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# The Effects of Fluoxetine and Buspirone on Self-Injurious and Stereotypic Behavior in Adult Male Rhesus Macaques

**M. Babette Fontenot, DVM, PhD,[1,*] E. Eugene Padgett, III,[1] Amy M. Dupuy,[1] Cheryl R. Lynch, PhD,[1] Paolo B. De Petrillo, MD,[2] and J. Dee Higley, PhD[3]**

**The effects of two serotonergic agents—fluoxetine, a serotonin (5-HT) reuptake inhibitor, and buspirone, a 5-HT $1_a$ agonist—on rates of self-injurious and stereotypic behavior were examined in 15 adult male *Macaca mulatta*. All animals received a placebo for 2 weeks followed by either buspirone or fluoxetine for 12 weeks. Behavior was monitored using a focal sampling technique throughout the study and for 2 weeks post-study. Cerebrospinal fluid (CSF) samples and body weights were obtained pre-study, at the ends of placebo and treatment phases, and post-study. Fluoxetine and buspirone were significantly effective in reducing rates of self-biting during treatment weeks 1 to 8 and self-directed stereotypic behavior during weeks 5 to 12 and post-treatment. No significant effect of either treatment on hair-plucking, stereotypic pacing, saluting, or head tossing was identified. The duration of neutral behavior increased, and rates of scratching and yawning decreased in the buspirone-treated condition. In the fluoxetine-treated condition, rates of yawning, scratching, and self-directed grooming were higher overall compared with those of buspirone-treated animals, and rates of scratching increased significantly ($P < 0.05$) in weeks 9 to 12; these findings suggest that animals in the fluoxetine-treated condition experienced higher levels of anxiety throughout the study. In both treatment conditions, concentrations of CSF 5-HIAA (5-HT metabolite) were significantly lower ($P < 0.05$) than placebo concentrations. Fluoxetine and buspirone may be efficacious for treatment of self-injurious and self-directed stereotypic behavior in macaques. Further studies are required to determine the optimal dosages and treatment length.**

Studies have shown that self-injurious behavior (SIB) is a serious problem in adult rhesus macaques socially deprived in infancy and individually housed in captivity (5, 9, 19, 21, 26, 30, 43, 44). Jorgensen and colleagues (14) found that the incidence of self-injury may be as high as 14% in captive populations of rhesus monkeys, the vast majority of which are males, with self-biting being the most prevalent form of injury. Severe cases of self-biting require prolonged veterinary care and often result in the removal of animals from research protocols. The most severe forms of self-injury may require digit or limb amputation and in the worst cases, in which currently known treatments fail, euthanasia becomes the only option.

Current research has focused on identifying an etiology of SIB with the ultimate goal of prevention (29). It appears that compared with others, some monkeys have an increased vulnerability that is associated with stressful social experiences in the first 2 years of life, such as early weaning. In susceptible adult animals, the disorder may be triggered by the separation of sexual partners (6), separation from social groups (2), contact with fear-provoking personnel (33), or disruption of daily routines (14). Once the condition develops, manipulation of the environment by increasing cage space (15, 16) or providing toys (28), puzzle-feeders (30), or forage boards (17) appears to have little effect. The results of these studies suggest that pharmacological intervention would be highly useful if it was found to be an effective means to alleviate SIB.

Although several neurotransmitters systems may be involved in the initiation and maintenance of SIB, most studies to date suggest the central serotonergic system (for review, see reference 18). Decreased serotonin (5-HT) function is associated with depression, suicide, and obsessive–compulsive disorder (OCD) in humans (for review, see reference 23). In rhesus macaques, low central 5-HT concentration is associated with impulsive and aggressive behavior (12, 25). Further, exposure of adult cynomolgus macaques to chronic social stress is associated with low precortical 5-HT concentrations (7). In rhesus monkeys, early social deprivation (e.g., early weaning or social isolation) results in decreased 5-HT function and increased rates of stereotypic behavior and SIB (13, 19). Many adult rhesus monkeys display, in addition to SIB, a repertoire of self-directed stereotypic behaviors (22). The association between low 5-HT function and rates of SIB is less clear in adult monkeys that have not been socially deprived. Concentrations of 5-hydroxyindole acetic acid (5-HIAA) in cerebrospinal fluid (CSF) were measured in an attempt to identify alterations in pre-synaptic 5-HT function among adult rhesus monkeys with SIB. Although no significant differences in CSF 5-HIAA were associated with SIB compared with levels in controls (43, 44), Weld and coworkers (44) found that treatment with tryptophan, the amino-acid precursor to 5-HT, decreased the duration of self-biting and increased CSF 5-

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*[1]University of Louisiana at Lafayette—New Iberia Research Center, 4401 W. Admiral Doyle Drive, New Iberia, Louisiana 70560; [2]National Institutes of Health, Section on Clinical and Biochemical Pharmacology, Bethesda, Maryland 20837; [3]National Institutes of Health, Laboratory of Clinical Studies, NIH Animal Center, Poolsville, Maryland 20837.*
*[*]Corresponding author.*

HIAA concentrations in adult rhesus macaques with a history of SIB. Interestingly, after receiving the same dose as the SIB subjects, the control animals showed no changes in CSF 5-HIAA.

The overall aim of the present study was to assess the acute effects of fluoxetine, a selective 5-HT reuptake inhibitor (SSRI) and buspirone (a 5-$HT_{1A}$ agonist) on SIB and stereotypic behavior in rhesus macaques. Although their mechanisms of action differ, both compounds have demonstrated clinical efficacy in the treatment of disorders associated with alterations in serotonergic function (e.g., depression, obsessive–compulsive disorder, panic disorder, and post-traumatic stress disorder) in humans (11, 42). Self-mutilation or SIB in humans is associated with psychopathology such as depression, anxiety, and obsessive–compulsive behavior (41). Fluoxetine is useful for treatment of OCD and dominance aggression in dogs. Buspirone has been used effectively in treating canine dominance aggression, canine and feline stereotypic behavior, self-mutilation, OCD, phobias, and inappropriate feline spraying (31).

