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Review Article

Clinical and Toxicological Profile of NBOMes: A Systematic Review

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Background: *NBOMes are a new class of potent hallucinogens widely present in illicit drugs. Little is known about this class of drugs, regarding its detection and clinical manifestations of intoxication.* **Objective:** *This study aims to enhance care involving NBOMes by reviewing the literature on their clinical manifestations and laboratory detection.* **Methods:** *A systematic review was performed on the clinical manifestations and laboratory tests of NBOMEs ingestion. Embase, Pubmed, PsycINFO, and Cochrane databases were employed in this analysis.* **Results:** *Forty-five articles met the inclusion criteria out of the 2814 nonduplicated studies on the theme. Seventy case reports of intoxication were found in the analyzed articles (64.3% were men and 11.4% were women, mean age of 22.5). The technique most employed for NBOMes identification was chromatography of blood, urine, and oral fluids. Moreover, the studies identified 13 chemical structures different from the NBOMes on their toxicological analyses. According to these studies, most of these drugs were ingested orally—nasal use was the second preferred administration route, followed by intravenous administration.* **Conclusion:** *Better identification of the clinical manifestations and laboratory profile of NBOMes is crucial to the recognition of intoxication as well as to its effective treatment.*

(Psychosomatics 2018; ■:1–10)

Key words: designer drugs, NBOMes, hallucinogens, clinical and laboratorial.

INTRODUCTION

New psychoactive substances have arrived in the last few years, creating public health challenges for regulatory agencies.[1] In 2012, more than 250 new drugs were developed, and in 2015 this number doubled, which makes management of intoxication, challenging.[2]

Among the new psychoactive substances, is N-benzylmethoxy, better known as NBOMes.[3] The ingestion of these substances has most often been reported in young male adults, these drugs can be easily bought online.[4,5] NBOMes are derived from the 2C-X

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family of hallucinogenic phenethylamines and they are sold under different names as "designer drugs," "herbal highs," "synthetic drugs," "research chemicals," "legal highs," "smile," "synthetic lysergic acid," "Nbomb," "Acid," "25B," and "25C." They can be administered sublingually, buccally, or by insufflation[4,6,7]. As the NBOMes are often falsely sold as lysergic acid, users are mostly not aware of which substance is being ingested.[8]

Some studies describe psychiatric manifestations of intoxication by NBOMes (e.g., euphoria, panic attacks).[9–13] Its consumption can also increase risky behaviors (e.g., suicide attempts, unprotected sex with multiple partners).[14,15]

The toxicological profile involves the detection, identification, and quantification of the substance which allows for the establishment of a cause and effect relationship, thus helping the health professionals to choose the best clinical management for it.[16–19]

Because there are no experimental studies or quantitative studies of NBOMes, the potential harm and effects of these drugs remain unknown. The recent rise of this new class of drugs, its selling as lysergic acid, and its a online purchasing increases public health concerns. Thus, this study aims to review the literature on NBOMes, as well as the identification of their clinical manifestations.

METHODS

This review was based on methodologic PRISMA PROTOCOL.[20] The recent search for these papers was performed in March 2017 in 4 databases: Embase, Pubmed, PsycINFO, and Cochrane.

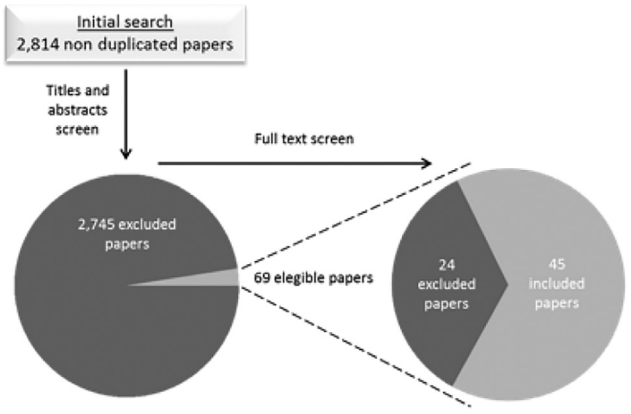
The strategy for doing this research was based on each of the databases found in Appendix 1.

