be closely monitored.

Key Words: quetiapine, cocaine, abuse, self-administration, monkeys

Introduction

Quetiapine is an atypical, or second generation, antipsychotic that has approved labeling from the Food and Drug Administration (FDA) for the treatment of schizophrenia, acute manic or mixed episodes associated with bipolar I disorder (as monotherapy or in combination with lithium or divalproex), bipolar I disorder (in combination with lithium or divalproex), acute depressive episodes associated with bipolar disorder and as an adjunctive treatment of major depressive (Lexi-Comp Online, 2013). 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). Thus, recent literature has characterized quetiapine as an antipsychotic, anxiolytic and antidepressant (Borison et al., 1996; Pisu et al, 2010; Prieto et al., 2010; Sajatovic et al., 2002). The pharmacological mechanism of action of quetiapine is multifunctional with it acting as an antagonist at serotonin 5-HT_{1A} and 5-HT_{2A}, the dopamine D_1 and D_2 receptor subtypes, histamine H_1, and adrenergic α_1 and α_2 receptors (Lexicomp, 2013; Goldstein, 1999; Reeves and Brister, 2007; Riedel et al., 2007).

While this mechanism of action would not suggest abuse potential of quetiapine, there are multiple case reports of quetiapine abuse and via multiple routes of administration (e.g., Morin, 2007). 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 by Hussain and colleagues, it was reported that a female prisoner would dissolve two tablets in water

and subsequently inject herself (Hussain et al., 2005). It was also reported that this patient had a history of substance abuse, depressive episodes, and borderline personality disorder. The drug was described as having a calming effect and has been referred to as "quell" or "baby heroin" among the prison population (Waters and Joshi, 2007).

While the abuse of quetiapine is pharmacologically perplexing, a survey of buyers and sellers of black-market drugs revealed that quetiapine (25 mg dose) sells for $3.00-$8.00 that is comparable to the amount charged for benzodiazepines (Tarasoff and Osti, 2007), indicating demand for the drug. Although lacking a definitive explanation, one hypothesis has gained much attention for explaining the abuse of quetiapine. That hypothesis postulates that the abuse is a result of quetiapine's sedative and anxiolytic effects (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, Hanely 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. Finally, the calming and sedating effects of quetiapine appear to be helpful in patients experiencing anxiety, restlessness, and insomnia associated with withdrawal and craving from central nervous system stimulants (Morin, 2007), which could help explain the use by prison inmates with limited access to more typical drugs of abuse. 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 (either in humans or animal models) examining the abuse potential of quetiapine. 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 this study was to investigate the reinforcing effects of quetiapine in rhesus monkeys. A second goal of this study is to examine the reinforcing effect of combinations of i.v. cocaine and quetiapine in a separate group of monkeys responding under a cocaine-food choice schedule of reinforcement.

Methods and Materials

Subjects: Eleven (4 female and 7 male) individually housed adult (age 16-18) rhesus monkeys (*Macaca mulatta*) with extensive experimental histories, including > 5 years of cocaine self-administration (Hamilton et al., 2010, 2011; Brutcher and Nader, 2013), served as subjects. Monkeys were weighed weekly and body weights maintained at approximately 95% of free-feeding weights by food earned during experimental sessions and by supplemental feeding of LabDiet Monkey Chow 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 2003 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. All monkeys were surgically implanted with an indwelling intravenous catheter and vascular access port (described next) for drug self-administration.

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.) and maintained with ketamine (5 mg/kg, i.m.) as needed. Vital signs were monitored for the duration of the surgery. Briefly, 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 switches (5 cm wide) were located on one side of the chamber with a horizontal row of three stimulus lights 14 cm

above each switch and a food receptacle between the response keys. 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.K. Noyes Co., Lancaster, NH). An infusion pump (Cole-Palmer, 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 betadine and 95% EtOH, and the port was connected to the infusion pump located outside the chamber via a 20-gauge Huber Point Needle (Access Technologies). The pump was operated for approximately 3 s to fill the port and catheter with the concentration of drug or saline available for the session. Experimental sessions were conducted daily (M-F) at approximately 9:00 a.m. with each session lasting until 30 reinforcers were earned or 60 minutes elapsed. Initially, all monkeys responded under an FR 30 schedule of food reinforcement (1.0-g banana-flavored pellets). Once responding was stable (average response rate ± 20% for 3 consecutive sessions with a minimum of 5 sessions) saline was substituted for food for a minimum of 5 sessions and until response rates declined by at least 80% and were deemed stable. Following a return to food reinforcement, various doses of quetiapine (0.01-0.1 mg/kg per injection) were substituted for food for at least the same number of sessions as was required for stable saline-contingent responding. Doses were tested in random order, with a return to food-reinforced responding for at least 3 sessions prior to another substitution. Following each experimental session, the

port and catheter was filled with heparinized saline solution (100 U/ml) to prolong patency.

After completing the quetiapine dose-response curve, each monkey was treated chronically with quetiapine (25 mg p.o., b.i.d.). The first treatment occurred at approximately 0730 (90 min prior to the experimental session) and the second treatment at approximately 1700. During the first 4 weeks of treatment, only food-maintained responding was examined, after which, the quetiapine dose-response curve was redetermined as described above.

Experiment 2. Examination of the combination of quetiapine and cocaine on self-administration. Each morning (~0730), Monday-Friday, another group of monkeys (N=7) self-administered cocaine under conditions, in which food reinforcement was concurrently available (i.e., choice procedure). For these studies, food reinforcement (three 1.0-gram banana-flavored pellets) was contingent upon completing 30 consecutive responses on one switch (i.e., FR 30), while cocaine (0.003-0.1 mg/kg per injection) presentation was contingent on 30 consecutive responses on the other lever. Sessions ended after 30 total reinforcers or 60 min. Each session began with a forced trial for each reinforcer; a 30 second timeout separated forced trials. Also, following five consecutive same-choice reinforcers, there was a forced trial on the opposing switch manipulandum. The cocaine dose remained constant for at least 5 sessions and until choice was deemed stable (choice was within 20% of the mean responding for 3 consecutive sessions without trends) before adding quetiapine solution (0.03 or 0.1 mg/kg per injection) to the cocaine

solution. Once responding for the quetiapine/cocaine combination met stability criteria, another cocaine dose was examined alone prior to the addition of quetiapine.

Data Analysis: Experiment 1: For quetiapine self-administration studies, the primary dependent variable was the response rate (responses/sec) that was analyzed using one-way (compared to saline) or two-way (comparing quetiapine self-administration during chronic treatment to baseline conditions) repeated measures ANOVA followed by Bonferroni post-hoc tests for pair wise 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. Experiment 2: For combination quetiapine and cocaine self-administration studies, the primary dependent variable was the number of injections, which was analyzed using a repeated measures t-test comparing the combination vs. cocaine alone. Data are presented as mean (± SD) for individual subjects and as means (± SEM). 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. When tested orally, 25 mg or 50 mg capsules were placed inside treats and given to the monkey.

Results

Experiment 1. Evaluation of the reinforcing effects of quetiapine. Quetiapine (0.01-0.1 mg/kg per injection) did not function as a reinforcer in any monkey tested (Figure 1). Individual-subject data revealed significant interactions in two (R-1553, R-1559) monkeys ($p<0.05$ and $p=0.0001$, respectively) with significantly lower response rates at the highest quetiapine dose (0.1 mg/kg per injection) compared to saline (Figure 1). Following twice-daily oral quetiapine treatment, there was a significant effect of Dose ($F_{1,12} = 22.69$; $p=0.0005$), with post-hoc comparisons revealing significant ($p<0.01$) decreases in response rates during saline self-administration (Figure 2). Analysis of individual-subject data (Figure 3) revealed a significant effect of treatment in three (R-1553, R-1554, R-1555) monkeys ($p<0.0001$, $p<0.0001$, and $p<0.05$ respectively) and a significant effect of dose in two (R-1555, R-1559; $p<0.05$, $p<0.01$). The total number of reinforcers was affected in a manner similar to response rate results (data not shown).

FIGURE 1.

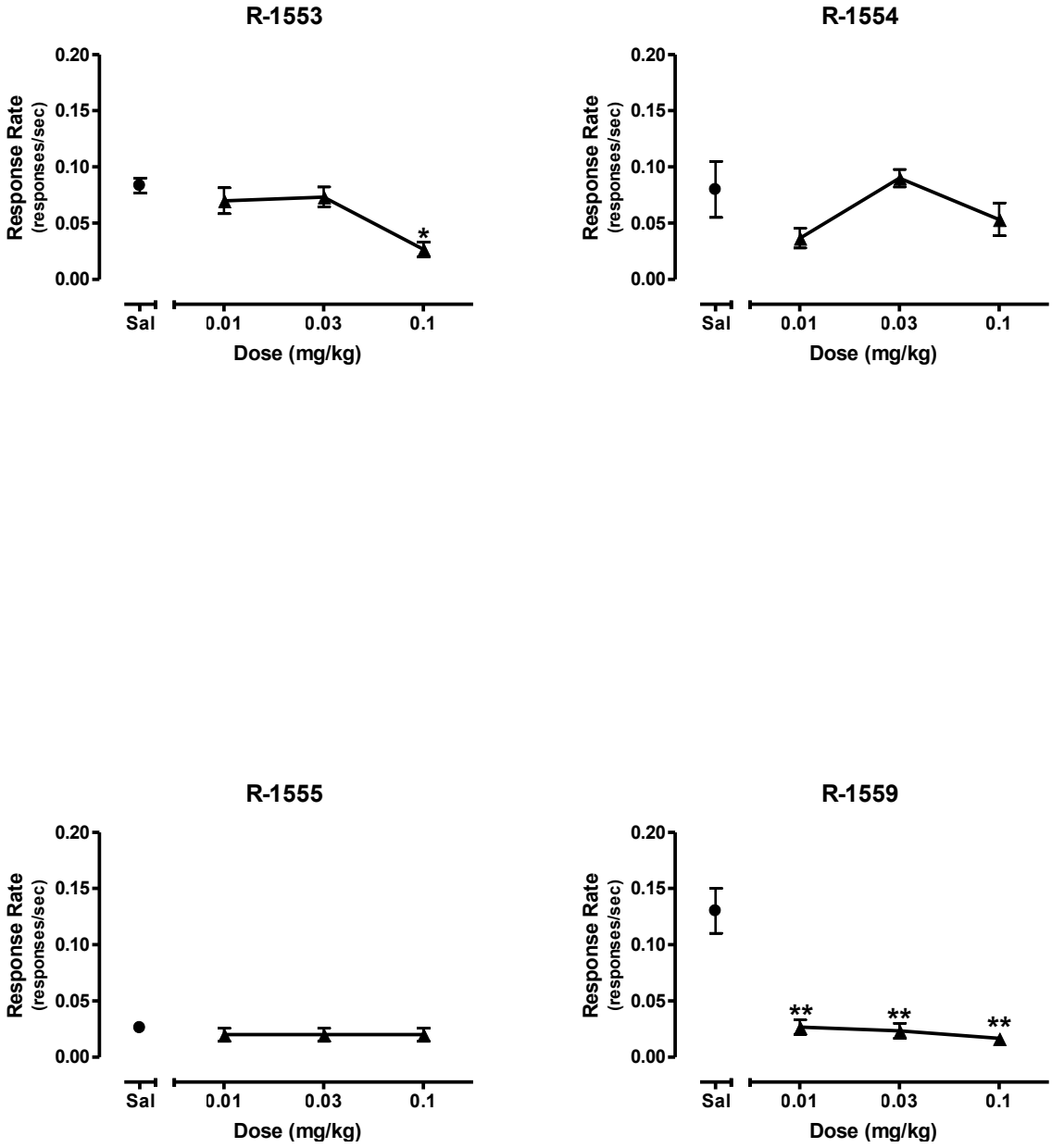

FIGURE 1. Response rates (responses per second) when saline (circle) and quetiapine (triangle) were substituted for food presentation under an FR 30 schedule of reinforcement. Each point represents the mean (± SD) for the last 3 sessions of availability. *$p < 0.05$, **$p < 0.001$

FIGURE 2.

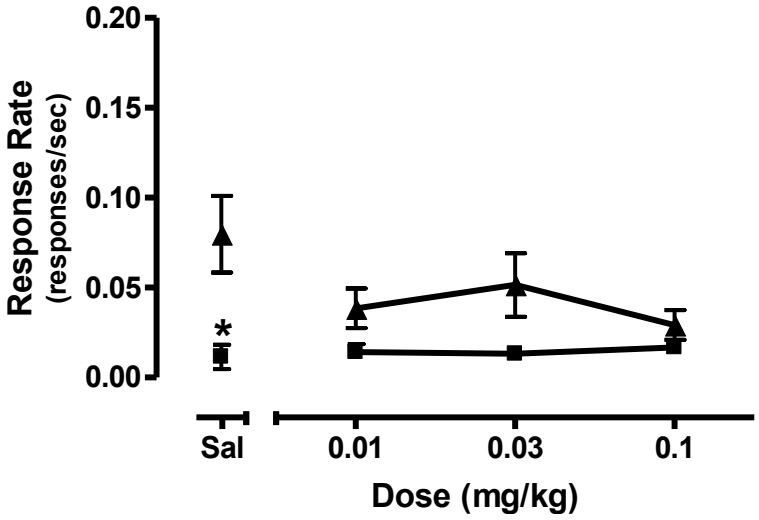

FIGURE 2. Group mean (± SEM) response rates (responses per second) for quetiapine self-administration at baseline (triangle) and during chronic quetiapine treatment (square). *$p < 0.01$, n=4

FIGURE 3.

