

# International Conference on New Drugs 2014 Rome, 14<sup>th</sup> May Clinical and Toxicological aspects



## *The clinical toxicity of PMA/PMMA and NBOMe compounds*

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NPIS is commissioned by Public Health England  
on behalf of UK Health Departments

- I have no financial interests or relations to declare

# A recent case - Reece

- Pulseless VT 200/min
- GCS 3/15
- No respiratory effort
- Temp 41.5°C
- Pupils fixed and dilated bilaterally
- Increased muscle tone
- Potassium 6.8
- Lactate 8.1
- Creatinine 261
- ALT 539
- PT 12
- Fibrinogen 3.7
- Hypoglycaemia 1.2

- Resuscitation & 5xDC cardioversion
  - Magnesium 2g iv
  - Calcium gluconate 10ml 10%
- Cooling
- Rapid sequence induction
  - Fentanyl/midazolam/rocuronium
- Dantrolene 2mg/kg
- Cyproheptadine 12mg ng
- Dextrose then Insulin

# Clinical course – multiorgan failure

- Disseminated intravascular coagulopathy
  - (PT 23, APTT 53, Plt 19, fibrinogen 2.1, D-Dimers 49789)
  - Managed with FFP and Platelet transfusion
- Rhabdomyolysis
  - (CK peak at 130764)
  - Managed with IVT and urinary alkalinisation
- Acute Renal Failure
  - CVVH
- Acute liver failure
  - Acetylcysteine
- Ventilator associated pneumonia

1 July 2013 Last updated at 16:36



## Peter Robinson calls drug-linked deaths

Northern Ireland's First Minister Peter Robinson has said "police need to act" following the deaths of eight people that could be linked to a lethal batch of drugs.

Police are investigating to establish whether those who died took a tablet that they thought was ecstasy.

It is understood five of the people who died are from east Belfast.

Mr Robinson said police needed to pursue the matter.

"It must be a massive concern to people, particularly beyond, that this kind of thing can happen," the member said.

"It indicates that the police cannot relax on these because it is well-known who is selling drugs in the area."

"It is well-known the outlets for the sale of drugs are in the area."

Over the past number of weeks, seven people died in the North West of Northern Ireland. They were all aged 18 to 25.

The health minister said he was "very concerned" linked to a lethal batch of drugs, although he said that this was the case.

12 July 2013 Last updated at 06:50



## Arrest over 'fake ecstasy' death in Alexandria

A man has been arrested in connection with the death of an 18-year-old who had taken fake ecstasy tablets.

The woman died in Alexandria, West Dunbartonshire, on Tuesday. She and three friends had taken green tablets with a Rolex Crown logo on them.

Similar tablets have been linked to the deaths of six other people in the west of Scotland in the past two months.

A 24-year-old man has been arrested over allegations he was concerned about the supply of controlled drugs.

He was detained in police custody, and is expected to appear at Dumfries Sheriff Court on Friday.

Police said the teenager had taken the tablets in Alexandria with three friends in the early hours of Tuesday.

The three men, aged 18, 21 and 25, were all admitted to hospital.

### Festival warning

Posters warning about the dangers of the tablets, which cause extreme temperatures, hallucinations and convulsions, have been put up at weekend's T in the Park music festival.

Extra doctors and medical supplies are also being taken to the festival. Balado in Perth and Kinross and leaflets have been handed out to festival-goers.



