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NBOMe DESIGNER DRUG EXPOSURES REPORTED TO TEXAS POISON CENTERS

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Use of 2-methoxybenzyl analogues of 2C-X phenethylamines (NBOMe) is increasing in the United States. Twenty-five NBOMe exposures reported to Texas poison centers during 2012–2013 were identified; 76% involved 25I-NBOMe, 12% involved 25C-NBOMe, and 12% involved an unknown NBOMe. Eighty-eight percent of the patients were men; mean age was 17 years (range, 14–25 years). The exposure route was 72% from ingestion alone, 12% from inhalation alone, 4% from ingestion and inhalation, and 12% from an unknown route. The most common clinical effects were tachycardia (52%), agitation (48%), hallucinations (32%), hypertension (32%), confusion (24%), and mydriasis (20%). Two patients died.

KEYWORDS. NBOMe, 25I-NBOMe, 25C-NBOMe, designer drug, poison center

INTRODUCTION

There has been an increasing trend in the use of designer drugs in the United States, among which are variants of the 2C-X series of phenethylamines (2,5-dimethoxyphenethylamines). In these variants, a 2-methoxybenzyl is added onto the nitrogen (N) of the phenethylamine, hence the designation "NBOMe." These include 2-(4-iodo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine (25I-NBOMe; 2CI-NBOMe; 25I; Cimbi-5), 2-(4-chloro-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine (25C-NBOMe; 2C-C-NBOMe; 25C; Cimbi-82), and 2-(4-bromo-2,5-dimethoxyphenyl)-*N*-(2-methoxybenzyl)ethanamine (25B-NBOMe; 2C-B-NBOMe; 25B; Cimbi-36). These were developed in the early 2000s for the investigation of 5-HT_{2A} serotonin receptors in the mammalian brain.[1,2] The addition of the 2-methoxybenzyl enhances the potency of the phenethylamine. As a result, NBOMe is active at a low sub-milligram dose.[2] Currently, there is no approved medical use for NBOMe drugs nor are they approved by the U.S. Food and Drug Administration for human consumption.[1]

The published literature concerning the pharmacokinetics and pharmacology of NBOMe in humans is limited. One recent article reviewed the mechanism of action and pharmacological and toxicological effects of 25I-NBOMe.[3] The NBOMe drugs are potent 5-HT_{2A} serotonin receptor agonists.[4] This receptor is closely linked with complex behaviors such as working memory, cognitive processes, and affective disorders such as depression and schizophrenia. It also mediates the primary effects of hallucinatory drugs.[5] Hallucinatory effects are seen with 25I-NBOMe in doses as low as 50 to 250 μg, which is slightly less potent than lysergic acid diethylamine (LSD). Effects appear within 15 to 120 minutes of use and plateau in 2 to 4 hours. The duration of action depends on the route of administration: 4 to 6 hours by nasal insufflation and 6 to 10 hours with sublingual or buccal administration.[6]

The past several years have seen increasing public interest in these NBOMe drugs. A Google Trends search of several phrases (25I-NBOMe and 25I) associated with NBOMe drugs shows an increase in Google searches beginning in mid- to late-2011 (Figure 1). From November 2011 to June 2013, the System to Retrieve

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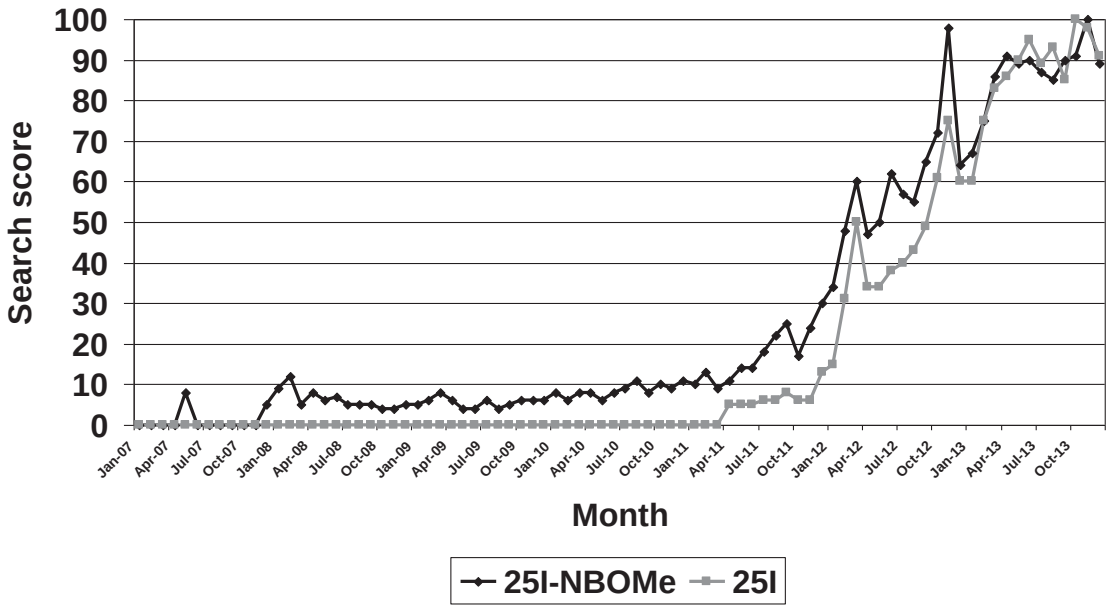

