NEW DRUGS 2014

Aspetti clinico-tossicologici

Roma, 14,05.2014

Problematiche cliniche e soluzioni: l'esempio italiano

Presidency of the Ministry Council
Dipartimento Politiche Antidroga
National Early Warning System

National Antidotes Stockpile
Ministry of Health - Civil Defense
Advisory Centre

Presidency of the Ministry Council
Dipartimento della Protezione Civile
Reference Centre

CENTRO ANTIVELENI PAVIA
CAV
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CENTRO NAZIONALE INFORMAZIONE TOSSICOLOGICA

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- Setting: Eds + PCC (NHS)
  - NEWS - clinical
  - Substances - poisonings
- Results and future needs

Carlo A Locatelli

Centro Antiveleni - Centro Nazionale di Informazione Tossicologica
IRCCS Fondazione Maugeri e Università degli Studi, Pavia

National Early Warning System (NEWS)

Società Italiana di Tossicologia - SITOX

Substances reported to N.E.W.S.

(from 2009 to April 2014
> 320 substances)

Pregabalin
4-MA
JWH-200
3-FMA
Etaqualone
Metamfepramone
Flefedrone (4-FMC; 4-fluorometcatinone)
Mitraginina (Mitragina Speciosa)
Bromo-Dragonfly
Levamisole
bk-PMMA (Metedrone)
2-PEA
MDPV
DNP (2,4-dinitrofenolo)
4-AcO-DMT
PMA
Petidine/Demerol (Meperidine o Pethidine)
Nortramadol (O-Desmetiltramadol)
Ketamina
mCPP
Piperonale
TMA-6
Carbarile

Desossi-D2PM
5-APB
Arecolina
Dibutilone
MDPBP
3-MeO-PCE
3-(4-idrossimetilbenzoil)-1-pentilindolo
Metossietamina
PMMA
JWH-019 – 023 – 203 - 250 – 200 -015
3,4-DMMC
Desossipipradrolo
Buflomedil
Diltiazem
Etafedrina
JWH-210
Pentedrone (β-etil-metcatinone)
5-MeO-DPT
Pentilone
M-ALPHA
Isomero del nafirone
Variante C8 + C2 del CP-47,497
4MBC MPPP
MPBP
Butilone ,Mefedrone (4-MMC) - Nafirone
Bufedrone
MDPV - 4-metiletcatinone (4-MEC)
JWH-122 AM-694- JWH-015
Metil derivato del JWH-073
Dimetocaina DMC
DMAA
Iso-Etcatinone
pFBT
JWH-081 Analogo del JWH-018
Fentanil
4-FMA
Metamizolo (novalgina)
pFPP
MDAI
β-Me-PEA
N,N-dimetilfenetilamina
N-benzil-1-feniletilamina
JWH-073 JWH-018
GHB
2C-B-BZP

1-Fenil-1-propanamina
(1-[(5-Cloropentil)-1H-indol-3-il]-(2-iodofenil)metanone
α-Pirrolidinobutirrofenone (α-PBP)
3-Amino-1-fenil-butano (3-APB) / 4-APB - 6-APB
AM-2232- JWH-022 - WIN 55,212-2 - AM-679
Etizolam
Etilfenidato
Camfetamina
4-Metilbufedrone - 4-EMC 4-BMC (Brefedrone)
CP 47,497-C8-omologo
Propossifene/destroprossifene
bk-MDDMA
Benzilpiperidina
Desomorfina
Metorfano
Isopentedrone
WIN 48,098 (Pravadoline)
Pirovalerone
Dipipanone
Sildenafil
Metilone (MDMCAT; bk-MDMA)
4-Fluoroamfetamina (4-FA)
Metamfetamina
N-etilbufedrone
Org-29647 / 27569 / 27759 AM-2233 JWH-307
Caffeina (in eroina)
Benzoin isopropil etere (BIE)
Pseudoefedrina
Nandrolone
JWH-412 - JWH-387 RCS-4(C4) Ostarine
Fenazepam
JWH-122 - fluoropentil derivato - JWH-182
2C-C-NBOMe
Colofonia in hashish
OMMA
Metanandamide
AM-1220-azepan-derivato - AM-1220
JWH-007 JWH-251 AM-2201
N-etilamfetamina / α-PVP
DMMA / Tropicamide
Diazepam
3-FMC
5-IAI
MPA
CRA-13
4-MeO-PCP

Etizolam
AM-2232 - AM-679
3-amino-1-fenil-butano
alfa-pirrolidinobutirrofenone
Metanandamide,
AM-694, CP 47-497 omologo C8, CRA-13,
JWH-019, JWH-081, JWH-122, JWH-203,
WH-250, WIN48098/pravadolina, WIN-55212-2
JWH-022, AM-2201 HU-331 JWH-073
nitrito di isopropile
eroina tagliata con paracetamolo, caffeina e
metorfano tetramisolo/levamisolo
metossietamina
eroina con destrometorfano
4-FA; 2-fluoroamfetamina
MDAI
4-MEC, metilone, bufedrone
N-idrossi-MDA
N-propilamfetamina
3-(p-metossibenzoil)-N-metilindolo
trans-CP47,497-C8 omologo
1-cicloesil-x-metossibenzolo
3-FiMC
1-(3-metilbenzil)piperazina
1-(tiofen-2-il)propan-2-amina
URB754; AM-694-cloro derivato;
1-fenil-1-propanamina
eroina/antrace
4-MA / 2-FMA
5-APDB / 6-APDB
Phenibut
MAM-2201 / JWH-370 / AM-2233, JWH-307
PMA
ECX
4-Fluoroefedrina
3-MeO-PCP
UR-144 - 5FUR-144
metorfano
energy drink
6-APB
25D-NBOMe
MPA
AMT
A-796,260 4-AcO-DALT RCS-4
5-IT
2,4,5-TMMC; Apinaca