The inclusion criteria were (1) papers that discuss clinical and laboratorial usage and/or identification of NBOMes, (2) papers written in English, Spanish, and Brazilian Portuguese, and (3) papers published in the last 10 years.

Research on animals as well as reviewed articles and letters to the editor was removed from the study.

Four researchers (A.Z. and M.R.; R.O. and M.P.) implemented the screening process from the papers found based on inclusion and exclusion criteria, as well as the extraction of data through a prearranged protocol.

FIGURE 1. Proportion of included and excluded papers



The initial search identified 2814 nonredundant publications, among which 45 met the inclusion criteria.

There were 70 case reports in the included papers (Figure 1). Figure 2 summarizes the search for recent papers and the methods employed.

APPENDIX I. SEARCH STRATEGIES

Results

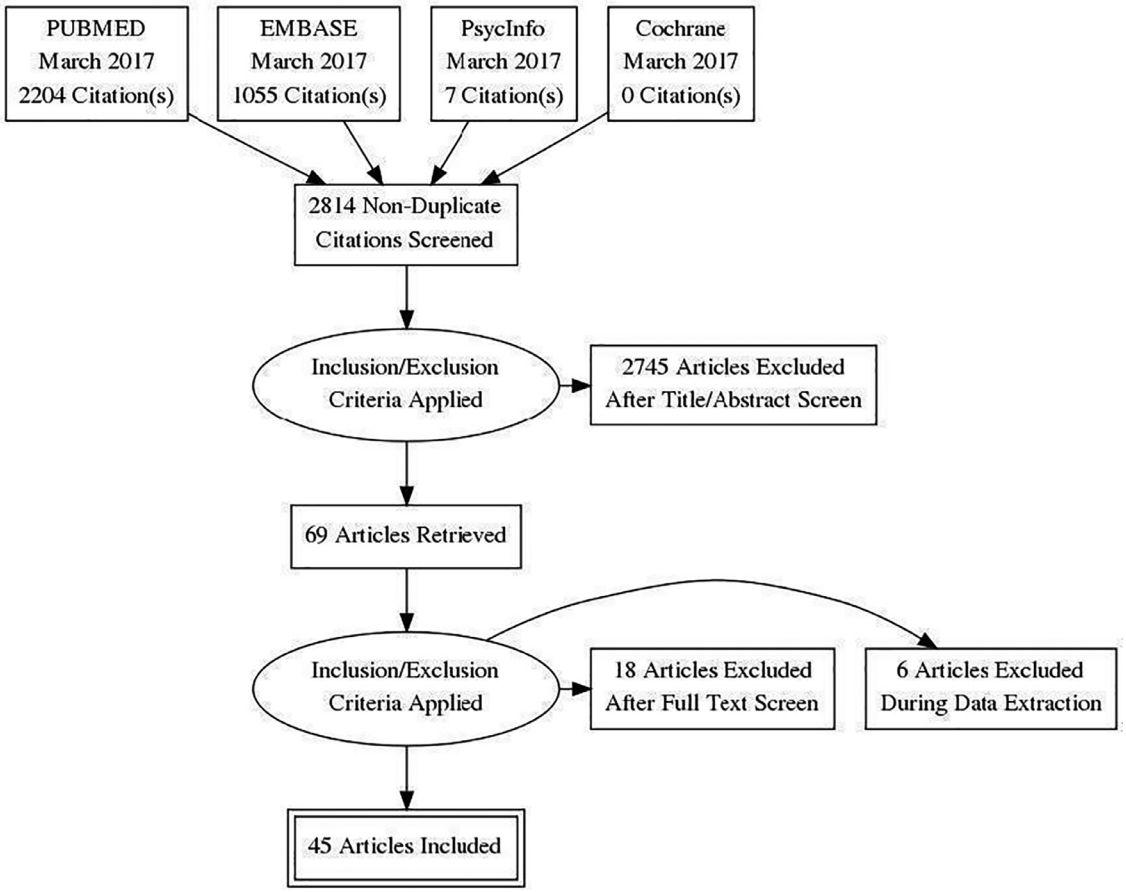
Studies Selected

The initial search in PUBMED, EMBASE, PsycInfo, and Cochrane databases identified 2814 nonduplicated publications among which 69 were considered eligible after screening of their titles and abstracts. Eighteen studies were excluded after the screening and 6 were excluded during data extraction. In the end, 45 studies met the inclusion criteria for this review. A summary of the published reports regarding laboratory and clinical data is presented in Table 1.