## Materials and Methods

**Animals.** The study included 15 adult male rhesus macaques (*Macaca mulatta*; age, 6 to 12 years) with a history of at least one episode of self-mutilation requiring veterinary intervention (Table 1). All of the animals had been housed individually since weaning. One animal (Subject 6) was weaned at 1 month of age and nursery-reared. All other animals were maternally reared and weaned at 6 to 9 months of age. During the study, the animals were housed individually in 0.56-$m^2$ cages located in a room that exclusively contained animals on this study. They were fed a commercially available primate chow twice daily, and water was provided ad libitum. Additional fresh fruit and foraging devices were provided 5 days per week for enrichment. All animals were provided with manipulanda, which included commercially available toys and wood.

The animals were serologically negative for simian retrovirus, simian T-cell leukemia virus, simian immunodeficiency virus, and herpes B virus (Cercopithecine herpesvirus 1). All experimental procedures were approved by the Institutional Animal Care and Use Committee. The University of Louisiana at Lafayette–New Iberia Research Center operates in full compliance with federal guidelines and is accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care, International.

**Experimental conditions**. The animals were randomized by age and number of previous incidents of severe SIB (i.e., self-wounding requiring veterinary intervention) to one of two treatment conditions (i.e., buspirone treatment versus fluoxetine treatment). During the 12-week treatment phase, animals received either buspirone (5 mg/kg orally once daily) or fluoxetine (2 mg/kg orally once daily) in a fruit-flavored (raspberry or banana) wafer between 0700 and 0830. The wafers were prepared by a pharmacist (Professional Arts Pharmacy, Lafayette, La.). After receiving the wafer or food treat, observers documented the amount the animals consumed. For animals that refused to consume the wafer, medication was placed in a food treat such as fruit. The doses used were extrapolated from human regimens by using the following formula:

$$\text{Dosage}_{\text{macaque}} = \text{dosage}_{\text{human}} [\text{body weight}_{\text{human}}/\text{body weight}_{\text{macaque}}]^{0.25} \quad \text{Eq. 1}$$

This equation is based on allometric scaling from therapeutic dosages in humans (34). Protein binding, capacity-limited biotransformation, and genetic polymorphisms of cytochrome $P_{450}$ isoenzymes may all influence the application of this equation. A fruit-flavored placebo was administered 2 weeks prior to and after treatment. Body weights were obtained prior to the study and again after the placebo, treatment, and post-treatment phases.

**Table 1.** Ages of study animals and numbers of previous incidents of severe self-injurious behavior (SIB)

| Animal | Treatment condition | Age (years) | Incidents of severe SIB during the previous 5 years | Months since last incident of severe SIB |
|---|---|---|---|---|
| 1 | B | 7 | 4 | 6 |
| 2 | B | 7 | 1 | 15 |
| 3 | B | 11 | 4 | 7 |
| 4 | B | 7 | 1 | 15 |
| 5 | B | 6 | 1 | 9 |
| 6 | B | 12 | 3 | 26 |
| 7 | B | 7 | 1 | 15 |
| 8 | F | 8 | 1 | 13 |
| 9 | F | 7 | 1 | 12 |
| 10 | F | 7 | 1 | 4 |
| 11 | F | 11 | 2 | 51 |
| 12 | F | 8 | 2 | 8 |
| 13 | F | 7 | 1 | 12 |
| 14 | F | 7 | 2 | 14 |
| 15 | F | 7 | 6 | 7 |

B, buspirone; F, fluoxetine.

**Behavioral observations.** Behavioral data balanced for time of day (a.m. or p.m.) were collected twice a week per subject by using a 20-min focal sampling technique. The behavior collected was categorized as SIB, stereotypic, agonistic, and general (Table 2). Stereotypic behaviors are repetitive behaviors associated with SIB (21). Agonistic behaviors are ritualized gestures indicative of aggressiveness and conflict. General behaviors are those associated with normal activity.

Behaviors that occurred nearly instantaneously were categorized as events and calculated as rates (i.e., number/min). Behaviors that occurred over a period of time were categorized as states and calculated as percentage of time. All behavior was averaged over 2-week time periods to yield eight time periods: pretreatment (Pre-Rx), treatment periods 1 through 6 (Rx1, Rx2, Rx3, Rx4, Rx5, and Rx6), and post-treatment (Post-Rx). Behavioral data were collected by three independent observers using handheld computers with The Observer software (Noldus Information Technology, Leesburg, Va.); Cohen's kappa for inter-observer reliability was 0.70 or above.

**CSF samples and analysis.** Approximately 0.5- to 1.0-ml samples of CSF were obtained from the cisterna magna within 30 min of injection with ketamine HCl (10 mg/kg intramuscularly) by using a 25-gauge, 1 1/2-in. (ca. 3.75-cm) needle and 3.0-cc syringe. The samples were checked for blood contamination; any contaminated sample was discarded. All samples were placed on dry ice, then they were frozen at –70°C until assayed. The samples were assayed for 5-hydroxyindoleacetic acid (5-HIAA; a serotonin metabolite), homovanillic acid (HVA; a dopamine metabolite), and 3-methoxy-4-hydroxyphenylglycol (MHPG; a norepinephrine metabolite) by using high-performance liquid chromatography with electrochemical detection (35, 36). Samples were obtained pre-study, at the end of the placebo and treatment phases, and post-study. Samples from every time point were not obtained from two animals in the buspirone-treated condition and one animal in the fluoxetine-treated condition. These data were excluded from the CSF statistical analyses.