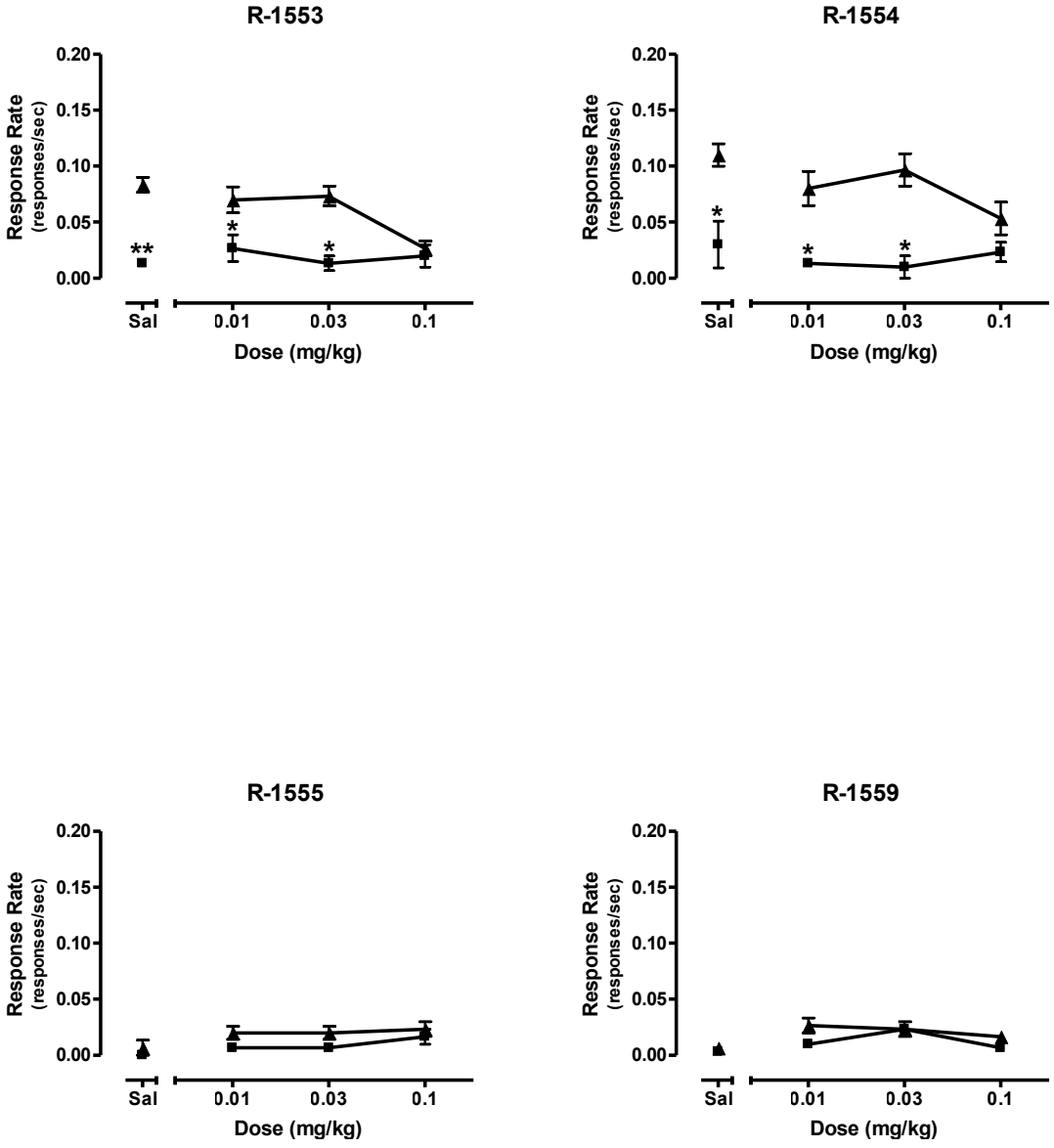

FIGURE 3. Individual response rates for quetiapine self-administration at baseline (triangle) and during chronic quetiapine treatment (square). *$p < 0.01$, **$p < 0.001$

Experiment 2. Examination of the combination of quetiapine and cocaine on self-administration. There was individual-subject variability in sensitivity to cocaine when studied under a concurrent schedule of reinforcement, with the lowest preferred dose (≥ 80% cocaine choice) being 0.01 (n=3), 0.03 (n=2) and 0.1 (n=2) mg/kg (Figure 4). Addition of quetiapine (0.03 or 0.1 mg/kg) to doses of cocaine that did not engender maximum (30) cocaine injections resulted in significant increases in the number of injections in five (R-1663, R-1662, R-1563, R-1568 and R-1570) of seven monkeys (Table 1).

Table 1. Mean (±SEM) number of reinforcers earned for cocaine (COC) and quetiapine (0.03 mg/kg (a) or 0.1 mg/kg (b)) and cocaine (QTP + COC) combination for monkeys where quetiapine increased the reinforcing strength of COC. *p<0.05

Monkey	COC Dose (mg/kg)	COC Injections	COC + QTP Injections	P value
R-1663	**0.01**	**4.3 (1.5)**	**9.7 (1.7)[a],***	**0.0153**
R-1662	**0.1**	**14.7 (0.3)**	**21.0 (0.6)[a],***	**0.0188**
	0.01	**16.8 (0.9)**	**26.0 (1.5)**	**0.0759**
R-1563	**0.01**	**20.7 (0.3)**	**27.0 (1.5)[a],***	**0.0416**
	0.003	**1.3 (0.9)**	**18.7 (2.4)[b],***	**0.0059**
R-1568	**0.01**	**15.0 (1.7)**	**29.3 (0.3)[a],***	**0.0101**
R-1570	**0.03**	**18.8 (0.2)**	**29.4 (0.6)[a],***	**<0.0001**

FIGURE 4.

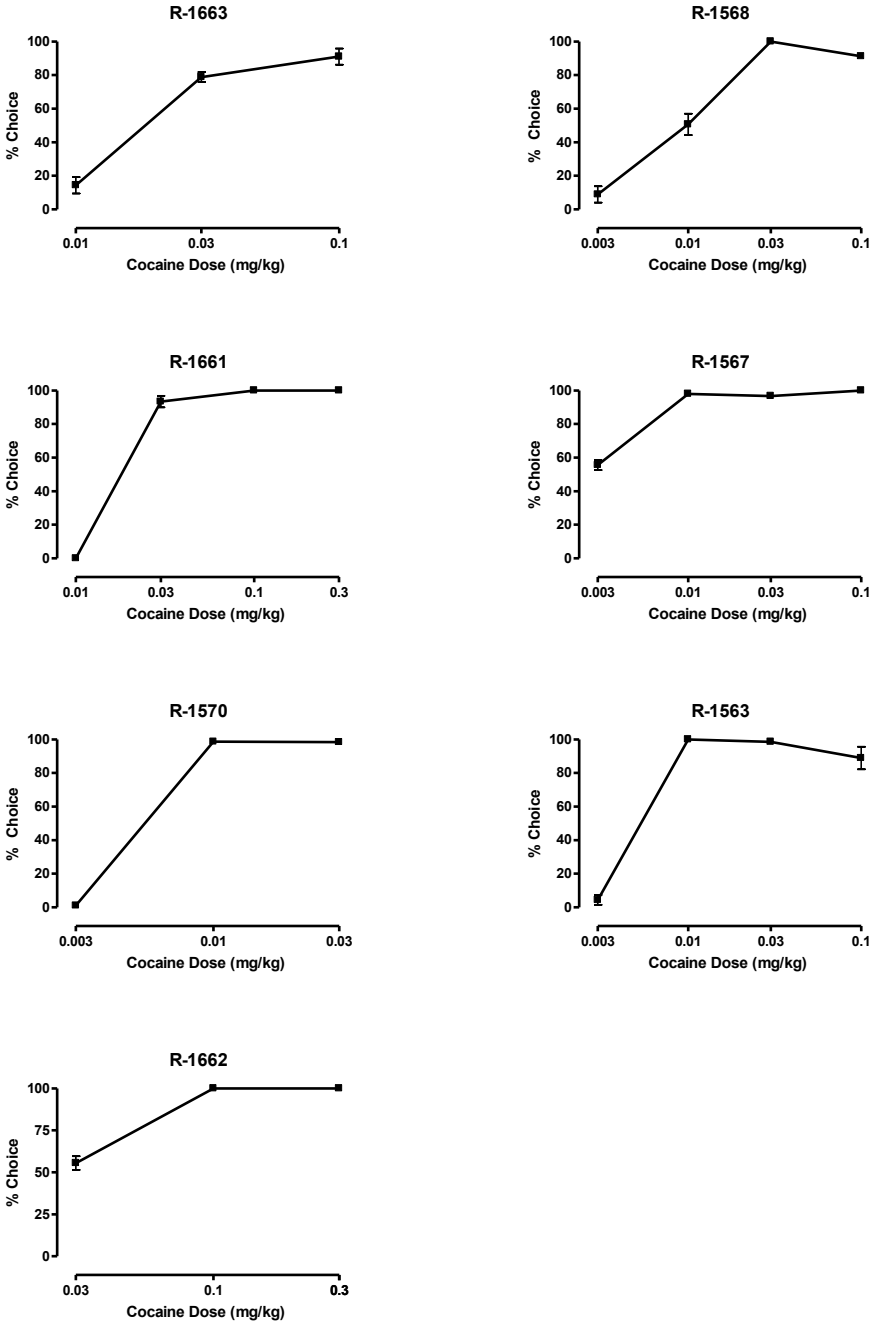

FIGURE 4. Cocaine choice dose-response curves for monkeys responding under a concurrent cocaine (0.003-0.3 mg/kg) vs. food (3 pellets) reinforcement schedule. Each point represents the mean of the last 3 sessions of availability.

Discussion

The present study sought to investigate the potential abuse liability 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 enhance the reinforcing effects of intravenous quetiapine and, in fact, resulted in response rates lower than saline rates for several quetiapine doses. In contrast to these negative results, when quetiapine was co-administered with cocaine, it enhanced the reinforcing effects of cocaine. Thus, while 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. Importantly, 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 patient population. Although we did not observe quetiapine functioning as a reinforcer, it is possible that the patients who have reported abusing quetiapine have also possessed other psychiatric comorbidities and polysubstance abuse that may have 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 eight times more likely to report quetiapine misuse (McLarnon et al., 2012). Further, it has been suggested that the misuse of quetiapine is motivated by self-medication of insomnia (Reeves and Brister, 2007), anxiety (Chen et al., 2009; Reeves and Brister, 2007; Morin, 2007) or depression (Chen

et al., 2009). These principles fall in line with Khantzian's "self-medication hypothesis" that suggests that substances are abused to overcome anxiety of the distressing effects of illness or its treatment (Khantzian, 1985) and may provide an explanation of the lack of an observed effect in our model.

As a secondary measure of the reinforcing effect of quetiapine, quetiapine was combined with cocaine in a concurrent choice paradigm. Adding quetiapine to cocaine resulted in an increase in the number of injections earned in the majority of monkeys (5/7). Our results are similar to a documented case report in the literature that a patient reported injecting himself with a mixture of cocaine and quetiapine, referred to as "Q-ball," so he could experience hallucinogenic effects (Waters and Joshi, 2007). It has been suggested that a quetiapine's reduced affinity for the D_2 receptor would support a possible abuse potential due to a reduced extrapyramidal side effect profile (Kapur et al., 2000; Tauscher et al., 2004; Morin, 2007; Farah, 2005) and therefore is not likely to produce euphoria or enhance dysphoria associated with drug withdrawl (Morin, 2007). Potentially supporting this explanation, low and intermediate dose chlorpromazine and haloperidol has been shown to increase the frequency of cocaine choice (Woolverton and Balster, 1981), which would also have reduced D2 receptor binding compared to higher doses that eliminated responding for both cocaine and food. Further, the 5-HT_2-selective antagonist, ritanserin, resulted in increased response rates for intravenous self-administration of cocaine over a range of cocaine doses (Howell and Byrd, 1995) and it is possible that the 5-HT_{2A} antagonism by quetiapine may be partially responsible for the enhancing effect observed. The results of our experiments suggest that quetiapine

demonstrates the potential to increase the reinforcing effects of cocaine, and therefore caution should be used in prescribing this medication in cocaine addicts.

It has been suggested that a likely explanation for the abuse of quetiapine is due to its high affinity for the histamine H1 receptor (Fischer and Boggs, 2010), especially in relationship to its lower affinity for D2 receptors (Kroeze et al., 2003). Reports have indicated that antihistamines are misused in humans (Bailey and Davies, 2008; Halpert et al., 2002; Thomas et al., 2009) and would further support the Fischer and Boggs (2010) suggestion. Further, it has been reported that individuals with a history of abusing sedatives have ranked antihistamines significantly higher on "liking" versus placebo (Preston et al., 1992) and not significantly different from the benzodiazepine lorazepam (Mumford et al., 1996). Pre-clinical data also document the abuse potential of antihistamines. Specifically, in nonhuman primates and rodents, antihistamines demonstrate behavioral effects similar to cocaine (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 a 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 resulted in significantly increased response rates compared to cocaine alone in rhesus monkeys (Banks et al., 2009). Taken together these results would support our findings that a combination of quetiapine and cocaine was more reinforcing than cocaine alone.