Clinical Aspects

This review found 70 cases of intoxication, among which 45 (64.3%) were male and 8 (11.4%) were female, with a mean age of 22.5 for both genders. In 17 cases (24.3%), no gender was reported (Table 1). Among the

FIGURE 2. The strategic search for papers and selections in the databases



reported cases, 7 (10%) died, whereas the rest were treated with benzodiazepines (in cases of convulsions) or needed intubation and mechanical ventilation due to extreme agitation. The most common administration route of the NBOMes was oral, followed by nasal and intravenous (IV) routes. In terms of clinical profile, the most common adverse signs and symptoms were convulsions, aggressive behavior, agitation, sudden movements, hallucinations, paranoia, panic, altered mental state, impaired speech, tachycardia, hypertonia, hypertension, hyperthermia, clonus, and mydriasis (Figure 3).

Toxicological Analysis

Forty-two of the articles presented analytic methodologies for the detection and quantification of the NBOMes and derived substances in biologic matrices (blood, serum, plasma, urine, brain, liver, bile, vitreous humor, and gastric content), apprehension, analytic patterns, or natural products. The analytic methods most employed in the analyses included liquid and gas chromatography mass spectrometry and variations (GC–MS, LC–MS, LC–MS/MS, LC–MS/QQQ, HPLC–MS/MS, UPLC–MS/MS, UPLC–HRTOF/MS, UPLC–ESI–MS, LC–QTOF/MS, UHPLC–QTOF/MS, HPLC–QTOF/MS, GC–HRMS, LC–HRMS, and LC–HRMS/MS), high-performance liquid chromatography diode array detection (HPLC–DAD), Fourier transform infrared spectroscopy, magnetic resonance spectroscopy, and attenuated total reflectance Fourier transform infrared spectroscopy. The most commonly identified substances were 25C-NBOMe, 25B-NBOMe, 2CC-NBOMe, 25I-NBOMe, 25H-NBOMe, 25D-NBOMe, 2CT-NBOMe, 25I-NBMD, 25G-NBOMe, NBOMe, 25E-NBOMe, 2C-N-NBOMe, and 25T2-NBOMe.