**Table 2.** Ethogram for Rhesus Macaques

| Behaviors | Definition | Units |
|---|---|---|
| | Self-injurious behaviors | |
| Bite with injury | Self-wounding (severe SIB) | #/h |
| Bite with no injury | Teeth contacting skin with no apparent wound | #/h |
| Hair pluck | Pulling/eating of fur | #/h |
| | Stereotypic behaviors | |
| Head toss | Stereotypic backwards movement of head | #/h |
| Pacing | Repetitive locomoting | % time |
| Salute | Poking/covering eyes with hands or fingers | #/h |
| Abnormal masturbation | Genital manipulation with mouth | #/h |
| Stereotypic to self | Repetitive behavior towards self including cheek pouch manipulation, digit sucking or flipping, chasing tail or limb, strenuous shaking of legs/feet, banging head into cage, rubbing face on cage, or touching hands to mouth | % time |
| Stereotypic to environment | Repetitive behavior towards surroundings including biting/licking/sucking/picking cage, rubbing hand or feet on cage, repetitive non-purposeful grabbing at objects in the cage. | % time |
| | General behaviors | |
| Resting | Rest/sleep, lying down; with a body position at 45°–180°, in a relaxed state with or without eyes closed | % time |
| Investigating | Exploration of surroundings; manipulating toys | % time |
| Locomoting | Walking, running, climbing, or other major positional change | % time |
| Eating | Acts of ingesting food or water | % time |
| Grooming | Self-directed picking or spreading of fur | % time |
| Neutral | Maintenance of static position with no simultaneous behavior; withdrawn with head down and or sitting with eyes closed; sitting upright while looking up with chin resting on cage | % time |
| Scanning | Observing in a repeated sweeping pattern or observing attentively in assigned cage | % time |
| Playing | Apparently non-purposeful behavior mimicking agonistic or locomotive behaviors | % time |
| Masturbation | Genital manipulation | #/h |
| Yawn | Inhalation of air, mouth open, teeth bared | #/h |
| Scratch | Movement of arms or legs, brushing skin | #/h |
| | Agonistic behaviors | |
| Open mouth threat | Aggressive open mouth stare | #/h |
| Stare threat | Fixedly looking; aggressive | #/h |
| Treeshake/display | Aggressive stereotyped treeshaking | #/h |
| Fear grimace | Submissive parting of the lips, bearing the teeth | #/h |
| Lip smack | Mouth and lips rapidly opening and closing | #/h |
| Scream | Fearful vocalization | #/h |
| Submissive present | Display hind end toward another | #/h |

**Statistical analysis.** The experiment model was an ABA split-plot design [S(2) × 8] comparing the efficacy of two treatment conditions (buspirone versus fluoxetine) across eight time periods (Pre-Rx, Rx1, Rx2, Rx3, Rx4, Rx5, Rx6, and Post-Rx). A 2 × 8 repeated measures analysis of variance (rmANOVA) was done to compare the effects of buspirone and fluoxetine on each behavior before, during, and after treatment. Significant within-subjects main effects or interactions for each behavior were analyzed using univariate comparisons of Pre-Rx versus treatment time periods averaged across weeks 1 through 4, 5 through 8, and 9 through12 and the Post-Rx time periods. The rates or duration of each behavior during treatment averaged across weeks 1 through 4, 5 through 8, and 9 through 12 were compared with Post-Rx. Significant between-subjects main effects were analyzed using repeated-measures analysis of covariance (rmANCOVA) with Pre-Rx as the covariate. We used a square-root transformation of the data to equalize variance and normalize distribution for all behavioral analyses.

Body weights were compared using rmANOVA. Cerebrospinal fluid monoamine metabolites were compared using rmANCOVA with pre-study concentrations as a covariate. All statistical procedures were done using the software package Statistica (Statsoft, Inc., Tulsa, Okla.).

## Results

**SIB and stereotypic behavior.** Results of the rmANOVA indicated a significant effect of time period on rates of self-biting (Fig. 1, $F_{7,91} = 4.30$, $P < 0.001$). Self-biting rates decreased significantly from Pre-Rx rates during Rx weeks 1 to 4 ($F_{1,13} = 9.46$, $P < 0.05$) and weeks 5 to 8 ($F_{1,13} = 9.70$, $P < 0.05$). Post-Rx rates were significantly higher than rates during the Rx weeks 1 through 4 ($F_{1,13} = 6.50$, $P < 0.05$) and 5 through 8 ($F_{1,13} = 9.06$, $P < 0.05$) but did not differ significantly from rates during Pre-Rx or Rx weeks 9 through 12.

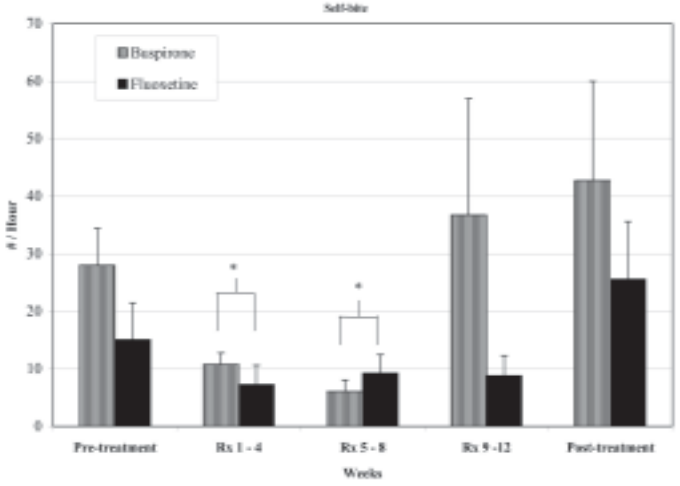


**Figure 1.** Rates of self-biting (mean ± 1 SD). *, Rates of self-biting were significantly ($P < 0.05$) lower during treatment weeks 1 to 4 and 5 to 8 than during pre-treatment (Pre-Rx) and post-treatment (Post-Rx).

