Clinical Effects of Psychedelic Substances Reported to United States Poison Centers: 2012 to 2022

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Study objective: Psychedelic substances use is increasing in the United States (US). The approval of new psychedelic drugs and legalization of natural psychedelic substances will likely further increase exposures and subsequent adverse events. The study objective is to describe the clinical effects, therapies, and medical outcomes of patients with psychedelic exposures reported to US poison centers.

Methods: We performed a retrospective, cross-sectional study on psychedelic exposures reported to the National Poison Data System from January 1, 2012, to December 31, 2022. We categorized exposures into groups: hallucinogenic amphetamines, lysergic acid diethylamide, tryptamines (such as N, N-dimethyltryptamine), phencyclidine, hallucinogenic mushrooms, hallucinogenic plants, and ketamine and ketamine analogs. We summarized effects, treatments, and outcomes and evaluated associations with logistic regression and odds ratios.

Results: Our sample included 54,605 cases. There were concomitant exposures in 41.1% (n=22,460) of cases. Hallucinogenic mushroom exposures increased most over the study period from 593 in 2012 to 1,440 in 2022. Overall, 27,444 (50.3%) psychedelic exposures had symptoms that required treatment, severe residual or prolonged symptoms, or death. Cardiovascular effects were common, especially with hallucinogenic amphetamine exposures (31.1%). Patients managed in or referred to a health care facility received medical therapies in 62.4% of cases, including sedation (32.9%) and respiratory interventions (10.3%).

Conclusion: Over half of psychedelic exposures reported to US poison centers had symptoms that required treatment, severe residual or prolonged symptoms, or death. Increases in psychedelic use may lead to increased frequency of adverse events and health care utilization. [Ann Emerg Med. 2024;■:1-14.]

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INTRODUCTION

Psychedelic substances are a diverse group of drugs that alter perception, mood, and cognition through several mechanisms.[1,2] The understanding of the mechanisms, therapeutic potential, and adverse effects of psychedelic substances has rapidly evolved, and recent studies demonstrate that psychedelic substances can modulate brain connectivity, neuronal synaptic plasticity, and functional neuronal activity during wakeful rest.[3-7] Much of these effects involve serotonin neurotransmission.[2] Psychedelic substances commonly work through structural homology to serotonin, which allows for direct activation of postsynaptic serotonin receptors or increased synaptic release, decreased synaptic reuptake, and inhibited metabolism of biogenic amines such as serotonin.[8,9] This provides the basis for the therapeutic benefits of psychedelic-assisted treatment for conditions such as depression, anxiety, and posttraumatic stress disorder.[10-16] However, increased serotonin neurotransmission may also lead to some adverse manifestations seen after psychedelic exposure, such as delirium, cardiovascular effects, and serotonin toxicity.[17]

Currently, ketamine and esketamine are approved by the United States (US) Food and Drug Administration (FDA) for anesthesia and treatment-resistant depression, respectively.[18,19] There is also increasing medical utilization of historically illicit drugs, such as lysergic acid diethylamide (LSD), 3,4-methylenedioxy-methamphetamine (MDMA), psilocybin, and N, N-dimethyltryptamine (DMT), in clinical trials and patient-attempted self-medication for a range of non-FDA approved mental health indications.[20] Clinicaltrials.gov lists

Editor's Capsule Summary

What is already known on this topic

The use of psychedelic drugs is increasing.

What question this study addressed

What are the types and severity of psychedelic-associated complications being reported to poison centers?

What this study adds to our knowledge

This 10-year review of the Nation Poison Data System included 54,605 psychedelic exposures. Of these, 42% had symptoms that required treatment, 8% had severe residual or prolonged symptoms, and 0.5% died.

How this is relevant to clinical practice

Clinically important adverse events can occur with psychedelic use.

hundreds of ongoing phase II and III clinical trials of psychedelic substances for the treatment of a myriad of neuropsychiatric diseases.[21]

Importance

The legal landscape of psychedelic substances in the US and other countries is rapidly changing, resulting in increased utilization.[22] In 2019, Denver, Colorado was the first US city to decriminalize psilocybin, followed by other cities.[23] In 2020, Oregon legalized psilocybin through licensed service centers, and, in 2022, Colorado decriminalized the growth, possession, and sale of natural psychedelics such as psilocybin, psilocin, DMT, ibogaine, and mescaline.[24,25] As of 2023, more than half of US states had introduced bills or ballot initiatives to liberalize psychedelic regulations.[26-28]

Legalization for therapeutic purposes can be a prelude to increased exposure in the general population outside of approved indications. States that legalized or decriminalized cannabis use for medical and recreational purposes experienced a subsequent increase in intentional use and unintentional exposures.[29-31] Similar effects are now being seen with psychedelics, even before legalization in many states.[22] The National Survey on Drug Use and Health reported that 4.7 million Americans used a hallucinogen in the last year in 2015, and 8.5 million used a hallucinogen in the last year in 2022.[22,32,33] This increase is even more pronounced when looking at areas that have legalized or decriminalized natural psychedelics. The Survey of Nonmedical Use of Prescription Drugs demonstrated the prevalence of overall psychedelic use and past year initiation increased more rapidly in Oregon and Colorado than other states after state-wide legalization and decriminalization laws were passed.[22,34] Legalization of these traditionally Schedule 1 drugs and the FDA approval of others is likely to lead to increased use in the population and a subsequent increase in the frequency of adverse events. Poison center data remain a vital surveillance tool for these adverse events in the general population.

Goal of This Investigation

Many laypersons and medical providers perceive psychedelic substances as safe, natural, and with minimal adverse effects.[1,35] However, similar claims of safety were made when certain opioids, amphetamines, and cocaine were introduced as new pharmaceuticals.[1,35-39] A baseline description of psychedelic substance exposures is imperative to anticipate and detect the effects of increased availability of these substances. To that end, the objective of this study is to describe the clinical effects, therapies, and medical outcomes of patients with psychedelic exposures reported to US poison centers from 2012 to 2022.

METHODS

Study Design and Setting

This was a retrospective, cross-sectional study using the National Poison Data System. America's Poison Centers maintain the National Poison Data System, which stores deidentified case data from calls made to all 55 US poison centers. Specialists in poison information, typically nurses and pharmacists with specialty training in toxicology, receive calls from patients, patient representatives, or medical providers; provide information; and manage exposures. These specialists perform standardized documentation of the calls, which are collected by the National Poison Data System. This study included psychedelic exposures reported to the National Poison Data System from January 1, 2012, to December 31, 2022. Our institutional review board deemed this study to be exempt.

