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Matthew Lipow
Drexel University College of Medicine, Philadelphia, PA

Syed Zane Kaleem
Drexel University College of Medicine, Philadelphia, PA

Eduardo Espiridion
Reading Hospital - Tower Health

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Review

NBOMe Toxicity and Fatalities: A Review of the Literature

Matthew I. Lipow[1], Syed Z. Kaleem[1], Eduardo D. Espiridion[2]

1. Drexel University College of Medicine, Philadelphia, PA, USA
2. Department of Psychiatry, Reading Hospital – Tower Health, West Reading, PA, USA

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ABSTRACT

INTRODUCTION: In the decade since the introduction of the novel synthetic hallucinogen NBOMe into the consumer market, this drug has become an increasingly prevalent, yet poorly understood cause of altered mental status (AMS) resulting in hospitalization.

METHODS: In this literature review, we conducted a PubMed query for mentions of NBOMe ingestion since Suzuki et al.'s publication of their 2015 review. Among English language publications published between October 2014 and June 8, 2021, were sixteen case reports and six case series detailing a total of 42 cases of NBOMe toxicity.

RESULTS: Notably, 26 (62%) patients experienced tachycardia, 22 (52%) had hypertension, 34 (81%) experienced hallucinations. Nine of 42 cases ended in fatality, including six cases of apparent direct NBOMe toxicity, one death by suicide, and two cases of fatalities from trauma after "excited delirium." At least seven individuals believed that they had purchased and consumed LSD.

CONCLUSION: This updated review of the literature underlines the high prevalence of fatality associated with NBOMe ingestion, as well as the need for increased knowledge among law enforcement and emergency medical providers of the toxidrome of NBOMe when responding to cases of AMS.

INTRODUCTION AND BACKGROUND

2-(4-iodo-2,5-dimethoxy-phenyl)-N-[(2-methoxyphenyl)methyl] ethanamine, or 25I-NBOMe, is a "2C" ring phenethylamine and full 5HT-2A agonist first described by German chemist Ralf Heim in 2003 in his search for novel compounds with activity at the 5HT-2A receptor[1]. Also called "Smiles," "N-Bombs," and "N-benzylmethoxy," recreational use of NBOMe as a hallucinogen was first documented in the early 2010s, infused in blotter paper for oral use or a powder for nasal insufflation[1].

NBOMe has been compared to lysergic acid diethylamide (LSD), as both drugs are 5HT-2A agonists and induce similarly altered sensorium; indeed, NBOMe is often sold as LSD[1]. Neither NBOMe nor LSD are tested for in routine urine drug screening. Multiple NBOMe variants have been discovered[1], and in 2013, three NBOMe compounds, 25I, 25C, and 25B, were first categorized under the US Controlled Substances Act as Schedule I compounds[2].

In their review of the literature through October 2014, Suzuki et al. identified 20 cases of NBOMe toxicity[3], with 17 cases involving males and an average age of 20.3 years. They note that NBOMe's toxidrome regularly includes "autonomic instability," with the majority of individuals experiencing tachycardia (85%) and hypertension (65%), and some experiencing fever (25%) or elevated creatine kinase (45%), indicative of rhabdomyolysis[3]. They argue that unlike LSD, which does not cause serotonin syndrome despite 5HT-2A agonism, these autonomic symptoms in NBOMe toxicity may represent a serotonin syndrome-like condition[3].

Correspondence to Matthew Lipow
matthew.lipow@gmail.com

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Among published cases, Suzuki et al. recorded three fatalities and eight intensive care unit admissions[3]. This is in direct contrast to LSD, for which there have been no documented fatal overdoses and "rarely reported" true suicide attempts[4,5].

In 2014, Lawn et al. performed a large anonymous online survey of NBOMe users, recording a peak psychoactive effect of two hours after oral ingestion and 45 minutes after nasal insufflation, with duration of activity lasting 3-13 hours[5].

Since the publication of Suzuki et al.'s systematic review, numerous published case reports and case series have expanded the present knowledge of NBOMe toxicity and management strategies. Here, we conduct an updated review of the literature detailing cases of NBOMe ingestion and toxidrome.

