

Fentanyl and Methamphetamine Mixture Interactions on Drug Choice in Male and Female Sprague Dawley Rats

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Introduction

Illicit substance usage is an insidious problem in America and has contributed to an increase in drug-related overdose deaths, many of which can be attributed to the synthetic opioid fentanyl. In addition, the practice of mixing fentanyl with other addictive substances also continues to increase. Combining fentanyl with other addictive substances, such as the monoamine transporter substrate methamphetamine may enhance the reinforcing effects and may contribute to a greater chance of a fatal overdose or other undesirable effects. Furthermore, men have higher rates of substance use disorders compared to women and are more likely to take illicit substances at a young age, which may be due to various reasons such as hormones or societal factors. Therefore, the purpose of this experiment was to study interactions of fentanyl and methamphetamine on reinforcement endpoints and their variations between the different sexes. We hypothesized fixed-dose proportions of fentanyl and methamphetamine would interact synergistically on drug self-administration.

Procedure

Subjects:

- 75 Sprague-Dawley rats
 - 42 Females
 - 33 Males

Independent Variables:

- Unit drug dose/associated stimuli & fentanyl/methamphetamine mixture ratios

Dependent Variables:

- Percent infusion choice and choices per component

Training:

- Sprague-Dawley rats were trained on a specific drug, drug ratio, or saline and food (32% vanilla-flavored Ensure) up to a fixed ratio 5 schedule of reinforcement and then moved to a choice behavior experiment.
- Each training session spanned 2 hours.

Choice:

- Each session is separated into five components. Each component is characterized by a half-log increase in the unit drug or drug mixture dose.

Drug Training	FR1: 7-10 days	FR2: 2 days	FR3: 2 days	FR4/5: 5 days
Food Training	FR1: 2-3 days	FR5: 3 days		
Choice	9 days			

Figure 1: Timeline of training and choice experiment. Drug training goal is to maintain >13 reinforcers. Food training goal is to maintain >70 reinforcers.

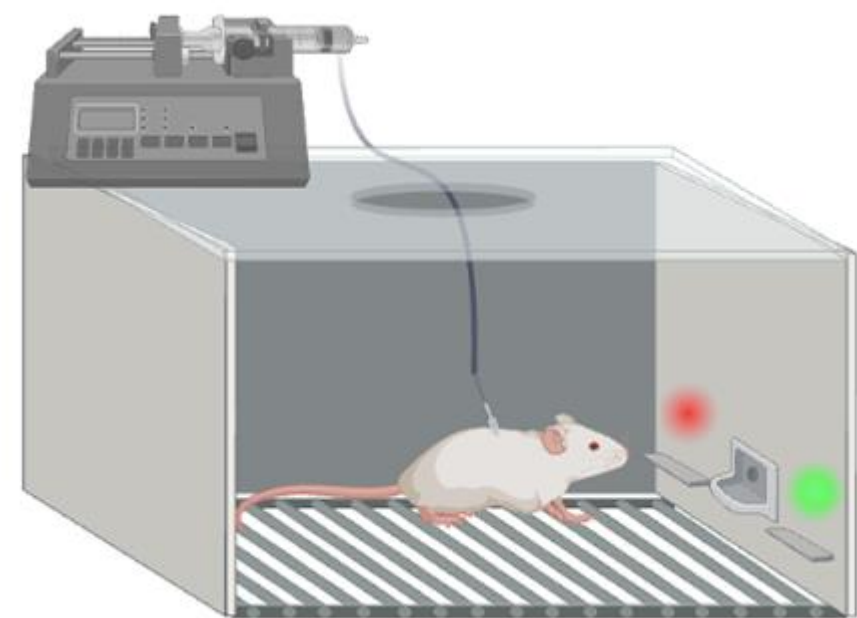


Figure 2: Illustration of operant box used for drug and food training and choice behavioral experiments. Left lever dispenses 32% vanilla-flavored Ensure via a small dipper through a hole in the middle compartment. Right lever infuses drug/saline via intravenous catheter & tether connected to a drug syringe.