In summary, quetiapine alone did not function as a reinforcer but when available in combination with cocaine increased the reinforcing strength of cocaine. With reports of off-label quetiapine use increasing (Murphy et al., 2008) future experiments need to further investigate the abuse potential of quetiapine. Taken together, the results of these experiments should serve as a caution to prescribers who are considering using quetiapine in cocaine-addicted patients.

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Chapter V

EFFECTS OF SLEEP DISRUPTION OR QUETIAPINE ADMINISTRATION ON COGNITIVE PERFORMANCE IN ADULT RHESUS MONKEYS

Robert E. Brutcher and Michael A. Nader

The following manuscript is in preparation to be submitted to *Neuropharmacology* in April, 2013. Stylistic variations are due to the requirements of the journal. Robert E. Brutcher performed the experiments, analyzed the data and prepared the manuscript. Michael A. Nader acted in an advisory and editorial capacity.

Abstract

*Rationale***:** Clinical and pre-clinical studies show that cocaine use is associated with sleep disturbances and cognitive impairment, and that these consequences may perpetuate continued drug use. It has been suggested that quetiapine may be beneficial in treating cocaine addiction and also that it has cognitive-promoting capabilities. *Objective*: This study examined the effect of sleep disruption on cognitive performance, and also the effect of quetiapine administration on working memory in rhesus monkeys. *Methods***:** Four adult rhesus monkeys trained to respond on a delayed-match-to-sample (DMS) task served as subjects. Percent accuracy was measured at short, medium and long delays and the effect of one night of sleep disruption or quetiapine administration (25 mg, p.o., 45 min presession and 25-100 mg, b.i.d. for 10 days) was examined. *Results***:** Under baseline conditions, there was a delay-dependent decrease in cognitive performance; sleep disruption did not significantly alter this behavior. However, quetiapine administration (both acute and chronic) did result in significant disruptions in DMS task performance. *Conclusions***:** Based on these findings, our method of sleep disruption does not result in cognitive disruptions, and therefore would not be a suitable method to examine potential treatment options for examining the cognitive promoting capabilities in future models of cocaine self-administration. Our findings do indicate that quetiapine causes cognitive disruptions in working memory and therefore may perpetuate the drug use cycle.

Key Words: cognition, quetiapine, sleep disruption, monkeys

Introduction

Cocaine addiction in the United States continues to be a significant disorder that plagues the population. Specifically, recent reports are that for all substance abuse treatment admissions, 12.9% were for treatment of cocaine abuse (SAMHSA, 2011). Currently, there are no medically approved treatments for cocaine addiction (Vocci et al., 2005), although several novel pharmacological avenues have been considered (O'Brien, 2005; Elkashef et al., 2007). There are multiple deleterious consequences associated with cocaine abuse, one of which is poor cognitive performance, as it is understood that chronic cocaine use results in disruptions of executive function (Kelley et al., 2005; Verdejo-Garcia et al., 2006; Tomasi et al., 2007). Executive function includes all of the processes involved in learning, monitoring and adapting to stimuli to produce complex, goal-oriented behaviors.

Interestingly, some abused substances (amphetamine, nicotine, and cocaine) have been shown to acutely enhance learning and/or attention (Del Olmo et al., 2007; Kenney and Gould, 2008; Mattay, 1996). Compared to control groups, chronic cocaine users show impaired cognitive performance across multiple cognitive domains, and it is suggested that these effects extend into abstinence and influence both treatment outcomes and predicting vulnerability to relapse. For example, results from several studies indicate that chronic users of opiates and psychostimulants share some deficits in memory, cognitive flexibility and decision making (Bechara, 2005; Fu et al., 2008; Fernandez-Serrano et al., 2010; Ornstein et al., 2000). The present study utilized a working memory task in monkeys that assessed the effects of cocaine self-administration and a potential treatment on executive function.

To assess executive functioning, working memory tasks have been traditionally used, and cocaine use has been shown to produce poorer performance on these tasks (Verdejo-Garcia et al., 2006; Tomasi et al., 2007). Importantly, research has shown that nonhuman primates can be trained to perform tasks probing specific cognitive domains that are known to be imparied in human cocaine users. In terms of developmental and aging processes, neurotransmitter distribution, and complex social and cognitive behavioral repertoires macaques have a close homology to humans (Weerts et al., 2007). Cognitive performance has been shown to be significantly disrupted in rhesus monkeys with a history of cocaine self-administration (Gould et al., 2012, 2013). One task that has been traditionally used is the delayed-match-to-sample test (DMS). In this test, a visual stimulus is presented to the animal that must be retained across a variable delay interval. Following a predetermined delay, the animal must select the previously presented stimulus from an array of stimuli. If the animal chooses the correct stimulus, a reinforcer is earned. Increasing the cognitive demand can be accomplished by either increasing the delay value or increasing the number of distracter images presented. The present study utilized the Cambridge Neuropsychological Test Automated Battery (CANTAB) in rhesus monkeys, using procedures described previously (Weed et al., 1999).

There is also evidence available that sleep deprivation can cause cognitive disruptions and thus, may further perpetuate the drug-use cycle (Morgan et al., 2006). It has been reported that sleep deprivation negatively affects levels of alertness and cognitive performance in both humans and animal models (Habeck et al., 2005; Thomas et al., 2000; Chee and Choo, 2004; Drummond and Brown, 2001; Habeck et al., 2004; Choo et al., 2005; Drummond et al., 2001), which may be due, in part, to sleep

deprivation being reported to cause subjects to lapse and miss the deadline for responding during the probe phase of memory trials (Habeck et al. 2004). Further, it has been suggested that an absence of sufficient sleep may be as important to learning deficits in chronic cocaine users as it is to sleep-dependent learning in healthy subjects (Morgan et al., 2006). The effects of sleep deprivation on cognition has been extensively studied in the rhesus monkey and the DMS task and have proven useful to examine the ability of medications to effectively block or attenuate those deficits (Hampson et al., 2004, 2009; Porrino et al., 2005; Deadwyler et al., 2007). One goal of the present studies is to evaluate a model of sleep disruption on cognition in adult rhesus monkeys.

There is evidence to link the importance of cognitive performance for treatment retention (Aharonovich et al., 2003) and outcome (Teichner et al., 2001, 2002) and it has been reported that some of the most promising candidate pharmacotherapies for cocaine addiction either promote sleep or daytime wakefulness (Morgan et al., 2006). Quetiapine, an atypical antipsychotic, has been reported to be prescribed off-label for the treatment of sleep withdrawal (Robert et al., 2005; Rowe, 2007; Philip et al., 2008) and insomnia (Wine et al., 2009; Dolder and McKinsey, 2010). However, a recent meta-analysis reported inconclusive evidence regarding the efficacy of quetiapine for treating insomnia (Maher et al., 2011). Quetiapine has been shown to improve cognitive function in several patient populations. For example, in an open-label trial examining the effect of quetiapine in patients with comorbid schizophrenia and substance use disorders, the authors reported significant improvements in substance abuse measures, psychiatric symptoms, and cognition (Potvin et al., 2006). Adding evidence to the cognitive-promoting capabilities of quetiapine another study showed that quetiapine improved executive functioning in

patients with borderline personality disorder (Van den Eynde et al., 2009) and partially improved cognitive functions in schizophrenic patients (Zhang et al., 2009). Furthermore, it has been reported that quetiapine has improved self-rated cognitive dysfunction and subjects' performance on neurocognitive tasks (Voruganti et al., 2007). Thus, a second goal of this study is to examine the effects of quetiapine treatment on cognitive performance in adult rhesus monkeys.

Methods and Materials

Subjects: Four individually housed adult (age 16-18) male rhesus monkeys (*Macaca mulatta*) trained to respond in a delayed-match-to-sample (DMS) task served as subjects. All monkeys had an extensive history of performance on this task (Gould et al., 2012, 2013). Monkeys were weighed weekly and body weights maintained at approximately 95% of free-feeding weights by food earned during experimental sessions and by supplemental feeding of LabDiet Monkey Chow and fresh fruit no sooner than 30 minutes after the session; water was available *ad libitum* while in the home cage. Each monkey was 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 experimental manipulations were performed in accordance with the 2003 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.

Apparatus: Cognitive testing was conducted using the CANTAB apparatus (Lafayette Instruments, Lafayette, IN). Each CANTAB cognition station (0.38 x 0.56 x 0.31 m) was located in sound-attenuating, ventilated chambers (0.8 x 0.8 x 1.32 m) and included a touch-sensitive computer screen (0.3 x 0.23 m) with a stimulus light, a non-retractable response lever, and a pellet receptacle located to the right side of the front panel.

Cognition: Monkeys were trained on a DMS task as previously described (Gould et al., 2012, 2013). Briefly, at the start of each trial the house light was illuminated for 5 seconds followed by the appearance of a "target" stimulus in the center of the computer screen (sample phase). A response on this stimulus was followed by a delay (short, medium, long) and the presentation of 2 or more shapes around the edges of the screen (match phase) that remained on the screen for a maximum of 10 seconds or until a response was registered. One stimulus was "target" and the others served as distracter images. Responding on the matching image during this phase resulted in delivery of 1, 190-mg sucrose pellet, whereas a response on any distracter image resulted in trial termination. The house light remained illuminated during each delay and remained lit throughout post-trial timeouts (5 sec) following correct trials but was extinguished following incorrect responses. If no response was emitted within 10 seconds during the sample or match phase, the house light was extinguished and the trial was terminated (omitted trial). Delays (0-175 seconds, see Table 1) were randomly distributed throughout each session for a total of 60 trials (20 trials/delay). Delay values (short, medium, and long) were individualized to result in delay-dependent reductions in the

percent accuracy. Delay values and the number of distracter images (3-7, see Table 1) were altered periodically in an effort to maintain delay-dependent decreases in accuracy.

Table 1. Individual delay (short or no, medium and long) and number of image distractors (D) for the DMS task.

Monkey	Short (sec)	Medium (sec)	Long (sec)	D
R-1681	5	130	175	7
R-1682	0	90	175	4
R-1696	5	75	150	3
R-1756	5	100	175	3

Experiment 1. Effects of sleep disruption on working memory. For these studies, the effect of sleep disruption on working memory was examined using the DMS task. Sleep disruption occurred while the monkey was in their home cage and was achieved by keeping the lights on during the typical lights-out period and by having an investigator (R.E.B.) enter the room hourly to awaken the monkeys by tapping on their cage with a stick (see Brutcher and Nader, 2013). This protocol was designed to disrupt sleep each hour, not to produce sleep deprivation by forcing the monkeys to stay awake all night. On the morning (0730) immediately following a night of sleep disruption, the monkeys were again studied in the DMS task and the percentage of accuracy (at each delay) and total number of trials omitted was determined.

Experiment 2. Effects of quetiapine on working memory. These studies examined the effects of quetiapine on working memory, and also used the DMS task. Once performance was deemed stable (± 20% accuracy), quetiapine (25 mg; TEVA Pharmaceuticals USA, Sellersville, PA; placed inside a food treat) was given orally 45

minutes prior to the next session. This dose of quetiapine was shown to be behaviorally active in a previous study in our lab (unpublished). After a return to baseline performance, the effect of chronic quetiapine (25-100 mg, p.o., b.i.d. for 10 days) treatment on working memory was examined. Doses of quetiapine were individualized to a behaviorally active dose (Table 2). DMS sessions were conducted daily approximately 45 min after the morning dose.

Table 2. Individual, oral quetiapine doses for continuous treatment studies.

Monkey	Quetiapine Dose (mg)
R-1681	**50**
R-1682	**50**
R-1696	**25**
R-1756	**100**

Data Analysis: Experiment 1: the primary dependent variables were the percent accuracy and number of trials omitted. A two-way repeated measures ANOVA was conducted using condition (baseline or sleep-disrupted) and delay (short, medium, long) to compare percent accuracy. A repeated measures t-test was conducted to compare number of omitted trials between groups. Experiment 2: the primary dependent variables were the percent accuracy, the percent total accuracy, and the number of trials omitted. For these experiments, two-way repeated measures ANOVAs were conducted using condition (baseline or quetiapine treated) and delay (short, medium and long) to compare percent accuracy (trials correct/trials completed out of 20) and percent total accuracy (trials correct/20 total trials). To examine chronic quetiapine treatment on omitted trials, one-way repeated measures ANOVA was conducted, while a repeated measures t-test

was used to compare the effects of acute treatment. For all analyses, $p<0.05$ was considered statistically significant.

Results

Experiment 1. Effects of sleep disruption on working memory. For each monkey, delay values were individualized such that short-, mid- and long-delay values resulted in delay-dependent reductions in percent accuracy (see Table 1). For these studies there was a significant effect of the length of delay ($p<0.0001$) on cognitive performance measured by the DMS task (Figure 1). One night of sleep disruption did not significantly alter cognitive performance in this task nor did it significantly affect the number of trials omitted (Figure 1).

FIGURE 1.