METHODS

A PubMed query for terms including "NBOMe," "N-bomb," "nbomb,"and "N-benzylmethoxy" revealed 160 publications between October 2014 and June 8, 2021. Among English language publications were sixteen case reports [6–21] (*Supplemental Table 1*) and six case series[22–27] (*Supplemental Table 2*) of NBOMe toxicity, encompassing a total of 44 patients. Two cases within an included case series were excluded due to lack of presentation characteristics beyond demographic information, leaving a total of 42 cases[25]. Extracted data included:

Demographics and characteristics of ingestion: age, sex, and country

Characteristics of ingestion: NBOMe variant, analytic confirmation, presence of other substance, and source of drug

Toxidrome: hallucinations, agitation, duration of altered mental status (AMS), seizure, tachycardia, hypertension, hyperthermia, diaphoresis, increased muscle tone or creatine kinase, additional information, and fatality.

Management: use of benzodiazepines, intubation, and intensive care unit (ICU) admission.

Table 1: Demographic and Purchase Characteristics

Average age	20.96	
Sex		
male	32	(76%)
female	10	(24%)
Country		
USA	21	
New Zealand	10	
Australia	3	
Singapore	1	
Austria	1	
Canada	1	
Denmark	1	
Germany	1	
Italy	1	
Poland	1	
U.K.	1	
Analytic confirmation	29	(69%)
Other substance	19	(45%)
Source/ Purchase characteristics		
Believed was LSD	9	(21%)
Purchased on internet	3	(7%)
Purchased at party	3	(7%)

RESULTS

In demographic information (*Table 1*), 32 patients (76%) were male, with an average age of 20.96 years. Toxidrome (*Table 2*) included tachycardia in 26 (62%) patients, while 22 (52%) had hypertension, and 11 (26%) had one or more seizures. 34 (81%) experienced hallucinations and 22 (52%) experienced agitation or aggression. Management (Table 2) included treatment with benzodiazepines in 31 cases (74%), and 13 individuals (31%) required ICU-level care.

Nine (21%) cases ended in fatality, with six appearing to result from direct NBOMe toxicity, including one case labeled as "serotonin syndrome"[6]. One fatality occurred by suicide, while two other patients

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Table 2: Toxidrome and Management

Hallucinations	34	(81%)
Agitation or aggression	22	(52%)
Seizure	11	(26%)
Tachycardia	26	(62%)
Hypertension	22	(52%)
Hyperthermia	6	(14%)
Diaphoresis	13	(31%)
Increased muscle tone	7	(17%)
Increased creatine kinase	5	(12%)
Fatality	9	(21%)
Use of benzodiazepines	31	(74%)
Intubation	13	(31%)
ICU admission	13	(31%)

attempted suicide without completion. One fatality occurred after reported "excited delirium and forcible restraint" by police[25], while another occurred after "blunt craniofacial trauma as a manifestation of excited delirium"[10].

Additional rare but notable observations included increased muscle tone in seven patients (17%) and significantly elevated creatine kinase (CK) indicative of rhabdomyolysis in five cases (12%). One patient experienced acute vasospastic limb ischemia[19].

It has been noted that NBOMe is regularly sold under the label of LSD; Suzuki et al. noted in their review that four individuals (20%) who consumed NBOMe believed that they had ingested LSD[3]. Our review of the literature revealed a continuation of this trend: at least nine patients (21%) believed that they had obtained and consumed LSD rather than NBOMe.

In all but one case detailing a timeline of AMS that did not end in fatality, AMS lasted less than 24 hours, the majority of AMS resolving in less than half that time. The exception occurred with one individual who experienced recurrent hallucinations over the course of 18 months[28].

DISCUSSION

Consistent with Suzuki et al.'s 2015 review[3], the majority of recent cases of NBOMe ingestion occur in young adult males, with average age of 20.96 years old. The prior documentation of autonomic instability remains prevalent, with most individuals experiencing tachycardia and hypertension. Most individuals (81%) likewise experienced AMS with hallucinations.

Although there is no point-of-care test for NBOMe, clinical suspicion for NBOMe ingestion may prompt off-site laboratory confirmation through high performance liquid chromatography mass spectrometry[3]. To represent a more accurate snapshot of the types of cases that may present to the emergency department, we did not exclude unconfirmed reports of NBOMe ingestion; many institutions may not have the resources to send away samples for confirmation, while other clinicians may deem a patient's report of ingestion as sufficient. Indeed, 29 of 42 (69%) cases were analytically confirmed, and 19 (45%) individuals ingested another substance(s) along with NBOMe. As a limitation of this review, some toxidromes were likely influenced by substances other than NBOMe.