FIGURE 1. Results of Google Trends analysis of Google searches for NBOMe designer drugs in United States.

Information from Drug Evidence (STRIDE), which includes data on analyzed Drug Enforcement Administration (DEA) laboratory samples, reported 54 exhibits involving 27 cases for 25I-NBOMe, 27 exhibits involving 12 cases for 25C-NBOMe, and 4 exhibits involving 4 cases for 25B-NBOMe.[1] From June 2011 to June 2013, the National Forensic Laboratory Information System (NFLIS), a database of scientifically verified samples in state and local forensic laboratories, registered 959 reports involving these NBOMe drugs (25I-NBOMe: 795 reports; 25C-NBOMe: 144 reports; 25B-NBOMe: 20 reports) across 35 states. No instances of these NBOMe drugs were reported in NFLIS prior to June 2011.[1] In addition, the number of reports has increased in each of the past five quarters where data are complete.[1]

NBOMe drugs may be used for their hallucinogenic properties; they are reported to produce euphoria, hallucinations, empathic feelings, change in consciousness, and unusual body sensations.[4,7,8] These drugs can be obtained through the Internet, often being sold as a "research chemical," or from individual dealers.[1,2,4,9,10] They are sold under various names, such as N-bomb, Smiles, Solaris, and Cimbi. NBOMe drugs are available in powder, liquid, blotter paper, and food-laced forms.[1,2,4] They are taken through nasal insufflation, ingestion, or injection.[1,2,9,11] These drugs may be marketed to users as other hallucinogens such as LSD, resulting in users unknowingly taking NBOMe drugs.[1,4]

Adverse exposures to NBOMe drugs have been reported from hospital emergency departments and medical examiners.[4,9,11] The patients are often men ranging in age from adolescence to their 20s.[4,7,9–17] These drugs have been reported to have serotonergic and sympathomimetic adverse health effects, including tachycardia, hypertension, agitation, aggression, hallucinations, seizures, nausea, insomnia, paranoia, hyperpyrexia, clonus, elevated white cell count, elevated creatine kinase, hyperglycemia metabolic acidosis, rhabdomyolysis, and renal failure.[1,7,9–11,13,14,16,17] Users may become violent.[10] Several deaths implicating NBOMe drugs have been reported in various states, including Texas.[1,2,7,10,12,15]

On November 15, 2013, the DEA issued an order to temporarily schedule 25I-NBOMe,

25C-NBOMe, and 25B-NBOMe in schedule 1 of the Controlled Substances Act (CSA).[1]

Much of the literature on adverse exposures to NBOMe drugs consists of case reports and small case series. In these reports, the diagnosis often is presumptive because a specific history is not provided by the patient and laboratory testing is not obtained. In the United States, poison centers are telephone consultation services that assist in the management of potentially adverse substances, including designer drugs.[18] The objective of this investigation was to describe NBOMe exposures reported to a large poison center network.