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Table 2. Last 12-month prevalence (absolute number and %) of selected novel psychoactive substances and traditional drug use in entire sample.

	Last 12-month period of use	
	N	%
Cannabis, any form	13,965	62.7
MDMA, any form	7971	35.8
Cocaine	5290	23.7
Synthetic cannabis, herbal	1021	4.5
Mephedrone	871	3.9
Methoxetamine	545	2.4
Any NBOMe drug	526	2.4
Benzo-Fury (5/6-APB)	316	1.4
Methylone	279	1.2
Synthetic cannabis, powder	175	0.8
MDPV	95	0.4
N-ethyl ketamine	44	0.2
Flephedrone (4-FMC)	20	0.1

MDMA: 3,4-methylenedioxy-N-methylamphetamine; MDPV: methylenedioxypyrovalerone; NBOMe: hallucinogenic N-methoxybenzyl analogues of the 2C-X family of phenethylamines, agonists of the 5-HT_{2A} receptor; 2C-X: the generic name of a family of drugs called 2C, where an alphabetical letter replacing X would specify which one.

17,3%

2012 - on-line survey
22.289 answers

Age (average) 31 y-o

33.9%	UK
35.9%	Australia
17.3%	USA
10%	EU-zone
2.9%	Canada

Lawn W et al, 2014

Cost

Name of product	*Year of first appearance in the Netherlands*	*Supplied written information*	*Claimed dosage*	*Actual content*	*Price per tablet (€)*
2C-B	1994	None	5 mg of 2C-B	2C-B	Unknown
S-5 (synthetic herbs)	1997	Very limited information on the packing in Dutch	None	2C-T-2	11.34
2C-T-7	1997	Simple information on leaflet in Dutch	8 mg of 2C-T-7	2C-T-2	5.67
2C-T-2	1997	Simple information on leaflet in Dutch	8 mg of 2C-T-2	2C-T-2	3.78–10.21
Blue Mystics	2000	Extensive information on leaflet in Dutch and in English	10 mg of 2C-T-7	2C-T-7	3.78–6.81

de Boer et al., 2004

Clinical pictures and management priorities in EDs

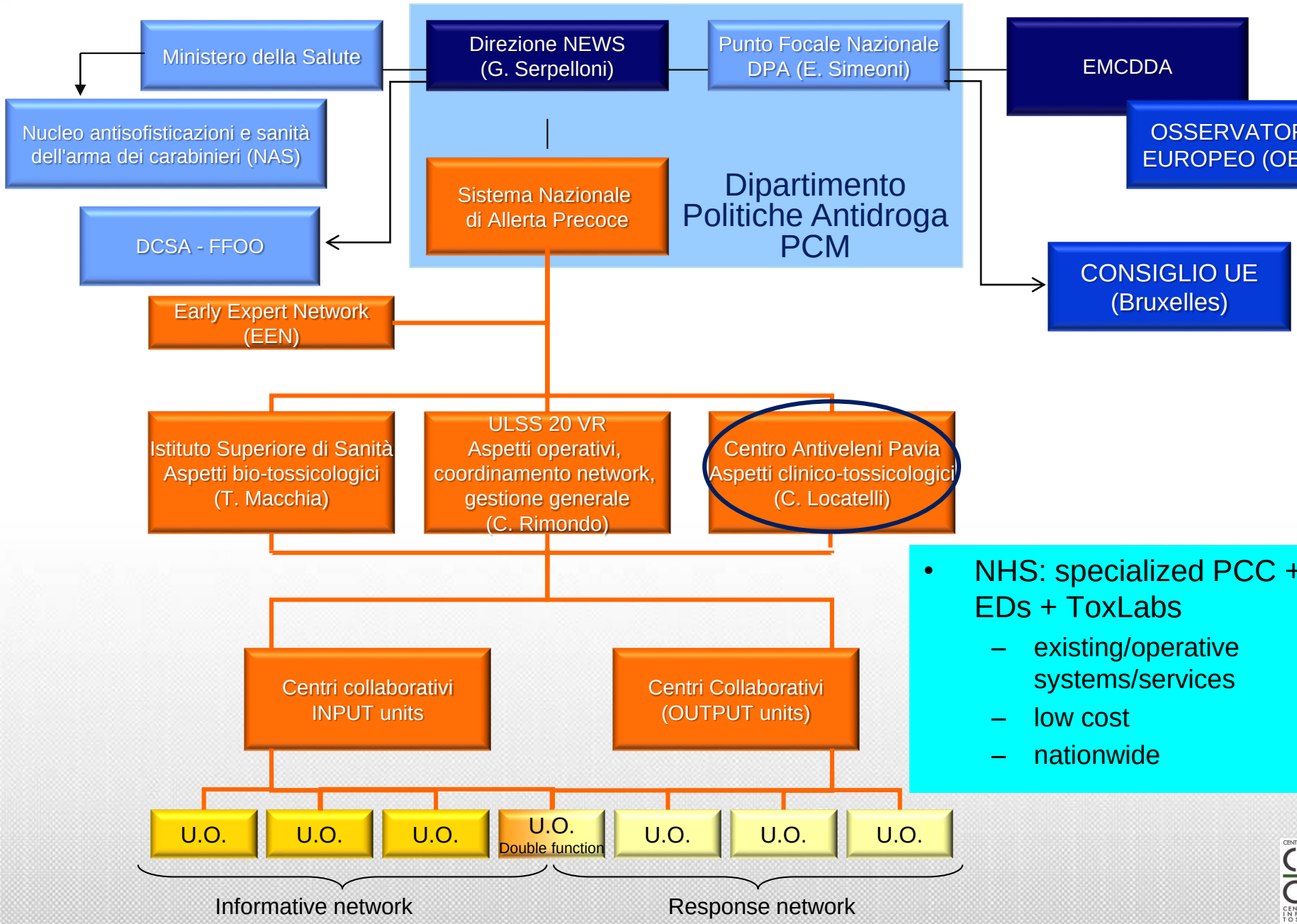
- Overdose clinical picture
  - sympathomimetic / excitatory syndrome
  - agitated / hallucinated patient in EDs
  - mixed syndromes / clinical effects
    - hallucination + agitation + violence + CNS depression
- management priorities at admission (first hours)
  - stabilization, decontamination, medications (antidotes ?)
  - specific toxicological diagnosis (clinical + analytical)
  - kind / level of monitoring (clinical and/or instrumental)
  - department/ward of hospital admission
    - OBI / emergency medicine / ICU
    - SPDC
    - other departments (paediatric ?)
  - transferability to less intensive Dpts / discharge