Perhaps the most concerning finding among these 42 recent cases of NBOMe ingestion is the extremely high rate of fatality: nine of 42 (21%) cases ended in death. This represents an increase since Suzuki et al.'s documentation of 17% fatality among cases prior to 2014[3]. Indeed, 5 of the 9 fatalities appeared to have occurred from direct NBOMe intoxication. Combined with the finding that at least 16.7% of individuals believed they had consumed LSD, which has no documentation of death from toxicity, this represents a disturbing reality. Suzuki et al. warned that "users familiar with LSD may have a false sense of security when ingesting NBOMe inadvertently"[3]. This warning should be reinforced: individuals purchasing what they believe to be LSD likely experience a heightened risk of decompensation and death. Clinicians interacting with individuals experiencing AMS, especially in the context of hallucinogen use, must have increased clinical suspicion for NBOMe and its potentially fatal toxidrome. This is especially true for males in late adolescence/early adulthood who have a negative UDS, and absent or limited psychiatric history. It is important to note the possibility of a bias towards publishing cases with catastrophic or unexpected outcomes: therefore, the published literature may overrepresent the true frequency of attempted suicide and fatalities

after NBOMe ingestion. Indeed, this review only captures cases which have come to the attention of emergency or medical responders.

The labelling of NBOMe's toxidrome as "excited delirium" in two fatal cases[10,25] is alarming, especially given that one of these deaths occurred after forcible restraint by police[25]. The term "excited delirium" was described in a 2009 white paper by the American College of Emergency Medicine to characterize an "agitated and delirious state with autonomic dysregulation" that "for some…progresses to death"[29]. In the years since, the label has been used to justify, often post-mortem, the police restraint of agitated patients with ketamine[30]. However, the American Medical Association stands in clear opposition to this term, as does the American Psychiatric Association, which recently published a memo noting that it "lacks any clear diagnostic criteria"[30]. The finding of fatal restraint of an individual intoxicated with NBOMe and labeled as "excited delirium," underlies the need for increased awareness and sensitivity to the toxidrome of NBOMe in the criminal justice system and among law enforcement.

Other serotonergic agonists like LSD are noted in some persons to cause a Hallucinogen Persisting Perception Disorder (HPPD)[31]. Our review revealed one prior case of altered sensorium appearing >24 hours after use: a 16-year-old who presented with multiple periods of hallucinations and seizure in the months following NBOMe ingestion, culminating in an episode 18 months after ingestion of progressive left-sided weakness, ataxia, facial droop, executive dysfunction and seizure activity; MRI revealed bilateral leukoencephalopathy[11,28]. Given the brief time since the first synthesis of NBOMe, and the even shorter period of documented NBOMe consumption – a little over ten years – the long-term effects and clinical presentations of NBOMe remain to be understood. Therefore, the prevalence of HPPD-like symptoms remote in time from NBOMe ingestion warrants continued investigation.

Emergency clinicians and consult-liaison psychiatrists should have heightened suspicion for both recent and remote use of novel synthetic hallucinogens among patients presenting to the emergency department with AMS.

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Supplemental Table 1: Case Reports of NBOMe Ingestion