Results of the rmANOVA revealed a significant effect of time period on self-directed stereotypy (Fig. 2, $F_{7,91} = 2.19$, $P < 0.05$). The duration of self-directed stereotypy decreased significantly

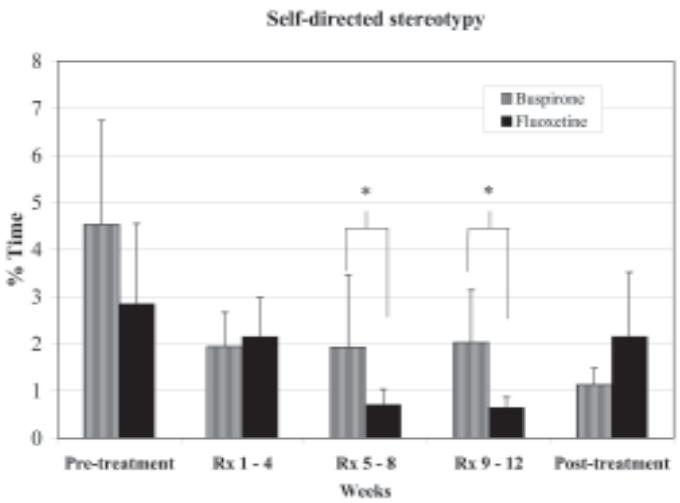


**Figure 2.** Duration of self-directed stereotypy (mean ± 1 SD). *, Mean durations during treatment were significantly ($P < 0.05$) lower than pre-treatment duration.

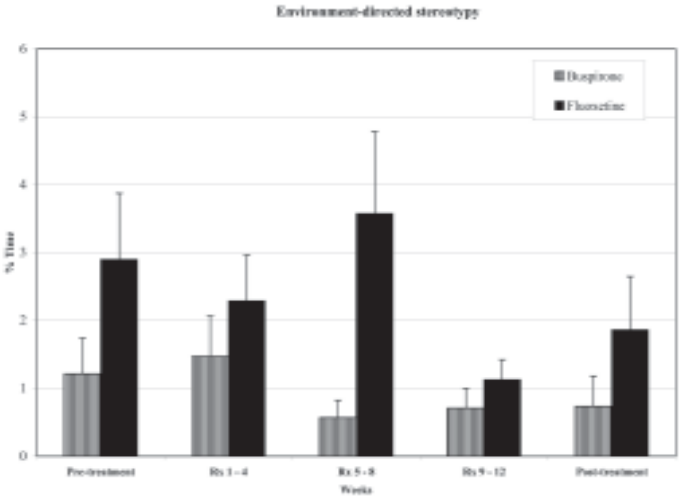


**Figure 3.** Duration of environment-directed stereotypy (mean ± 1 SD).

during Rx weeks 5 through 8 ($F_{1,13} = 10.50$, $P < 0.05$) and weeks 9 through 12 ($F_{1,13} = 6.45$, $P < 0.05$) compared with Pre-Rx duration. The duration of self-directed stereotypy during the Post-Rx phase did not differ significantly from those of Pre-Rx and Rx periods.

A significant main effect for treatment condition ($F_{1, 13} = 4.66$, $P = 0.05$) and time period ($F_{7,91} = 2.87$, $P < 0.01$) on overall duration of environment-directed stereotypy was identified (Fig. 3). Results of the rmANCOVA did not indicate significant main effects or interactions. Pre-Rx durations of environment-directed stereotypy were significantly correlated with treatment condition ($F_{1,12} = 8.50$, $P < 0.05$) and time period ($F_{6,72} = 2.21$, $P = 0.05$). Univariate comparisons of Pre-Rx versus Rx and Post-Rx versus Rx did not indicate significant differences in duration of environment-directed stereotypies.

Results of the rmANOVA indicated a significant effect for time period (Fig. 4, $F_{7,91} = 5.91$, $P < 0.001$) on rates of hair plucking. Rates of hair plucking increased significantly during Post-Rx compared with Pre-Rx ($F_{1,13} = 8.18$, $P < 0.05$) and Rx weeks 1 through 4 ($F_{1,13} = 7.90$, $P < 0.05$), 5 through 8 ($F_{1,13} = 9.67$, $P < 0.05$), and 9 through 12 ($F_{1,13} = 9.36$, $P < 0.05$).

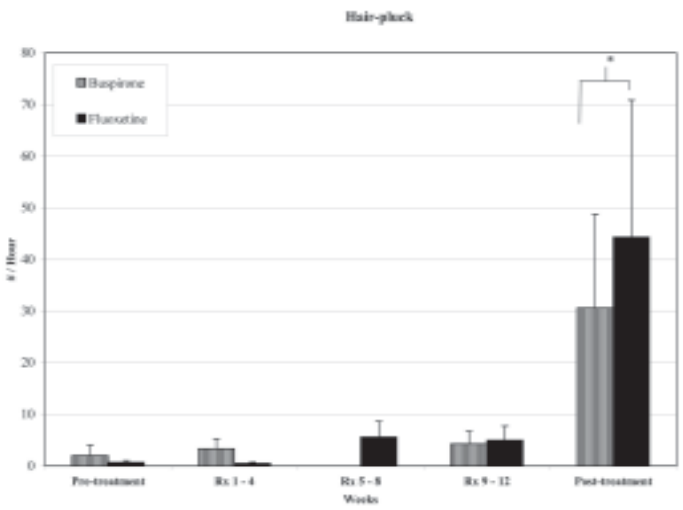


**Figure 4.** Rates of hair-plucking (mean ± 1 SD). *, Rates of hair-plucking were significantly ($P < 0.05$) higher during post-treatment (Post-Rx) compared with pre-treatment (Pre-Rx) and treatment (Rx) weeks 1 through 4, 5 through 8, and 9 through 12.