Sex Differences in Drug Alone Choice

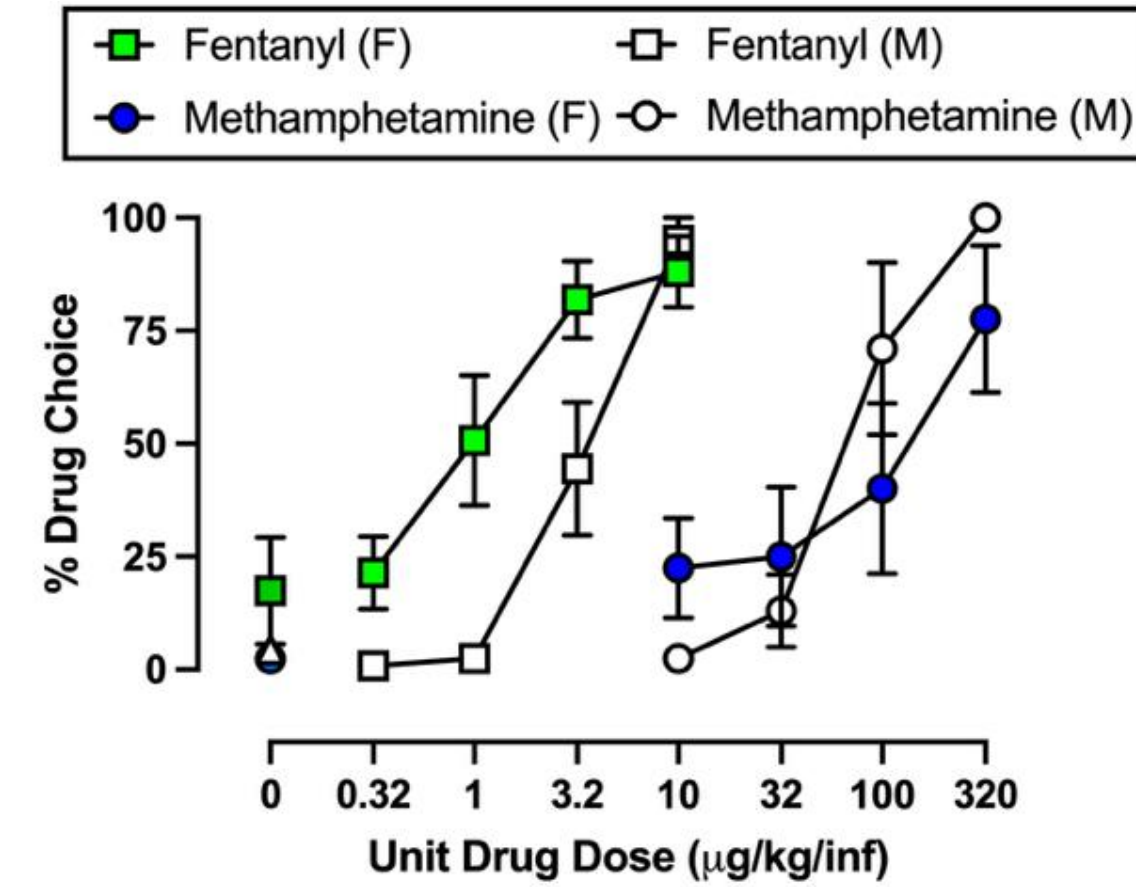
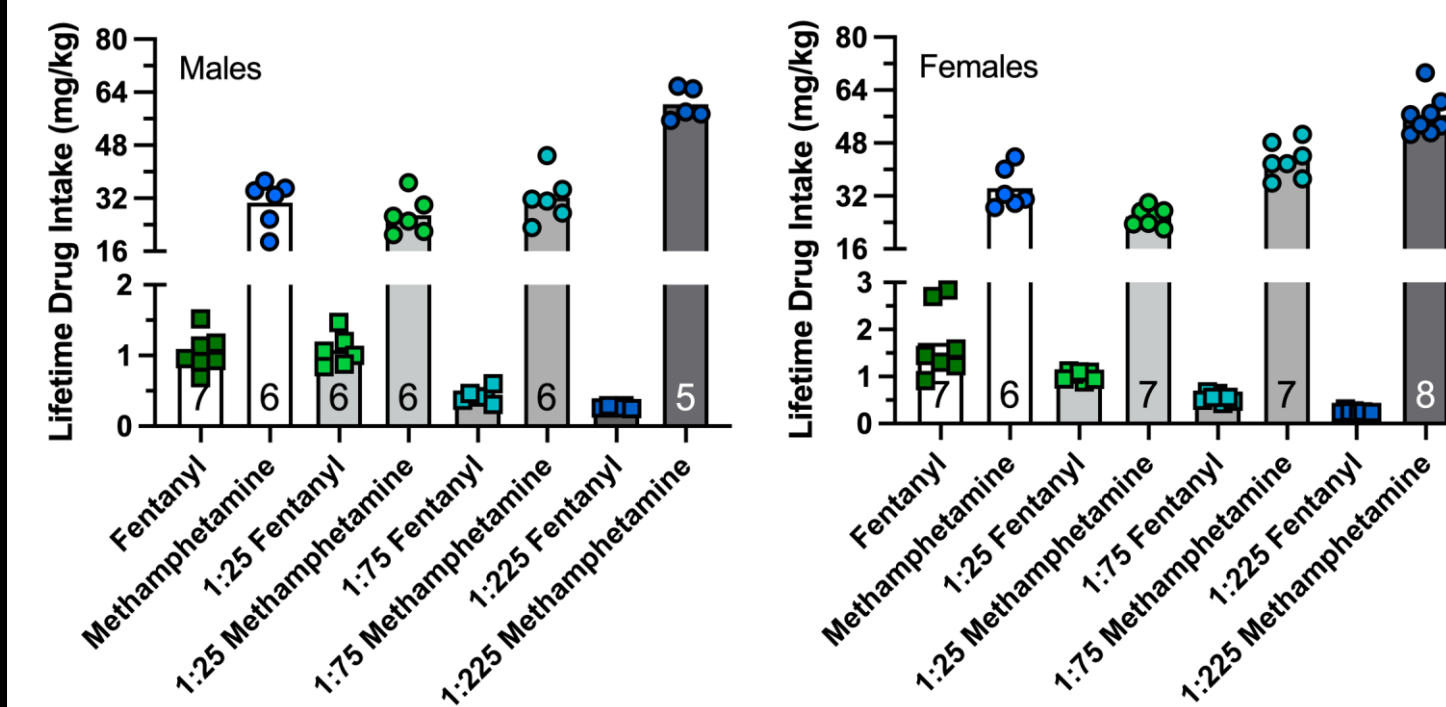


