A Behavioral Economic Analysis of Polysubstance Use: Studies with Cocaine, Fentanyl, and Cocaine–Fentanyl Mixtures in Sprague-Dawley Rats

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The co-use of stimulants and opioids has become increasingly evident in recent years, yet few studies have systematically investigated the reinforcing effects of cocaine-fentanyl mixtures. Behavioral economic demand analyses provide a translational approach to quantify the relative value of drug reinforcers across different classes (stimulant vs opioid), making it a viable method to help ascertain factors which promote polysubstance use in humans. The current study used a multiple component schedule of drug self-administration to assess economic demand for cocaine (0.032, 0.1, 0.32, 1.0 mg/kg/inf), fentanyl (0.00032, 0.001, 0.0032, 0.01 mg/kg/inf), and mixtures of cocaine:fentanyl (in 10:1, 3:1, 1:1, 1:3, 1:10, relative to the dose ranges above) in male and female rats. Available unit-doses of drug increased across 4, 20-min drug components, with increases in the response requirement (fixed ratio) occurring across sessions. Demand curves for cocaine, fentanyl, and their respective mixtures were generated by normalizing consumption (number of infusions earned) to Q₀ (estimate of unconstrained demand) and plotted as a function of standardized price (FR × Q₀). Elasticity coefficients (α) generated from demand curve analyses were used to assess the relative value of each drug and mixture preparation. The elasticity coefficient of fentanyl was greater than that of cocaine (i.e., cocaine had a greater “essential value”). Similarly, demand for the 10:1 mixture of cocaine + fentanyl was found to be greater than demand for fentanyl alone but comparable to cocaine. Mixtures of 1:3 and 1:10 cocaine + fentanyl produced alpha values that were greater than that of cocaine but not that of fentanyl, further suggesting that interactions may be strictly additive in respect to their reinforcing effects. Results from the current study complement reports from nonmedical opioid users who combine opioids with stimulants to “enhance the high”. Taken together, the co-use of cocaine and fentanyl may increase the risk for developing a substance use disorder. Additionally, treatment targeting opioid use may be less effective in individuals who co-use stimulants such as cocaine with opioids. Future studies are warranted to assess how opioid dependence and withdrawal may impact the reinforcing effectiveness of cocaine-fentanyl mixtures compared to either drug alone.

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