TABLE 1. Systematic Review Summary of NBOMe Clinical and Toxicological Profile

Author	N	Product consumed by user	Matrix/sample	Substance identified	Analytical technique/ quantitative results	RA	Patient characteristic	Effects	Management	Outcomes
Ameline et al., 2017	2	White creamy powder	Plasma	25I-NBOMe	UPLCMS/MS/37 and 72 ng/mL	Nasal	Males	Visual hallucinations and alteration of behavior	Clinical examination and supervision	Discharged from the hospital 5 hours later
Andrade et al., 2017	20	-	Blotter paper	25B NBOMe and 25I NBOMe	GC−MS	-	-	-	-	-
Arantes et al., 2017	-	-	Blotter paper	25I-NBOH	GC−MS/2 mg/mL	-	-	-	-	-
Botch-Jones et al., 2017	14	-	Blotter paper	NBOMe	HPLC−QTOF/MS	-	-	-	-	-
Pasin et al., 2017	-	-	-	2C-X, DOX2 and 25X-NBOMe derivatives	UPLC−QTOF−MS	-	-	-	-	-
Rajotte et al., 2017	1	Blotter paper	Urine	25C-NBOMe	GC/MS	Oral	20 y.o. female	Mumbled and irrational speech, mental confusion	-	-
Wiergowski et al., 2017	3	-	Blood	25B-NBOMe and 4-CMC	HPLC−QTOF−MS, UPLC−MS−MS/ 17.5−6619 ng/mL (25B-NBOMe)	-	23 y.o. male/ 24 y.o. male	Aggressive, very agitated, ineffective verbal contact, convulsions, heavy breathing, and salivation	-	2 obits
Boumrah et al., 2016	-	-	-	25B-NBOMe	UHPLC−QTOF/MS	-	-	-	-	-
Caspar et al., 2016	-	-	Standardt + urine	25B-NBOMe and 25C-NBOMe	LC−HRMS/MS	-	-	-	-	
Ezquiaga et al., 2016	56	-	-	25I-NBOMe	GC−MS	-	-	-	-	-
Gee et al., 2016	10	White powder	Plasma and urine	25B-NBOMe	LC−MS/MS/0.7−10.1 ng/mL	Nasal and Oral	21−30 y.o. male/ 26 y.o. female	Hallucinations, violent agitation, tachycardia, hypertension, and hyperthermia	The majority (7/10) required sedation with benzodiazepines.	-
Kaizaki-Mitsumoto et al., 2016	22	Unknown liquid/Powder	-	25H-NBOMe, 25D-NBOMe, 25E-NBOMe, 25I-NBOMe, ADB-CHIMINACA, 5F-ADB, 25I-NBMD, RH34, escaline, 5-DBFPV, 3,4-MDPHP, 3,4-dime-thyl-NEB, 3, 4-dimethyl-a-ethylamino-pentiophenone, 3, 4-dimethyl-a-PVP, 4F-a-ethylaminopentiophe-none, bk-IVP, bk-IBP, MMXE and butane-1, 4-diol	GC/HRMS, NMR	-	-	-	-	-
Kristofic et al., 2016	3	-	Blood and urine	25C-NBOMe, 2C-C	LC−MS/MS/ 2.07−27.43 ng/mL (25C-NBOMe), 0.12−0.38 ng/mL (2C-C)	-	23, 24, and 30 y.o male	Agitated and combative, respiratory difficulties	-	-
Lum et al., 2016	-	Blotter paper	-	25C-NBOMe, 25I-NBOMe	GC−MS	-	-	-	-	-
Wohlfarth et al., 2016	2	-	Urine	25B-NBOMe e 25I-NBOMe	LC−HRMS	-	-	-	-	-
Adamowicz and Tokarczyk, 2015	20	-	Blood	cathinones, phenethyl-amines, tryptamines, piperazines, piperidines, synthetic cannabinoids, arylalkylamines, arylcy-clohexylamines and aminoindanes	LC−MS/MS	-	-	-	-	-

(*continued on next page*)

TABLE 1. (*continued*)