Diagnostic problems in the emergency setting

- NPS use in “non abusers” → “recreational” use (non daily use?)
- incomplete / wrong history (unawareness of use ?)
- Illegal use (e.g. sexual assault, incapacitation)
- difficult / impossible (at the moment) analytical identification in ED
- Effects of cutting or “co-formulating” substances
- Contemporary use of → Incomplete/wrong diagnosis ! and treatments?
  - old and detectable substances of abuse
  - several (more than one) NPS
  - medications (benzo, SSRI, Ca-chanel blockers, …)
  - ethanol
- insufficient characterization / knowledge of acute / post-acute / chronic effects (e.g. kind, severity, length of toxic effects) for the majority of NPS

- trauma / accidents and NPS
- surgical emergencies and NPS
- ……

NEWS - National Early Warning System



- NHS: specialized PCC + EDs + ToxLabs
  - existing/operative systems/services
  - low cost
  - nationwide

Activities in the emergency system

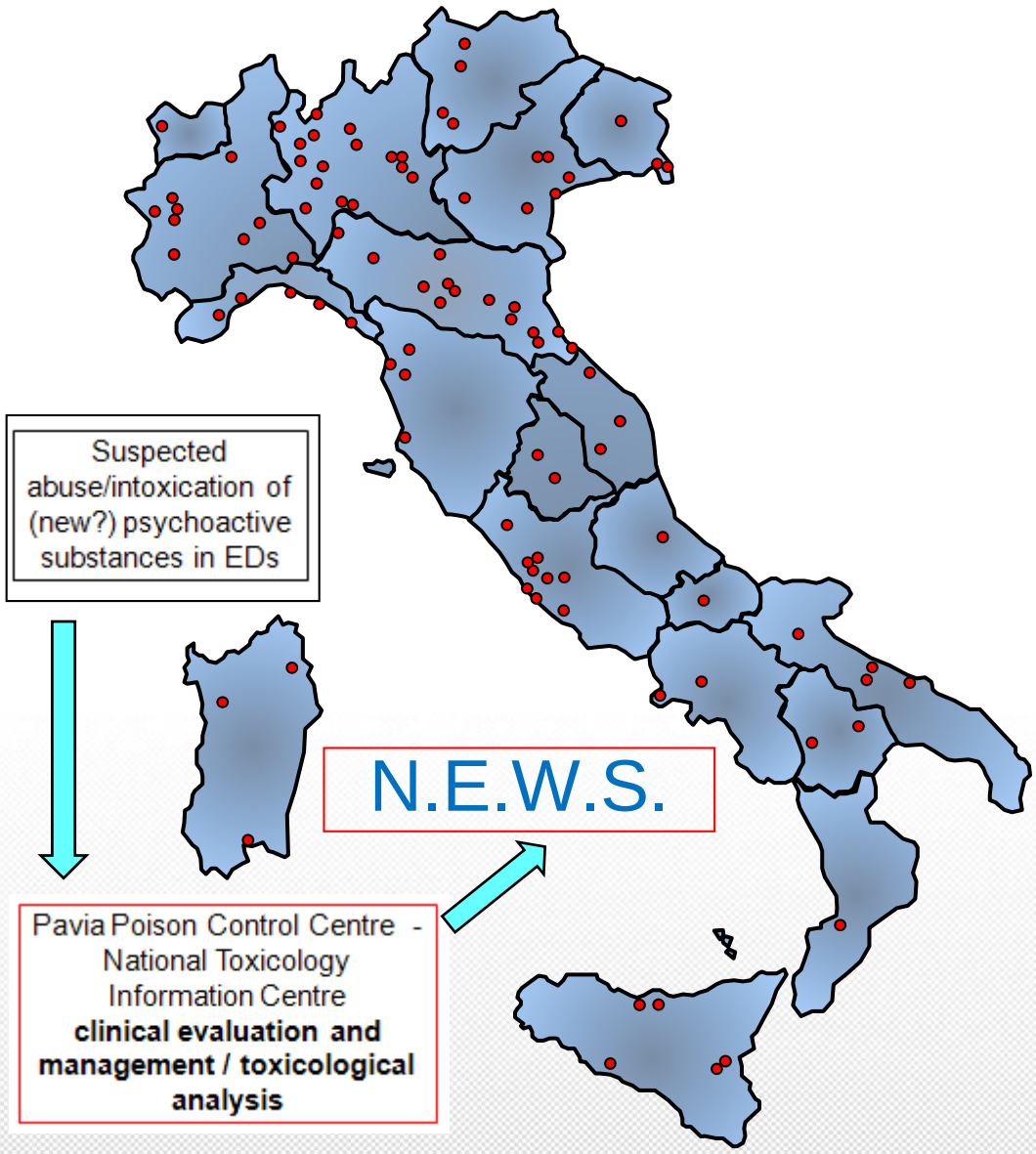
advantages and limits

- collection of clinical cases → relevant data regarding
  - assumed product (street product, medications, …)
  - characteristic of abuse
  - clinical effects related to abuse → evaluation / identification of
    - "toxidromes"
    - severity of poisoning / new toxic effects
    - treatments (acute phase)
- prevention of mortality (rapid identification → treatments)
- more confident evaluation of the prevalence
- promptness in alerting the national health system → early warning system