Selection of Population

We categorized psychedelic exposures by the National Poison Data System generic and specific product codes into the following groups: ketamine and ketamine analogs (ketamine/analogs), hallucinogenic amphetamines including MDMA, LSD, tryptamines (such as DMT), phencyclidine (PCP), hallucinogenic mushrooms (such as psilocybin), and hallucinogenic plants (such as *Salvia divinorum*) (Table E1, available at http://www.annemergmed.com). We included all psychedelics and

dissociatives, given their similar therapeutic use for mental health conditions and their similar clinical effects of altered perception, mood, and cognition. LSD and d-lysergic acid amide were classified in the LSD category due to patterns of use, although they are structurally tryptamines. We included all sexes, ages, exposure routes, exposure reasons, and single- and multiple-agent exposures. We excluded confirmed nonexposure cases.

Demographics, Clinical Effects, and Therapies

We obtained demographic data, exposure year, state, clinical effects, and therapies administered from the National Poison Data System. Specialists document clinical effects from lists with standardized data definitions. We included therapies coded "performed" or "recommended and performed." Clinical effects and therapies may be attributable to any exposure reported in the case; effects are not definitively caused by the psychedelic drug and therapies may be used to treat symptoms not associated with psychedelic drugs.

Given that serotonin toxicity is a feared severe adverse event attributable to psychedelics, that National Poison Data System does not record this finding, and there is no diagnostic method validated for retrospective capture of this clinical condition from National Poison Data System data, we developed a data definition for patients with clinical findings consistent with serotonin toxicity. A triad of neuromuscular findings, autonomic dysfunction, and mental status change after exposure to a serotonergic agent characterizes serotonin syndrome after the exclusion of alternate etiologies.[17,40,41] Neuromuscular findings were defined as clonus or myoclonus. Autonomic dysfunction was defined as tachycardia, hypertension, or fever/hyperthermia. Mental status change was defined as coma, mild, moderate, or severe central nervous system depression, confusion, drowsiness/lethargy, hallucinations/delusions, or agitation/irritability. Cases of potential serotonergic toxicity had at least 1 finding in all 3 components of the clinical effect triad: neuromuscular, autonomic, and mental status changes.

Medical Outcomes

The National Poison Data System defines medical outcomes according to the most severe related effect observed during poison center involvement.[42] These outcomes include no effect, minor, moderate, major, death, or not followed. According to National Poison Data System, minor effects are minimally bothersome, usually resolve rapidly, and the patient recovers with no disability; moderate effects have more pronounced or prolonged effects that usually require treatment but are not life-threatening; major effects are life-threatening or result in significant residual disability.[42] Table E2 (available at http://www.annemergmed.com) displays examples of effects for each medical outcome code.[42]

Analysis

We used descriptive statistics to compare demographics, reasons for use, clinical effects, therapies, and the National Poison Data System medical outcomes between psychedelic substance classes. The population used for the medical outcome analysis were exposures to each psychedelic substance category. The exposures included in the clinical effects analysis were those that had at least 1 reported clinical effect. The exposures included in the therapies analysis were those managed in or referred to a health care facility. We used logistic regression analyses to calculate pairwise odds ratios of moderate or worse medical outcomes between psychedelic substance classes. The model included individuals who used a single-psychedelic substance, regardless of the use of other nonpsychedelic substances, and were followed to a known medical outcome. We calculated adjusted pairwise odds ratios by logistic regression analysis with moderate or worse medical outcomes as the dependent variable; psychedelic substance classes as the independent variable; and age, sex (man as a reference group), exposure reason (unknown as reference group), and presence of coexposure of a nonpsychedelic substance as covariates (positive coexposure as reference group). We used SAS® (Cary, NC) for analyses. We used RStudio (R Core Team 2023) package ggplot for figure creation. A second analyst performed validation on all substance categorization and data analyses.

RESULTS

There were 55,678 total cases of psychedelic substance exposure reported to the National Poison Data System during the study period. There were 54 cases excluded for confirmed nonexposures and 1,019 cases for incorrect coding of a nonpsychedelic substance as psychedelic exposures, such as acetaminophen categorized under the category of hallucinogenic amphetamines. The final analysis included 54,605 cases.

Demographics

Table 1 displays the patients' demographic information. Exposures were most common in men (65.7%), with a median age of the overall population of 22.0 years (interquartile range [IQR] 17.0 to 31.0 years). Those between 20 to 29 years old were exposed more than any

Table 1. The demographics of the study population.