Author	N	Product consumed by user	Matrix/sample	Substance identified	Analytical technique/ quantitative results	RA	Patient characteristic	Effects	Management	Outcomes
Andreasen et al., 2015	1	Capsule	Blood, urine, vitreous humor, liver and gastric content	25C-NBOMe	UPLC−HRTOF−MS/ blood (0.60 mcg/kg), urine (2.93 mcg/kg), vitreous humor (0.33 mcg/kg), liver (0.82 mcg/kg), and gastric content (0.32 mcg total)	Nasal	22 y.o. male	Incoherent, hallucination, jerky movements, clenched jaw, and unconsciousness	Clinical examination, intubation, treatment with benzodiazepines, mechanic ventilation, blood transfusion, coma induced in the intensive care unit.	Death due to multi-organ failure and clinical picture consistent with serotonin syndrome
Brandt et al., 2015	18	-	Analytical standards	25I-NB2OMe, 25I-NB3OMe, 25I-NB4OMe, 25I-NB2B,25I-NB3B and 25I-NB4B	GC−MS, HPLC−DAD, UPLC−MS/MS, UHPLC/QTOF−MS/MS	-	-	-	-	-
Caspar et al., 2015	1	-	Urine	25I-NBOMe	GC−MS, LC−MS, LC−HRMS/MS	-	-	-	-	-
Coelho et al., 2015	77	-	Blotter paper	25B-NBOMe, 25C-NBOMe and 25I-NBOMe	ATRFTIR	-	-	-	-	-
Hieger et al., 2015	10	-	Serum	25I-NBOMe	HPLC−MS/MS/ 0.76 ng/mL.	Nasal and oral	14−20 y.o. male and female	Tachycardia, hypertension, hyperglycemia, agitation and hallucinations, status epilepticus, multiple discrete intraparenchymal cerebral hemorrhages, and acute kidney injury	Six patients were admitted to the ICU, 2 were treated in the ED, and one each was admitted to psychiatry or managed in a clinical decision unit. Three patients required emergent intubation, and all admitted patients (7/10) were given intravenous benzodiazepines for sedation	All were discharged after treatment.
Isbister et al., 2015	1	Blotter paper	Blood	25B-NBOMe	HPLC−MS/MS/0.089 μg/L	Oral	16 y.o. male	Seizures and coma	Treatment with benzodiazepines, intubation, mechanical ventilation at the intensive care unit	-
Kueppers et al., 2015	1	White powder	Blood	25I-NBOMe	LC−QTOF/MS, LC−MS/QQQ	Nasal	23 y.o. female	Strange and aggressive behavior, confusing speech, agitation, seizures, vomit followed by collapse and death	Bystanders and ambulance staff unsuccessfully attempted cardiopulmonary resuscitation	Obit
Laskowiski et al., 2015	2	Blotter paper	Serum and urine	25C-NBOMe and 25B-NBOMe	GC/MS, HPLC/MS/MS/ 0.025−1.0 ng/mL (25C-NBOMe) and 0.51−1.2 ng/mL (25B-NBOMe)	Oral	16 y.o. female/ 15 y.o. male	Increased muscle tone in all extremities, altered mental status, garbled speech, visual hallucinations, tonic-clonic seizure, dilated and reactive pupils, diaphoresis, dry mucous membranes, and generalized muscle rigidity	Seizures managed with benzodiazepines	Discharged hospital on day 8 (female) and within 24 h (male)

(*continued on next page*)

TABLE 1. (*continued*)

Author	N	Product consumed by user	Matrix/sample	Substance identified	Analytical technique/ quantitative results	RA	Patient characteristic	Effects	Management	Outcomes
Lowe et al., 2015	1	Mushrooms and unknown clear liquid	Blood and urine	25I-NBOMe, 25C-NBOMe, 25H-NBOMe and Psilocin	LC−MS/MS/ 0.076 ng/mL (25I-NBOMe)	Oral	15 y.o. male	Vomiting, convulsion, fainting, acute renal failure, liver failure, multisystem organ failure and cardiopulmonary arrest.	-	Death 3 days after drug ingestion
Poklis et al., 2015a	2	-	Urine	25I-NBOMe	UPLC−MS/MS	-	20 y.o. male/ 28 y.o. male	-	-	-
Poklis et al., 2015b	-	Blotter paper	-	25I-NBOMe, 25C-NBOMe, 25B-NBOMe, 25H-NBOMe and 25D-NBOMe	HPLC−MS/MS	-	-	-	-	-
Shanks et al., 2015	2	Blotter paper	Blood and urine	25B-NBOMe and 25I-NBOMe	UPLC−MS/MS/ 1.59 ng/mL (25B-NBOMe), 19.8 ng/mL (25I-NBOMe)	Oral	18 y.o. male/ 16 y.o. male	Destructive behavior, followed by collapse and unconsciousness	-	Obit
Tarpgaard et al., 2015	-	-	-	-	-	-	-	Generalized seizures	Intubation	-
Uchiyama et al., 2015	-	-	Chemical-type or herbal-type products	25H-NBOMe, 25B-NBOMe, 2C-N-NBOMe	UPLC−ESI−MS, GC−MS	-	-	-	-	-
Yoshida et al., 2015	1	Blotter paper	Plasma	NBOMe	LC−MS/MS	Oral	20 y.o. male	Violent behavior, convulsion, stupor, systolic hypotension, tachycardia, tachypnea, hyperthermia, mydriasis, sluggish light reflex and hyperthermia	-	Obit
Armenian et al., 2014	3	Blotter paper	Blotter paper	2C-C-NBOMe and 2C-I-NBOMe	LC−QTOF/MS	Oral	24 y.o. female	Agitation, confusion, paranoia, dilated pupils, moist and hot skin, amnesia, tachycardia, tachypnea and agitated delirium	Treatment with benzodiazepines	-
Johnson et al., 2014	6	-	Blood, plasma and urine	25B-NBOMe, 25C-NBOMe, 25D-NBOMe, 25H-NBOMe, 25I-NBOMe, and 25T2-NBOMe	LC−MS/MS	-	-	-	-	-
Poklis et al., 2014a	-	-	Urine	25H-NBOMe, 2CC-NBOMe, 25I-NBF, 25D-NBOMe, 25B-NBOMe, 2CT-NBOMe, 25I-NBMD, 25G-NBOMe, and 25I-NBOMe.	HPLC−MS/MS	-	-	Tachycardia, hypertension, severe agitation and seizures	-	-
Soh and Elliott 2014	-	-	Blood and Plasma	4-MEC, MDAI, 5-MeO-DALT, 6-APB, MPA, 5-IAI, MDAT, 2-AI, AMT, 25C-NBOMe, AH-7921, 5-MAPB, methoxetamine	HPLC−DAD, LC/MS/MS, UHPLC−QTOF−MS	-	-	-	-	-