- …….
- Unsystematic collection of cases → not a monitoring system
- Chronic effects ? Treatmentts iin the post-acute phase ?

Pavia Poison Control Centre - National Toxicology Information Centre

- NHS Hospitals-dedicated service
- major toxicological accidents and emergencies
- availability of clinical toxicology labs (national reference) for poisonings / chemical emergencies
- Italian national administration reference PCC (in addition to the routine activities planned by the national decree, 2008)
  1. Drugs of abuse – NEWS clinical toxicology (Italian Department for Antidrug Policies, Presidency of the Council of Ministers)
  2. Chemical accidents (Civil Protection, Presidency of the Council of Ministers)
  3. CBRN reference Centre (Civil Defence – Ministry of Health)
- specialized / specifically trained MD and other personnel to face these functions

Network of EDs (n. 197)



Pavia PCC and EDs network

Detection, collection/evaluation of "new drugs" of abuse (NPSs) poisonings as national point of view

- variation in the consumption pattern
- new drugs involved
- incidence op poisonings
- sentinel cases
- clinical pictures at admission (identification of new "toxidromes")
- diagnostic and therapeutic pathways
- new analytical needs usefulm in the emergency setting
- post-acute consequences
- ……

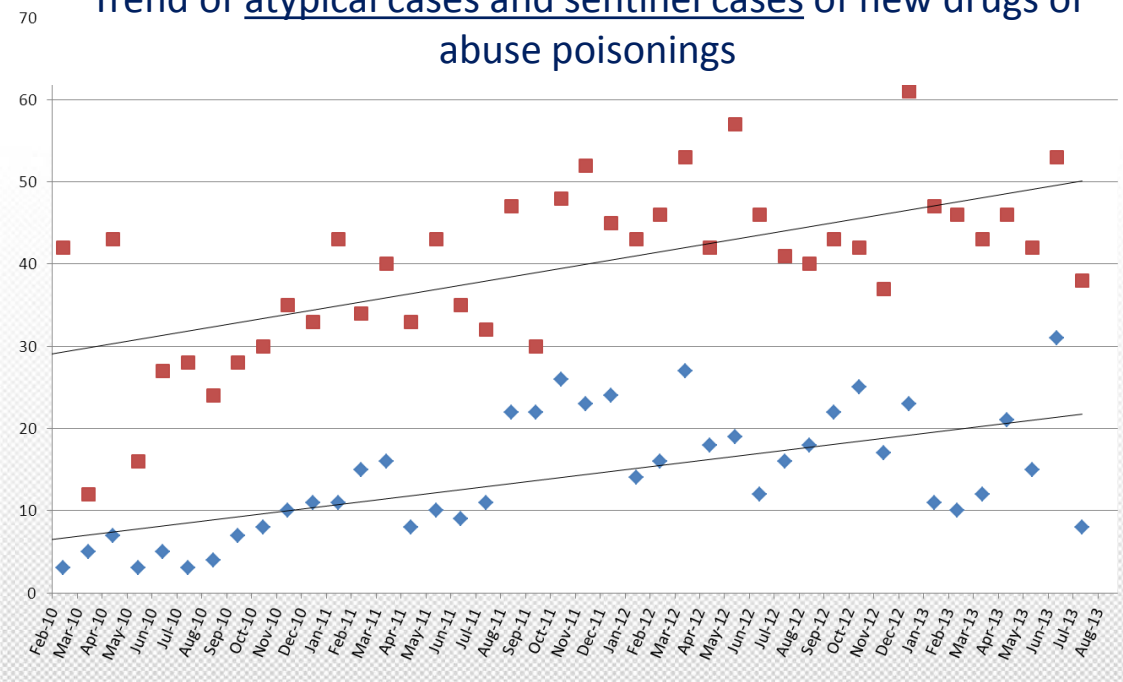
- advantages
  - national point of view
  - standardized procedures
  - one system, one method