Demographics	Characteristics	Ketamine and Analogs	Hallucinogenic Amphetamines	Lysergic Acid Diethylamide	Tryptamines	Phencyclidine	Hallucinogenic Mushrooms	Hallucinogenic Plants	All Psychedelics
Cases	Total	3,418 (6.3%)	22,156 (40.6%)	9,677 (17.7%)	1,103 (2.0%)	6,007 (11.0%)	7,543 (13.8%)	6,299 (11.5%)	54,605 (100%)
Age (y)	Median (interquartile range)	27.0 (20.0 to 36.0)	23.0 (19.0 to 30.0)	18.0 (16.0 to 22.0)	22.0 (18.0 to 30.0)	33.0 (25.0 to 42.0)	20.0 (17.0 to 27.0)	20.0 (11.0 to 33.0)	22.0 (17.0 to 31.0)
Sex	Woman	1,333 (39.0%)	8,241 (37.2%)	2,552 (26.4%)	221 (20.0%)	1,960 (32.6%)	2,103 (27.9%)	2,379 (37.8%)	18,374 (33.6%)
	Man	2,039 (59.7%)	13,786 (62.2%)	7,079 (73.2%)	881 (79.9%)	4,024 (67.0%)	5,394 (71.5%)	3,866 (61.4%)	35,888 (65.7%)
	Unknown	46 (1.3%)	129 (0.6%)	46 (0.5%)	1 (<0.1%)	23 (0.4%)	46 (0.6%)	54 (0.9%)	343 (0.6%)
Region*	New England	761 (22.3%)	3,778 (17.1%)	1,417 (14.6%)	165 (15.0%)	1,496 (24.9%)	1,204 (16.0%)	998 (15.8%)	9,530 (17.5%)
	South	986 (28.8%)	9,465 (42.7%)	3,583 (37.0%)	340 (30.8%)	2,765 (46.0%)	1,955 (25.9%)	2,026 (32.2%)	20,603 (37.7%)
	Midwest	731 (21.4%)	4,576 (20.7%)	2,672 (27.6%)	264 (23.9%)	1,053 (17.5%)	1,770 (23.5%)	1,282 (20.4%)	11,940 (21.9%)
	West	920 (26.9%)	4,226 (19.1%)	1,935 (20.0%)	329 (29.8%)	675 (11.2%)	2,567 (34.0%)	1,958 (31.1%)	12,229 (22.4%)
	Other US territories	4 (0.1%)	14 (<0.1%)	21 (0.2%)	0 (0.0%)	3 (<0.1%)	5 (<0.1%)	7 (0.1%)	54 (<0.1%)
	Unknown	16 (0.5%)	97 (0.4%)	49 (0.5%)	5 (0.5%)	15 (0.2%)	42 (0.6%)	28 (0.4%)	249 (0.5%)
Exposure Reason	Adverse reaction	310 (9.1%)	212(1.0%)	57(0.6%)	17 (1.5%)	46 (0.8%)	98 (1.3%)	612 (9.7%)	1,347 (2.5%)
	Intentional abuse/misuse	1,584 (46.3%)	15,542 (70.1%)	7,487 (77.4%)	886 (80.3%)	3,137 (52.2%)	5,669 (75.2%)	2,419 (38.4%)	35,483 (64.5%)
	Suspected suicide	494 (14.5%)	3,403 (15.4%)	1,053 (10.9%)	58 (5.3%)	1,313 (21.9%)	541 (7.2%)	271 (4.3%)	6,918 (12.7%)
	Therapeutic error	305 (8.9%)	48 (0.2%)	2 (<0.1%)	3 (0.3%)	40 (0.7%)	9 (0.1%)	78 (1.2%)	484 (0.9%)
	Unintentional	382 (11.2%)	1,162 (5.2%)	432 (4.5%)	59 (5.3%)	456 (7.6%)	878 (11.6%)	2,514 (39.9%)	5,850 (10.7%)
	Other	105 (3.1%)	461 (2.1%)	147 (1.5%)	20 (1.8%)	118 (2.0%)	59 (0.8%)	121 (1.9%)	1,017 (1.9%)
	Unknown	238 (7.0%)	1,328 (6.0%)	499 (5.2%)	60 (5.4%)	897 (14.9%)	289 (3.8%)	284 (4.5%)	3,506 (6.4%)
Management Site	Managed on site (non-HCF)	334 (9.7%)	1,165 (5.3%)	485 (5.0%)	45 (4.1%)	264 (4.4%)	953 (12.6%)	2,744 (43.6%)	5,971 (10.9%)
	Patient in/enroute to HCF	2,692 (78.8%)	17,571 (79.3%)	7,982 (82.5%)	953 (86.4%)	5,239 (87.2%)	5,379 (71.3%)	2,537 (40.3%)	40,889 (74.9%)
	Patient referred to HCF	324 (9.5%)	3,008 (13.6%)	1,040 (10.8%)	91 (8.3%)	416 (6.9%)	1,067 (14.2%)	848 (13.5%)	6,702 (12.3%)
	Other	23 (0.7%)	183 (0.8%)	64 (0.7%)	6 (0.5%)	44 (0.7%)	44 (0.6%)	100 (1.6%)	458 (0.8%)
	Unknown	45 (1.3%)	229 (1.0%)	106 (1.1%)	8 (0.7%)	44 (0.7%)	100 (1.3%)	70 (1.1%)	585 (1.1%)
Route	Ingestion	1,298 (38.0%)	16,818 (75.9%)	7,376 (76.2%)	668 (60.6%)	2,714 (45.2%)	6,647 (88.1%)	5,276 (83.8%)	39,833 (72.9%)
	Inhalation/nasal	477 (14.0%)	897 (4.1%)	211 (2.2%)	168 (15.2%)	1,151 (19.2%)	79 (1.1%)	263 (4.2%)	3,200 (5.9%)
	Parenteral	587 (17.2%)	247 (1.1%)	18 (0.2%)	15 (1.4%)	44 (0.7%)	16 (0.2%)	18 (0.3%)	941 (1.7%)
	Dermal	106 (3.1%)	49 (0.2%)	83 (0.9%)	7 (0.6%)	98 (1.6%)	14 (0.2%)	452 (7.2%)	809 (1.3%)
	Ocular	142 (4.2%)	15 (<0.1%)	12 (0.1%)	2 (0.2%)	6 (0.1%)	2 (<0.1%)	277 (4.4%)	456 (0.8%)
	Rectal	22 (0.6%)	22 (0.1%)	2 (<0.1%)	0 (0.0%)	5 (<0.1%)	3 (<0.1%)	0 (0.0%)	54 (1.3%)
	Other	41 (1.2%)	92 (0.4%)	31 (0.3%)	2 (0.2%)	32 (0.5%)	2 (<0.1%)	15 (0.2%)	215 (0.4%)
	Unknown	799 (23.4%)	4,157 (18.8%)	1,982 (20.5%)	255 (23.1%)	2,028 (33.8%)	800 (10.6%)	260 (4.1%)	9,698 (17.8%)

HCF, Health care facility.

*Region of exposure was based on United States Census Bureau Region.[62]

other age group (32.4%, n=17,685), followed by ages 13 to 19 years old (29.6%, n=16,147) (Table E3, available at http://www.annemergmed.com). Patients exposed to LSD had the youngest median age (18 years, interquartile range [IQR] 16-22 years), and patients exposed to PCP had the oldest median age (33 years, IQR 25 to 42 years). Over half of all LSD exposures were between ages 13 and 19 years (57.4%, n=5,554). Overall, 4.5% (n=2,473) of exposures were in patients 6 years old or less, including 18.3% (n=1,151) of hallucinogenic plants and 5.4% (n=409) of hallucinogenic mushroom exposures. Coexposure with another substance was seen in 41.1% (n=22,460) of cases. A total of 47,591 (87.2%) exposures were either referred by the poison center to a health care facility or already in a health care facility at time of contact.

Longitudinal Trends

There was an overall decrease of 6.6% in total psychedelic exposures per year reported to US poison centers from 2012 (n=4,858) to 2022 (n=4,555) (Figure 1). However, exposure to several psychedelic substances increased, with the largest relative increase seen in hallucinogenic mushrooms from 593 exposures in 2012 to 1,440 exposures in 2022, representing a 242% increase over the study period. The largest relative decrease in annual exposures was in PCP, which decreased by 60.3% from 2012 (n=786) to 2022 (n=312). In states where psilocybin was legalized (Oregon and Colorado), total psychedelic exposures increased from 2012 (n=161) to 2022 (n=194).

