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Fentanyl-xylazine interaction induces transcriptional modifications in the nucleus accumbens of Sprague Dawley rats

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The opioid crisis is an escalating public health emergency, that is intensifying as polysubstance use rises, exemplified by the combination of fentanyl and xylazine. The relaxing, euphoric, and respiratory-depressant effects associated with fentanyl use are amplified when paired with xylazine—an animal tranquilizer not approved for human use. Individuals injecting this combination, coined "tranq dope," report severe health consequences, including profound sedation and the formation of severe bruises with necrotic wounds, which may lead to limb amputation. The molecular mechanisms behind opioid polysubstance use are poorly understood. This study begins to elucidate the molecular consequences of the synergistic effects of fentanyl combined with xylazine by analyzing the neural gene expression patterns in male and female Sprague Dawley rats receiving twice-daily intraperitoneal injections of fentanyl (45 ug/kg), xylazine (2.5 mg/kg), fentanyl with xylazine, or saline (n=4/sex/treatment) for 14 days. Using isoform-resolved transcriptomics, we evaluated total RNA from the nucleus accumbens (NAc) to identify differentially expressed genes and isoforms. Our findings revealed significant alterations in gene expression within the NAc when comparing the fentanyl and xylazine group to those receiving the drugs individually, with evident distinctions between sexes. Regulatory mechanisms and biological pathways were disturbed in the drug-administered groups, underscoring the urgency for in-depth investigations into xylazine polysubstance abuse. Understanding the molecular effects of different combined drugs is crucial for developing specific treatments to address the evolving problems of the ongoing drug epidemic.