The girl and her friends had taken a Rolex Crown



HOME NEWS SPORT ENTERTAINMENT LIFESTYLE IN YOUR AREA

News > Scottish News > Drugs

By John Ferguson | 20 Aug 2013 00:01

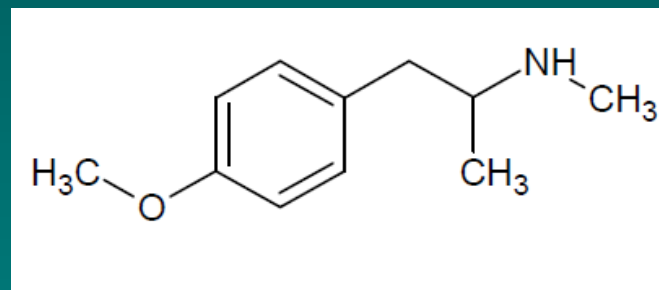
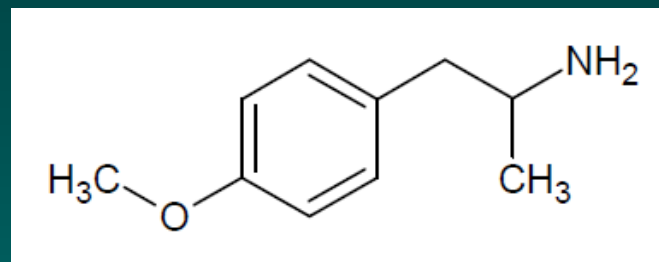
## Fears grow that 'Green Rolex' fake ecstasy tablets could have claimed eighth Scottish victim

THE 18-year-old died in his home village of Ecclefechan last week, and police and drugs experts have warned that tablets being sold in the area contain substances which are largely unknown and untested.

Tweet 1 Like 18 Send



- Analysis
  - **PMA** “Death”
  - **PMMA**
  - **MDMA\***
  - **BZP\***





## Case Report

Med J Aust. 2001 May 7;174(9):453-5.

# Poisoning with the recreational drug paramethoxyamphetamine ("death").

Ling LH, Marchant C, Buckley NA, Prior M, Irvine R

Department of Clinical

S. F.  
Depu

## Abstract

### OBJECTIVE:

To

### DESIGN:

Retrospective

### PARTICIPANTS:

metropolitan teaching

### RESULTS:

Patient

seizures (32%),

self-reported ecstasy

accompanied by

### CONCLUSIONS:

Hypoglycaemia and

"ecstasy", and

PMID: 11386590 [PubMed]

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### CRITICAL CARE

## Severe paramethoxyamphetamine poisoning

Yael Lurie<sup>1</sup>, Asher Gopher<sup>2</sup>

<sup>1</sup>Rambam Health Care Campus, Haifa

<sup>2</sup>Sheba Medical Center, Institute of

<sup>3</sup>Technion-Israel Institute of Technology

**Context.** Paramethoxyamphetamine (PMMA) is a synthetic stimulant drug. In Israel, PMMA is controlled under the Israeli Controlled Substance Act. **Objectives.** The Israeli national immunosassays and chromatographic analysis of PMMA. **Design.** Retrospective analysis of PMMA poisoning cases. **Setting.** Rambam Health Care Campus, Haifa. **Patients.** Patients with PMMA poisoning. **Results.** PMMA or PMA were detected, we screen for amphetamines, 32 were males, post mortem whole blood were detected in 17 (70.8%) fatal cathinone derivatives, cephedrine/p years, four had co-exposures to cocaine in July 2007, resulting in only three resulting in 24 fatalities, and the PMMA metabolism. Stimulant poison center co-operation is important.

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journal homepage: [www.elsevier.com/locate/forensiint](http://www.elsevier.com/locate/forensiint)



## The PMMA epidemic in Norway: Comparison of fatal and non-fatal intoxications

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### ARTICLE INFO

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Paramethoxyamphetamine  
PMMA  
Fatal intoxication  
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Blood concentration  
Forensic toxicology