Medical Outcomes

There were 27,444 (50.3%) exposures with moderate or worse medical outcomes. Exposures had moderate effects in 22,689 (41.6%) cases, major effects in 4,490 (8.2%) cases, and death in 265 (0.5%) cases (Table 2). Exposure severity did not increase over the study period. The percentage of moderate or worse outcomes fluctuated by year, with a low of 47.3% in 2012 and high of 53.2% in 2017. Of the cases with a known medical outcome, there were 40,654 single-psychedelic exposures included in the logistic regression to predict the adjusted odds of moderate or worse medical outcome between psychedelic substance categories (Figure 2). There were 13,951 cases excluded due to either not having a known medical outcome or for exposure to multiple psychedelic substances. Hallucinogenic plants had the lowest pairwise adjusted odds ratio (aOR) for moderate or worse medical outcomes compared to other psychedelics (range of aORs: 0.4 [95% confidence interval 0.6 to 0.8] to 0.7 [0.3 to 0.5]), which served as the reference. Tryptamine exposures had the highest adjusted odds of moderate or worse outcomes (aOR 2.4 [2.0 to 3.0]), followed by LSD (aOR: 2.3 [2.1-2.5]), hallucinogenic amphetamines (aOR 1.9 [1.7 to 2.1]), PCP (aOR 1.7 [1.5 to 1.9]), hallucinogenic mushrooms (aOR 1.6 [1.5 to 1.8]), and ketamine/analogs (aOR 1.5 [1.3 to 1.7]) (Table E4, available at http://www.annemergmed.com). Although the period of observation following legalization/decriminalization in Oregon and Colorado after January 2021 was short, our preliminary data demonstrate that the proportion of patients with moderate or worse medical outcomes after hallucinogenic mushroom exposures was

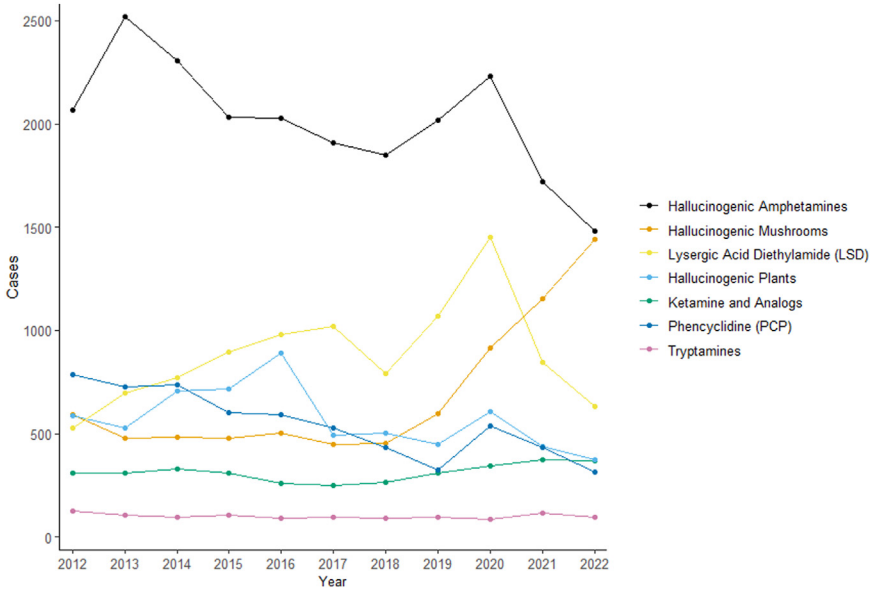

Figure 1. Annual exposures to psychedelic substances reported to US poison centers.

Table 2. Medical outcome reported after psychedelic substance exposure.

Medical Outcome	Ketamine and Analogs (N=3,418)	Hallucinogenic Amphetamines (N=22,156)	Lysergic Acid Diethylamide (N=9,677)	Tryptamines (N=1,103)	Phencyclidine (N=6,007)	Hallucinogenic Mushrooms (N=7,543)	Hallucinogenic Plants (N=6,299)	All Psychedelics (N=54,605)
Death	31 (0.9%)	152 (0.7%)	22 (0.2%)	7 (0.6%)	54 (0.9%)	9 (0.1%)	6 (<0.1%)	265 (0.5%)
Major effect	417 (12.2%)	2,115 (9.5%)	740 (7.6%)	96 (8.7%)	873 (14.5%)	317 (4.2%)	178 (2.8%)	4,490 (8.2%)
Moderate effect	1,254 (36.7%)	9,473 (42.8%)	5,049 (52.2%)	602 (54.6%)	2,453 (40.8%)	3,285 (43.6%)	1,430 (22.7%)	22,689 (41.6%)
Minor effect	746 (21.8%)	4,497 (20.3%)	1,945 (20.1%)	191 (17.3%)	1,198 (19.9%)	1,663 (22.0%)	1,261 (20.0%)	11,227 (20.6%)
No effect	230 (6.7%)	1,227 (5.5%)	411 (4.2%)	37 (3.4%)	325 (5.4%)	414 (5.5%)	729 (11.6%)	3,326 (6.1%)
Not followed/ other/unknown	740 (21.7%)	4,692 (21.2%)	1,510 (15.6%)	170 (15.4%)	1,104 (18.4%)	1,855 (24.6%)	2,695 (42.8%)	12,608 (23.1%)

similar (69 cases of 154 total cases, 44.8%) compared to all other states (1,083 cases of 2,438 total cases, 44.4%), despite an increase in hallucinogenic mushroom exposures in those states.

Clinical Effects

Table 3 displays the related clinical effects of the 42,790 cases with observed effects. Cardiovascular effects were common, seen in 29,251 (68.4%) exposures. The most common clinical effect across all exposures was tachycardia, seen in 17,604 (41.1%) cases. The most common organ system involved was neurologic in 34,760 (81.2%) cases, including seizures in 2,046 (4.8%), mild central nervous system depression in 1,809 (4.2%), moderate central nervous system depression in 1,149 (2.7%), and coma in 2,067 (4.8%) cases. Gastrointestinal effects were seen in 6,718 (15.7%) cases, most commonly nausea or vomiting in 5,467 (12.8%) exposures.

The observed effects differed by psychedelic substance category. Cardiovascular effects were most frequent after hallucinogenic amphetamine exposure (n=14,602 [80.9%]), and least frequent after hallucinogenic plant exposure (n=1,596 [45.2%]). Gastrointestinal effects were most frequent after hallucinogenic plant (n=1,148 [32.5%]) and hallucinogenic mushroom (n=1,587 [26.7%]) exposures.

Overall, 176 (0.4%) cases met the data definition of serotonin toxicity. These patients had at least 1 clinical symptom in all 3 components of the serotonin toxicity triad: neuromuscular findings, autonomic dysfunction, and mental status change. Serotonin toxicity was most common after hallucinogenic amphetamine (n=81 [0.4%]) exposure. Clinical effects representing possible serotonin toxicity included clonus (n=151 [0.4%]), myoclonus (n=107 [0.9%]), fever/hyperthermia (n=2,181 [5.1%]), tachycardia (n=17,604 [41.1%]), hypertension (n=7,560 [17.7%]), agitation (n=14,784 [34.6%]), central nervous system mild depression (n=1,809 [4.2%]), central nervous system moderate depression (n=1,149 [2.7%]), coma (n=2,067 [4.8%]), and confusion (n=8,165 [19.1%]).