Figure 3: Effect of unit drug dose in µg/kg/inf on drug-vs-food choice in females (F) and males (M). Percent infusion choice increases as unit drug dose increases for both Fentanyl and Methamphetamine alone. Each point represents the mean ± SEM of 5-7 rats per sex.



Figures 4 and 5: Lifetime fentanyl or methamphetamine intake in both males and females during self-administration of fentanyl alone, methamphetamine alone, or a fentanyl/methamphetamine mixture. Samples are denoted in the bars. Bars represent mean intakes and symbols denote individual subject data points

Summary/Conclusions

- 1:225 Fentanyl/Meth mixture showed the largest leftward shift compared to Fentanyl alone in males, but not females, which may support the hypothesis that meth may enhance fentanyl reinforcement.
- In contrast, 1:25 Fentanyl/Meth mixture was slightly rightward shifted compared to Fentanyl alone in females, but not males, suggesting a small amount of Meth may attenuate Fentanyl reinforcement.
- Higher drug or drug mixture doses resulted in decreased behavior (data not shown), suggesting either motor or cognitive impairment based on choices per component data.
- Overall, these results suggest that the relative mixture of fentanyl and Meth self-administered simultaneously may differentially influence drug reinforcement processes and that these interactions depend upon sex as a biological variable.
- 1:75 and 1:225 Fentanyl/Meth mixtures in male rats demonstrated a greater infusion choice per unit drug mixture dose compared to female rats, suggesting that males may be more susceptible to polysubstance use disorders such as opioid/stimulant mixtures.