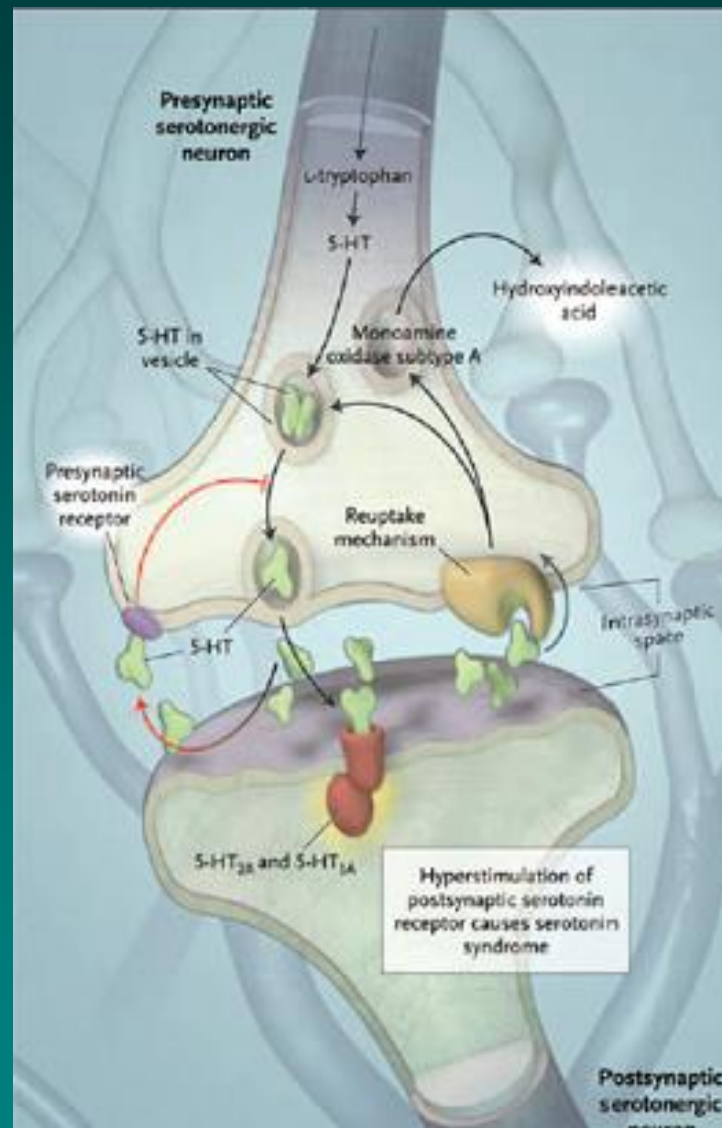
### ABSTRACT

During a 6 month period (July 2010–January 2011) we observed 12 fatal intoxications and 22 non-fatal cases related to the drug paramethoxymethamphetamine (PMMA) in Norway (4.8 mill inhabitants). This toxic designer drug, also known as "Death", is occasionally found in street drugs offered as "ecstasy" or "amphetamine". The present study aimed to evaluate the cause of death, and to compare the PMMA blood concentrations in fatal and non-fatal cases. Methods for identification and quantification of PMMA are presented. The median age of fatalities was 30 years (range 15–50) with 67% males; in non-fatal cases 27 years (20–47) with 86% males. In the 12 fatalities, the median PMMA blood concentration was 1.92 mg/L (range 0.17–3.30), which is in the reported lethal range of 0.6–3.1 mg/L in peripheral blood and 1.2–15.8 mg/L in heart blood. In the 22 non-fatal cases, the median PMMA concentration was 0.07 mg/L (range 0.01–0.65). Poly-drug use was frequent both in fatal and non-fatal cases. The PMA concentrations ranging from 0.00 to 0.26 mg/L in both groups likely represented a PMMA metabolite. Three fatalities were attributed to PMMA only, six to PMMA and other psychostimulant drugs, and three to PMMA and CNS depressant drugs, with median PMMA concentrations of 3.05 mg/L (range 1.58–3.30), 2.56 (1.52–3.23) and 0.52 mg/L (0.17–1.24), respectively. Eight victims were found dead, while death was witnessed in four cases, with symptoms of acute respiratory distress, hyperthermia, cardiac arrest, convulsions, sudden collapse and/or multiple organ failure. In summary, all fatalities attributed to PMMA had high PMMA blood concentrations compared to non-fatal cases. Our sample size was too small to evaluate a possible impact of poly-drug use. A public warning is warranted against use and overdose with illegal