Case series from the Pavia PCC

Specialist consultation → cases of poisoning by substances of abuse
(Pavia PCC activity from February 2010 to August 2013)
n = 5593

Ethanol abuse + body-packers (stuffers) cases

Trend of atypical cases and sentinel cases of new drugs of abuse poisonings



"atypical" cases
n = 1723

"sentinel" cases
n = 604 / 1723 (35%)

NPS detection in emergency setting (ToxLabs)

NATIONAL EARLY WARNING SYSTEM

Screening 1 - CS

1. JWH-200
2. JWH-073
3. JWH-302
4. JWH-250
5. JWH-007
6. JWH-081
7. JWH-098
8. JWH-398
9. JWH-147
10. JWH-016
11. JWH-018
12. JWH-307
13. JWH-122
14. JWH-019
15. AM-2233
16. AM-2201
17. AM-694
18. MAM-2201
19. WIN-55212
20. WIN-48,098
21. RCS4
22. RCS8

Screening 2

1. ketamine
2. metoxyetamine
3. atropine
4. scopolamine
5. mephedrone
6. butylone
7. dimethylcathinone
8. dimethylmetcathinone
9. bufedrone
10. etcathinone
11. 4-fluormetcathinone
12. pentedrone
13. metedrone
14. etilone
15. pentilone
16. 1-naphyrone
17. MDPV
18. 4-MEC
19. 5-APB/6-APB
20. dimethyltriptiamine
21. 2-C-I
22. 2-C-T7
23. 2-C-B
24. DOB

Screening 3

1. 4-fluoroamhetamine
2. MDAI
3. PMMA-PMA

Screening 4

1. heroine/morphine
2. 6-MAM
3. cocaine
4. THC
5. amphetamine
6. MDMA
7. ethanolo

Screening 5

1. .. otrther, on demand
2. ……

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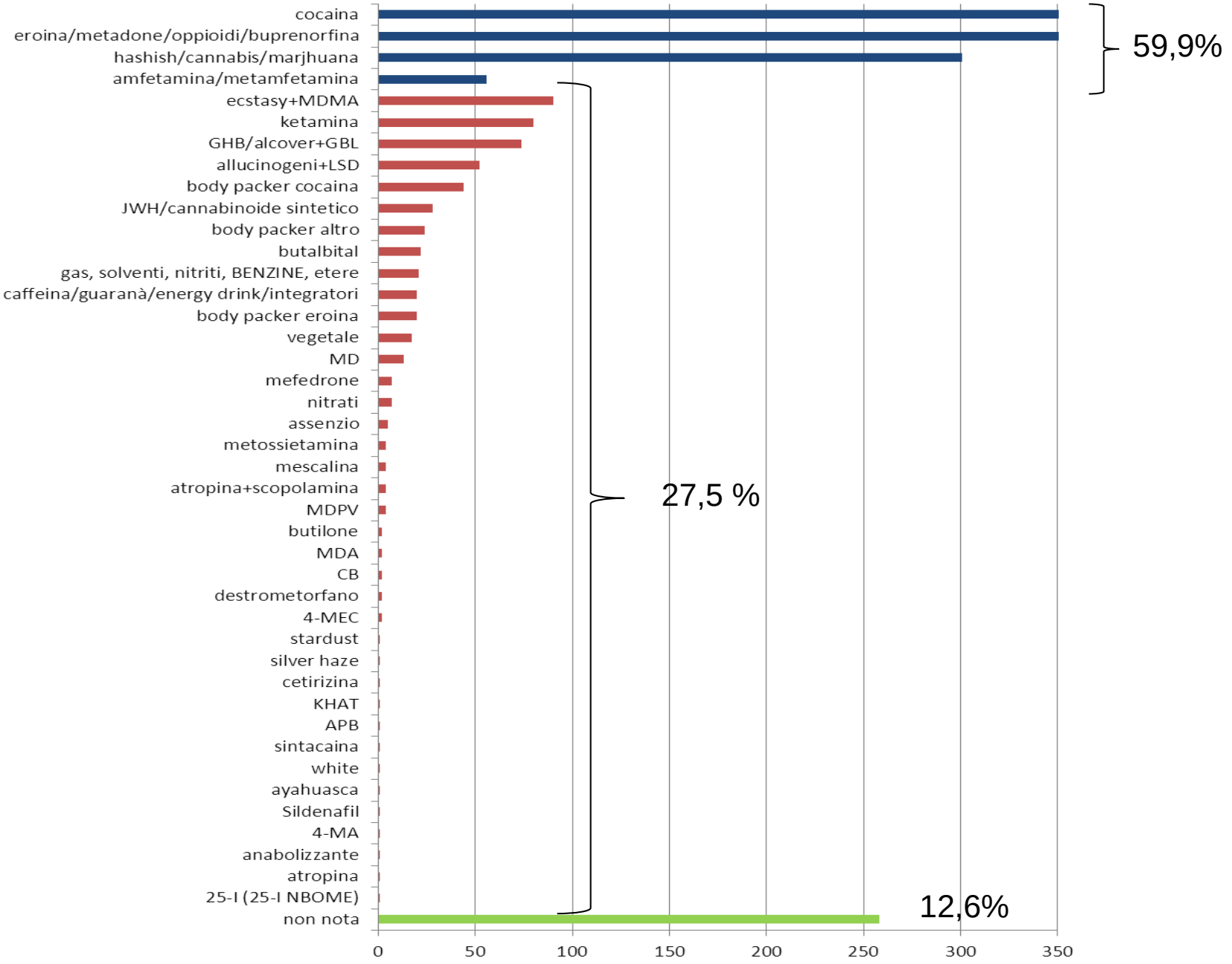
1723 “atypical” cases of poisoning → identified substances