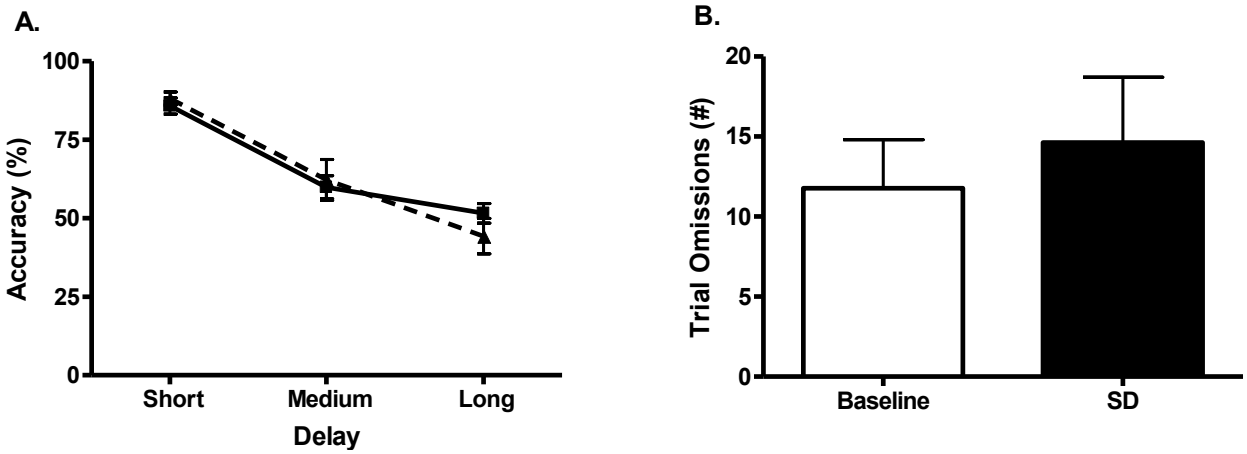

FIGURE 1. (A) Mean (± SEM) percent accuracy for baseline (square, solid line) and following sleep disruption (triangle, dashed line) at three (short, medium and long) delays. (B) Mean (± SEM) number of trial omissions for baseline (white bar) and following sleep disruption (black bar), n=4.

Experiment 2. Effects of quetiapine on working memory. When examining the effect of acute quetiapine treatment on percent accuracy, analysis revealed a significant effect of delay ($p=0.0003$) with no effect of quetiapine (Figure 2A). Acute quetiapine treatment significantly increased the number of omitted trials ($p=0.0084$) (Figure 2B) and two-way repeated measures ANOVA revealed a significant effect of delay and quetiapine treatment on total accuracy ($p<0.0001$; Figure 2C). Further analysis revealed significant decreases in total accuracy at short ($p<0.001$) and medium ($p<0.01$) delays, following acute quetiapine treatment (Figure 2C). Analysis of chronic quetiapine treatment on percent accuracy revealed a significant effect of delay ($p=0.0009$) and a significant decrease in performance at day 5 ($p<0.05$) [data not shown]. A one-way ANOVA revealed a significant main effect of chronic quetiapine treatment ($p=0.002$) on number of omissions and significant increases were present at day 5 and day 10 ($p<0.01$) compared to baseline (Figure 3). Finally, chronic quetiapine treatment resulted in significant cognitive impairment at all time points except at the long delay on the first day of treatment (Table 3).

FIGURE 2.

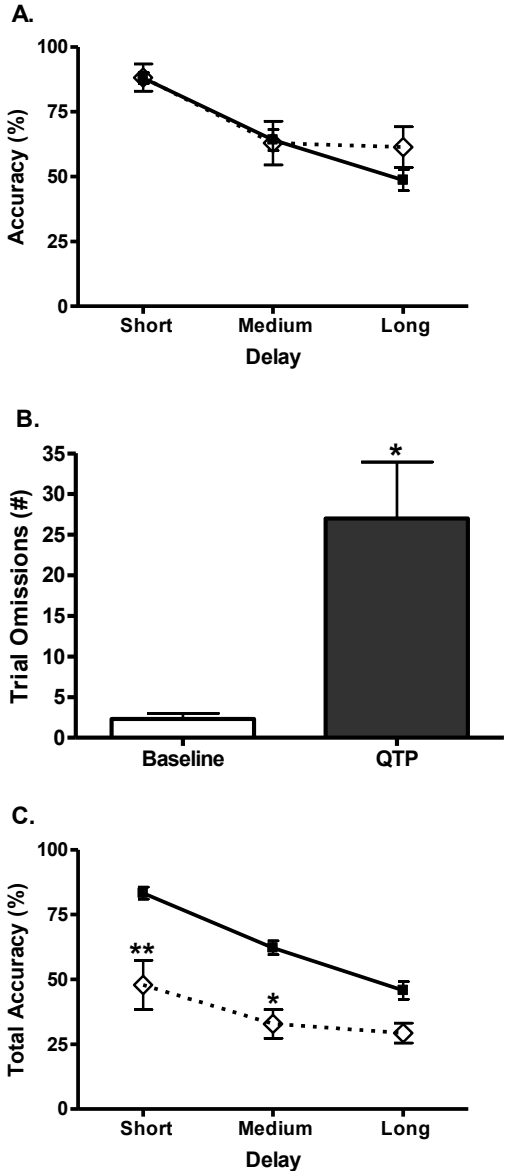

FIGURE 2. (A) Percent accuracy for baseline (square, solid line) and following quetiapine (25 mg) administration (diamond, dashed line) at three (short, medium and long) delays. (B) Number of trial omissions for baseline (white bar) and following quetiapine (gray bar). (C) Percent of total trial accuracy for baseline (square, solid line) and following quetiapine administration (diamond, dashed line). Each point is the mean (± SEM) for four monkeys; *$p < 0.01$, **$p < 0.001$.

FIGURE 3.

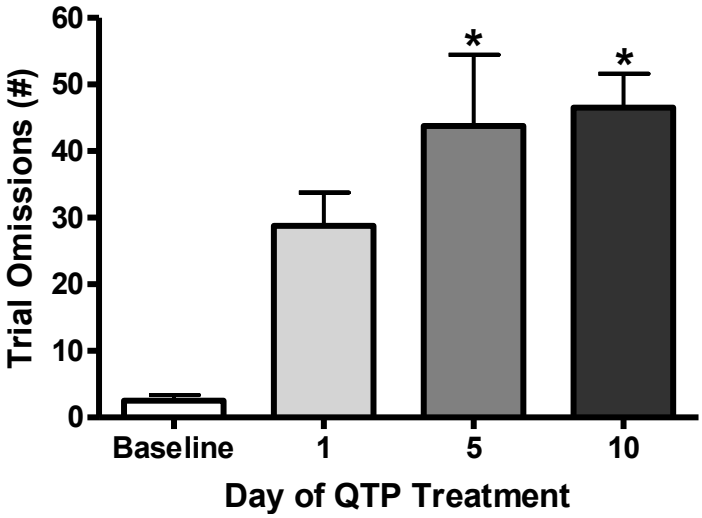

FIGURE 3. Mean (± SEM) number of trial omissions for baseline (white) and following twice-daily quetiapine treatment for one (light gray bar), five (gray bar), and ten (dark gray bar) days. *p < 0.01; n=4

Table 3. Average percent of total accuracy, at multiple delays, at baseline and following quetiapine (QTP) treatment (expressed as the mean ± SEM) for rhesus monkeys. *p<0.05; **p<0.01; ***p<0.001; compared to baseline; n=4

Delay	Baseline	Day 1 QTP	Day 5 QTP	Day 10 QTP
Short	82.0 ± 4.4	38.3 ± 6.3**	21.3 ± 14.2***	21.3 ± 5.2***
Medium	60.3 ± 5.5	23.8 ± 5.5*	10.0 ± 8.4***	13.8 ± 7.7**
Long	51.4 ± 6.3	25.0 ± 2.0	18.8 ± 12.1*	12.5 ± 4.3**

Discussion

The present study investigated the effects of sleep disruption and quetiapine treatment on cognitive performance using a DMS task in adult rhesus monkeys. To achieve significant disruptions in sleep measures, the lights remained on during the night in the animal housing room and monkeys were awakened each hour. This method of sleep disruption was not intended to provide complete sleep deprivation, but it does produce significant disruption in several measures of sleep (Brutcher and Nader, 2013). Under these conditions, we did not observe disruptions in cognitive performance as measured using delayed match-to-sample tasks. However, when quetiapine was tested, both acute and chronically, there was evidence of cognitive disruption, as assessed with DMS performance.

Our results using sleep disruption are in contrast to results published that reported sleep deprivation caused significant cognitive deficit in the DMS task (Hampson et al., 2004; Porrino et al., 2005; Deadwyler et al., 2007; Hampson et al., 2009). Possible explanations for the lack of an observed deficit in the present study may be due to the disruption allowing enough opportunity to sleep (see Brutcher and Nader, 2013). The studies that showed sleep deprivation was responsible for producing cognitive deficits all used a method of complete sleep deprivation that consisted of 30-36 hours of continued sleep prevention. In those studies, the monkeys were continuously monitored to ensure they did not fall asleep at all for an extended period of time. It is also possible that due to our monkeys having a previous history with the DMS task (Gould et al., 2012, 2013) that we did not observe deficits due to the monkeys' experience at this task. Their skill level at performing this task may have been higher than an animal that had just learned the

task. Although this is a possible explanation, we feel that because delay-dependent decreases in performance were still present that it must be due to something else, particularly the length or method of disruption.

The present study also examined the effect of quetiapine on cognitive performance. Acute and chronic quetiapine treatment caused cognitive disruption of performance in a working memory task. Further, our results indicate that initial treatment (acute and chronic) resulted in disruption of total accuracy at short and medium delays, which would suggest quetiapine may cause attentional deficits. However, chronic treatment resulted in disruption at all delays that would be suggestive of an overall disruption of performance and tolerance did not develop to this effect following ten days of treatment.

Our results that quetiapine disrupts cognitive performance are supported by other reports. A pre-clinical study reported that quetiapine administration resulted in disruption of performance in the 5-choice serial reaction time task in rats (Amitai and Markou, 2009). There is also clinical literature available to support our findings. A study examining the effects of quetiapine on cognition in a group of first-episode antipsychotic-naïve patients concluded that there was very little evidence of the efficacy of quetiapine on cognition (Anderson et al., 2011) and further, results from another study reported no efficacy of quetiapine on cognitive improvement in a sample of adolescents with psychosis (Robles et al., 2011). There is also a report that indicated that initiation of quetiapine treatment was associated with immediate adverse cognitive effects and increased somnolence (Harvey et al., 2007). Finally, the combination of quetiapine with an SSRI resulted in no effect on cognitive functioning although the authors proposed that

the failure may be caused by attention difficulties owing to somnolence (de Geus et al., 2007). While it is possible that the disruptions we observed following quetiapine were a result of somnolence, sleep disruption in these same monkeys did not affect working memory. There are also data, which are in stark contrast to what we observed, showing that quetiapine enhanced cognitive function in several patient populations (Potvin et al., 2006; Van den Eynde et al., 2009; Zhang et al., 2009; Voruganti et al., 2007). The reasons for the equivocal results between clinical studies and preclinical studies remain to be determined.

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CHAPTER VI

DISCUSSION

There were an estimated 22.1 million people in the U.S. that met DSM-IV criteria for substance abuse or dependence in 2010 (NSDUH, 2010) with currently no approved treatment for cocaine abuse. Although those numbers have remained stable, or slightly declined, over the past few years, cocaine abuse/dependence represents an important area of concern to healthcare professionals and scientists alike. Drug abuse is also a growing problem among our military members with surveys reporting that 7.1% of veterans met criteria for a past-year substance use disorder (NIDA, 2009) and the percentage of the DoD active duty force using illicit drugs rose from 5% in 2005 to 12% in 2008 (RTI, 2009). Further, post-traumatic stress disorder (PTSD) has plagued both the military and civilian populations and had a profound affect on the substance abusing population.

The lifetime prevalence of PTSD among adult Americans is estimated to be 6.8% (Kessler et al., 2005a,b) with the prevalence of current PTSD in soldiers serving in Iraq/Afghanistan being 13.8% (Tanielian and Jaycox, 2008). Further, the self-reported rates of current symptoms of PTSD within the Department of Defense increased between the year 2005 to 2008 (Military Health System, 2009). PTSD has been described as consisting of three types of symptom clusters: 1) reexperiencing symptoms; 2) avoidance symptoms; and 3) arousal symptoms (Jacobsen et al., 2001), and some of those symptoms are subject to animal modeling. The experiments in each Chapter were designed to provide information related to aspects of PTSD, of which there are numerous diagnostic criteria (APA, 2000; see Figure 1). For example, sleep disturbances following a stressful event have been suggested to be predictive of future development of PTSD (Lavie, 2001; Spoormaker and Montgomery, 2008). To complicate PTSD and development of

treatment strategies is the fact that PTSD has been associated with substance abuse (Stein and McAllister, 2009). The rates of current PTSD among patients with substance use disorder is substantially higher than the rates of PTSD in the general population (Cottler et al., 1992; Jacobsen et al., 2001; Brady et al., 2004; Kessler at al., 2005a and 2005b) suggesting a link between these two conditions. Animal models of PTSD typically involve the presentation of multiple stressors using rodent models. To date, the research on PTSD in nonhuman primate models has involved early life stress (rearing) in rhesus (Spinelli et al., 2009) and bonnet macaques (Smith et al., 1997).

The overall goal of the work presented in my dissertation was to systematically evaluate a potential monkey model of PTSD by examining different aspects of the disorder – sleep disturbance, cognitive disruptions and drug abuse - while trying to identify a potential treatment for cocaine dependence and PTSD. The development of a valid nonhuman primate model of PTSD is crucial for future development of treatment strategies and examination of the neurochemical and neurobiological effects of PTSD, and this model needs to be built from the ground up.

Figure 1

A. The person was exposed to one or more of the following event(s): death or threatened death, actual or threatened serious injury, or actual or threatened sexual violation, in one or more of the following ways: **

- Experiencing the event(s) him/herself
- Witnessing, in person, the event(s) as they occurred to others
- Learning that the event(s) occurred to a close relative or close friend; in such cases, the actual or threatened death must have been violent or accidental
- Experiencing repeated or extreme exposure to aversive details of the event(s) (e.g., first responders collecting body parts; police officers repeatedly exposed to details of child abuse); this does not apply to exposure through electronic media, television, movies, or pictures, unless this exposure is work related.