Therapies

There were 47,591 patients managed in or referred to a health care facility, of which 29,720 (62.4%) exposures received at least 1 therapy (Table 4). The most common therapy was intravenous fluid administration (n=20,759 [43.6%]), followed by sedative administration (n=15,639 [32.9%]). Sedative administration included benzodiazepines alone (n=10,702 [22.5%]), antipsychotics alone (n=147 [0.3%]), other sedatives alone (n=1,278

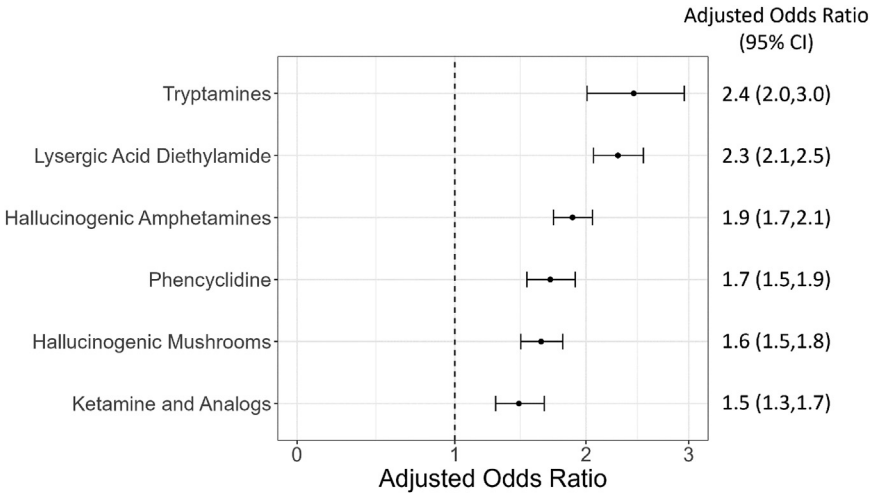

Figure 2. Adjusted odds ratio for moderate or worse medical outcome by psychedelic substance category compared to the lowest risk category (hallucinogenic plants).

[2.7%]), or a combination of these therapies (n=3,512 [7.4%]). Sedation was most frequently administered after LSD exposure (n=3,805 [42.2%]) in patients managed in or referred to a health care facility and least frequently after hallucinogenic plant exposure (n=706 [20.9%]). Respiratory interventions (supplemental oxygen, positive pressure ventilation, or intubation) were administered in 4,919 [10.3%] patients. Respiratory interventions were most frequently administered after PCP exposure (n=1,064 [18.8%]), followed by ketamine/analogs exposures (n=548 [18.2%]).

LIMITATIONS

The National Poison Data System data source has limitations that affect conclusions made from this study. This data set only reflects cases reported to US poison centers, which typically occur due to adverse or unexpected effects, and does not capture the outcome prevalence of all psychedelic exposures. These findings apply to those who had poison center involvement and underrepresent those who have uneventful psychedelic exposures and therefore do not have contact with a poison center. However, this information is essential to understand patients who interact with the medical system after psychedelic exposure. These data display important clinical effects and medical resources utilized for these patients, who will be primarily managed in the emergency department and will likely increase in the coming years.

Furthermore, missing data are possible in the National Poison Data System data set given the most pertinent clinical exposures, symptoms, and therapies are the focus of specialists managing and documenting cases. Additionally, these cases included single- and multiple-agent exposures, generally without laboratory confirmation. Confounding from concomitant substance use was minimized by excluding those that used multiple psychedelic products and adjusting for those that used another substance outside of psychedelics in the medical outcome regression. Miscoding of the reason for use is possible, given that many of these drugs remain illegal, and the reason may be inferred rather than confirmed with the patient. It is possible that this data source differentially under-reports adverse events from therapeutic use of FDA-approved drugs, such as ketamine in health care facilities, due to provider comfort with these adverse events. This would falsely suggest increased safety of drugs used in monitored settings.

This data source does not differentiate specific products due to limited product code definitions, miscoding, failure to capture product names during prioritized medical care, and the perpetual introduction of new psychedelic substances with similarities to current drugs. Therefore, we have not stratified the clinical effects, therapies, or outcomes associated with specific drugs. This study utilized a data definition for serotonin toxicity based on the triad of clinical findings consistent with this toxidrome and reflecting multiple-system organ involvement. The National Poison Data System does not document cases of serotonin toxicity and diagnostic criteria are not validated for application to this database.[43-45] Thus, our data definition has yet to be validated against a gold standard diagnosis. This study did not assess exposure dose as a limited number of cases reported dose and accuracy of dose is difficult to verify. Exposure dose likely affects clinical effects and outcome; however, further study is needed to