NATIONAL EARLY WARNING SYSTEM

"new" hallucinogenic/stimulants/psychoactive drugs (NPSs)

analytical confirmation in 604 «sentinel» cases

most frequent

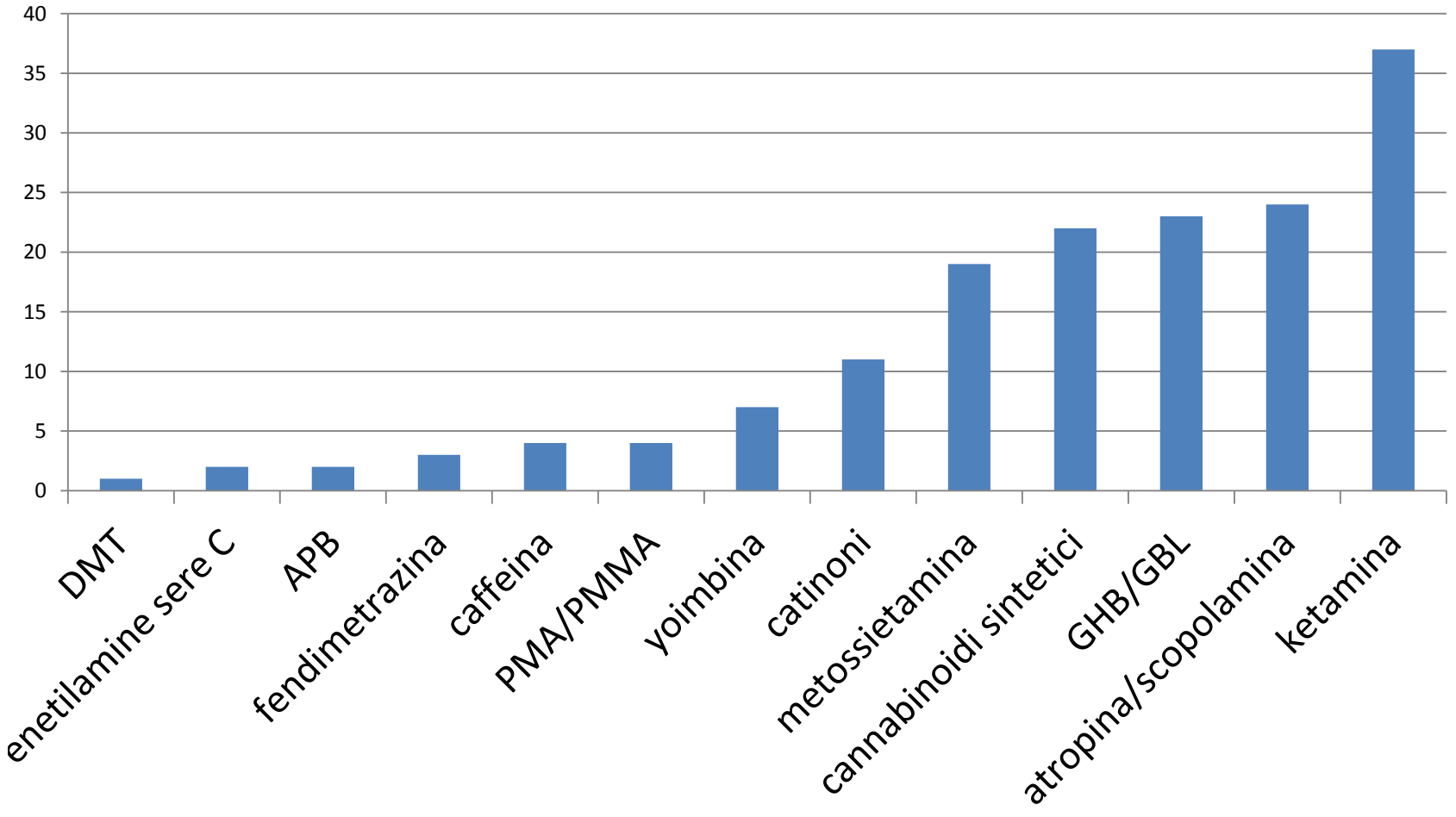
- synthetic cannabinoids
- synthetic cathinones
- ketamine → synthetic ketamines (e.g. metoxyetamine)
- caffeine (+ cocaine and/or heroin)
- GHB / GBL
- anticholinergic agents (seeds, atropine, scopolamine)
- amphetamines-type substances (PMA/PMMA, 4-FA, …)