B. Intrusion symptoms that are associated with the traumatic event(s) (that began after the traumatic event(s)), as evidenced by 1 or more of the following:

- Spontaneous or cued recurrent, involuntary, and intrusive distressing memories of the traumatic event(s).
- Recurrent distressing dreams in which the content and/or affect of the dream is related to the event(s).
- Dissociative reactions (e.g., flashbacks) in which the individual feels or acts as if the traumatic event(s) were recurring (Such reactions may occur on a continuum, with the most extreme expression being a complete loss of awareness of present surroundings.)
- Intense or prolonged psychological distress at exposure to internal or external cues that symbolize or resemble an aspect of the traumatic event(s)
- Marked physiological reactions to reminders of the traumatic event(s)

C. Persistent avoidance of stimuli associated with the traumatic event(s) (that began after the traumatic event(s)), as evidenced by efforts to avoid 1 or more of the following:

- Avoids internal reminders (thoughts, feelings, or physical sensations) that arouse recollections of the traumatic event(s)
- Avoids external reminders (people, places, conversations, activities, objects, situations) that arouse recollections of the traumatic event(s).

D. Negative alterations in cognitions and mood that are associated with the traumatic event(s) (that began or worsened after the traumatic event(s)), as evidenced by 3 or more of the following:

- Inability to remember an important aspect of the traumatic event(s) (typically dissociative amnesia; not due to head injury, alcohol, or drugs).
- Persistent and exaggerated negative expectations about one's self, others, or the world (e.g., "I am bad," "no one can be trusted," "I've lost my soul forever," "my whole nervous system is permanently ruined," "the world is completely dangerous").
- Persistent distorted blame of self or others about the cause or consequences of the traumatic event(s)
- Pervasive negative emotional state -- for example: fear, horror, anger, guilt, or shame
- Markedly diminished interest or participation in significant activities.
- Feeling of detachment or estrangement from others.
- Persistent inability to experience positive emotions (e.g., unable to have loving feelings, psychic numbing)

E. Alterations in arousal and reactivity that are associated with the traumatic event(s) (that began or worsened after the traumatic event(s)), as evidenced by 3 or more of the following:

- Irritable or aggressive behavior
- Reckless or self-destructive behavior
- Hypervigilance
- Exaggerated startle response
- Problems with concentration
- Sleep disturbance -- for example, difficulty falling or staying asleep, or restless sleep.

F. Duration of the disturbance (symptoms in Criteria B, C, D and E) is more than one month.

G. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

H. The disturbance is not due to the direct physiological effects of a substance (e.g., medication or alcohol) or a general medical condition (e.g., traumatic brain injury, coma).

Figure 1. DSM-IV diagnostic criteria for PTSD (adapted from APA, 2000)

CHOICE PROCEDURE VS. FIXED-RATIO RESPONDING

Preclinical assays of drug self-administration provide a valuable experimental tool that can be used to assess potential pharmacotherapies for the treatment of drug abuse (Mello and Negus, 1996). Throughout the majority of the experiments in this dissertation, a choice paradigm was chosen over a simple fixed-ratio (FR) schedule of reinforcement. A choice paradigm was chosen to avoid the possible reinforcement-independent rate altering effects of quetiapine, since quetiapine is reported to possess sedative effects. This factor in the experimental design was driven by the concept that the measures of self-administration response rate can be influenced by both the reinforcing effect of the self-administered drug and also by other direct effects of the self-administered drug that can either increase or decrease response rates (Zernig et al., 2004). Also, important in the design of the experiments contained in this dissertation was evidence from a recent review that although many therapeutic agents have shown promise in preclinical models, they have failed to translate into the human condition (Jupp and Lawrence, 2010) and therefore we must continue to pursue the best models of addiction (Koob et al., 2009).

Drug addiction has been classically defined as a disorder of choice and behavioral allocation (Hernstein and Prelec, 1992; Heyman, 2009) and in regard to viewing addiction as a disorder of choice, choice procedures have emerged as the standard approach in clinical studies of drug reinforcement (Comer et al., 2008; Haney and Spealman, 2008). To parallel clinical studies, the choice procedure was chosen for the experiments in Chapters II, III, and IV. Importantly, when studied under food-drug choice conditions, cocaine produces dose-dependent increases in drug choice (Negus, 2003; Czoty et al., 2005; Banks et al., 2011, 2013). Comparing the dose of cocaine that

engendered the peak response rate under a FR 30 schedule of reinforcement to the lowest preferred dose of cocaine in a choice procedure reveals interesting results (Table 1). Comparisons reveal that, in the choice procedure, the dose of cocaine was higher in four monkeys (R-1563, R-1570, R-1662, R-1663), lower in one (R-1567) and the same in two (R-1568, R-1661). Comparing the dose of cocaine that engendered the peak response rate under a FR 30 schedule demonstrates individual variability in the relative reinforcing strength of cocaine when food is the alternative reinforcer, and may suggest different responses to manipulations. Interestingly, in Chapter IV, a combination of quetiapine and cocaine increased the reinforcing strength of cocaine in five (R-1563, R-1568, R-1570, R-1662, R-1663) monkeys, and the lowest preferred dose of cocaine in these monkeys was higher (4) or the same (1) than the cocaine dose that produced peak response rates. Thus, these results support individualized treatment strategies and may suggest the potential to identify a relationship between fixed-ratio schedules of reinforcement and concurrent choice procedures, however further research would need to be done to support this suggestion.

Table 1. Cocaine dose (mg/kg) that engendered peak response rates under a fixed-ratio (FR) schedule of reinforcement and was the lowest preferred (≥80% cocaine choice, P) in a concurrent choice procedure.

Monkey	FR (mg/kg)	P (mg/kg)
1563	0.003	0.03
1567	0.03	0.01
1568	0.01	0.01
1570	0.003	0.01
1661	0.1	0.1
1662	0.03	0.1
1663	0.001	0.1

THE RELATIONSHIP BETWEEN COCAINE SELF-ADMINISTRATION AND SLEEP IN ADULT RHESUS MONKEYS

Hypothesis: *Monkeys will demonstrate disruptions in behavioral indices of sleep following cocaine self-administration, and these disruptions will occur in a dose-dependent manner. Following sleep disruption, an increase in cocaine choice curve will be observed indicating the monkeys find cocaine more reinforcing compared to food.*

Drug addiction has been defined in the literature as a chronically relapsing disorder involving repeated bouts of compulsive drug seeking and use despite potential adverse consequences (Koob and LeMoal, 1997; Witkiewitz and Marlatt, 2004). Reports indicate that relapse rates for addicted humans range from 40-90%, even after a prolonged period of abstinence (DeJong 1994; McLellan et al., 2000; Paparrigopoulos et al., 2011). It is known that most drugs can affect sleep patterns, usually adversely, impacting both the duration and frequency of sleep stages (Barkoukis and Avidan, 2007) and literature suggests cocaine abusers encounter a vicious cycle between relapse and sleep dysregulation when trying to abstain from the drug. Thus, it is possible that sleep disturbances contribute to cocaine addiction and are not just a consequence of the illness. Further, clinical literature suggests that sleep deprivation is a factor that can induce patients to relapse to drug-taking behavior. Acute sleep deprivation was shown to increase the rate at that rats self-administer cocaine (Puhl et al., 2009). Research has shown that with sustained abstinence from cocaine, human chronic cocaine users exhibit decreased sleep, impaired vigilance and sleep-dependent procedural learning, and spectral activity suggestive of chronic insomnia (Morgan et al., 2006). Chapter II examined the relationship between cocaine self-administration and sleep disturbances

using actigraphy in adult rhesus monkeys. A key step in developing potential pharmacologic treatment agents will be aided by understanding this relationship.

Following cocaine self-administration, monkeys demonstrated significantly lower sleep efficiencies, while total lights out activity significantly increased and modest increases in the latency to fall asleep were observed. For latency to sleep and activity, these measures varied as a function of dose in an inverted U-shaped fashion. Interestingly, these effects were noted at the lowest preferred dose of cocaine ($\geq$ 80% cocaine choice) and they were present at least 12 hrs following cocaine self-administration. Combining the results of the sleep disturbances noted at the lowest preferred dose, with the results of cocaine doses that were one-half log-unit above and below this dose failed to produce a similar response lead to the suggestion that there may be other non-pharmacological mechanisms involved in this response as well. Further research is necessary to elucidate other possible mechanisms that cocaine self-administration is disrupting actigraphy-based sleep measures.

Results from Chapter II would suggest that cocaine self-administration is responsible, either directly or indirectly, for causing some of the observed and reported sleep disturbances reported by human cocaine users; the present results are similar to a study conducted in humans where REM sleep was found to be shortest on nights following cocaine use (Morgan et al., 2008). These are also similar to findings that, following an acute intraperitoneal (i.p.) cocaine injection in rats, the time spent in wakefulness increased and slow wave sleep decreased in a dose-dependent manner compared to controls (Knapp et al., 2007). The present results in monkeys are also supported by a vast literature showing that the use of stimulant medications is associated

with sleep problems. For instance, dopamine transporter (DAT) inhibitors have been shown to affect the sleep-wake cycle of nonhuman primates (Andersen et al., 2010). These investigators also examined several measures of sleep in rhesus monkeys during chronic treatment with the DAT inhibitor RTI-336 and found significant increases in evening activity, sleep latency and sleep fragmentation, while sleep efficiency was decreased (Andersen et al., 2012).

Finally in Chapter II, when choosing between a low, non-preferred dose of cocaine and food, nighttime sleep disruption did not significantly increase cocaine choice. To achieve significant disruptions in behavioral indices of sleep, the lights were left on in the animal housing room all night and the room was entered hourly to awaken the monkeys. The decision to use this form of sleep disruption, and not total sleep deprivation, was based on the concept that this would model sleep disturbances encountered by chronic cocaine users. Although significant disruptions in several behavioral indices of sleep were observed, as represented by increases in nighttime activity, we did not observe increases in the percent of cocaine choice for a dose of cocaine that was one-half log-unit below the preferred dose, as had been hypothesized. One possible explanation for the lack of an effect on the percent of cocaine choice could be a result of the alternative reinforcer (food pellets) that was available. Clinical literature suggests that sleep loss will increase food intake (Brondel et al., 2010), enhance the drive to consume food (Benedict et al., 2012), and that the associated stress of sleep loss may lead to increased hunger and appetite (Pejovic et al., 2010). Thus, it is possible that sleep disruption increased the reinforcing effects of both food and cocaine, which would cancel each other out and yield no chance in allocation of responses under the choice procedure.

Other preclinical data supports this hypothesis. In a study using a choice procedure in rhesus monkeys, it was reported that withdrawal from extended cocaine access failed to alter the reinforcing strength of cocaine as measured by cocaine vs. food choice (Banks and Negus, 2010). For extended cocaine access, daily cocaine choice procedures were immediately followed by 21 hour supplemental sessions where cocaine was also available and large intakes were noted. The authors suggested that a possible explanation for the negative results was that it is possible that increases in cocaine's reinforcing strength were masked by a concurrent increase in the reinforcing strength of food to produce no net change in choice (Banks and Negus, 2010). Thus, the effect of sleep disruption on cocaine choice with a food reinforcer as the competing stimulus may have negated any effect that we had hypothesized. Based on previous literature that indicates that early withdrawl from cocaine (Morgan et al., 2008) and cocaine abstinence (Morgan et al., 2006) is associated with sleep disturbances, and that sleep deprivation has been documented to increase cocaine self-administration (Puhl et al., 2009) it is interesting that no effect on cocaine choice was observed in the Banks and Negus (2010) study and similarly, that no effect on cocaine choice following sleep disruption was observed in Chapter II. Specifically for the lack of an observed effect in Chapter II, it is possible that while we examined sleep disruption on low-dose cocaine self-administration, it may be that the higher, reinforcing doses are more vulnerable to sleep disturbances. Thus, another limitation of the present choice paradigm is that intake for the lowest preferred dose could not be substantially increased if we had tested sleep disruption when that dose was available. Future studies will need to be conducted to more thoroughly examine the

relationship between sleep disruption and the consequences on cocaine self-administration.

With sleep problems being important risk factors for substance abuse (Breslau et al., 1996; Wong et al., 2004) it is important to understand the relationship when evaluating potential treatment option. The results presented in Chapter II indicated cocaine self-administration affects sleep, but sleep disruption did not affect cocaine reinforcement. Studies in Chapter III looked at whether treatments that improve sleep efficiency will subsequently decrease cocaine reinforcement. Further, the results of Chapter II provide evidence that sleep disturbances induced by cocaine use can be measured in rhesus monkeys using actigraphy and this technique could be applied for future experiments targeting sleep disturbances associated with PTSD.

THE EFFECT OF QUETIAPINE TREATMENT ON COCAINE SELF-ADMINISTRATION AND SLEEP EFFICIENCY IN ADULT RHESUS MONKEYS

Hypothesis: Quetiapine treatment will shift the cocaine choice curve down and to the right following either acute or chronic administration. Based on the pharmacology of quetiapine, quetiapine administration will increase the sleep efficiency of cocaine self-administering monkeys.