# Serotonin Toxicity

- Central serotonin excess
  - Increased release
  - Reuptake inhibition
  - MAO inhibition



# Principles of management

- Cooling
- Serotonin toxicity
  - **Specific 5HT2a antagonist eg cyproheptadine**
- Malignant hyperthermia like
  - **Ryanodine receptor closure eg dantrolene**
- Adrenergic excess
  - **Mixed alpha and beta adrenoceptor antagonists**
- Central hyperthermia
  - **Benzodiazepines**
- Muscle hyperactivity
  - **Non-depolarising neuromuscular blockade eg rocuronium**

Table 1  
Rat mortality classified according to group

	Dose	Deaths / total no.
Saline		6 / 6
WAY 100635	1 mg/kg	5 / 5
Propranolol	10 mg/kg	5 / 5
Ritanserin	3 mg/kg	0 / 5
Pipamperone	20 mg/kg	0 / 6
Chlorpromazine	20 mg/kg	6 / 6
	40 mg/kg	0 / 5
Cyproheptadine	5 mg/kg	5 / 5
	10 mg/kg	0 / 5
Dantrolene	20 mg/kg	6 / 6

# Clinical evidence for dantrolene

Table 2. Survival data from 71 cases of MDMA-related hyperpyrexia

Survival	No. of survivors (%)			
	Dantrolene		No dantrolene	
Total survival	21/26	(80.8)	25/45	(55.6)
Survival $\geq 42^{\circ}\text{C}$	8/13	(61.5)	0/4	(0.0)
Severe complications	6/8	(75.0)	—	
Mild-moderate complications	2/8	(25.0)	—	
Survival 40–41.9°C	10/10	(100.0)	15/27	(55.6)
Severe complications	5/10	(50.0)	12/15	(80.0)
Mild-moderate complications	5/10	(50.0)	3/15	(20.0)
Survival 38.0–39.9°C	3/3	(100.0)	7/8	(87.5)
Severe complications	1/3	(33.3)	3/7	(42.9)
Mild-moderate complications	2/3	(66.7)	4/7	(57.1)
Survival: temperature identified as $> 38^{\circ}\text{C}^*$	—		3/6	(50.0)
Severe complications	—		2/3	(66.6)
Mild-moderate complications	—		1/3	(33.3)