Fent/Meth interactions in Females

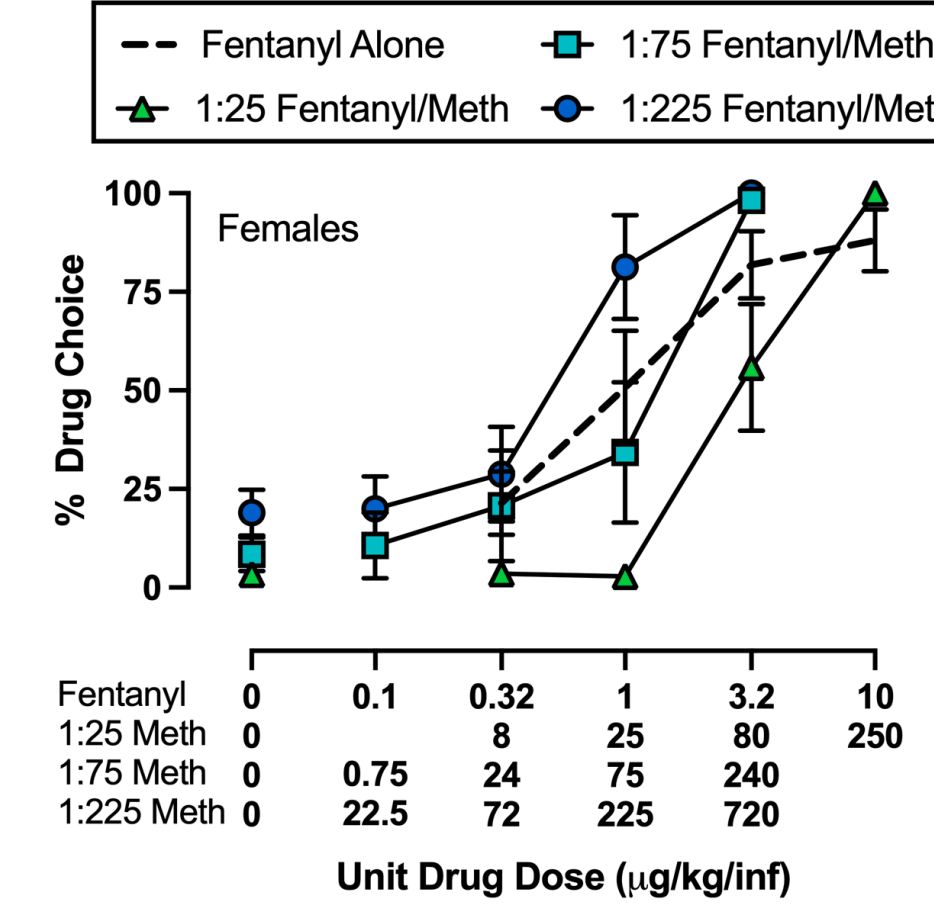


Figure 6: Effect of unit drug mixture dose in µg/kg/inf on percent infusion choice. As unit fentanyl dose increases, the percent infusion choice increases towards drug choice. Each point represents the mean±SEM of 6-8 rats.