METHODS

The source of data for this study was the Texas Poison Center Network (TPCN), a system of six poison centers that together service the entire state, a population currently greater than 25 million. When a TPCN agent receives a call about an exposure, they obtain details about the exposure (e.g., substance involved, dose, exposure route, patient demographics, and circumstances of the exposure). The agent also determines what, if any, adverse clinical effects have occurred and anything about the patients current state of health (e.g., vital signs, medical history), other circumstances (e.g., family situation), or current treatments that might affect the management of the patient. From this information, the agent determines a course of management (treatment) to recommend for the patient. If the patient is not already at or en route to a healthcare facility at the time of the initial call, the TPCN agent will determine whether to recommend that the patient go to a healthcare facility or other healthcare provider or to suggest the patient be managed outside of a healthcare setting. Depending on the substance involved, the anticipated severity of the outcome, or other circumstances of the exposure, the agent may make follow-up calls until they have decided that the patient should no longer be followed. In these follow-up calls, the agent may ask for the patient's current vital signs and symptoms and any changes in the patient's status or management that have occurred. It should be noted that is not always possible to collect all of these items of information or to follow a patient as long as the agent would like. Moreover, the TPCN agent usually only has access to information on the patient provided to them over the telephone. The six poison centers all use a common electronic database to collect the demographic and clinical information on the calls. The data fields, their format, and allowable field options/codes were standardized by the American Association of Poison Control Centers.[18]

Cases included were all NBOMe exposures reported to Texas poison centers during January 1, 2012, to December 31, 2013. (A search indicated that no such exposures had been received prior to 2012.) Calls received from outside of Texas were excluded. Exposures involving other substances in addition to the NBOMe and patients not followed to a final medical outcome were included. The distribution of cases was determined for year, type of NBOMe drug, patient age and gender, exposure route, circumstances of (reason for) the exposure, exposure site, management site, medical outcome, specific adverse clinical effects, and specific treatments. The institutional review board of the Texas Department of State Health Services considers this investigation exempt from ethical review.

RESULTS

Twenty-five total cases were identified, 8 in 2012 and 17 in 2013. Nineteen (76%) of the exposures were reported to have involved 25I-NBOMe, 3 (12%) involved 25C-NBOMe, and 3 (12%) involved an unknown type of NBOMe; no cases of 25B-NBOMe were reported. Mean patient age was 17 years (range, 14–25 years); 21 (84%) patients were aged between 14 and 19 years. Twenty-two (88%) patients were men and 3 (12%) were women.

The exposure route was ingestion alone (n = 18, 72%), inhalation alone (n = 3, 12%), ingestion and inhalation (n = 1, 4%), and unknown route (n = 3, 12%). Twenty-three

(92%) of the exposures were reported to have occurred due to intentional abuse, 1 (4%) was a suspected attempted suicide, and 1 (4%) was due to contamination or tampering. Eighteen (72%) exposures occurred at the patient's own residence, 3 (12%) in a public area, 2 (8%) in a school, and 2 (8%) at an unknown location.

Twenty-one (84%) did not involve other substances. Of the remaining four, one each were also reported to involve alcohol, marijuana, marijuana and alprazolam, and mushrooms and synthetic cathinone ("bath salts"). Eighteen (72%) of the patients were already at or en route to a healthcare facility when the poison center was contacted; the other seven (28%) were referred to a healthcare facility by the poison center. The distribution by medical outcome was no effect (n = 1, 4%), minor effect (n = 3, 12%), moderate effect (n = 13, 52%), major effect (n = 3, 12%), unable to follow but judged as potentially toxic (n = 3, 12%), and death (n = 2, 8%).

Table 1 presents the adverse clinical effects reported in the exposures. Most of the clinical effects involved the cardiovascular and neurological systems. The most common clinical effects were tachycardia (52%), agitation (48%), hallucinations (32%), hypertension (32%), confusion (24%), and mydriasis (20%). The most frequently reported treatments were intravenous fluids (68%) and benzodiazepines (52%) (Table 2).

Table 1. Adverse Clinical Effects Among NBOMe Exposures Reported to the Texas Poison Center Network During 2012–2013

Clinical effect	Number	Percent total
Cardiovascular		
Asystole	2	8
Cardiac arrest	1	4
Chest pain	1	4
Conduction disturbance	1	4
Dysrhythmia	1	4
Hypertension	8	32
Hypotension	2	8
Tachycardia	13	52
Dermal		
Erythema/flushed	2	8
Gastrointestinal		
Vomiting	1	4
Neurological		
Agitation/irritability	12	48
Coma	1	4
Confusion	6	24
Drowsiness/lethargy	4	16
Hallucination/delusions	8	32
Muscle rigidity	1	4
Seizure	1	4
Tremor	1	4
Ocular		
Mydriasis	5	20
Renal		
Urine color change	1	4
Respiratory		
Cyanosis	1	4
Hypervenilaton/tachypnea	1	4
Respiratory arrest	1	4
X-ray findings	1	4
Miscellaneous		
Creatine phosphokinase elevated	1	4
Diaphoresis	1	4
Electrolyte abnormality	2	8
Fever/hyperthermia	3	12
Pain	1	4
Other (unspecified)	4	16
Total	25	100