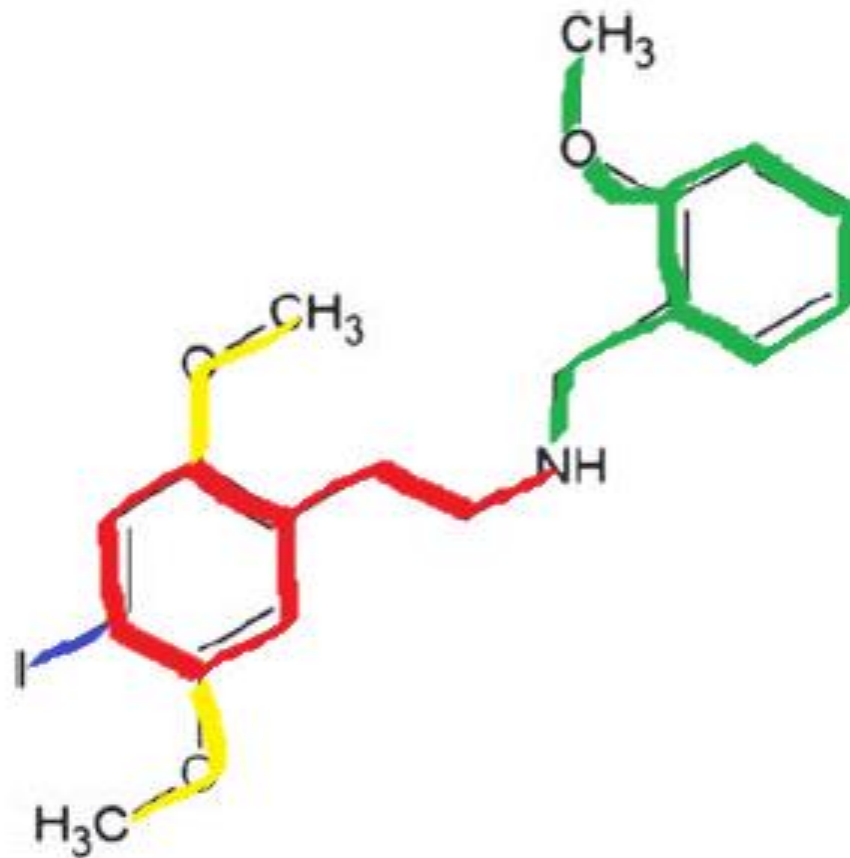
\*In the following case reports, patients were described as being hyperpyrexial, but the authors did not cite a specific temperature: Patel et al. (first case);<sup>37</sup> Karlovsek et al.;<sup>60</sup> Ben-Abraham et al. (3 cases);<sup>63</sup> Garcia-Repetto et al. (first case).<sup>65</sup>

## Dantrolene in the treatment of MDMA-related hyperpyrexia: a systematic review

### Review Articles

Brian E. Grunau, MD,\* Matthew O. Wiens, PharmD,† Jeffrey R. Brubacher, MD‡

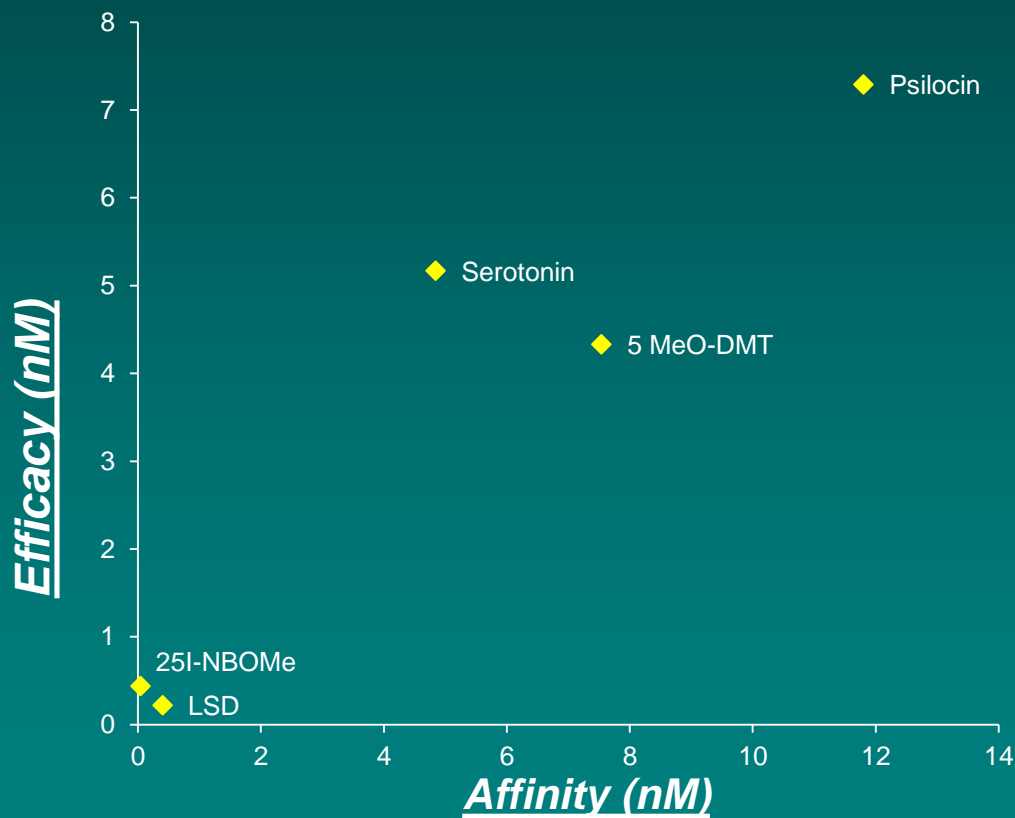
- Structure Activity relationship compares with known stimulants and hallucinogens



