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215. Intentional single-agent or predominant-agent herbal, dietary supplement, and vitamin exposures in the ToxIC registry: therapeutic intent versus misuse, phenotype clusters, and severe clinical course

Justin Cupps[a], Kim Aldy[b,c], Rachel Culbreth[b], L. Claire Epperson[d] and on Behalf of the Toxicology Investigators Consortium (ToxIC)

[a]University of Oklahoma College of Medicine, University of Oklahoma Health Campus, Oklahoma City, OK, USA; [b]American College of Medical Toxicology, Phoenix, AZ, USA; [c]Baylor University Medical Center, Houston, TX, USA; [d]Oklahoma Poison Center, Oklahoma City, OK, USA

Background: Herbal, dietary supplement, and vitamin (HDSV) exposures are heterogeneous and have increased substantially over the past decade, accounting for an estimated 23,000 emergency department visits and 2,100 hospital admissions annually in the United States. Large descriptions of single-agent cases remain limited. We sought to characterize single-agent HDSV exposures classified as misuse or therapeutic use, identify phenotype clusters, and compare severe clinical courses by coded intent.

Methods: We conducted a secondary analysis of the single-agent HDSV cases classified as misuse or therapeutic use reported to the Toxicology Investigators Consortium (ToxIC) Core Registry from 2010 through 2025. Pediatric exploratory ingestions less than 10 years old were excluded as intent is difficult to reliably interpret in this age group. The primary composite outcome of severe clinical course was defined as critical care unit admission, intubation/ventilatory management, vasopressor/inotropic support, or in-hospital death. The secondary composite outcome of intensive medical treatment was defined as hemodialysis (HD), insulin euglycemic therapy (IET), transplantation, extracorporeal membrane oxygenation (ECMO), or cardiopulmonary resuscitation (CPR). Exploratory principal component analysis with Varimax rotation was performed on 11 binary clinical variables.

Results: A total of 275 cases met criteria for the misuse versus therapeutic-use comparison. The most common agents were caffeine (19.6%, n = 54), melatonin (14.9%, n = 41), and unknown HDSV products (13.0%, n = 36). When stratified by intent, the cases more frequently associated with misuse included caffeine (64.8%, n = 35 of 54, p = 0.0037) and melatonin (90.2%, n = 37 of 41, p < 0.001), whereas unspecified HDSV products were more predominantly associated with therapeutic use (72.2%, n = 26 of 36, p < 0.001). Sampling adequacy for phenotype analysis was acceptable (Kaiser-Meyer-Olkin = 0.673), and Bartlett's test was significant ($\chi^2(55) = 472.5$, p < 0.001). Four

phenotype clusters explained 59.3% of total variance and reflected the following: a sedative/unstable pattern (hypotension, ventricular dysrhythmias, respiratory depression, rhabdomyolysis), metabolic derangements (seizures, metabolic acidosis, elevated anion gap), end-organ damage (acute kidney injury and hepatotoxicity), and a sympathomimetic pattern (tachycardia and hypertension). Severe clinical course occurred in 15 of 150 misuse cases (10.0%) and 12 of 125 therapeutic-use cases (9.6%; p = 0.91). Intensive medical treatment occurred in 6 of 150 misuse cases (4.0%) and 3 of 125 therapeutic-use cases (2.4%; p = 0.46). Hepatotoxicity occurred more often in therapeutic-use cases than misuse cases (11/125 [8.8%] vs 3/150 [2.0%], p = 0.011), as did N-acetylcysteine treatment (5.6% [7 of 125] vs 0.7% [1/150], p = 0.015).

Conclusions: Misuse and therapeutic use HDSV exposures were not associated with meaningful differences in severe outcomes in this patient cohort. Product-specific patterns and phenotype clustering were more informative than intent alone. The higher frequency of hepatotoxicity in therapeutic-use cases is concerning for clinically significant toxicity, and could be targeted through patient education and clear product labeling.