less frequent

- myristic acid (nutmeg)
- ergine
  - *Rivea corymbosa* (seeds)
  - *Argyreia nervosa* (Hawaiian Baby Woodrose seeds)
  - *Ipomea violacea* (Morning glory)
- ayahuasca (dimethyltriptamine + harmine)
- benzofurans (APB isomers)
- 2C-E
- 2-CB
- 5-IT
- performing agents
- anorectic agents (e.g. sybutramine)
- bupropion
- …..

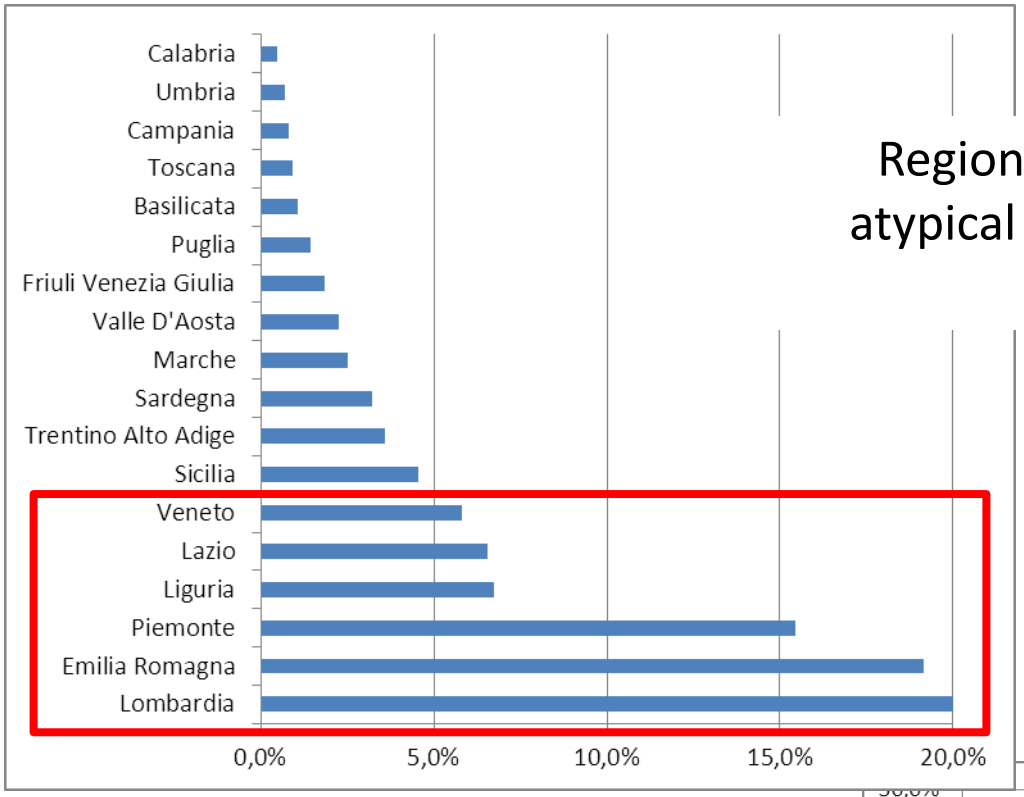
NATIONAL EARLY WARNING SYSTEM