25I-NBOMe

# Summary of Pharmacology for clinicians

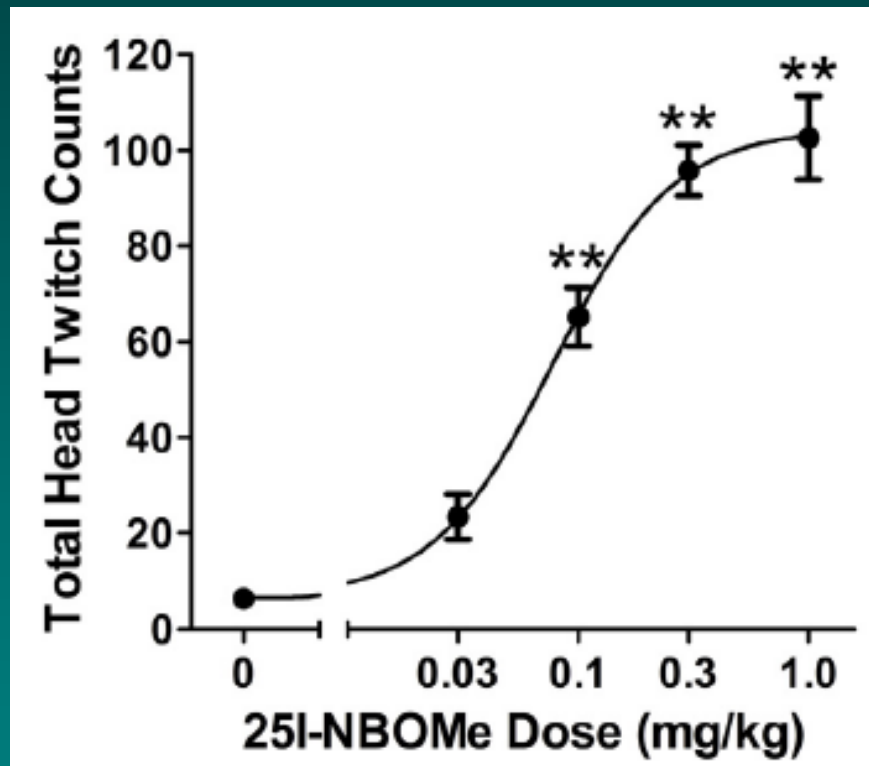
- In vitro studies
  - Braden et al, 2006
  - Affinity
    - Displacement of DOI
  - Efficacy
  - Ettrup et al
    - PET radiotracers
    - Cimbi – series
    - Confirm nM affinity