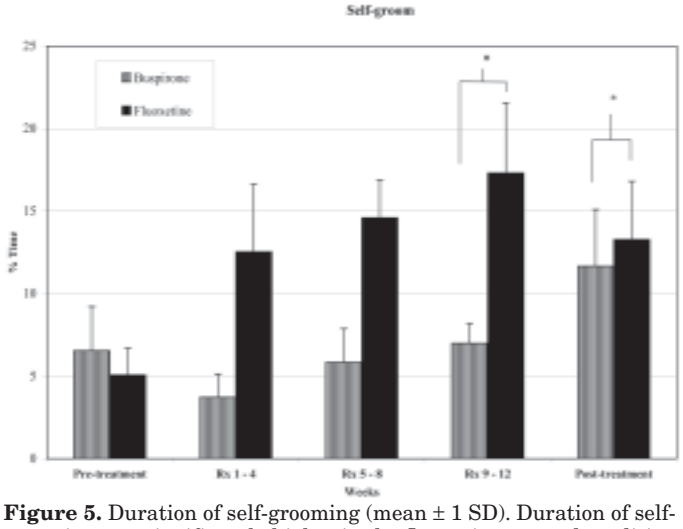


**Figure 5.** Duration of self-grooming (mean ± 1 SD). Duration of self-grooming was significantly higher in the fluoxetine-treated condition compared with the buspirone-treated condition ($P < 0.05$). *, Rate was significantly higher than pre-treatment (Pre-Rx) rate ($P < 0.05$).

No significant main effects or interactions were observed for other stereotypic behaviors including pacing, saluting, head tossing, or abnormal masturbation. No incident of severe biting occurred during the study.

**General behavior**. The results of the rmANOVA indicated significant main effects for treatment condition ($F_{1,13} = 10.14$, $P < 0.01$) and time period ($F_{7, 91} = 2.25$, $P < 0.05$) on duration of self-grooming (Fig. 5). The results of the rmANCOVA indicated that the duration of self-grooming was significantly higher in the fluoxetine-treated compared with the buspirone-treated conditions ($F_{1,12} = 11.88$, $P < 0.05$). In both conditions, duration of self-grooming increased significantly during Rx weeks 9 to 12 ($F_{1,13} = 9.30$, $P < 0.05$) and Post-Rx ($F_{1,13} = 6.45$, $P < 0.05$) compared with Pre-Rx.

A significant main effect of treatment condition was identified for duration of neutral behavior (Fig. 6, $F_{1,13} = 4.60$, $P = 0.05$). The

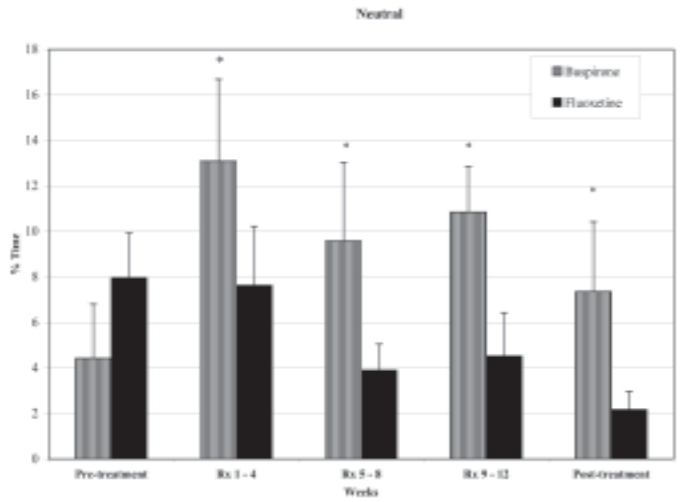


**Figure 6.** Duration of neutral behavior (mean ± 1 SD). *, Durations were significantly ($P < 0.05$) higher in the buspirone-treated condition compared with the fluoxetine-treated condition.

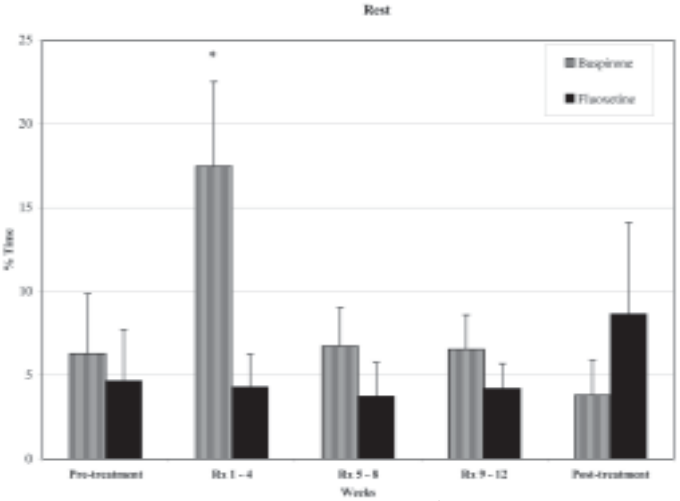


**Figure 7.** Duration of resting (mean ± 1 SD). *, Durations were significantly higher ($P < 0.05$) in the buspirone-treated condition than the fluoxetine-treated condition during treatment (Rx) weeks 1 through 4.