Table 3. Clinical effects reported after psychedelic substance exposure.*

Clinical Effects	Ketamine and Analogs N=2,583 (6.0%)	Hallucinogenic Amphetamines N=18,058 (42.3%)	Lysergic Acid Diethylamide N=8,273 (19.4%)	Tryptamines N=938 (2.2%)	Phencyclidine N=4,898 (11.5%)	Hallucinogenic Mushrooms N=5,954 (13.9%)	Hallucinogenic Plants N=3,530 (8.3%)	All Psychedelics N=42,790 (100.0%)
Cardiovascular	**1,607**	**14,602**	**6,070**	**717**	**3,250**	**2,695**	**1,596**	**29,251**
Asystole	37 (1.4%)	143 (0.8%)	12 (0.1%)	1 (0.1%)	59 (1.2%)	8 (0.1%)	4 (0.1%)	255 (0.6%)
Bradycardia	117 (4.5%)	281 (1.6%)	90 (1.1%)	23 (2.5%)	89 (1.8%)	47 (0.8%)	33 (0.9%)	646 (1.5%)
Cardiac arrest	12 (0.5%)	97 (0.5%)	11 (0.1%)	7 (0.7%)	58 (1.2%)	3 (<0.1%)	8 (0.2%)	185 (0.4%)
ECG change - QRS prolongation	23 (0.9%)	78 (0.4%)	27 (0.3%)	8 (0.9%)	20 (0.4%)	16 (0.3%)	6 (0.2%)	163 (0.4%)
ECG change - QTc prolongation	45 (1.7%)	281 (1.6%)	136 (1.6%)	11 (1.2%)	69 (1.4%)	51 (0.9%)	19 (0.5%)	582 (1.4%)
High blood pressure	394 (15.3%)	3,774 (20.9%)	1,437 (17.4%)	214 (22.8%)	865 (17.7%)	778 (13.1%)	443 (12.5%)	7,560 (17.7%)
Hypotension	139 (5.4%)	604 (3.3%)	142 (1.7%)	32 (3.4%)	269 (5.5%)	86 (1.4%)	48 (1.4%)	1,260 (2.9%)
Other dysrhythmia	24 (0.9%)	260 (1.4%)	89 (1.1%)	12 (1.3%)	56 (1.1%)	36 (0.6%)	30 (0.8%)	477 (1.1%)
Pulseless electrical activity	3 (0.1%)	11 (<0.1%)	2 (<0.1%)	2 (0.2%)	4 (<0.1%)	1 (<0.1%)	0 (0.0%)	22 (<0.1%)
Syncope	25 (1.0%)	112 (0.6%)	26 (0.3%)	6 (0.6%)	40 (0.8%)	49 (0.8%)	27 (0.8%)	280 (0.7%)
Tachycardia	776 (30.0%)	8,829 (48.9%)	4,073 (49.2%)	393 (41.9%)	1,691 (34.5%)	1,609 (27.0%)	966 (27.4%)	17,604 (41.1%)
Torsade de pointes	0 (0.0%)	2 (<0.1%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)	0 (0.0%)	1 (<0.1%)	4 (<0.1%)
Troponin elevation	9 (0.3%)	76 (0.4%)	17 (0.2%)	3 (0.3%)	18 (0.4%)	6 (0.1%)	4 (0.1%)	127 (0.3%)
V. tachycardia/V. fibrillation	3 (0.1%)	54 (0.3%)	8 (<0.1%)	5 (0.5%)	11 (0.2%)	5 (<0.1%)	7 (0.2%)	86 (0.2%)
Gastroenterological	**264**	**2,703**	**738**	**116**	**327**	**1,587**	**1,148**	**6,718**
Abdominal pain	36 (1.4%)	369 (2.0%)	62 (0.7%)	9 (1.0%)	48 (1.0%)	227 (3.8%)	190 (5.4%)	921 (2.2%)
Diarrhea	8 (0.3%)	83 (0.5%)	27 (0.3%)	11 (1.2%)	13 (0.3%)	139 (2.3%)	58 (1.6%)	330 (0.8%)
Nausea or vomiting	220 (8.5%)	2,251 (12.5%)	649 (7.8%)	96 (10.2%)	266 (5.4%)	1,221 (20.5%)	900 (25.5%)	5,467 (12.8%)
Genitourinary	**100**	**921**	**283**	**29**	**321**	**117**	**54**	**1,702**
Creatinine increased	72 (2.8%)	672 (3.7%)	230 (2.8%)	20 (2.1%)	247 (5.0%)	82 (1.4%)	26 (0.7%)	1,263 (3.0%)
Renal failure	16 (0.6%)	151 (0.8%)	26 (0.3%)	4 (0.4%)	43 (0.9%)	11 (0.2%)	7 (0.2%)	240 (0.6%)
Urinary retention	12 (0.5%)	98 (0.5%)	27 (0.3%)	5 (0.5%)	31 (0.6%)	24 (0.4%)	21 (0.6%)	199 (0.5%)
Hematologic	**0**	**2**	**1**	**0**	**0**	**0**	**0**	**3**
Hemolysis	0 (0.0%)	2 (<0.1%)	1 (<0.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (<0.1%)
Hepatic	**71**	**487**	**106**	**18**	**166**	**77**	**44**	**905**
AST, ALT>1,000 IU/L	21 (0.8%)	163 (0.9%)	33 (0.4%)	7 (0.7%)	58 (1.2%)	22 (0.4%)	8 (0.2%)	288 (0.7%)
AST, ALT 100 to 1,000 IU/L	50 (1.9%)	324 (1.8%)	73 (0.9%)	11 (1.2%)	108 (2.2%)	55 (0.9%)	36 (1.0%)	617 (1.4%)
Metabolic	**115**	**866**	**387**	**36**	**306**	**102**	**40**	**1,743**
Acidosis	115 (4.5%)	866 (4.8%)	387 (4.7%)	36 (3.8%)	306 (6.2%)	102 (1.7%)	40 (1.1%)	1,743 (4.1%)