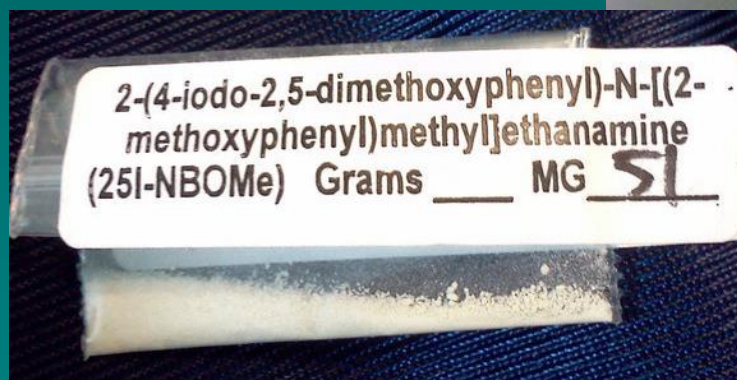


# Summary of Pharmacology for clinicians

- In vivo studies
  - Halberstadt and Geyer, 2013
- Head twitch response
  - High frequency
  - Paroxysmal
  - Rotational
  - 5HT 2a receptor activation
  - Proxy for human hallucination
  - Magnetometer



# 25I-NBOMe



- 29yr male liquid from dealer labelled 25I-NBOMe
- IV 3ml ?concentration
- ED
  - **violent (self) and agitated**
  - **Stimulant toxidrome**
  - **Renal impairment and rhabdomyolysis**
  - **Intubated and ventilated**
  - **Cerebral oedema**

# Case 1 – clinical course

- 43 days in hospital
- Acute respiratory distress syndrome
- Ventilator associated infection with abscesses
- Anuric renal failure
- Discharged without significant consequences / impairment

# Cases 2 to 7

- 6 young men (19-22years)
- Same party, internet purchased labelled '2C-B'
- Powder inside purple capsules
- Presented to ED together
- All agitated, hallucinating, stimulant toxidrome
- Pyrexia in 5 cases, seizures in 3 cases
- 1 man intubated and ventilated
- Moderate doses benzodiazepines / antipsychotics

- Poklis et al, 2013
  - 19 yr old male
  - Found prone, unresponsive on pavement below apartment
  - Trauma, multi storey fall
  - Sample of blotters – 25I-NBOMe
  - Body fluids / tissues – 25I-NBOMe
- Walterscheid JP et al, 2014, Am J Forensic Med Pathol.
  - 2 cases sudden death (21yr male, 15yr female)
  - Sudden onset disturbance of mental health
  - Self injury
  - External bruising
  - Hyperpyrexia



# Possible 25I-NBOMe fatalities

- Media/Erowid
- US
  - **7 deaths** (N. Dakota 1, Minnesota 1, N. Carolina 2, Louisiana 1, Florida 1 , Arizona 2)
- Australia
  - **3 deaths**
  - **1 pharmacological**
  - **2 behavioural**
- UK
  - **1 death**

**17 US deaths**

- 23 non-fatal cases
  - Hill et al, 2013 (7)
  - Rose et al, 2012 (1)
  - Rose et al, 2013 (10)\*
  - Kelly et al, 2012 (4)
  - Stellpflug et al, 2013 (1)

\* Exposure not analytically confirmed

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## BRIEF COMMUNICATION

### A case of 25I-NBOMe (25-I) intoxication: a new potent 5-HT<sub>2A</sub> agonist designer drug

S. RUTHERFOORD ROSE<sup>1</sup>, JUSTIN L. POKLIS<sup>2</sup>, and ALPHONSE POKLIS<sup>2,3</sup>

Departments of <sup>1</sup>Emergency Medicine, <sup>2</sup>Pharmacology and Toxicology and <sup>3</sup>Pathology, Virginia Commonwealth University, Richmond, VA, USA

*J. Med. Toxicol.*  
DOI 10.1007/s13181-013-0314-y

## TOXICOLOGY OBSERVATION

### 2-(4-Iodo-2,5-dimethoxyphenyl)-N-[(2-methoxyphenyl)methyl]ethanamine (25I-NBOMe): Clinical Case with Unique Confirmatory Testing

Samuel J. Stellpflug • Samantha E. Kealey •  
Cullen B. Hegarty • Gregory C. Janis

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ISSN: 1556-3650 print / 1556-9519 online  
DOI: 10.3109/15563650.2013.802795