DISCUSSION

In this study of 25 NBOMe exposures reported to Texas poison centers, no exposures were reported to prior to 2012 and the number more than doubled between 2012 and 2013. This is consistent with a Google Trends search, which showed that the rate of Google searches in the United States involving several terms associated with NBOMe drugs were relatively rare prior to mid- to late-2011, when the rates began to increase (Figure 1). In addition, no NBOMe drugs were reported in the NFLIS prior to June 2011, and the number of reports has increased

Table 2. Treatments Among NBOMe Exposures Reported to the Texas Poison Center Network During 2012–2013

Treatment	Number	Percent total
Antiarrhythmic	1	4
Antiemetic	1	4
Antihistamine	1	4
Benzodiazepine	13	52
Cardiopulmonary resuscitation	2	8
Fluids IV	17	68
Intubation	3	12
Naloxone	1	4
Oxygen	4	16.7
Sedation (other)	2	8
Ventilator	1	4
Other (unspecified)	6	24
Total	25	100

in each of the last five quarters where data are complete.[1]

Among those cases where the specific type of NBOMe was mentioned, the majority were 25I-NBOMe, followed by 25C-NBOMe, with no cases of 25B-NBOMe mentioned. In both the STRIDE and NFLIS laboratory samples, 25I-NBOMe was found most frequently, followed by 25C-NBOMe, with 25B-NBOMe least common.[1]

The majority of patients were male. Eighty-four percent were adolescents, whereas the remainder was between ages 20 and 25 years. This demographic pattern was also found in the NBOMe case reports and case series reported in the literature.[4,7,9–17] Most of the exposures occurred by ingestion, followed by inhalation, with no instances of injection reported. Almost all of the exposures were for intentional abuse. Most of the exposures occurred at the patient's own residence, with the next common site being a public area. Similarly, of the 29 2C series phenethylamine exposures reported to Texas poison centers during 2005-2011, none of which were reported to be NBOMe, 86% of the exposures occurred by ingestion and 10% by inhalation.[19] Moreover, the 2C series phenethylamine exposures most frequently occurred at the patient's own residence followed by a public area.[19]

Almost three quarters of the patients were already at or en route to a healthcare facility when the poison center was contacted; the remainder was referred to a healthcare facility by the poison center. The majority of exposures were known or expected to result in serious outcomes; the patient died in two of the exposures, although NBOMe may not have necessarily have caused the death. This pattern was similar to that observed among the 2C series phenethylamine exposures reported in Texas.[19]

The most frequently reported adverse clinical effects—tachycardia, agitation, hallucinations, and hypertension—had been reported in the literature.[1,7,9–11,13,14,16,17] These adverse effects also were reported among the 2C series phenethylamine exposures in Texas,[19] although the rates of many of these adverse effects tended to be higher among the NBOMe exposures. Likewise, the most commonly reported treatments for NBOME exposures were also the most frequently reported treatments for 2C series phenethylamine exposures,[19] although the rates were mostly higher among the NBOMe exposures.

This study is subject to various limitations. NBOMe exposure was based on reports by the caller and not independently confirmed by toxicological testing. Considering that the substances the patients thought they had taken might actually have been mixed with other substances or been another substance entirely,[1,4] some of the exposures included in this investigation might not actually have involved an NBOMe drug. In addition, reporting of NBOMe exposures to Texas poison centers is voluntary. As a result, those exposures that were reported might not be representative of all such exposures that occurred in the state. Furthermore, there were only 25 cases included in this study. However, these were more cases than what have been included in most the other studies, and the current analysis might serve as impetus for investigations using larger data sets.

The majority of NBOMe exposures reported to Texas poison centers involved men; the patients were all adolescents or young adults. Most of exposures occurred by inhalation. All of the exposures required management by healthcare facilities. The majority were known or expected to have serious outcomes.

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