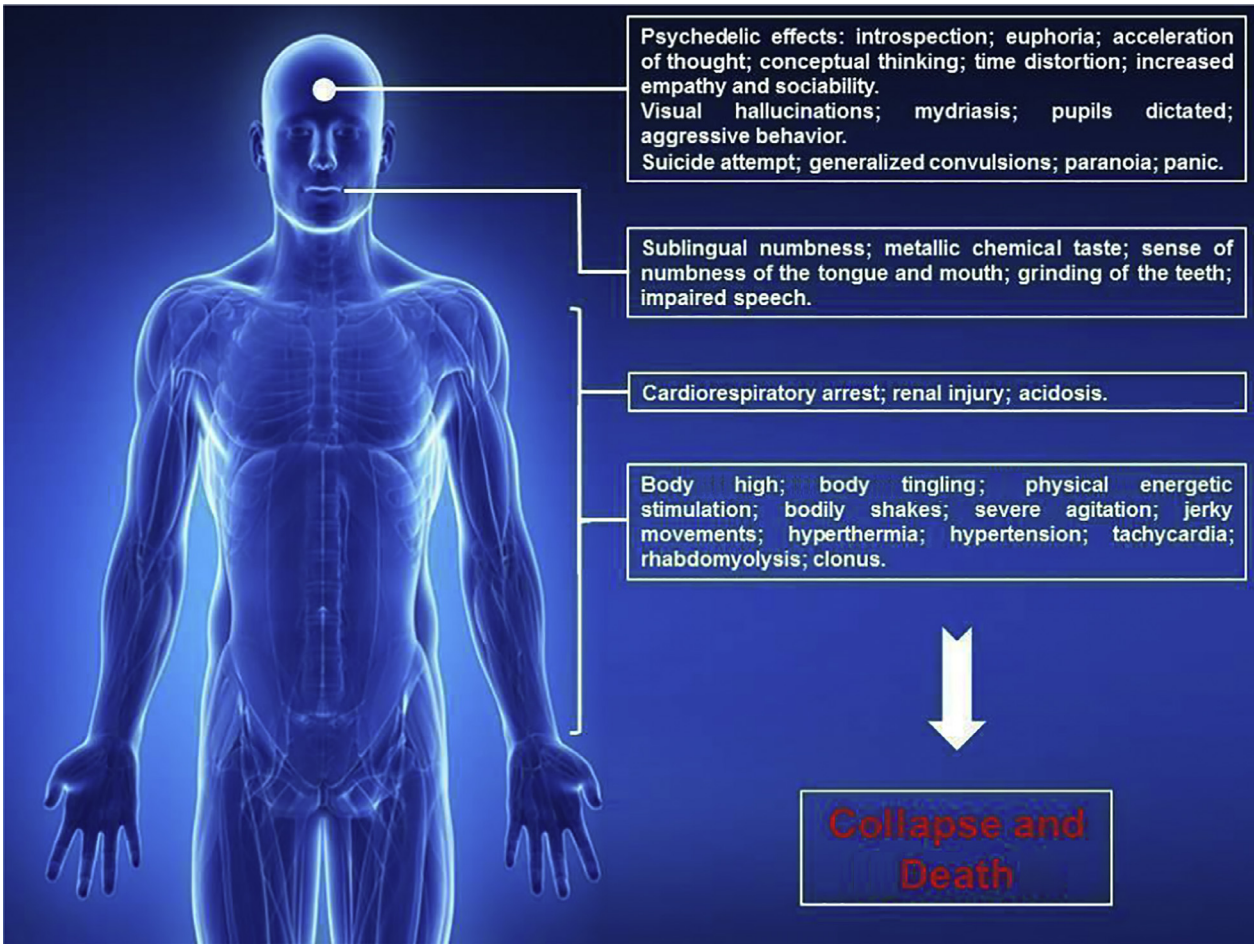
(*continued on next page*)