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## ORIGINAL ARTICLE

### Severe clinical toxicity associated with analytically confirmed recreational use of 25I-NBOMe: case series

SIMON L. HILL<sup>1,2</sup>, TOM DORIS<sup>2</sup>, SHIV GURUNG<sup>3</sup>, STEPHEN KATEBE<sup>3</sup>, ALEXANDER LOMAS<sup>3</sup>, MICK DUNN<sup>1</sup>, PETER BLAIN<sup>1,2</sup> and SIMON H. L. THOMAS<sup>1,2</sup>

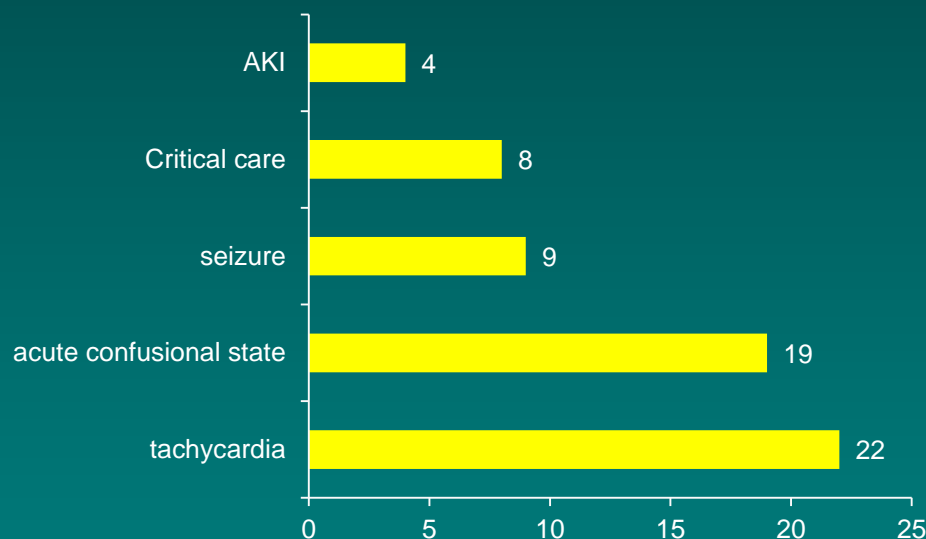
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<sup>2</sup>Department of Clinical Toxicology, Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK

<sup>3</sup>Departments of Anaesthesia and Critical Care, South Tyneside Hospital, UK

- Demographics
  - **Age**  
Mean 18yrs, [14-29]
  - **Sex**  
Male 13, female 1, not recorded 9
  - **Route**  
All recorded as oral or insufflated except 1 IV

- Clinical features



- Hyperpyrexia, hypertension, dilated pupils, flushing
- Aware of other cases; 1 Ireland, 3 Belgium

# Management

- Supportive care
- Stimulant toxidrome
  - **Intravenous fluids**
  - **Cooling**
- Mental health disturbance
  - **Benzodiazepines**
  - **antipsychotics**
- Serotonin toxicity specific



- Serotonin mediated toxicity
- Variations of toxidrome among related substances
- Understanding the pharmacology directs management
- Aggressive cooling is vital for hyperpyrexia
- Harm reduction work is highly important



# Thanks for listening.

- Hill SL et al. Clin Tox, 2013;
- Braden MR et al. Mol. Pharmacol, 2006;70:1956
- Ettrup A et al. J.Nucl.Med, 2010; 51:1763
- Halberstadt AL et al. Neuropharmacology,2014;77:200
- Poklis JL et al, Forensic Sci International, 2013 early online
- Walterscheid JP et al. Am J Forensic Med Pathol 2014 (early online)
- Rose R. Clin Tox,2013;51:174
- Stellpflug SJ et al. J.Med.Toxicol, 2013 early online
- Rose SR et al. Clin Tox, 2012;50:707
- Kelly A et al. Clin Tox, 2012;50:702