Quetiapine, an atypical antipsychotic, has been used off-label as a treatment for patients who present with insomnia. It has been proposed that quetiapine exerts its activity primarily through a combination of DA D2 and serotonin (5-HT) 2 (5-HT_2)

antagonism. However, quetiapine is an antagonist at multiple neurotransmitter receptors in the brain including serotonin 5-HT_{1A} and 5-HT2, DA D1- and D2-like, histamine H_1, and adrenergic $alpha_1$- and $alpha_2$- receptors. In addition to its supposed efficacy in sleep disturbances, quetiapine has also been reported to significantly reduce cocaine craving in humans (Brown et al., 2002, 2003; Kennedy et al., 2008). The experiments in Chapter III were designed to examine the effect of quetiapine treatment on cocaine self-administration in a monkey model of cocaine abuse. Secondarily, Chapter III examined the effect of quetiapine treatment on cocaine-induced disruptions of sleep efficiency that were reported in Chapter II.

Positive individual-subject responses to acute quetiapine treatment were observed, but tolerance developed and this effect diminished with chronic twice-daily treatment. These results are similar to another preclinical study where aripiprazole, also an atypical antipsychotic, administration decreased cocaine choice in rats following acute treatment, however this effect was not sustained during repeated treatment (Thomsen et al., 2008). Our results are inconsistent with some reports in the literature of quetiapine showing positive results for reducing substance abuse (Brown et al., 2003; Sattar et al., 2004; Pinkofsky et al., 2005; Potvin et al., 2008). Differences in response may be attributable to several different factors. It is highly possible that in the clinical studies that reported positive results, enrolled patients exhibited polysubstance abuse and therefore the results may be confounded. However, positive results have been reported in other preclinical studies examining the effects of treatments on cocaine administration where polysubstance abuse was not present. Clozapine, a pharmacological agent in the same category as quetiapine, was shown to reduce cocaine self-administration in rats (Roberts

and Vickers, 1984) and diazepam, an agent that can induce sleep, administration decreased cocaine choice in rats (Augier et al., 2012).

Further, many of the studies that reported positive results occurred in patients with a comorbid psychiatric condition. The lifetime prevalence rates of substance abuse in patients with bipolar disorder are as high as 60% (Regier et al., 1990; Strakowski and DelBello, 2000). Interestingly, a group of authors observed decreases in the quantity of substance abuse following administration of antipsychotic medications to control psychotic symptoms (Volkow et al., 2002). These findings would lead us to hypothesize that in the absence of a psychotic disorder quetiapine treatment may lack efficacy in treating cocaine abuse. To support this hypothesis are multiple reports in the literature where the efficacy of quetiapine for treating substance abuse is coupled with a comorbid psychiatric condition (Brown et al., 2002; Martinotti et al., 2008). Further, it has been suggested that substances are abused to overcome anxiety of the distressing effects of illness or its treatment, which has been referred to the "self-medication hypothesis" (Khantzian, 1985). More recently it has been suggested that substance-dependent individuals have obsessive thoughts related to the substance they abuse and the antipsychotic effect of quetiapine may help in reducing those thoughts (Martinotti et al., 2008). Although literature supports the hypothesis that quetiapine treatment effectively reduces cocaine use in the presence of a comorbid psychiatric condition, quetiapine efficacy was also investigated for the treatment of cocaine dependence in individuals who lacked psychotic symptoms and positive results were reported (Kennedy et al., 2008). Also, in a study comparing risperidone and quetiapine, administration of either drug resulted in decreases in cocaine and methamphetamine craving with those reductions

predicting less frequent drug use (Nejtek et al., 2008). However, in contrast to the Khantzian "self-medication hypothesis" the authors of this study reported that they found no direct evidence that improved mood was associated with less overall drug use. Taken together with the results from Chapter III, these conflicting results would suggest that the reductions in substance abuse observed following quetiapine administration are not a direct result of improved sleep or improvements in psychiatric symptoms. It is possible that the combination of improvements in sleep and psychiatric symptoms, are coupled with an unknown condition or particular neurobiology and it is in those patients that positive results are observed. Future experiments need to be conducted to further examine the possible mechanisms by which quetiapine exerts a positive effect of reducing cocaine abuse.

Although single doses of quetiapine (given orally the morning prior to cocaine self-administration) did not improve the sleep efficiency the following night, Chapter III reported that chronic, twice daily oral administration of quetiapine was able to significantly improve the sleep efficiency suggesting that quetiapine may be beneficial in treating substance abuse by inhibiting the sleep disturbances induced by substance abuse as observed in Chapter II. Quetiapine has been commonly used off-label for a variety of conditions, one of which being insomnia (Hartung et al., 2008; Philip et al., 2008; Wine et al., 2009; Dolder and McKinsey, 2010) although results from a meta-analysis reported inconclusive efficacy (Maher et al., 2011). Importantly, results from Chapter III indicated that following discontinuation of chronic quetiapine administration the sleep efficiency declined to baseline self-administration percentages as early as one day. A recent study showed that sedation associated with quetiapine administration was reported in 100% of

the participants receiving quetiapine in the absence of psychotic symptoms, which decreased to 75% by the end of week 1 of treatment to 29% at the end of week 6 (Kennedy et al., 2008). We showed that improvements in sleep disruption were still evident following two weeks of twice-daily quetiapine administration. There are several possible explanations for the reported tolerance to the sedation associated with quetiapine use reported in the Kennedy and colleagues (2008) study. The most obvious reason for the conflicting results could be that the majority of the patients in their study received lower than the target dose of quetiapine (600 mg/day) due to complaints of sedation. Thus, it is possible that if all of the participants were to receive the target dose, despite complaints of sedation, that tolerance to the sedative effect would not be observed. Further, the results from that study are based on patient reports and it has been shown that, patient reports and measured sleep do not always coincide. In a study in abstinent cocaine users, patients reported improvements in sleep while objectively measured sleep was actually shown to be deteriorating (Morgan et al., 2006). Importantly, the results of our study are supported by a study that examined the efficacy of mirtazapine (a sleep-promoting agent) in patients with comorbid depression and cocaine dependence showed that mirtazapine was superior to placebo in improving sleep, however it was not more effective than placebo in reducing cocaine use (Afshar et al., 2012).

Taken together, the findings in Chapter III do not support quetiapine treatment as a monotherapy for cocaine abuse; the results do suggest the potential of quetiapine to be used as an adjunct therapy in cocaine abuse to treat sleep disturbances associated with stimulant abuse. However, results obtained in Chapter IV and V would also caution the use of quetiapine in substance abusing individuals based on the potential for further

cognitive disruption and/or and increased co-abuse potential. Finally, based on variability in individual response to quetiapine treatment, it is important to remember to treat the individual and not the condition.

EXAMINING THE REINFORCING EFFECT OF QUETIAPINE, ALONE AND IN COMBINATION WITH COCAINE, IN ADULT RHESUS MONKEYS

Hypothesis: Quetiapine will not have reinforcing effects in monkeys compared to saline conditions, nor will quetiapine exhibit reinforcing effects while monkeys are concurrently treated with chronic oral quetiapine. Addition of quetiapine to cocaine will not increase the relative reinforcing strength of cocaine in monkeys.

Quetiapine, an atypical antipsychotic, has been used off-label as a treatment for patients who present with insomnia. In addition to its supposed efficacy in sleep disturbances, quetiapine has also been reported to significantly reduce cocaine craving in humans (Brown et al., 2002, 2003; Kennedy et al., 2008). One concern, however, is the abuse potential of quetiapine, with intravenous abuse first being reported in the literature in 2005 (Hussain et al., 2005). Experiments in Chapter IV were designed to examine the abuse potential of quetiapine in rhesus monkeys self-administering cocaine under two different schedules of reinforcement.

When quetiapine was substituted for food it did not function as a reinforcer. Concurrent chronic quetiapine treatment had no effect on the reinforcing effect of intravenous quetiapine self-administration. Importantly, response rates for quetiapine were lower than baseline conditions when the subject was concurrently given oral

quetiapine treatment. Thus, although individual case reports are available reporting the abuse of quetiapine, the results of Chapter IV indicate that quetiapine, alone, does not function as a reinforcer in rhesus monkeys.

To date, it doesn't appear that the reinforcing effects of quetiapine in nonhuman primates have been characterized. Importantly, 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 (> 5 years) history of cocaine self-administration (Hamilton et al., 2010, 2011) and therefore we felt they would serve as suitable subjects to model this patient population. Although quetiapine did not function as a reinforcer, it is possible that the patients who have reported abusing quetiapine have also possessed other psychiatric comorbidities and polysubstance abuse that may have contributed to their percieved reinforcing properties associated with quetiapine and therefore our model may have lacked these concomitant disorders. Specifically, it has been reported that individuals with a history of anxiolytic/sedative misuse were more than eight times more likely to report quetiapine misuse (McLarnon et al., 2012). Further, it has been suggested that the misuse of quetiapine is motivated by self-medication of insomnia (Reeves and Brister, 2007), anxiety (Reeves and Brister, 2007; Morin, 2007; Chen et al., 2009) or depression (Chen et al., 2009). These principles fall in line with Khantzian's "self-medication hypothesis" that suggests that substances are abused to overcome anxiety of the distressing effects of illness or its treatment (Khantzian, 1985) and may provide an explanation of the lack of an observed effect in our model.

Based on the "self-medication hypothesis" it is possible that quetiapine may be abused for its ability to reduce the symptoms of withdrawl from drugs of abuse and may be combined with the drugs in a manner similar to "speedball" use (i.e., cocaine plus heroin). Interestingly, it has been reported in the literature that a patient injected himself with a mixture of cocaine and quetiapine, referred to as "Q-ball," so he could experience hallucinogenic effects (Waters and Joshi, 2007). To examine this co-abuse hypothesis, experiments in Chapter IV also examined the reinforcing strength of quetiapine and cocaine in combination. Results from those experiments indicated that a majority of monkeys (5/7) demonstrated an increased relative reinforcing strength of the combination compared to cocaine alone. A possible explanation for this may be due to the ability of quetiapine to block the α_1-adrenergic receptor, therefore blocking some of the untoward effects that cocaine has (i.e. tachycardia). Further, it has been suggested that the reduced affinity of quetiapine for the D_2 receptor would support a possible abuse potential due to a reduced extrapyramidal side effect profile (Kapur et al., 2000; Tauscher et al., 2004; Morin, 2007; Farah, 2005) and therefore is not likely to produce euphoria or enhance dysphoria associated with drug withdrawl (Morin, 2007). Potentially supporting this explanation, low and intermediate dose chlorpromazine and haloperidol has been shown to increase the frequency of cocaine choice (Woolverton and Balster, 1981), which would also have reduced D2 receptor binding compared to higher doses that eliminated responding for both cocaine and food. Further, the 5-HT_{2A} selective antagonist, ritanserin, resulted in increased response rates for intravenous self-administration of cocaine over a range of cocaine doses (Howell and Byrd, 1995) and it is possible that the 5-HT_{2A} antagonism by quetiapine may be partially responsible for the enhancing effect observed.

It has also been suggested that another likely explanation for the abuse of quetiapine is due to its high antagonistic affinity for the histamine H1 receptor (Fischer and Boggs, 2010), especially in relationship to its antagonistic affinity for the D2 receptor (Kroeze et al., 2003). Reports have indicated that antihistamines are misused in humans (Halpert et al., 2002; Bailey and Davies, 2008; Thomas et al., 2009) and would further support the Fischer and Boggs (2010) suggestion. Pre-clinical data are also available documenting the abuse potential of antihistamines. Specifically, in nonhuman primates and rodents, antihistamines demonstrate behavioral properties similar to cocaine (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 a greater reinforcing strength than was predicted based on additivity alone (Wang and Woolverton, 2007). Finally, self-administered combinations of cocaine (0.03 mg/kg/injection) and diphenhydramine resulted in significantly increased response rates compared to cocaine alone in rhesus monkeys (Banks et al., 2009). Taken together these results suggest H1 receptor antagonism as a mechanism underlying our findings that a combination of quetiapine and cocaine was more reinforcing than cocaine alone.

Future experiments should be designed to examine the relative reinforcing strength of quetiapine alone compared to food reinforcement, and alternatively the effect of combinations of quetiapine and cocaine should be examined in a single-response self-administration procedure. Based on the results in Chapter IV, while a prior history of substance abuse may not be a requirement for a patient to subsequently abuse quetiapine,

it could serve as a potential indicator of a patient to be closely monitored if started on quetiapine.

EFFECTS OF SLEEP DISRUPTION OR QUETIAPINE TREATMENT ON COGNITIVE PERFORMANCE IN ADULT RHESUS MONKEYS

Hypothesis: Following sleep disruption, monkeys will demonstrate impaired working memory compared to baseline conditions. Since quetiapine treatment has been shown to improve sleep, quetiapine administration will result in improvement of working memory in monkeys.

Cocaine use is also associated with deficits in cognitive flexibility (Kelley et al., 2005) making abstinence more difficult. Further, the deficits associated with cocaine use may perpetuate the cycle of drugs use and increase relapse (cf. Rogers and Robbins 2001) and therefore it is possible that tending to an individual's cognitive disruptions may in part decrease relapse. Available literature has suggested that quetiapine has cognitive promoting abilities and therefore an examination of the effect of quetiapine on working memory (Chapter V) was assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB). CANTAB is comprised of a series of visual and spatial tasks designed to probe regional brain function by challenging specific cognitive components (Weed et al., 1999) and has been shown to be a valid model for examining working memory in rhesus monkeys. Further, as cocaine use is associated with sleep disturbances, and previous literature has shown sleep deprivation causes cognitive

deficits, the effect of sleep disruption, not total sleep deprivation, on working memory was also examined as part of Chapter V.