TABLE 1. (*continued*)

Author	N	Product consumed by user	Matrix/sample	Substance identified	Analytical technique/ quantitative results	RA	Patient characteristic	Effects	Management	Outcomes
Suzuki et al., 2014	1	Blotter paper	Blood	25I-NBOMe	34 pcg/mL	Oral	18 y.o. male	Euphoria, tachycardia, visual hallucinations, and panic. Attempted suicide to end the experience.	Surgery and outpatient psychiatric follow-up	-
Tang et al., 2014	2	Pill/packet of a drug	Urine	25C-NBOMe and 25B-NBOMe	LC−MS/MS	Oral	17 y.o. male/ 31 y.o. male	Confusion, agitation, convulsion, sweating, hyperthermia and pupils dilatation	Intubation and sedation with benzodiazepines	-
Hill et al., 2013	7	-	-	25I-NBOME	-	Nasal and IV	19−22 y.o. male	Tachycardia, hypertension, agitation, aggression, visual and auditory hallucination, seizures, hyperpyrexia, clonus, leukocytosis, elevated creatine kinase, metabolic, acidosis, respiratory failure, and acute kidney injury	Intensive care unit, treatment with benzodiazepines	Discharged after 15 h of observation
Poklis et al., 2013a	12	-	Serum	2CC-NBOMe e 25I-NBOMe	HPLC−MS/MS/250-2780 pg/mL (25I-NBOMe)	-	-	-	-	-
Poklis et al., 2013b	1	Blotter paper	Blood, brain, liver and bile	25I-NBOMe	HPLC−MS/MS	Oral	19 y.o. male	Bizarre and paranoid behavior	-	Death due to unknown fall
Poklis et al., 2013c	1	-	Serum and urine	25B-NBOMe	HPLC−MS/MS	-	19 y.o. male	Jerking movements and seizures	Intubation and seizure control with sedation	-
Prabhakar 2013	1	-	-	25I-NBOMe	-	-	17 y.o. male	Aggressive behavior, hallucinations	-	-
Richeval et al., 2013	1	Pink liquid	Serum and urine	25I-NBOMe	LC−HRMS, LC−MS/MS/0.9 ug/L	Nasal	29 y.o. male	Acute unconsciousness, hypertonia, tremors, partial seizures with secondary generalization, bilateral and reactive mydriasis, tachycardia, hypertension, hyperthermia and profuse sweating	-	-
Rose et al., 2013	1	-	Serum	25I-NBOMe	LC−MS/MS	-	18 y.o. male	Severe agitation, hallucination, tachycardia and hypertension	Sedation with benzodiazepines	-
Zuba et al., 2013	-	-	Blotter paper	25C-NBOMe	GC−MS, LC−QTOF−MS, FTIR, NMR	-	-	-	-	-