		Demographics			Characteristics of Ingestion				Toxidrome								Management	
Authors	Year	Age	Sex	Country	NBOMe Variant	Analyt. Conf.	Other subst.	Source	Hallucinations, Agitation	AMS Duration	Seizure	Tachycardia, HTN	Hyper-thermia	Diaphoresis	↑muscle tone, CK	Additional info	Fatality?	Benzo. admin.	Intubation, ICU admiss
Andreasen et al.	2015	22	M	Denmark	25C	Y	Amphetamine, THC	Internet	Y, Y	12 hrs (death at 12 hrs)	Y	Y, N (70/45)	Y (40)	Not reported	Y, 42670	"Died at the hospital at approximately 12h after ingestion, with preceding signs of serotonin toxicity"	Fatal serotonin toxicity	Y	Y, Y
Armenian and Gerona	2014	24	F	USA (Nevada)	25C, 25I	Y	Marijuana, wine	Believed "like acid": from person who got directly from supplier	Y, Y	<10hrs	N	Y, not reported	Not reported	Y	Not reported		N	Y	Not reported
Boulos et al.	2015	15	M	USA	25I	Not reported	Not reported; prior cannabis & EtOH	Believed to be LSD	N, Y	<24 hrs (not specified)	N	Not reported	Not reported	Not reported	Not reported	Extreme sadness + suicidal ideation after ingestion	Suicide attempt: self-inflicted stab wound	Not reported	Not reported
Brooks et al.	2017	17	M	UK	25G	N	Not reported	Purchased over the internet	Not reported	Not reported	Y	Y, N (97/76)	Y	Not reported	Not reported, 24253	"Severe respiratory and metabolic acidaemia"	N	Y	Y, Y
Byard RW et al.	2016	19	M	Australia	25B	Y	Ecstacy, MDPBP	Believed to be LSD	Y, Y	Unknown, ended in death (<24 hrs)	Not reported	Not reported	Not reported	Not reported	Not reported	"Death was due to blunt cranial trauma against a background of mixed drug toxicity" Death occurred in context of "excited delirium"	Fatal trauma	N	N, N
Creagh et al.	2018	16	M	USA	25I	Not reported	N	Not reported	Y, not reported	Intermittent in 18 mo after ingestion	Y	Not reported, Y at 18 mo	Not reported	Not reported	Not eported	N	N	Not reported	Y, Y
Hermanns-Clausen et al.	2017	42	M	Germany	25I	Y	EtOH	Accidental ingestion - son replaced analgesic syrup with ethanolic solution of 25I-NBOMe	Y, Y	<6hrs	N	N, N	N	Y	Not reported, unremarkable	Developed "auditory and somatic hallucinations, and complex visual hallucinations (particularly serious traffic accidents)"	N	Y	N,N
Isbister et al.	2015	16	M	Australia	25B	Y	Not reported	Believe to be LSD. Purchased from friend	Not reported	<24 hrs (unclear 2/2 intubation	Y	Not reported	Not reported	Not reported	Not reported	Acidosis	N	Y (medazolam)	Y, Not reported
Kueppers and Cooke	2015	23	F	Australia	25I, 25H, 25C	Y	EtOH, methylamphetamine, promethazine, THC	Believed to be "synthetic LSD"	Y, Y	Likely within 1-2 hours: ended with death	Y	Not reported	Not reported	Not reported	Not reported	Seizure followed by collapse and death	Fatal toxicity	N	N, N
Lowe LM et al.	2015	15	M	USA (Washington)	25I, 25C, 25H, 25C	Y	Mushrooms, THC, carboxy-THC	Sold by DJ at party	Not reported	<2 hrs (ended with death)	Y	Not reported	Not reported	Not reported	Not reported, 66000	Liver failure, coagulopathic w/DIC-like pres. Multi-system organ failure following cardiopulm arrest 3 days after ingestion	Fatal toxicity		Y
Morini et al.	2017	"teenager"	M	Italy	25C and 25H	Y	Marijuana	Purchased at party	"altered state of mind", Y	Hours	N	Not reported	Not reported	Not reported	Not reported	Acute suicidal ideation, jumped off bridge. Death by drowning	Suicide	Not reported	Not reported
Rajotte et al.	2017	20	F	Canada	25C	Y	Cocaine, marijuana, "antidepressant medication"	Not reported	AMS, N	Unclear end time	N	Y, N	N (34.8)	Not reported	N		N	Not reported	Not reported
Suzuki J et al.	2014	18	M	USA	25I	Y	marijuana	Believe to be LSD. Purchased from friend	Y, Y	11 hrs (~max)	N	Y, Y	Not reported	Not reported	Not reported, 0	Extreme anxiety: suicide attempt "as a way to end the experience." Stabbed self with scissors in neck & chest	Suicide attempt	Not reported	Not reported
Wadowski et al.	2019	30	M	Austria	25I, 25C, 25H, pentylon	Y	Amphetamine, buprenorphine, cotinine, and benzodiazepine	Purchased on internet.	Not reported	Not reported	Not reported	Not reported, Y	Not reported	Not reported	Not reported	Acute limb ischemia w/o thrombus Hx of Schizophrenia LMWH and IV alprostadil	N	Not reported	Not reported
Waldman W et al.	2018	20	M	Poland	25I	Y	None	Obtained at party	Not reported	Not reported	Y	N, N (hypotensive)	Y (up to 40°–41°C)	Not reported	Y, 516455	Called "Alice in Wonderland"	N	Not reported	Y, Y
Zygowiec et al.	2017	27	M	USA	25C	Y	Lisdexamphetamine	Not reported	Y, Y	4.5hrs	N	Y, Y	N	N	No myoclonus, not reported		N	Y	N, N

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Supplemental Table 2: Case Series of NBOMe Ingestion

