This study is the first to systematically investigate whether benzodiazepines are positive reinforcers in rats trained to self-administer heroin (15 μg/kg/infusion) on a fixed ratio (FR) schedule of reinforcement in 2 hr training sessions. After establishment of consistent heroin self-administration (acceptance criterion: mean of ≥12 infusions/2 hr session over 3 consecutive sessions), the rats were subjected to saline extinction (acceptance criterion: mean of ≤6 infusions/2 hr session over 3 consecutive sessions). The reinforcing effects of diazepam (1.0, 3.0, 4.5 or 10 μg/kg/infusion) and midazolam (0.3, 1.0, 1.5, 2.25 or 3 μg/kg/infusion) were then evaluated on a FR3 schedule in 2 hr sessions.

In the first part of the experiment, if a benzodiazepine served as a positive reinforcer (>6 infusions/2 hr session) in an individual rat, a 4 hr progressive ratio (PR)/break-point analysis was performed.

Results are presented as mean ± SEM.

### RESULTS

Heroin maintained robust levels of self-administration in the group of rats used to evaluate the possible reinforcing effects of diazepam and midazolam (17.6 ± 0.5 infusions/2 hr session, n=39) and these rats showed excellent extinction when given access to saline (3.7 ± 0.2 infusions/2 hr session, n=39), significantly different p<0.001.

Figure 1 shows that diazepam served as a positive reinforcer in heroin-maintained rats and it exhibited the typical inverted U-shaped dose-response function. The group mean results revealed that the 3 μg/kg/infusion dose of diazepam maintained self-administration at levels significantly greater than saline (p<0.05). The number of infusions of all doses of diazepam were significantly (p<0.001) lower than heroin.

Figure 2 is the scatter plot for the diazepam results showing that this benzodiazepine met the criterion for a positive reinforcer (>6 infusions/2 hr session) in 50% (4/8) and 43% (3/7) rats at 3 μg/kg/infusion and 10 μg/kg/infusion, respectively.

Figure 3 shows that midazolam also served as a positive reinforcer with an inverted U-shaped dose-response relationship in heroin-maintained rats. Analysis of the group mean results revealed that the 1.5 μg/kg/infusion dose of midazolam maintained self-administration at levels significantly greater than saline (p<0.05). The number of infusions of all doses of midazolam were significantly (p<0.001) lower than heroin.

Figure 4 is the scatter plot for the midazolam results showing that this benzodiazepine met the criterion for a positive reinforcer (>6 infusions/2 hr session) in 14% (1/7), 29% (5/17) and 69% (11/16) 12.5% (1/8) and 12.5% (1/8) rats at 0.3, 1, 1.5, 2.25 and 3.0 μg/kg/infusion, respectively.

Table 1 reports the break-points for responding (mean lever-presses/infusion) for diazepam, midazolam and heroin.

Table 2 is a summary of the break-points for a wide range of strong and weak positive reinforcers that have been evaluated in our laboratory. It is clear that diazepam and midazolam are weak reinforcers.

### CONCLUSIONS

- This study is the first to systematically investigate whether benzodiazepines substitute for heroin in rats, and to compare their reinforcing effects relative to heroin.
- Diazepam and midazolam maintained self-administration at some, but not all, doses in heroin-maintained rats indicating their reinforcing effects are weak in this species. This was confirmed by their low break-points for drug reinforcement.

### REFERENCES


### INTRODUCTION

It is well established that benzodiazepines are sedative euphoriant drugs in man (Evans et al, 1990; Busto et al, 1994; Farré et al, 1998) and subject to moderate levels of recreational abuse. In animal models benzodiazepines have been reported to serve as positive reinforcers in self-administration studies in both New World and Old World monkeys (Gomez et al, 2002; Broadbear et al, 2005; Fischer et al, 2010) and baboons (Griffiths et al, 1981).

On the other hand, there have been only 3 published articles that have investigated the reinforcing effect of benzodiazepines in USA experiments conducted in rats (Naruse & Asami, 1987; Szostak et al, 1987; Finlay et al, 1989), in the last 25 years.

To address this deficit in our knowledge about the possible reinforcing effects of benzodiazepines in rats, we investigated whether diazepam or midazolam would maintain self-administration in rats that had been established on a low dose of heroin.

#### Figures

- **Figure 1:** Effect of diazepam in rats trained to self-administer heroin
- **Figure 2:** Scatter plot of diazepam results
- **Figure 3:** Effect of midazolam in rats trained to self-administer heroin
- **Figure 4:** Scatter plot of midazolam results

#### Summary Table

<table>
<thead>
<tr>
<th>Treatment and dose</th>
<th>Break-point (lever-presses/infusion)</th>
<th>n</th>
<th>Statistical significance versus heroin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heroin (15 μg/kg/infusion)</td>
<td>39.4 ± 6.9</td>
<td>10</td>
<td>N/A</td>
</tr>
<tr>
<td>Diazepam (3 μg/kg/infusion)</td>
<td>18.9 ± 2.8</td>
<td>4</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Midazolam (10 μg/kg/infusion)</td>
<td>17.1 ± 2.8</td>
<td>3</td>
<td>p &lt; 0.05</td>
</tr>
<tr>
<td>Midazolam (1.5 μg/kg/infusion)</td>
<td>13.2 ± 0.7</td>
<td>5</td>
<td>p &lt; 0.05</td>
</tr>
</tbody>
</table>

N/A = not applicable
Criterion for positive reinforcement: ≥6 infusions/2 hr session