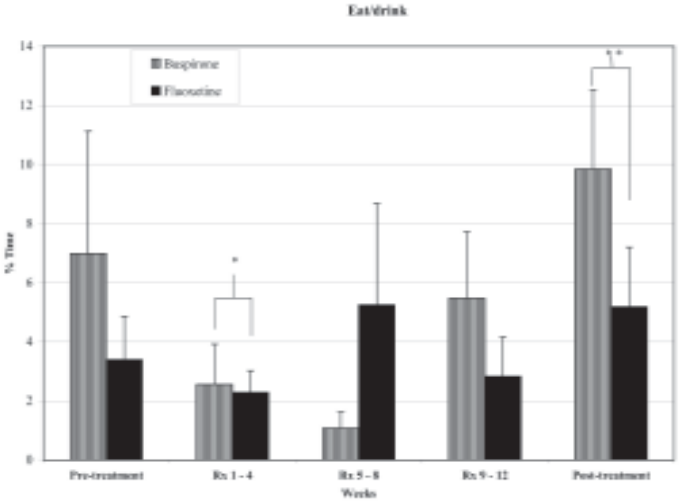


**Figure 8.** Duration of eating (mean ± 1 SD). *, Mean duration was significantly ($P < 0.05$) lower than pre-treatment (Pre-Rx) duration. **, Mean duration was significantly ($P < 0.05$) higher than durations during treatment (Rx) weeks 1 through 4, 5 through 8, and 9 through 12.

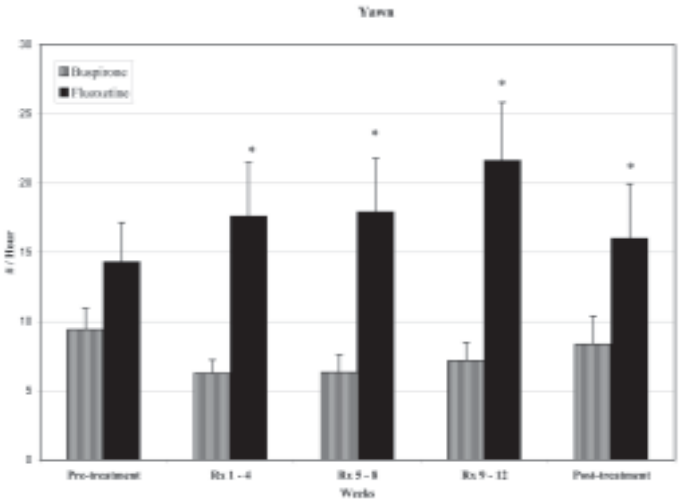


**Figure 9.** Rates of yawning (mean ± 1 SD). *, Rates of yawning were significantly ($P < 0.05$) higher in the fluoxetine-treated than the buspirone-treated condition.

results of the rmANCOVA revealed that duration of neutral behavior was significantly higher in the buspirone-treated compared with the fluoxetine treatment conditions ($F_{1,12} = 11.74$, $P < 0.01$).

Results of the rmANOVA revealed a significant interaction of treatment and time period for resting duration (Fig. 7, $F_{7,91} = 2.45$, $P < 0.05$). The buspirone-treated animals spent significantly more time resting during Rx weeks 1 through 4 ($F_{1,13} = 4.88$, $P < 0.05$) compared with Pre-Rx ($P < 0.05$).

A significant main effect for time period on duration of eating and drinking was identified (Fig. 8, $F_{7,91} = 2.86$, $P < 0.01$). Eating duration was significantly lower in Rx weeks 1 to 4 compared with Pre-Rx ($F_{1,13} = 4.88$, $P < 0.05$). Duration of eating during Post-Rx was significantly higher than during Rx weeks 1 through 4 ($F_{1,13} = 10.56$, $P < 0.05$), 5 through 8 ($F_{1,13} = 10.76$, $P < 0.05$), and 9 through 12 ($F_{1,13} = 6.97$, $P < 0.05$).

Results of the rmANOVA indicated a significant main effect for treatment condition on rates of yawning (Fig. 9, $F_{1,13} = 12.32$, $P < 0.01$). Subsequent rmANCOVA indicated that rates of yawning were significantly higher in the fluoxetine-treated compared with the buspirone-treated animals ($F_{1,12} = 8.88$, $P < 0.05$).

A significant main effect for treatment condition on rates of scratching was indicated (Fig. 10, $F_{1,13} = 11.44$, $P < 0.05$). Results of the rmANCOVA indicated that rates of scratching were significantly higher in the fluoxetine-treated compared with buspirone-treated condition ($F_{1,12} = 16.50$, $P < 0.05$). A significant interaction between time period and treatment condition was indicated for rates of scratching ($F_{7,91} = 3.34$, $P < 0.01$). In the buspirone-treated condition, rates of scratching were significantly lower during Rx weeks 1 through 4 ($F_{1,13} = 8.07$, $P < 0.05$), 5 through 8 ($F_{1,13} = 16.16$, $P < 0.05$), and 9 through 12 ($F_{1,13} = 7.67$, $P < 0.05$) compared with Pre-Rx rates. Post-Rx rates were not significantly different than Pre-Rx rates but were significantly higher than rates during Rx weeks 5 through 8 ($F_{1,13} = 5.11$, $P < 0.05$). In the fluoxetine-treated condition, rates of scratching were significantly higher in Rx weeks 9 through 12 compared with Pre-Rx rates ($F_{1,13} = 8.47$, $P < 0.05$). Post-Rx rates did not differ significantly from Pre-Rx rates but were signifi-

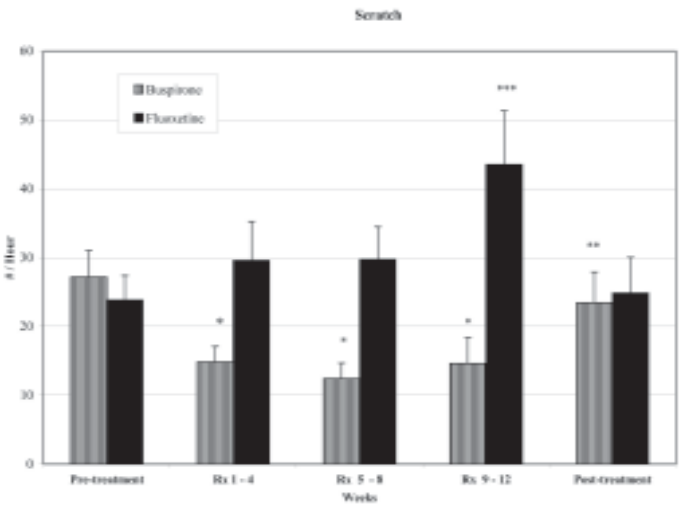


**Figure 10.** Rates of scratching (mean ± 1 SD). Rates of scratching were significantly higher in the fluoxetine-treated compared with the buspirone-treated condition ($P < 0.05$). *, In the buspirone-treated condition, rates were significantly ($P < 0.05$) lower than pre-treatment (Pre-Rx) rates. **, In buspirone-treated condition, post-treatment (Post-Rx) rates were significantly higher ($P < 0.05$) than rates during Rx weeks 5 through 8. ***, In the fluoxetine-treated condition, rates were significantly ($P < 0.05$) higher than Pre-Rx and Post-Rx rates.