Neurologic	**2,918**	**18,072**	**10,977**	**1,214**	**6,239**	**6,684**	**2,539**	**46,697**
Agitation	543 (21.0%)	6,242 (34.6%)	3,861 (46.7%)	353 (37.6%)	1,836 (37.5%)	1,852 (31.1%)	692 (19.6%)	14,784 (34.6%)
CNS depression (mild)	187 (7.2%)	751 (4.2%)	347 (4.2%)	26 (2.8%)	176 (3.6%)	312 (5.2%)	93 (2.6%)	1,809 (4.2%)
CNS depression (moderate)	173 (6.7%)	496 (2.7%)	164 (2.0%)	21 (2.2%)	191 (3.9%)	138 (2.3%)	13 (0.4%)	1,149 (2.7%)
CVA	0 (0.0%)	11 (<0.1%)	0 (0.0%)	0 (0.0%)	1 (<0.1%)	0 (0.0%)	0 (0.0%)	12 (<0.1%)
Clonus	11 (0.4%)	72 (0.4%)	45 (0.5%)	8 (0.9%)	11 (0.2%)	17 (0.3%)	4 (0.1%)	151 (0.4%)
Coma	320 (12.4%)	930 (5.2%)	201 (2.4%)	43 (4.6%)	514 (10.5%)	104 (1.7%)	62 (1.8%)	2,067 (4.8%)
Confusion	483 (18.7%)	2,884 (16.0%)	2,187 (26.4%)	229 (24.4%)	1,173 (23.9%)	1,199 (20.1%)	395 (11.2%)	8,165 (19.1%)
Dizziness/vertigo	95 (3.7%)	572 (3.2%)	118 (1.4%)	19 (2.0%)	92 (1.9%)	184 (3.1%)	249 (7.1%)	1,310 (3.1%)
Drowsiness/lethargy	594 (23.0%)	2,222 (12.3%)	608 (7.3%)	99 (10.6%)	1,208 (24.7%)	372 (6.2%)	363 (10.3%)	5,313 (12.4%)
Hallucinations/ delusions	216 (8.4%)	2,427 (13.4%)	2,793 (33.8%)	354 (37.7%)	493 (10.1%)	2,233 (37.5%)	542 (15.4%)	8,677 (20.3%)
Myoclonus	12 (0.5%)	56 (0.3%)	19 (0.2%)	3 (0.3%)	8 (0.2%)	14 (0.2%)	2 (<0.1%)	107 (0.3%)
Nystagmus	191 (7.4%)	242 (1.3%)	106 (1.3%)	14 (1.5%)	273 (5.6%)	53 (0.9%)	20 (0.6%)	862 (2.0%)
Paranoia	3 (0.1%)	55 (0.3%)	87 (1.1%)	9 (1.0%)	12 (0.2%)	77 (1.3%)	6 (0.2%)	245 (0.6%)
Seizures	90 (3.5%)	1,112 (6.2%)	441 (5.3%)	36 (3.8%)	251 (5.1%)	129 (2.2%)	98 (2.8%)	2,046 (4.8%)
Pulmonary	**352**	**1,961**	**537**	**64**	**594**	**234**	**175**	**3,758**
Dyspnea	23 (0.9%)	373 (2.1%)	54 (0.7%)	4 (0.4%)	53 (1.1%)	50 (0.8%)	48 (1.4%)	592 (1.4%)
Hyperventilation/ tachypnea	68 (2.6%)	906 (5.0%)	348 (4.2%)	29 (3.1%)	146 (3.0%)	120 (2.0%)	61 (1.7%)	1,596 (3.7%)
Pulmonary edema	4 (0.2%)	32 (0.2%)	3 (<0.1%)	0 (0.0%)	9 (0.2%)	0 (0.0%)	1 (<0.1%)	48 (0.1%)
Respiratory arrest	35 (1.4%)	133 (0.7%)	16 (0.2%)	10 (1.1%)	68 (1.4%)	8 (0.1%)	7 (0.2%)	266 (0.6%)
Respiratory depression	222 (8.6%)	517 (2.9%)	116 (1.4%)	21 (2.2%)	318 (6.5%)	56 (0.9%)	58 (1.6%)	1,256 (2.9%)
Muscular Skeletal	**207**	**2,489**	**897**	**108**	**737**	**259**	**111**	**4,554**
CPK elevated	77 (3.0%)	1,210 (6.7%)	451 (5.5%)	51 (5.4%)	384 (7.8%)	103 (1.7%)	60 (1.7%)	2,207 (5.2%)
Fasciculations	3 (0.1%)	44 (0.2%)	15 (0.2%)	0 (0.0%)	10 (0.2%)	3 (<0.1%)	4 (0.1%)	77 (0.2%)
Muscle rigidity	32 (1.2%)	264 (1.5%)	72 (0.9%)	10 (1.1%)	44 (0.9%)	25 (0.4%)	10 (0.3%)	436 (1.0%)
Rhabdomyolysis	95 (3.7%)	971 (5.4%)	359 (4.3%)	47 (5.0%)	299 (6.1%)	128 (2.1%)	37 (1.0%)	1,834 (4.3%)
Other	**414**	**4,799**	**2,436**	**262**	**793**	**1,425**	**662**	**10,267**
Diaphoresis	83 (3.2%)	1,265 (7.0%)	418 (5.1%)	44 (4.7%)	176 (3.6%)	190 (3.2%)	192 (5.4%)	2,261 (5.3%)
Erythema/flushed	24 (0.9%)	185 (1.0%)	83 (1.0%)	12 (1.3%)	26 (0.5%)	72 (1.2%)	152 (4.3%)	533 (1.2%)
Excess secretions	21 (0.8%)	49 (0.3%)	18 (0.2%)	3 (0.3%)	28 (0.6%)	17 (0.3%)	9 (0.3%)	137 (0.3%)
Fever/hyperthermia	105 (4.1%)	1,284 (7.1%)	415 (5.0%)	46 (4.9%)	271 (5.5%)	135 (2.3%)	53 (1.5%)	2,181 (5.1%)
Hypothermia	20 (0.8%)	106 (0.6%)	23 (0.3%)	1 (0.1%)	51 (1.0%)	6 (0.1%)	8 (0.2%)	206 (0.5%)
Mydriasis	161 (6.2%)	1,910 (10.6%)	1,479 (17.9%)	156 (16.6%)	241 (4.9%)	1,005 (16.9%)	248 (7.0%)	4,949 (11.6%)

ALT, alanine aminotransferase; *AST*, aspartate aminotransferase; *CPK*, creatine phosphokinase; *CVA*, cerebrovascular accident.
*The number of patient (N) utilized for each psychedelic category were those who had at least one reported clinical effect. Organ system totals reflect the total counts of findings from each organ system. Patient percentages are not reported for organ system totals as patients may have had multiple findings within an organ system (IU/L = international units per liter).

Table 4. Therapies performed after psychedelic substance exposure.*

Therapy	Ketamine and Analogs N=3,016 (6.3%)	Hallucinogenic Amphetamines N=20,579 (43.2%)	Lysergic Acid Diethylamide N=9,022 (2.2%)	Tryptamines N=1,044 (2.2%)	Phencyclidine N=5,655 (11.9%)	Hallucinogenic Mushrooms N=6,446 (13.5%)	Hallucinogenic Plants N=3,385 (7.1%)	All Psychedelics N=47,591 (100.0%)
Antiarrhythmic	22 (0.7%)	116 (0.6%)	34 (0.4%)	2 (0.2%)	32 (0.6%)	11 (0.2%)	10 (0.3%)	215 (0.5%)
Antiemetic	85 (2.8%)	776 (3.8%)	241 (2.7%)	40 (3.8%)	100 (1.8%)	387 (6.0%)	159 (4.7%)	1,742 (3.7%)
Antihistamine	62 (2.1%)	436 (2.1%)	243 (2.7%)	18 (1.7%)	161 (2.8%)	114 (1.8%)	48 (1.4%)	1,035 (2.2%)
Antihypertensive	26 (0.9%)	237 (1.2%)	55 (0.6%)	8 (0.8%)	95 (1.7%)	26 (0.4%)	47 (1.4%)	475 (1.0%)
Antipsychotic	42 (1.4%)	265 (1.3%)	285 (3.2%)	36 (3.4%)	133 (2.4%)	151 (2.3%)	13 (0.4%)	875 (1.8%)
Atropine	25 (0.8%)	36 (0.2%)	8 (<0.1%)	4 (0.4%)	18 (0.3%)	9 (0.1%)	2 (<0.1%)	97 (0.2%)
Benzodiazepine	568 (18.8%)	6,665 (32.4%)	3,549 (39.3%)	366 (35.1%)	1,612 (28.5%)	1,455 (22.6%)	646 (19.1%)	14,194 (29.8%)
Intravenous fluids	1,151 (38.2%)	9,986 (48.5%)	4,167 (46.2%)	449 (43.0%)	2,623 (46.4%)	2,261 (35.1%)	986 (29.1%)	20,759 (43.6%)
Naloxone	286 (9.5%)	944 (4.6%)	177 (2.0%)	33 (3.2%)	550 (9.7%)	93 (1.4%)	101 (3.0%)	2,107 (4.4%)
Oxygen	510 (16.9%)	2,101 (10.2%)	666 (7.4%)	96 (9.2%)	969 (17.1%)	245 (3.8%)	170 (5.0%)	4,547 (9.6%)
Renal replacement therapy	19 (0.6%)	129 (0.6%)	23 (0.3%)	4 (0.4%)	43 (0.8%)	10 (0.2%)	10 (0.3%)	228 (0.5%)
Sedation (other)	303 (10.0%)	1,825 (8.9%)	981 (10.9%)	106 (10.2%)	801 (14.2%)	323 (5.0%)	151 (4.5%)	4,260 (9.0%)
Vasopressor	84 (2.8%)	290 (1.4%)	55 (0.6%)	8 (0.8%)	112 (2.0%)	28 (0.4%)	17 (0.5%)	569 (1.2%)
Ventilation/ intubation	348 (11.5%)	1,548 (7.5%)	511 (5.7%)	59 (5.7%)	722 (12.8%)	154 (2.4%)	121 (3.6%)	3,305 (6.9%)