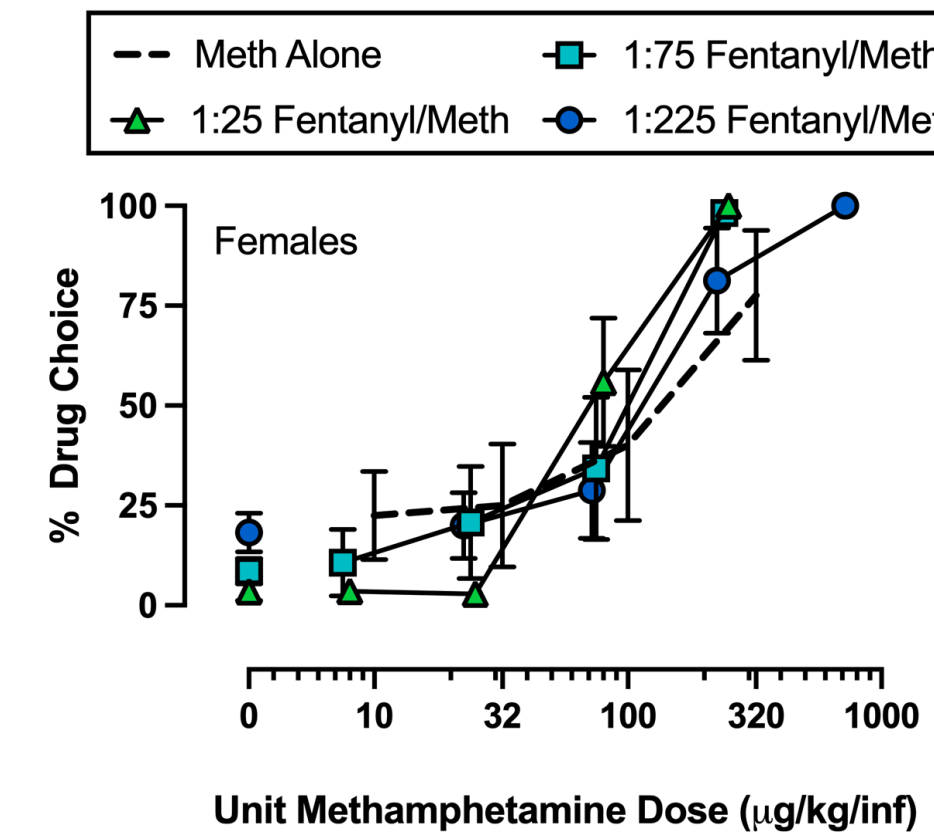


Figure 7: Effect of unit drug mixture dose in µg/kg/inf on percent infusion choice. As unit methamphetamine dose increases, the percent infusion choice increases towards drug choice. Each point represents the mean±SEM of 6-8 rats.