ATRFTIR = attenuated total reflectance Fourier transform infrared spectroscopy; FTIR = Fourier transform infrared spectroscopy; GC/HRMS = gas chromatography coupled to mass spectrometry; IV = intravenous; LC−HRMS/MS = liquid chromatography−high-resolution tandem mass spectrometry; LC−MS/QQQ = liquid chromatography−mass spectrometry triple quadrupole; LC−QTOF/MS = liquid chromatography quadrupole time of flight mass spectrometry; NMR = nuclear magnetic resonance spectroscopy; RA = route of administration; UHPLC−QTOF/MS/MS = ultrahigh-performance liquid chromatography quadrupole time of flight mass spectrometry; UPLC−HRTOF−MS = ultraperformance liquid chromatography with high-resolution time-of-flight mass spectrometry; UPLC−MS/MS = ultraperformance liquid chromatography tandem mass spectrometry.

FIGURE 3. Infographic of NBOMe clinical effects



DISCUSSION

This study clarifies the toxicological detection and clinical manifestations of intoxication with NBOMes. Currently, the greatest problem linked with NBOMes is the lack of knowledge about their adverse effects—there are scarce directives to these health care professionals on the clinical management in intoxication. Through a literature review, we aimed to enhance knowledge about the clinical manifestations of NBOMes and the toxicological profile found in the detection of these substances, to better guide health care professionals.

Regarding the toxicological profile, our study demonstrated that blotter paper is the most common form found by the users of this class of substances, and that most of the analyses were performed in blood or in urine samples. Toxicological analyses involved liquid or gas chromatography and mass spectrometry. The identification through immunoassays is limited to several substances, and the increasing number of new substances of this class represents an analytic challenge.[18] Hyphenated techniques are considered to be the best alternatives for the analysis of new substances, nevertheless they are not always available in laboratories for routine analysis due to their high cost and high analytic training required for the analyst.

The clinical effects found in this study, such as psychomotor agitation, violent behavior, hallucination, paranoia, confusion, and chest pain, as well as tachycardia, hypertension, and hypotension, hyperthermia, and mydriasis can be explain by a

serotonergic syndrome associated with 25I-NBOMe, because it is a highly potent 5-HT_{2A} receptor agonist.[21,22] Cardiovascular, respiratory, vasoconstriction of the smooth muscle, increase in blood pressure, and bronchoconstriction are also important symptoms that arise after the use of 25I-NBOMes.[23] Currently, benzodiazepines are used to treat psychiatric symptoms and excessive agitation caused by these substances.[24] The clinical examination of these patients also shows respiratory and metabolic acidosis, hyperpotassemia, high levels of lactic acid, anuria, and renal insufficiency. These effects are similar to those reported in users of synthetic cathinones ("bath salts"), phencyclidine, 34-methylenedioxymethamphetamine, anticholinergics, cocaine, and other stimulants, where agitation and cardiovascular effects are prominent.[25] The data resulting from this review are also similar to the previous reports of toxicity by NBOMes.[26]

Data found in this review show deaths and hospitalizations as a consequence of the ingestion of 25I-NBOMes and their subclasses.

Taking into account the brief time on the illicit market, the evidence about NBOMes's adverse effects and deaths from the consumption of these substances represent a challenge to public health. Current scientific literature corroborates our findings, indicating the lethal dangers that NBOMes and similar drugs may cause to their users.[4,27,28] The purity and concentration of proscribed drugs synthetized and fabricated in an illicit manner are generally uncertain.

CONCLUSION

Clinical-laboratory alignment is essential to aid health care professionals during emergency care of patients with acute intoxication with hallucinogens. Future studies on these interactions and their long-term effects may guide treatment for addiction on these substances, as well as the creation of public policies for users of these substances.

Limitations: Meta-analysis studies provide results over the best available evidence, but in some subjects that have specific characteristics, they may not be applicable.

Conflict of Interest: The authors declare no conflicts of interest.

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