			Demographics			Characteristics of Ingestion			Toxidrome								Management	
Authors	Year	# Cases	Age	Sex	Country	Analyt. Conf.	Other substance	Source	Hallucinations, Agitation	AMS Duration	Seizure	Tachycardia, HTN	Hyper-thermia	Diaphoresis	↑muscle tone, Creatine Kinase	Additional Info.	Fatality	Benzo. Manag.	Intubation, ICU admiss.
Gee et al.	2016	10			New Zealand	10/10	2/10	Not reported	10/10, 10/10		0/10	9/10, 7/10	3/10	9/10	3/10			7/10	1/10, 1/10
			24	M	New Zealand	Y	Carboxy-THC	Not reported	Y,Y	<9hrs	N	Y, Y	Y (to 38.5)	Y	Y, 18361	Patient was "running into walls and repeatedly head-butting concrete floor" Had inducible clonus	N	Y (+haloper-idol)	Y, Y
			21	M	New Zealand	Y	Not reported	Not reported	Y,Y	Unclear, though suggests behavior "managable" after hour	N	Y,Y	N	N	Y, not reported		N	Y	N, N
			22	M	New Zealand	Y	Not reported	Not reported	Y,Y	3 hr (cooperative enough to remove restraints)	N	Y, Y	Y (to 38)	Y	Not reported		N	Y	N, N
			26	M	New Zealand	Y	Not reported	Not reported	Y,Y	5 hrs	N	Y, Y	Y (to 38)	Y	Not reported		N	Y	N, N
			23	M	New Zealand	Y	Not reported	Not reported	Y,Y	7hrs	N	Not reported		Y	Not reported		N	Y (+ket-amine)	N, N
			42	M	New Zealand	Y	Not reported	Thought had taken "acid"	Y,Y	<13 hrs (d/c at 13 hrs)	N	Y, N		y	Y, not reported	Tremor, hyper-reflexia	N	Y	N, N
			30	M	New Zealand	Y	Alcohol	Not reported	Y,Y	5.5 hrs	N	Y, N		Y		Inducible clonus	N	Y	N, N
			30	M	New Zealand	Y	Not reported	Not reported	Y,Y	3.5 hrs after presentation	N	Y, Y	N (to 37.8)	Y		Inducible clonus	N	Y	N, N
			26	F	New Zealand	Y	Not reported	Not reported	Y,Y	<3 hrs	N	Y, Y		Y			N	N	N, N
			26	F	New Zealand	Y	Not reported	Not reported	Y,Y	<3 hrs	N	Y, Y		Y			N	N	N, N
Laskowski et al.	2015	2				2/2	1/2		2/2		2/2	2/2, 2/2	0/2	2/2	2/2, 2/2		0/2	2/2	Not report-ed, 2/2
			16	F	USA	Y	N		Y,Y	<24 hrs	Y	Y, Y	N	N	Y, 46906	Ankle clonus b/l	N	Y	Not reported, Y
			15	M	USA	Y	THC		Y,Y	<24 hrs (but > 8 hrs)	Y	Y, Y	N (to 99.8)	Y	Y, 429		N	Y	Not reported, Y
Kristofic et al.	2016	3 (excluded 2 which had only demographic data)																	
			23	M	USA	Y	N	Purchased bags labeled "LSD"	Not reported, Y	Unknown (appears to be short duration)	Not reported	Unknown	Unknown	Unknown	Not reported	Death via "25C-NBOMe toxicity temporally associated with excited delirium and forcible restraint"	Fatal police retraint w/"ex-cited delirium"	N	N, N
Chan et al.	2019	4 (1/4 with NBOMe ingestion)																	
			19	M	Singapore	Y	N	Purchased as "LSD"	Not reported, Y	Within hours	Not reported	Not reported	Not reported	Not reported	Not reported		Fatal toxicity	N	N
Hieger et al.	2015	10	17 (avg)	2F	USA	1/10	6 alone. 1 etha-nol, 1 DOET, 1 ketamine, one marijuana		5/10, 7/10	"Mean time to discharge was 14 hours (range, 2-36 hours) for uncomplicated patients. For more compli-cated cases, the mean time to discharge was 3 days (range, 2-5 days)."	2/10	9/10, 9/10	0/10	Not reported	Not reported	"One patient with seizures also had multiple discrete intraparenchymal cerebral hemorrhages and acute kidney injury"	All recovered	7/10	3/10, 6/10
Shanks et al.	2015	2			USA (Indiana)	2/2	1/2		Not reported, 2/2		Not reported	Not reported	Not reported	Not reported	Not reported		Two teen-age male deaths		
			18	M		Y	THC		Y, Y	"Short time" (likely within 1-2 hrs)						"Witness to collapse onto kitchen floor and became unresponsive" CoD: acute intoxication by 25B-NBOMe	Y		
			16	M		Y	N	Y,Y	<24 hrs (overnight)							Found unresponsive"acute intoxication by 25I-NBOMe	Y		