*The number of patient (N) utilized for each psychedelic category were those who were managed in or referred to a health care facility.

evaluate this. Finally, data on time from exposure to effects are not readily available in the National Poison Data System data set and will require further study.

DISCUSSION

This study displays the baseline adverse effects observed in psychedelic substance exposures reported to US poison centers. These patients had moderate or worse outcomes in 50.3% of cases, which indicates symptoms that required treatment, severe residual or prolonged symptoms, or death. Overall, 62.4% of cases received medical therapy, including 10.3% who received a respiratory intervention and 32.0% who received sedation. Hallucinogenic mushroom exposures increased most during the study period. Although we saw an increase in reports, we did not see an increased proportion of moderate or worse medical outcomes. Tryptamines and LSD had the highest odds, whereas hallucinogenic plants and ketamine/analogs had the lowest odds, of moderate or worse outcomes when adjusted for patient's sex, age, exposure reason, and coexposure of a nonpsychedelic substance. The reported reasons for psychedelic substance exposures were predominantly intentional abuse/misuse, which may pose a higher risk than use in approved medical settings.

Psychedelic substances show promise in treating numerous neuropsychiatric disorders.[10-16] The FDA approved ketamine and esketamine for use in monitored settings, and numerous clinical trials are investigating other drugs.[46] However, the adverse effects seen in those clinical trials are likely not representative of real-world use of the same drugs in unapproved and unmonitored settings. Furthermore, the scope of this study provides adverse effect data from more than 54,000 cases of psychedelic substance exposure in the real world. This contrasts with the smaller scope of clinical trials, which have enrolled only a few hundred patients to date.[46-49] The frequency of adverse effects associated with psychedelic exposures in the general population suggests the need for proactive surveillance as new psychedelic pharmaceuticals are approved and legislation to increase psychedelic availability is enacted.

Early legalization and decriminalization of psychedelic substances in Oregon and Colorado demonstrate that after legislation was passed, use of psychedelic substances increased, even before the infrastructure to monitor these substances was established.[22] This study demonstrated that there was both an increase in reports of hallucinogenic mushroom exposures to poison centers nationally and in Oregon and Colorado during this time. Monitoring these substances must parse the specific products and contexts of use to differentiate effects associated with therapeutic indications from unapproved and unmonitored use. This will become more complicated as states legalize and decriminalize these substances. For example, recent experience with cannabis legalization in the US demonstrated that legalization was associated with significant increases in unintended pediatric exposures.[29-31] We observed that 4.5% of exposures in this study were in children less than 6 years of age. Thus, education and safe storage initiatives are critical to minimize inevitable pediatric exposures as availability increases, as seen with cannabis.[50-52]

Despite increasing psychedelic substance use in the US, overall annual exposures to psychedelic substances reported to US poison centers decreased by 6.6% from 2012 to 2022.[32,33,53] However, there was a corresponding 9.2% decrease in total cases reported to US poison centers during that period.[54] There was a dramatic rise in psychedelic mushroom exposures, which accompanied legalization and decriminalization efforts. Additionally, different age groups had distinct patterns of psychedelic substance use. Over half of LSD reports were in patients between 13 and 19 years. This contrasts other substance categories for which patients between 20 and 29 years were among the most common. Overall, patients between 13 and 29 years were 62.0% of cases, which suggests the need for targeted harm reduction in this age group. Poison center data remain an important tool to surveil unmonitored use.[24,25] However, additional details will be necessary to define specific drugs and their source given that products have approved and unapproved uses through approved and unapproved programs, which are likely to have different medical outcomes.

These findings on the baseline profile of adverse effects and performed therapies after psychedelic substance exposure reported to US poison centers have multiple implications for medical providers, especially those in the emergency setting. Emergency medicine clinicians and emergency departments will be the front line in handling increased frequency of adverse events resulting from increased availability. Furthermore, these findings also demonstrate potential risks of psychedelic use in an unmonitored setting. Cardiovascular monitoring should be considered given the high proportion of cardiovascular effects, especially after hallucinogenic amphetamine exposure.[55,56] Consideration should be made for respiratory monitoring and the ability to intervene, especially in ketamine/analogs and PCP exposures given the high proportion of patients who received respiratory therapies and risk from delay of these interventions.[57,58] Finally, facilitators and observers of psychedelic therapies should prepare to provide sedative treatments, either

through medication administration or behavioral interventions, given that almost one third of all exposures received sedative medications.

Clinicians must consider intent, source of the drug, and coexposures to accurately interpret risk for their patients. However, these data display that even when we adjust for patient factors, intent, and coexposures, there are intrinsic differences in risk between psychedelic substances as seen by different odds for developing more severe presentations. Therefore, although clinical trials evaluate the adverse effects of these agents in monitored settings, this study demonstrates the risk of unmonitored illicit use in the general population. Although others have assessed individual psychedelic exposures in small geographic areas or small subpopulations, this is the first study to look at the most common psychedelic agents across the entire US in all demographics since decriminalization and legalization in some localities.[59-61]

In summary, psychedelic substance exposures reported to US poison centers commonly had moderate or worse medical outcomes, which indicates symptoms that required treatment, severe residual or prolonged symptoms, or death. These data do not reflect all psychedelic exposures; however, these data highlight important observations about the clinical influence of patients who have used predominantly outside of FDA approved or state programs and subsequently have an effect on the health care system. The rise in hallucinogenic mushroom exposures suggests that increased use is associated with increased frequency of adverse events reported to poison centers. These results indicate the need for active surveillance that differentiates specific products and assesses monitored and unmonitored use to differentiate the risks between these use patterns.

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