To achieve significant disruptions in sleep measures, the lights were left on in the animal housing room all night and the monkeys were awakened hourly. Although significant disruptions of several measures of sleep were reported in Chapter II, this method did not produce disruptions in cognitive performance measured by the percent accuracy and the number of omitted trials. While these findings did not show that sleep disruption resulted in cognitive impairment of working memory, delay-dependent deficits on cognitive performance were observed, as had been previously reported (Hampson et al., 2004; Porrino et al., 2005; Deadwyler et al., 2007; Gould et al., 2012, 2013).

The results presented in Chapter V were in contrast to results published that reported sleep deprivation caused significant cognitive deficits in the DMS task (Hampson et al., 2004, 2009; Porrino et al., 2005; Deadwyler et al., 2007). Possible explanations for the lack of an observed deficit in our studies are our model of disruption may have allowed too much time to sleep and therefore was not long enough. It appears that although our method of sleep disruption resulted in increases in total activity, those increases occurred early on during the normal "lights-out" period with less activity observed later (Figure 2). Thus, it is possible that although the monkeys were awakened hourly, they were able to still get some sleep and therefore no cognitive deficits were observed. The studies that showed sleep deprivation was responsible for producing cognitive deficits all used a method of complete sleep deprivation that consisted of 30-36 hours of continued sleep prevention. In those studies, the monkeys were continuously monitored to ensure they did not fall asleep at all for an extended period of time. It is also

possible that no effect was observed due to the monkeys having a previous extensive history with the DMS task (Gould et al., 2012, 2013) and their baseline performance was at a high level and was reported that baseline cognitive function may influence the response to manipulation (Rocca et al., 2007). However, this explanation seems unlikely, as delay-dependent decreases in performance were still present and therefore it was probably due to the length or method of disruption.

Figure 2

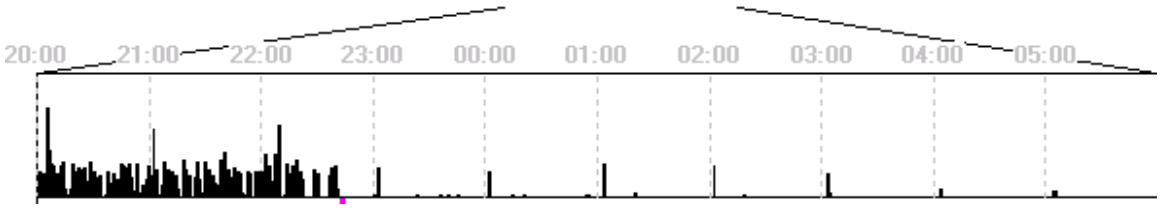

Figure 2. Individual (R-1563) actogram, representative of the group, recorded over the normal "lights-out" period during one night of sleep disruption.

Chapter V also examined the effect of quetiapine on cognitive performance and reported that acute and continuous quetiapine treatment resulted in cognitive disruption of performance in a working memory task. Those results also indicated that initial treatment (acute and continuous) resulted in disruption of total accuracy at short and medium delays, which would suggest quetiapine may be responsible for causing attentional deficits, an effect similar to that seen when humans are subjected to sleep deprivation they lapse and miss the deadline for responses during the probe phase (Habeck et al., 2004). However, continuous treatment resulted in disruption at all delays which would be suggestive of an overall disruption of performance and tolerance did not

develop to this effect following ten days of treatment. The results presented in Chapter V are supported by other reports of a similar effect. A pre-clinical study reported that quetiapine administration resulted in disruption of performance in the 5-choice serial reation time task in rats (Amitai and Markou, 2009). Clinical literature also fails to provide evidence of a cognitive-promoting effect of quetiapine (Anderson et al., 2011; Robles et al., 2011). Also, the combination of quetiapine with an SSRI resulted in no effect on cognitive functioning although the authors proposed that the failure may be caused by attention difficulties owing to somnolence (de Geus et al., 2007) and therefore it is possible that the disruptions observed in Chapter V are a result of somnolence induced by quetiapine administration. Finally, a report indicated that initiation of quetiapine treatment was associated with immediate adverse cognitive effects and increased somnolence (Harvey et al., 2007), which is supported by the findings in Chapter V and III, respectively. In conclusion, the findings indicate that quetiapine, an agent that has been suggested as a possible treatment option for cocaine addiction (Brown et al., 2002, 2003; Kennedy et al., 2008), caused cognitive disruptions in working memory and therefore may perpetuate the drug use cycle and therefore may not be a good treatment option for disorders where cognitive impairment is present. It is possible that if quetiapine is given only in the evening, to promote sleep, that quetiapine might function as a cognitive-enhancing agent. This suggestion would be supported by results that demonstrated the ability of quetiapine to promote sleep even in the presence of cocaine self-administration (Chapter III).

POST-TRAUMATIC STRESS DISORDER (PTSD)

While post-traumatic stress disorder (PTSD) continues to plague military veterans, it has been predicted that current treatment strategies for PTSD will meet no more than 20% of all veterans in need of treatment (Hoge, 2011). Not only does PTSD continue to be an under-treated condition, it poses a large economic burden as well, with estimates that the U.S. economy loses approximately $3 billion annually due to lost productivity associated with PTSD (Brunello et al., 2001). One factor that is largely known is there is significant individual variability in the vulnerability to severe stress or trauma as it relates to the development of PTSD (Liberzon and Knox, 2012), making treatments aimed at prevention much more difficult.

Interestingly, it has been suggested that PTSD is the only major mental disorder that a cause is considered to be known (Pitman et al., 2012), although effectively treating this disorder has been elusive. Some of that elusiveness can be partially attributed to the lack of a critical understanding of the neurobiological and physiological mechanisms of the disease and the overall lack of valid animal models. Identifying targets for effective treatments for PTSD are dependent on the development of suitable animal models of the disorder, which to date are limited. Developing an animal model of PTSD is challenging in that certain symptoms indicative of PTSD may be unique to humans (e.g., intrusive memories of the event, perception of event being life-threatening) and that there are currently no effective pharmacological treatments for PSTD (Cohen et al., 2011) that could be used in determining the validity of the animal model. The potential benefits of developing an effective animal model of PTSD in monkeys are abundant. An effective nonhuman primate model of PTSD would allow the opportunity to use within-subject

study designs, such that the etiology of the disorder could be examined. Also, with the development of an effective animal model of PTSD, the effects of cue presentation and situational reminders could be examined at a neurobiological and neurochemical level. Criteria have been developed to evaluate animal models of PTSD (for review see Yehuda and Antelman, 1993), although some criteria have proven difficult to model in animals. Specifically hard to model in animals is the interindividual variability in response to a stressor that should be present either as a function of experience, genetics, or an interaction of the two. Criteria that are more likely to be modeled include: 1) the stressor should be capable of inducing biological and behavioral sequalae of PTSD; 2) the stressor should be capable of producing PTSD-like sequalae in a dose-dependent manner; 3) the stressor produces biological alterations that persist or worsen over time; and 4) the stressor should induce biobehavioral alterations that can be enhanced or reduced (Yehuda and Antelman, 1993). Therefore, developing a model that encompasses the greatest number of symptoms is of utmost importance.

Sleep disturbances and substance use disorders are two symptoms frequently associated with PTSD. It has been reported that patients with comorbid PTSD and substance abuse have higher relapse rates compared to patients with substance abuse but without PTSD (Breslau et al., 1997; Najavits et al., 1998) and the symptoms of patients with comorbid PTSD and substance use are more severe and are more refractory to treatment (Jacobsen et al., 2001). Further, it has been suggested that PTSD may lead to the development of substance abuse via a self-medication pathway (Jacobsen et al., 2001) wherein patients begin abusing medications to treat symptoms associated with their condition. As described throughout this dissertation, this self-medication pathway may

lead to an exacerbation of symptoms and ultimately perpetuate the drug abuse cycle. Adding to that cycle, hallmark symptoms of PTSD involve alterations to cognitive processes such as memory, attention, planning, and problem solving, with evidence indicating memory and attention deficits in PTSD (Hayes et al., 2012). Patients with mental illness (including PTSD) are at high risk for substance abuse, and the adverse impact on cognition may be particularly deleterious in combination with cognitive problems related to their mental disorders (Gould, 2010) further complicating treatment outcomes.

As it relates to treatment of PTSD, the largest body of research available supports the efficacy of the SSRIs, while atypical antipsychotics and the α_1 antagonist, prazosin, have sown some efficacy (Ipser and Stein, 2012). Only two SSRIs, sertraline and paroxetine, have FDA approval to treat PTSD (Krystal et al., 2011). While treatment options are limited, the off-label use of atypical antipsychotics, particularly quetiapine, has gained wide popularity although it has been expressed that further studies are needed (Hoge, 2011). Clinical literature is reported that quetiapine treatment significantly improved subjective sleep quality, latency and duration; sleep disturbances, episodes of terror, and acting out dreams in a group of combat veterans diagnosed with PTSD (Robert et al., 2005). Similar to the results of this study, experiments in Chapter III revealed that quetiapine was able to significantly attenuate cocaine-induced disruptions of sleep efficiency and served in a sleep-promoting capacity. Taken together, these results suggest that quetiapine would be a potential treatment option for patients with comorbid PTSD and cocaine addiction.

Quetiapine treatment (both before and after enhanced single prolonged stress) was also shown to significantly ameliorate anxiety-like behavior, learning and spatial memory impairments and the authors concluded that quetiapine has preventive and protective effects against stress-associated symptoms (Wang et al., 2010), further suggesting quetiapine may have therapeutic efficacy for treating PTSD. However, results from Chapter V showed that quetiapine treatment was associated with significant cognitive impairments that were still evident after 10 days of treatment. Also problematic for the potential of quetiapine as a treatment option for PTSD are reports that quetiapine treatment increased marijuana craving and marijuana self-administration during relapse phase of a trial examining its use in non-treatment seeking abusers (Cooper et al., 2012) and Chapter IV reported that quetiapine and cocaine combinations were more reinforcing than cocaine alone.

A potential experiment for modeling PTSD might be accomplished by examining the effects of a compound stimulus, paired with a loud noise, on physiology, cognition, and the reinforcing effect of cocaine. To complete these studies, monkeys could be situated in primate restraint chair, with a blood pressure cuff (SunTech) wrapped around the bicep, directly above the antecubital space, and with three ECG probes placed (right elbow, left elbow, and left knee) for a 3-lead ECG recording of heart rate. Measurements can be recorded with a vital sign monitor (scil Vet View V5) to determine baseline measures. Prior to the loud noise/compound stimulus exposure, monkeys can be trained using CANTAB equipment to perform a memory task (delayed match to sample). Once a baseline has been established, the monkey would then be exposed to a loud noise (bomb blast or air horn) in the presence of a flashing light and menthol fragrance while blood

pressure and heart rate are recorded. Sleep activity could be monitored post-noise and stimulus exposure and compared to baseline activity. To determine if additional loud noise/compound stimulus pairings are needed, the effects of the compound stimulus on the physiological measures described above could be tested. Also, following stimulus and noise exposure, cognitive performance and the cocaine choice curve will be redetermined. Further, cue exposure could take place in different environments (e.g. home cage, self-administration chamber, CANTAB chamber) and behavioral measures could be monitored at several time points. Finally, after completion, chronic oral quetiapine treatment can be initiated and studies can be repeated using stimulus and noise exposure to examine the effect of quetiapine treatment on these measures. An experiment like this would meet the criteria established by Yehuda and Antelman (1993) that are necessary for a successful animal model of PTSD and would model at least five symptoms from the proposed DSM-V criteria. This model could then be used for future experiments involving imaging (both before and after exposure) in an effort to address the criteria that has been described as being difficult to model (interindividual variability in response to a stressor as a function of experience, genetics, or an interaction fo the two.

CONCLUSION

The research conducted in this dissertation demonstrated that several symptoms of PTSD (sleep disturbances, cognitive disruptions and drug abuse) could effectively be measured in rhesus monkeys and therefore can serve as a building block in the pursuit and an effective monkey model of PTSD. The next step in this pursuit would be to introduce a component of stress, associated with several cues, and evaluate the effects

(immediate and long-term) of this stress on the symptoms that were measured in this dissertation. Further, this research demonstrated that although quetiapine was able to effectively reduce cocaine induced sleep disturbances, the results of cognitive disruption and increased reinforcing strength would suggest using caution when determining the suitability of this treatment option for cocaine addiction or PTSD. Although the results presented for quetiapine treatment were not optimal, they do not totally discount the consideration of quetiapine as an adjunct treatment options for a variety of conditions. Finally, based on the results of this dissertation, evidence has been provided for individual variability in response to pharmacological manipulation so the strategy should be to treat the individual.

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SCHOLASTIC VITAE

ROBERT EDWIN BRUTCHER

EDUCATION

Current:	Ph.D., in Physiology and Pharmacology Wake Forest University Health Sciences, May 2013 Dissertation: Effects of sleep disruption and quetiapine on cocaine abuse: the path to development of a monkey model of PTSD Advisor: Michael A. Nader, Ph.D.
Degree: (High Distinction)	Pharm D, May 2004 Ohio Northern University Ada, OH
Degree: (High Distinction)	B.S. Biology / Pre-Medicine May 1999 Ohio Northern University Ada, OH

LICENSE/CERTIFICATION

Pharmacist:	Ohio State Board of Pharmacy, July 2004 - Present
Internship:	Rite Aid Pharmacy. Westlake, OH Dec. 2000 - Jun. 2004
Smoking Cessation:	Ohio Northern University, 2002
Adult Immunizations:	Ohio Northern University, 2002
CPR:	American Heart Association, 1999-present
EMT – Basic:	May 1999

MILITARY CAREER

Chief, Outpatient Pharmacy:

Evans Army Community Hospital, Fort Carson, Colorado
January 2008 – May 2009

Served as Chief, Outpatient Pharmacy at USA MEDDAC, Ft. Carson CO, a 78-bed hospital with three outlying medical clinics and a satellite pharmacy. Responsible for providing quality pharmaceutical care to over 145,000 beneficiaries, including 15,000 active duty Soldiers, with an annual pharmacy budget and expenditures in excess of $20 million. Provides direct leadership and guidance of 33 personnel; 14 pharmacists and 19 pharmacy technicians. Serves

as the Co-Chair of the Medication Management FMT. Supports continuous compliance with The Joint Commission standards. Active member of Pharmacy Quality Improvement and Performance Improvement teams. Serves as the Acting Chief in his absence. Maintains deployment readiness. Completes additional duties as assigned.

