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4. Fentanyl analogue overdose in emergency department patients: naloxone requirements and clinical outcomes in a national multicenter cohort

Alex F. Manini[a], Rachel Culbreth[a], Kim Aldy[a,b,c], Jeffrey Brent[a,d], Stephanie Abston[a,b], Alexandra M. Amaducci[a,e], Jennie Buchanan[a,f], Diane Calello[a,g], Sharan Campleman[a,b], Joseph E. Carpenter[a,h], Alyssa Falise[a,b], Adrienne Hughes[a,i], Bryan Judge[a,j], Alex J. Krotulski[a,k], Michael Levine[a,l], Barry Logan[a,m], Jennifer Love[a], Christopher W. Meaden[a,g], Evan Schwarz[a,l], Joshua Shulman[a,n], Paul Wax[a,b] and on Behalf of the Fentalog Study Group

[a]Center for Research on Emerging Substances, Poisoning, Overdose, and New Discoveries (RESPOND), Icahn School of Medicine at Mount Sinai, NYC Health + Hospitals/Elmhurst, New York, NY, USA; [b]American College of Medical Toxicology, Phoenix, AZ, USA; [c]Baylor University Medical Center, Dallas, TX, USA; [d]University of Colorado School of Medicine, Toxicology Associates, LLC, Littleton, CO, USA; [e]Lehigh Valley Health Network/USF Morsani College of Medicine, Allentown, PA, USA; [f]Denver Health and Hospital Authority, Denver, CO, USA; [g]Rutgers New Jersey Medical School, Newark, NJ, USA; [h]Emory University, Georgia Poison Center, Atlanta, GA, USA; [i]Oregon Health and Science University, Portland, OR, USA; [j]Corewell Health, Michigan State University, Grand Rapids, MI, USA; [k]Center for Forensic Science Research and Education, Fredric Rieders Family Foundation, Horsham, PA, USA; [l]University of California-Los Angeles, Los Angeles, CA, USA; [m]NMS Labs, Horsham, PA, USA; [n]University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Background: Novel synthetic fentanyl analogue (fentalog) use now drives the opioid epidemic in the US, as overdose (OD) deaths involving fentalogs have surpassed prescription opioids, and heroin. Despite this, the scope of the problem, incidence, prevalence and even the culprit molecules are not known. Therefore, we conducted a national cohort study of emergency department (ED) patients with nonfatal opioid OD to characterize the specific fentalog molecules, clinical severity, and naloxone use in fentalog OD. We hypothesized that naloxone dosing would be higher for fentalogs (vs. non-fentalogs), and that proportions requiring cardiopulmonary resuscitation (CPR), intensive care unit (ICU) admission, and mechanical ventilation would be higher for fentalogs (vs. non-fentalogs).

Methods: This multicenter, prospective cohort study enrolled adult patients with opioid OD who presented to one of 19 US EDs at 11 institutions between 2020 and 2025. Patients with suspected opioid OD were screened and eligible if waste serum was available for toxicology testing. Patient serum was de-identified and analyzed via liquid chromatography quadrupole time-of-flight mass spectroscopy to detect all current illicit opioids, novel synthetic opioids, and adulterants. Patients with confirmed opioid OD were included and classified by toxicology results into mutually exclusive exposure groups: fentalogs only (fentalog), fentanyl as the only opioid (FO), prescription opioids only (PO), heroin only (HO), or miscellaneous opioids (MO). The primary outcomes were naloxone

administration, total naloxone dose, and number of naloxone doses. Secondary outcomes included ICU admission, CPR, intubation or ventilatory support, in-hospital mortality, and composite severity indicators, with comparisons adjusted for age, sex, and region.

Results: Among 8,741 patients screened, 2,480 were eligible, of whom 2,129 were included for analysis after exclusion of 351 without an opioid detected. Among eligible patients, 1,090 (51%) were FO, 538 (25%) MO, 254 (12%) fentalogs, 210 (10%) PO, 13 (0.6%) HO, and 12 had novel potent opioids (0.6%). Among 411 (19.3% of all included) patients with fentalogs detected, fluorofentanyls were the most common class (246, 59.9%), followed by N-propionyl norfentanyl (169, 41.1%), acetyl fentanyl (36, 8.8%), methyl fentanyls (18, 4.4%), alkyl fentanyls (5, 1.2%), and carfentanil (4, 1.0%). In adjusted models of the primary outcome, fentalogs were associated with more naloxone doses compared to the FO group (incidence rate ratio [IRR], 1.14; 95% CI, 1.03-1.25), PO group (IRR, 1.63; 95% CI, 1.40-1.90), and HO group (IRR, 1.68; 95% CI, 1.06-2.86). In adjusted models of the secondary outcomes, fentalogs were not associated with ICU admission or the composite severity indicator but were associated with higher odds of CPR or death compared to the PO group (OR 6.1, CI 2.5-18.6); all other secondary outcomes were similar across groups.

Conclusions: In this large national multicenter cohort of ED patients with confirmed opioid OD, fentalogs were associated with a substantially higher need for repeat naloxone dosing compared with FO (14% more), PO (63% more), and HO (68% more). Additionally, fentalogs had higher risk of CPR or death compared to PO. Fentalog OD therefore represents a highly prevalent, distinct, high-risk OD phenotype which is the current greatest opioid threat to public health in the US.