Fent/Meth Interactions in Males

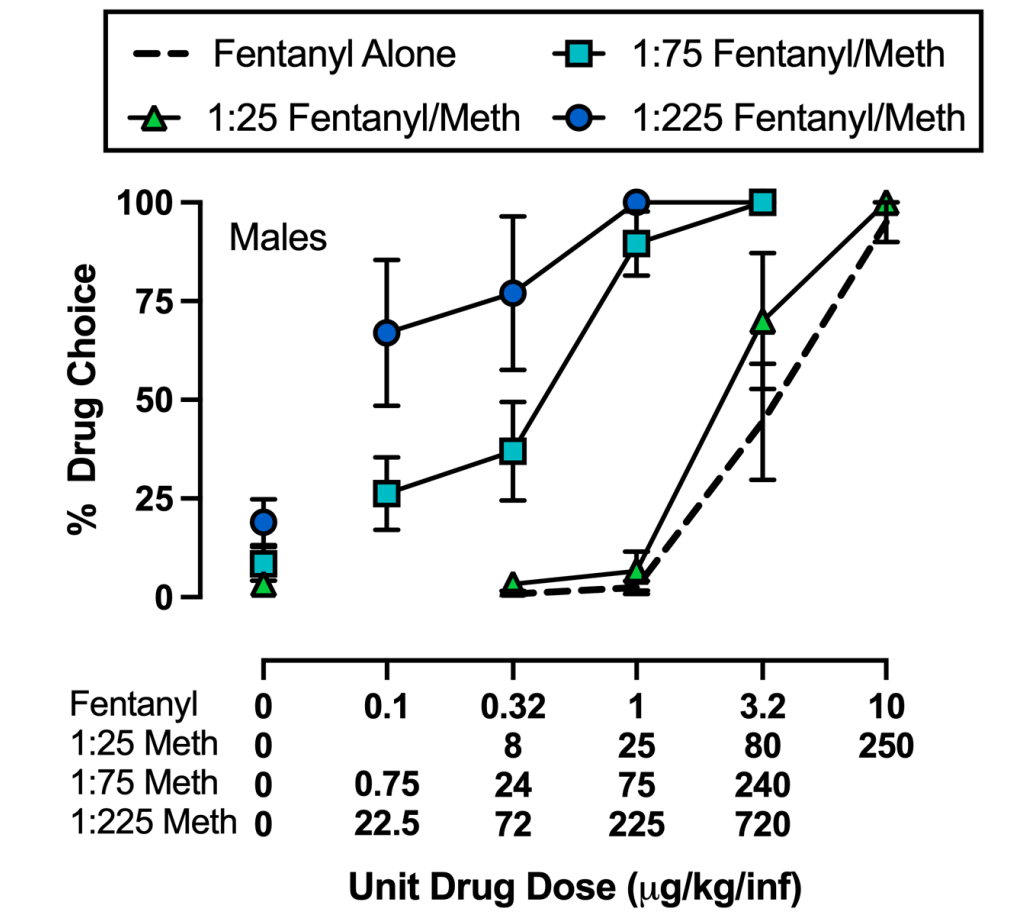


Figure 8: Effect of unit drug mixture dose in µg/kg/inf on percent infusion choice. As unit fentanyl dose increases, the percent infusion choice increases towards drug choice. Each point represents the mean±SEM of 5-7 rats.

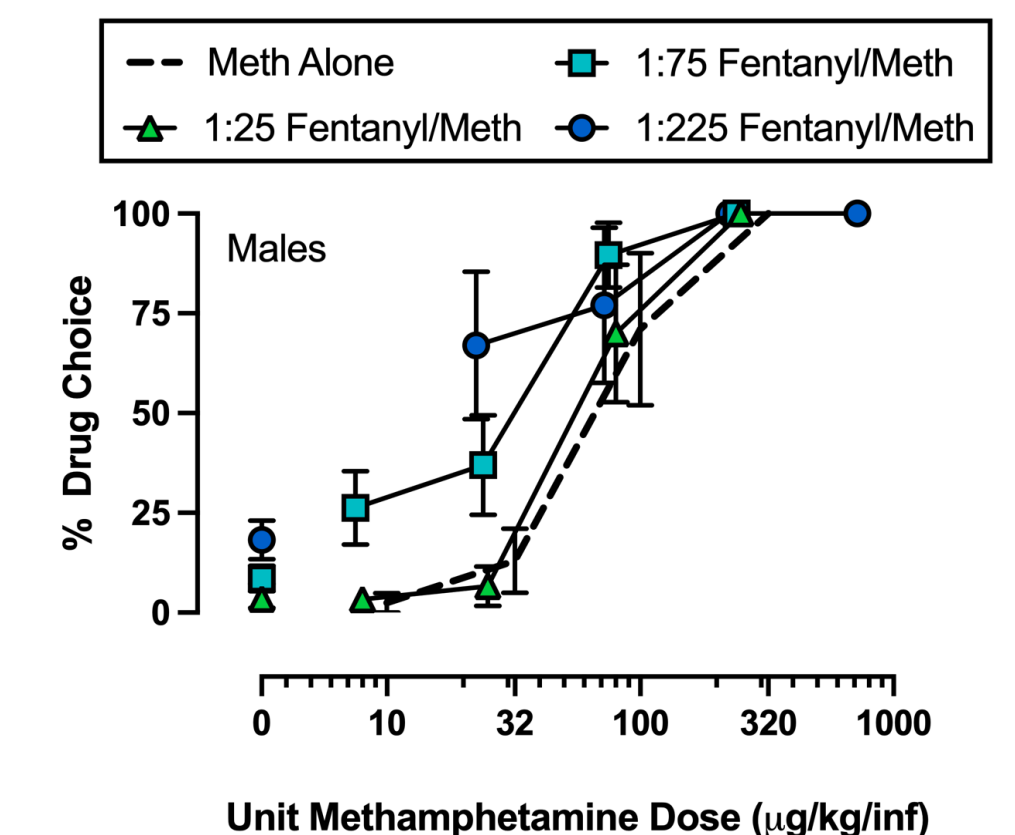


Figure 9: Effect of unit drug mixture dose in µg/kg/inf on percent infusion choice. As unit methamphetamine dose increases, the percent infusion choice increases towards drug choice. Each point represents the mean±SEM of 5-7 rats.

Future Directions

- Determine different ratios of fentanyl/methamphetamine mixtures on drug choice
- Determine the role of gonadal hormones on fentanyl, methamphetamine, fentanyl/methamphetamine mixture choice
- Determine effects of fentanyl and methamphetamine dependence and withdrawal on fentanyl/methamphetamine mixture choice
- Collect tissue for transcriptome analysis of prefrontal cortex to identify genes associated with cognitive function

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