The Effects of Oral Self-Administration of Fentanyl on Sleep Patterns, Precipitated Withdrawal, and Affective Behaviors in Female and Male Mice

Opioid Use Disorder has become a prominent health crisis over the last decade, often leading to overdose deaths among its users. Its prevalence can be attributed to the increased access to synthetic opioids, such as fentanyl, in the illicit drug supply. While there are some studies on intravenous fentanyl administration, there are limited studies on the effects of other routes of administration. In the following study, we used a Drinking in the Dark paradigm to model oral self-administration. The paradigm lasted five weeks, escalating from 10 ug/mL to 40 ug/mL fentanyl in normal drinking water. The fentanyl-drinking group consumed more fentanyl as the dose increased, peaking at the 30 ug/mL concentration. Females consumed more fentanyl, by weight, than males at all doses. During the paradigm, we observed a dose-dependent sleep dysregulation in both sexes during the dark cycle, where mice self-administering fentanyl slept significantly less while fentanyl was available and jumped into a “recovery sleep” immediately afterwards. However, we observed a larger decrease in sleep in the male fentanyl groups compared to the male controls. On the final day of fentanyl drinking, we performed precipitated withdrawal with naloxone and assessed withdrawal behaviors. Both fentanyl groups exhibited increased overall withdrawal behaviors, with the males showing more than the females. One and a half weeks into withdrawal, we performed the Light-Dark Box Assessment and found increased avoidance behaviors in male fentanyl-consuming mice. This study provides evidence that oral fentanyl consumption has potential acute and long-term effects on sleep and produces precipitated withdrawal symptoms. Our oral model of fentanyl self-administration could be used in future studies exploring different behaviors associated with fentanyl withdrawal syndrome and highlights the importance of sex differences when studying and treating fentanyl withdrawal syndrome.