Chief, Dept of Pharmacy:
28th Combat Support Hospital, Ibn Sina, Baghdad, Iraq
September 2006 – December 2008

Served as Chief of Pharmacy, Medical Task Force 28 (Baghdad), the primary Level III combat health care facility for MNF-I in support of Operation Iraqi Freedom 06-08. Plans, develops, coordinates, and executes pharmacy policies and procedures in support of over 113,000 beneficiaries. Responsible for the accuracy and appropriateness of drug therapy for all prescriptions dispensed. Responsible for the fiscal management of over a $1 million budget and over 2,000 expendable items. Enforces the principles of medication management throughout the hospital to ensure proper administration, dispensing, monitoring, storage, and security of all pharmaceuticals. Serves as the coordinator for the Pharmacy and Therapeutics Committee, ensuring proper management of the hospital formulary. Serves as the Clinical Pharmacy Consultant for providers of the 28th CSH, DoD, coalition forces, and Iraqi medical staff.

Pre-Deployment Training:
Fort Bragg, NC
August 2006

OIC Inpatient/Clinical:
Evans Army Community Hospital, Fort Carson, CO
June 2006 – July 2006

Served as Chief, Inpatient and Clinical Pharmacy, USA MEDDAC, Ft. Carson, CO. Responsible for providing quality pharmaceutical care to over 145,000 beneficiaries, including 15,000 active duty Soldiers. Provides leadership and management for 6 pharmacists and 11 pharmacy technicians/support staff. Assist in supporting medical SRP and mobilization activities as part of the Fort Carson Power Projection mission. Support continuous compliance with Joint Commission for Accreditation of Healthcare Organizations (JCAHO) standards. Serves as a member of the Medication Management FMT and as Pharmacy liaison on hospital JCAHO sustainment tracer team. Provide pharmaceutical oversight and care in the Disease Management Clinic and Anticoagulation Monitoring Service. Coordinate compliance with United States Pharmacopeia Chapter 797. Accomplish other duties as assigned.

Captains Career Course:
Fort Sam Houston, TX

March 2006 – May 2006

OIC Inpatient/Clinical:
Evans Army Community Hospital. Fort Carson, CO
December 2004 – March 2006

Served as Chief, Inpatient and Clinical Pharmacy, USA MEDDAC, Ft. Carson, CO. Responsible for providing quality pharmaceutical care to over 145,000 beneficiaries, including 15,000 active duty Soldiers. Provides leadership and management for 6 pharmacists and 11 pharmacy technicians/support staff. Assist in supporting medical SRP and mobilization activities as part of the Fort Carson Power Projection mission. Support continuous compliance with Joint Commission for Accreditation of Healthcare Organizations (JCAHO) standards. Serves as a member of the Medication Management FMT and as Pharmacy liaison on hospital JCAHO sustainment tracer team. Provide pharmaceutical oversight and care in the Disease Management Clinic and Anticoagulation Monitoring Service. Coordinate compliance with United States Pharmacopeia Chapter 797. Accomplish other duties as assigned.

Officer Basic Course:
Fort Sam Houston, TX
September 6, 2004 – November 23, 2004

MILITARY AWARDS/DECORATIONS

Bronze Star Medal (BSM)
Meritorious Service Medal (MSM)
National Defense Service Medal (NDSM)
Iraq Campaign Medal with 2 Campaign Stars (ICMCS)
Global War on Terrorism Service Medal (GWOTS)
Army Service Ribbon (ASR)
Overseas Service Ribbon (OSR)
Meritorious Unit Citation (MUC)

PHARMACY HONORARIES AND AWARDS

Mylan Pharmaceuticals Excellence in Pharmacy Award, Ohio Northern University, 2004
P-5 Class Honors, Ohio Northern University, 2002-03
Phi Kappa Phi: Ohio Northern University, Initiated April 2002
Rho Chi: Ohio Northern University, Initiated April 2002
P-4 Class Honors, Ohio Northern University, 2001-02
P-3 Class Honors, Ohio Northern University, 2000-01
President's Award: Ohio Northern University, 2002-03

Ohio Northern University, 2001-02
Ohio Northern University, 2000-01

Outstanding Academic Performance Award:
Ohio Northern University, 2001-02
Ohio Northern University, 2000-01
Ohio Northern University, 1998-99
Ohio Northern University, 1997-98
Outstanding Student in Organismic Biology, Ohio Northern University, 1999
Beta-Beta-Beta: Biology Honorary, Ohio Northern University, Ada, Ohio
1997-99

PRESENTATIONS/PROJECTS

Examining the relationship between cocaine self-administration and sleep in rhesus monkeys. Student Seminar Series, Integrative Physiology and Pharmacology Program, Wake forest University School of Medicine, DEC 2012.

Examining the relationship between cocaine self-administration and sleep in rhesus monkeys. Update Annual Wake Forest University-Emory University-Virginia Commonwealth University-Medical University of South Caronlina Lab Exchange, Winston-Salem, NC. 21 SEP 2012.

Examining the relationship between cocaine self-administration and sleep in rhesus monkeys. Student Seminar Series, Integrative Physiology and Pharmacology Program, Wake forest University School of Medicine, 16 APR 2012.

Drug Addiction: Not a problem to monkey around with……or is it? Joint Forces Pharmacy Seminar, Dallas, TX. 2 NOV 2012. ACPE accredited continuing pharmacy education lecture.

Effect of cocaine exposure *in utero* on the relative reinforcing strength of cocaine using delayed discounting. Emory University, Alanta, GA. 23 SEP 2011

Effect of cocaine exposure *in utero* on the relative reinforcing strength of cocaine using delayed discounting. Wake Forest University School of Medicine, Department of Physiology and Pharmacology Monday Seminar Series. 7 MAR 2011

Behavioral effects of chronic quetiapine and venlafaxine in an animal model of antidepressant activity. Annual Wake Forest University-Emory University-Virginia Commonwealth University-University of Michigan Lab Exchange. OCT 2010

Antivirals and Antifungals: The other trouble makers. Physiology and Pharmacology lecture, Winston-Salem State University, Physical Therapy program. OCT 2010, FEB 2012

Antibacterial drugs; What drugs kill what bugs? Physiology and Pharmacology lecture, Winston-Salem State University, Physical Therapy program. SEP 2010, FEB 2012

Pharmacology 500- Provided a lecture on the pharmacology of critical care medications to the Critical Care Registered Nurse Course which included: overview or sympathetic and parasympathetic nervous systems, receptors and subtypes, cardiac medications, misc. meds, and asthma overview. Ibn Sina Hospital, Baghdad, Iraq. 26 FEB 2007.

USP Chapter 797, Compounding Sterile Products- developed guide on implementation and guidance for compliance with the standard. Guide included: Revised SOP, Quality Assessment, Aseptic technique class, renovation plans, etc. Fort Carson, CO, 2005-06.

ABSTRACTS

Examining the relationship between cocaine and sleep in a monkey model of drug abuse. Student Seminar Series, Department of Physiology and Pharmacology, Wake Forest University School of Medicine. DEC 2012.

Examining the relationship between substance abuse and sleep. Joint Forces Pharmacy Seminar. NOV 2012.

Effects of *in utero* cocaine exposure on the relative reinforcing strength of cocaine in adult rhesus monkeys using a delay discounting procedure. Experimental Biology-ASPET, Poster session. APR 2011, APR 2012

Drug Abuse: Not a problem to monkey around with…..or is it? Joint Forces Pharmacy Seminar, Pharmacy Continuing Education. May 2011.

PUBLICATIONS

Brutcher RE, Nader MA (2013) The relationship between cocaine self-administration and actigraphy-based measures of sleep in adult rhesus monkeys. *Psychopharmacology (Berl),* in press

Sprague JE, **Brutcher RE**, Mills EM, Caden D, Rusyniak DE (2004) Attenuation of 3,4-methylenedioxymethamphetamine (MDMA, Ecstasy)-induced rhabdomyolysis with alpha1- plus beta3-adrenoreceptor antagonists. *Br J Pharmacol* 142(4):667-70

Hulisz D, **Brutcher RE** (2004) Drug-induced weight gain: a review for pharmacy technicians. www.continuingeducation.com/pharmtech/weightgain

RESEARCH PROJECTS

Effects of sleep disruption and quetiapine on cocaine abuse: the path to development of a monkey model of PTSD.
Dissertation

Advisor: Dr. Michael Nader

Brutcher RE, Nader MA (2013) The effect of quetiapine treatment on cocaine self-administration and sleep efficiency in adult rhesus monkeys. Submitted to *Journal of Pharmacology and Experimental Therapeutics* (Mar 2013)

Brutcher RE, Nader MA (2013) Examine the reinforcing effect of quetiapine, alone and in combination with cocaine, in adult rhesus monkeys. *In Preparation*

Brutcher RE, Nader MA (2013) Effects of sleep disruption or quetiapine treatment on cognitive performance in adult rhesus monkeys. *In Preparation*

Brutcher RE, Hamiliton LR, Nader MA (2013) Effect of cocaine exposure *in utero* on the relative reinforcing strength of cocaine using delayed discounting. *In Preparation*

Brutcher RE, Nader MA, Parvizi M, Hemby SE (2013) Behavioral and biochemical assessment of chronic quetiapine in a nonhuman primate model of stress-induced depression. *In Preparation*

The Effect of the Anabolic Steroid Stanozolol and Exercise on Muscle Weight, Size, and Fiber Type. Senior Research, Ohio Northern University. 1996-99
Advisors: Dr. Scott Swanson, Dr. Amy Aulthouse, and Dr. Nancy Woodley

OUTREACH ACTIVITIES

Kernersville Cares for Kids

Student visit held at the Piedmont Triad Community Research Center, Wake Forest University School of Medicine, 4 and 11 FEB 2011. Responsible for teaching students about the effects of different drugs of abuse on the body.

CLINICAL ROTATIONS

Research:	Ohio Northern University. Ada, OH. Dr. Jon Sprague. 7/1 - 7/31/03
Pediatrics:	Rainbow Babies and Children's Hospital. Cleveland, OH. Dr. Michael Reed, Pharm D. 8/1 – 8/31/03
Geriatrics:	University Hospital. Cleveland, OH. Dr. Darrell Hulisz, Pharm D. 9/1-9/30/03
Ambulatory Care:	University Hospital. Cleveland, OH. Dr. Darrell Hulisz, Pharm D. 10/1-10/31/03
Community Rx:	Giant Eagle. Cleveland Area, OH Dr. Kristian Miley, Pharm D. 11/1-11/30/03
Infectious Disease:	VAMC. Huntington, WV. Dr. James Allman, Pharm D. 1/1/04-1/30/04
General Medicine:	Cleveland Clinic Foundation. Cleveland, OH. Dr. Jeff Ketz, Pharm D. 2/2/01-2/27/04
Cardiology:	Cleveland Clinic Foundation. Cleveland, OH. Dr. Mike Militello, Pharm D. 3/1/04-3/31/04
Hospital Practice:	Fairview Hospital. Cleveland, OH. Don Zabriskie, Clinical Coordinator. 2/5/04-2/30/04

RELATED EXPERIENCE

Graduate Student:	Lab Rotation- Anthony Liguori, Wake Forest University School of Medicine (Fall 2009) – Effects of trazodone on sleep and next day performance.
Research Worker:	Drug Information Center Ohio Northern University 2001-2003
Teaching Assistant:	Biosciences Lab Ohio Northern University, 2001-2003
	Anatomy and Histology Ohio Northern University, 2001-2003

Volunteer:	Blood Pressure Monitoring Lima Community Church 2001-2002
	Hardin Hills Nursing Home, Fall 2000

GRADUATE COURSEWORK

Biochemical Techniques	Scientific Integrity
Fundamentals of Physiology/Pharmacology I, II	Intro to Professional Development
Quantitative Methods in Behavioral Science	Advanced Readings

RELATED COURSEWORK

GI/Oncology Module	Pharmacy Administration
Endocrine Module	CNS Module
Infectious Disease Module	Cardiovascular Module
Biomedical Science I, II	Pharmaceutical Science I, II
Patient Care Assessment I, II	Human Anatomy
Developmental Anatomy	Physiology
Biochemistry/ Inorganic Chemistry/ Organic Chemistry	
Physics	Cell Biology
Introduction to Genetics	Immunology
Microtechniques	Histology

ORGANIZATIONS

American Society for Pharmacological and Experimental Therapeutics	2010-Present
American Society of Health System Pharmacy:	2005-Present
Academy of Student Pharmacists:	2002- 2004
Student Society of Health Systems Pharmacists:	2001- 2004
Student Planning Committee:	1998-1999
Habitat for Humanity:	1995-1996