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7. Challenges of the fourth wave of the opioid epidemic: clinical presentations and risks of unmasked stimulant effects following naloxone in polysubstance overdoses

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Background: The “fourth wave” of the opioid epidemic is characterized by increasing polysubstance exposures, most commonly involving opioids and stimulants. We assessed for differences in clinical presentations after confirmed opioid versus polysubstance overdoses and whether patients with higher stimulant exposures were at greater odds of unmasked stimulant effects after naloxone.

Methods: The Toxicology Investigators Consortium Drug Overdose Toxico-Surveillance Reporting Program is an observational study. This study prospectively enrolled consentable patients ≥13 who presented to emergency departments at 17 U.S. institutions after suspected opioid and/or stimulant overdose from April 2023 to September 2024. Chart reviews and structured patient interviews were conducted. Blood specimens were collected and underwent comprehensive qualitative and quantitative testing by liquid chromatography-mass spectrometry for >1,200 xenobiotics. Each case was categorized for opioid tolerance, precipitated withdrawal versus unmasked stimulant toxicity (e.g., agitation after naloxone not attributed to opioid withdrawal), and overdose causality based on clinical presentation, structured interviews, and toxicologic testing. For this analysis, inclusion criteria were patients with detectable opioids, blood samples obtained within 12 h of hospital arrival, and classified as overdose-related by case adjudication. Patients were categorized into groups by stimulant concentrations: high (methamphetamine ≥400 ng/mL or cocaine ≥50 ng/mL), moderate (methamphetamine 10.0-399 ng/mL, cocaine 0.1- 49.9 ng/mL, or benzoylecgonine ≥120 ng/mL), and low (measurable but below these thresholds). Odds ratios (OR) were calculated for unmasked stimulant effects, precipitated withdrawal, and interventions.

Results: Of the 995 patients enrolled, 655 met the inclusion criteria. Only 14.4% had opioids detected without other illicit drugs or adulterants. Detected drugs included stimulants (80.6%); xylazine and

metabolites (22.6%); designer benzodiazepines (6.7%); medetomidine (2.6%); nitazene compounds (2.0%); cathinones (1.5%); cannabinoids (0.8%); and fentanyl analogs (0.6%). Patients with detectable opioids typically presented with an opioid toxidrome regardless of detectable non-opioid drugs. 92.5% had coma/central nervous system depression, 34.0% required invasive ventilatory support, and 9.3% had cardiac arrest. Naloxone was administered to 567 patients; of which 90.6% responded, 2.8% had no response, and 6.6% had an unknown response. Similar rates occurred in patients with opioids and high stimulant concentrations. Unmasked stimulant effects occurred in 6.5% of the 417 patients with detectable stimulants. This was more likely in those with high stimulant concentrations (17.9%) than with moderate (6.7%) stimulant concentrations (OR: 3.0; 95% confidence interval (CI): 1.2, 7.8). Two-thirds of patients with unmasked stimulant effects and 58.5% with precipitated withdrawal required sedative medications (OR: 1.4; CI: 0.5, 3.9). versus 12.0% of patients without adverse naloxone response (OR: 14.6; CI: 6.3, 34.2). No patients with unmasked stimulant effects died or had significant morbidity. Patients in the Western region were more likely than rest of the country to have high stimulant concentrations (16.1% versus 1.9%; OR: 10.4, CI: 4.5, 24.1) and unmasked stimulant effects (9.3% versus 2.4%; OR: 4.2, CI: 1.8, 9.5).

Conclusions: Patients exposed to both opioids and stimulants typically present with opioid toxicity and respond to naloxone, even with high stimulant concentrations. Unmasked stimulant effects after naloxone were uncommon and rarely associated with mortality or significant morbidity, although higher stimulant concentrations increased the odds.