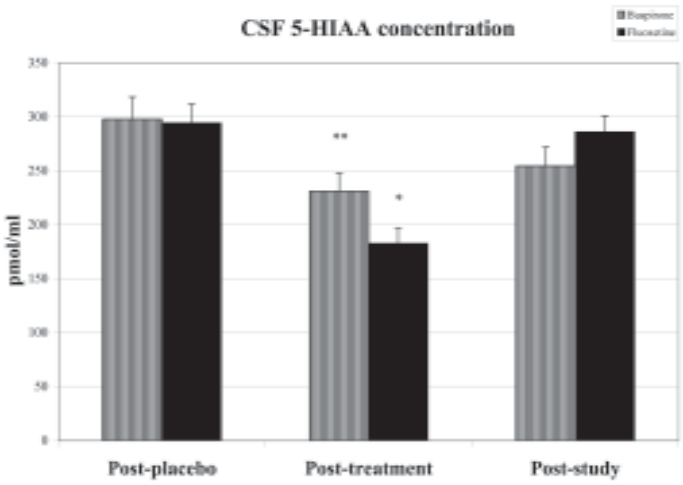


**Figure 11.** Concentrations of CSF 5-HIAA (mean ± 1 SD). *, Concentrations of CSF 5-HIAA were significantly ($P < 0.001$) lower than post-placebo and post-study concentrations. **, Concentrations of CSF 5-HIAA were significantly lower than post-placebo ($P < 0.05$) but not post-study concentrations.

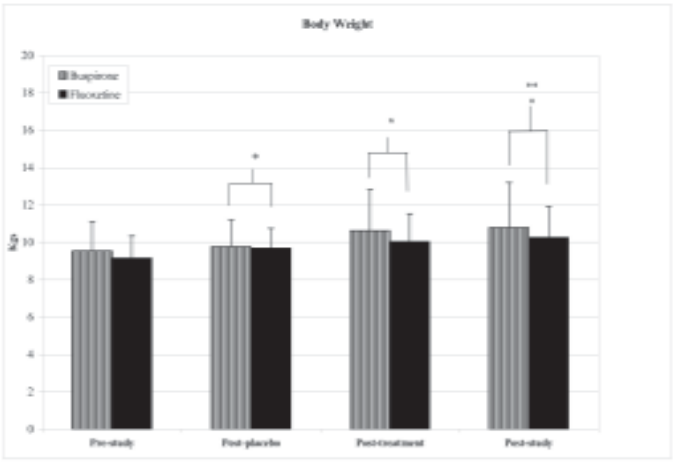


**Figure 12.** Body weight (mean ± 1 SD). *, Body weights were significantly ($P < 0.05$) higher at the end of the post-placebo, post-treatment, and post-study phases compared with the pre-study phase. **, Weights obtained at the end of the post-study phase were significantly ($P < 0.05$) higher than weights obtained at the end of the post-treatment phase.

cantly lower than rates during Rx weeks 9 through 12 ($F_{1,13} = 7.13$, $P < 0.05$).

No significant main effects or interactions were found in duration of locomotion, scanning, investigating, playing, or abnormal masturbation.

**Agonistic behavior.** No significant main effects or interactions were identified for rates of aggressive or submissive behavior.

**CSF monoamine metabolites**. A significant interaction between time period and treatment condition was identified for CSF 5-HIAA (Fig. 11, $F_{2,18} = 5.33$, $P < 0.05$). In the fluoxetine-treated condition, concentrations of CSF 5-HIAA was significantly lower than post-placebo ($F_{1,9} = 54.76$, $P < 0.001$) and post-study concentrations ($F_{1,9} = 38.94$, $P < 0.001$). In the buspirone-treated condition, concentrations of CSF 5-HIAA were significantly lower than post-placebo ($F_{1,9} = 10.30$, $P < 0.05$) but not post-study concentrations. There were no significant effects or interactions identified for concentrations of CSF HVA or MHPG.

**Body weight.** The results of rmANOVA revealed a significant effect of time on body weight (Fig. 12, $F_{4,52} = 7.88$, $P < 0.001$). In both treatment conditions, body weight increased significantly during the Pre-Rx ($F_{1,13} = 16.97$, $P < 0.05$), Rx ($F_{1,13} = 6.30$, $P < 0.05$), and Post-Rx periods ($F_{1,13} = 7.67$, $P < 0.05$) compared with the pre-study weight. Body weight at the end of the Pre-Rx phase did not differ significantly from the weight obtained at the end of the treatment phase. At the end of the Post-Rx phase, body weights were significantly higher than weights obtained at the end of treatment ($F_{1,13} = 10.67$, $P < 0.05$).

**Drug compliance.** In the fluoxetine-treated condition, five of eight animals readily consumed the raspberry wafers. One preferred a banana wafer and two animals preferred food or fruit treats. One animal refused all medication during the last 13 days of treatment. However, all data were included in the analyses. In the buspirone-treated condition, two of seven animals readily consumed raspberry wafers, one animal preferred wafers of various flavors (banana, tutti-frutti, strawberry), and four animals consumed only food or fruit treats. Overall, the bitter taste of buspirone was much harder to mask and required the addition of molasses or peanut butter to food or fruit items.

## Discussion

Fluoxetine and buspirone were effective in decreasing rates of self-biting during the first 8 weeks of treatment. Duration of self-directed stereotypic behavior decreased during weeks 5 to 12 and Post-Rx. However, rates of non-injurious self-biting were not significantly different from Pre-Rx levels during weeks 9 to 12. Rates of hair-plucking, while low, did not decrease with either treatment. We found no significant effect of either treatment on stereotypic pacing, saluting, or head tossing. The effects of treatment on self-biting and stereotypic behavior were not related to an overall lethargy as evidenced by the lack of significant changes in locomotion, scanning, play and only short-term effects on resting.

The behavioral effects of fluoxetine observed here are consistent with those of Weld and colleagues (44) who found that oral supplementation of the 5-HT precursor tryptophan decreased the duration of self-biting in adult rhesus monkeys. As in Weld and colleagues (44) fluoxetine treatment did not have a significant effect on some forms stereotypic behavior (i.e. pacing, saluting). Direct comparison of the effects of fluoxetine on stereotypic behavior is difficult due to differences in categorization of abnormal behavior between studies. These differences are likely due to the idiosyncratic nature of the stereotypies. The behavioral effects of buspirone found in this study are consistent with those of Kraemer and Clarke (19), who found that buspirone reduced "self aggression" (e.g., self-bite, head slap, and head bang) in mother- and peer-deprived juvenile rhesus monkeys. Overall, the most significant decreases in self-biting occurred during the initial 8 weeks of treatment. The lack of significant treatment effects on these behaviors during weeks 9 to 12 may reflect the need for dosage adjustment or may in part be related to compliance failures. Evaluation of serum drug concentrations, which were not obtained in the current study, would be required to clarify these issues.

While both compounds have demonstrated anti-anxiety effects (40), the results of this study suggest that only buspirone had significant anti-anxiety effects as evidenced by an increase in neutral behavior as well as a significant decrease in rates of scratching and yawning throughout the treatment period. In the fluoxetine-treated animals rates of yawning, scratching and self-directed grooming were higher overall compared to buspirone-treated animals and rates of scratching increased significantly in Rx weeks 9 to 12, which suggests that animals in the fluoxetine-treated condition experienced higher levels of anxiety throughout the study compared to the buspirone condition. It is unclear why rates of self-directed grooming increased in both conditions during Rx weeks 9 to 12 but may indicate an increased level of anxiety in both groups.

Combination therapy with a benzodiazepine such as diazepam may be an appropriate means of reducing anxiety in the first 3 to 4 weeks of treatment. For cases that present with severe wounding, treatment is initiated with diazepam (1.0 mg/kg orally twice daily) in conjunction with fluoxetine for several weeks with empirical success (8). In humans, combination therapy with buspirone and fluoxetine has been used to treat refractory depression. While synergistic effects have been reported (39), the combination has been associated in rare instances with increased incidence of extrapyramidal effects and 5-HT syndrome characterized by hyperpyrexia, convulsions and coma (20, 24). Further research is ongoing to determine the efficacy of combination therapies for SIB.

As shown in previous studies, concentrations of CSF 5-HIAA were significantly decreased by both treatments (3, 4, 27, 37). In the fluoxetine-treated condition, decreased CSF-5-HIAA may result from reductions in the metabolism of 5-HT secondary to reuptake inhibition. Fluoxetine blocks the reuptake of 5-HT at dendritic synapses and axon terminals (38). The resultant increase in 5-HT causes somatodendritic autoreceptors to down-regulate which results in increased impulse flow release of 5-HT at the axon terminals. In response to the increase in 5-HT, post-synaptic receptors down-regulate (38). Downregulation of post-synaptic receptors or regulation of receptor-coupled intracellular signal transduction pathways may require weeks of therapy and is thought to underlie the clinical effects.

Buspirone has mixed CNS effects in that it is a potent 5-$HT_{1A}$ receptor agonist and a moderate $D_2$-dopamine receptor agonist and antagonist (38). It is proposed that buspirone first slows neuronal firing, helping the system to replenish 5-HT. In the buspirone-treated condition, reductions in CSF 5-HIAA may result from decreased 5-HT turnover secondary to blockade of 5-HT autoreceptors. Buspirone acts as a partial agonist of somatodendritic autoreceptors directly, which may allow desensitization to occur with smaller amounts of available 5-HT (38). Over time post-synaptic receptors are desensitized and downregulated, which is associated with SSRI treatment. Research is ongoing to determine whether the therapeutic effects of 5-$HT_{1a}$ agonists are related to the modulation of second messenger systems (38). The actions of both treatments were specific to the 5-HT system as evidenced by the lack of significant effects on CSF HVA and MHPG concentrations in the present study. Decreases in self-biting were apparent in both treatment conditions within 4 weeks of treatment.

Upon discontinuation of treatment, rates of self-biting and hair-plucking increased significantly over Pre-Rx levels in our animals. These results suggest that the drugs, although efficacious during dosing do not induce long-lasting changes or that treatment for 12 weeks is insufficient to sustain the effects. It is recommended that human patients receive 4 to 9 months of treatment after remission of clinical symptoms of depression (32) and at least 6 months for generalized anxiety disorders (10). Further research is required to determine optimal treatment length for SIB.

Overall, the results of the present study suggest that fluoxetine and buspirone may be effective pharmacological agents for treatment of SIB in adult macaques. However, optimal dosages and treatment length require further study. In the absence of appropriate blood levels, we extrapolated from dosages used in humans and canines. Although metabolite blood levels are generally not associated with clinical response in humans (1), this information may nonetheless be useful in titrating dosages in the future.

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