604 “sentinel” cases of NPS poisoning in Italy → identified substances



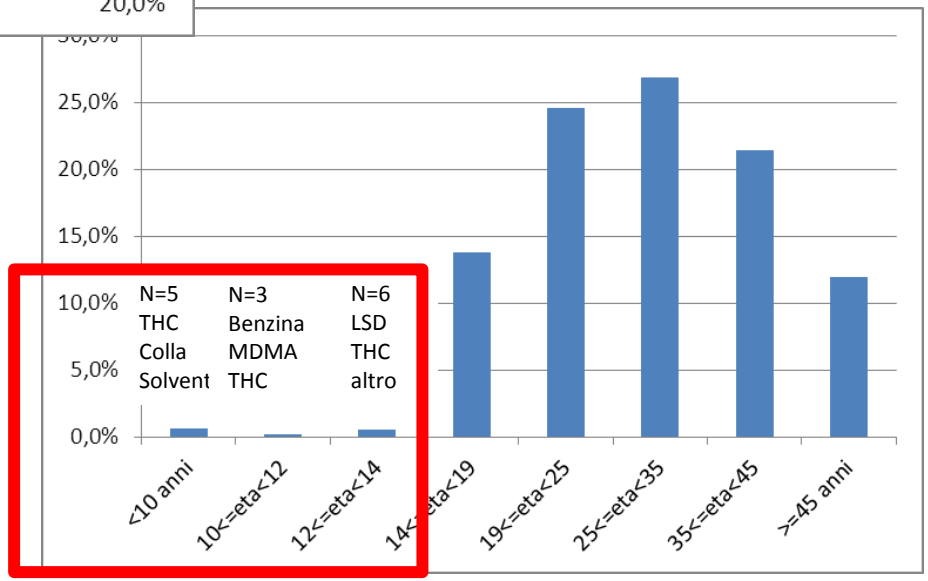
Results: 1723 “unusual” cases of poisoning

NATIONAL EARLY WARNING SYSTEM



Regional distribution of 1408 atypical cases of drugs of abuse poisonings

Age distribution of 1408 atypical cases of drugs of abuse poisonings



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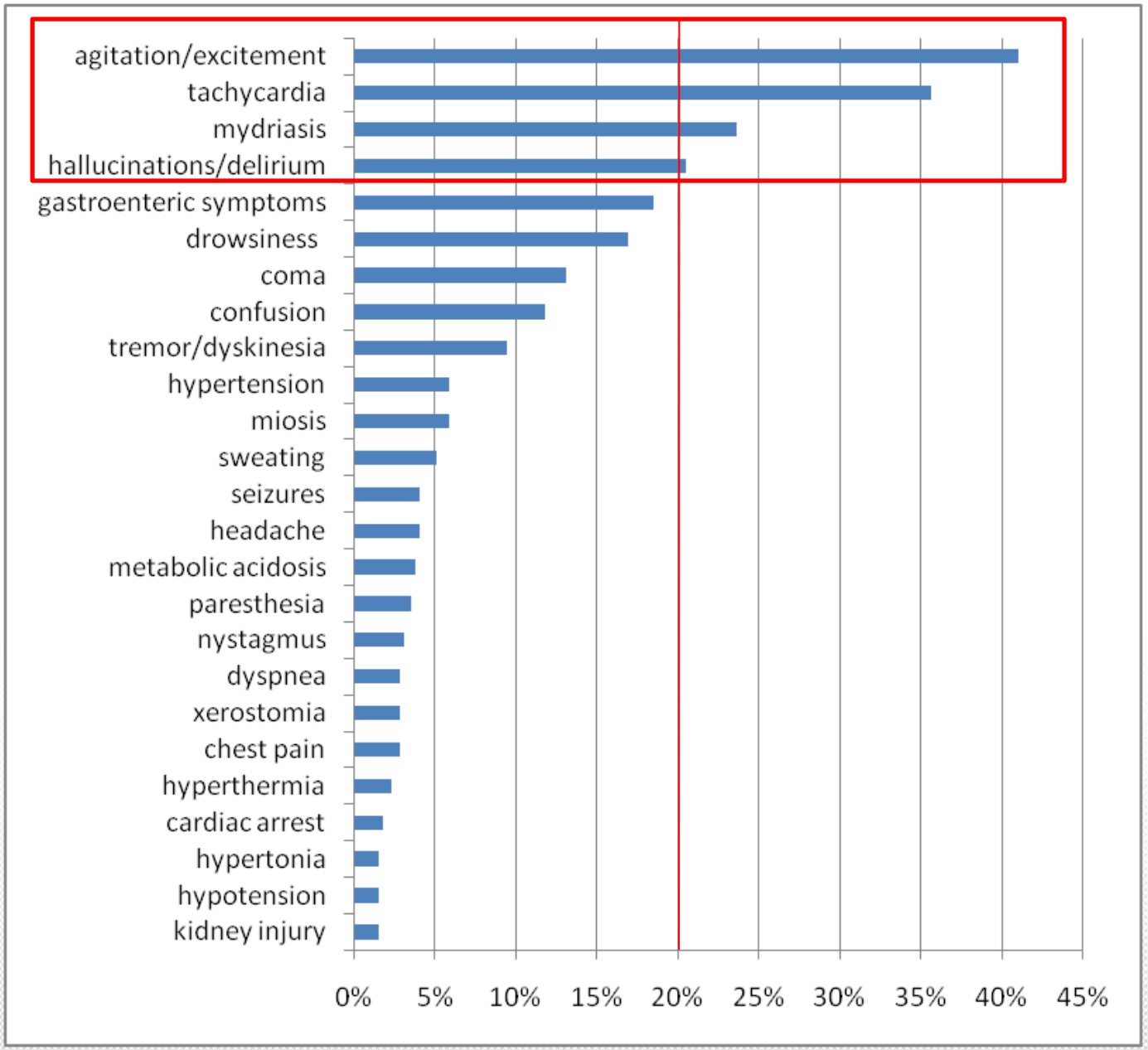
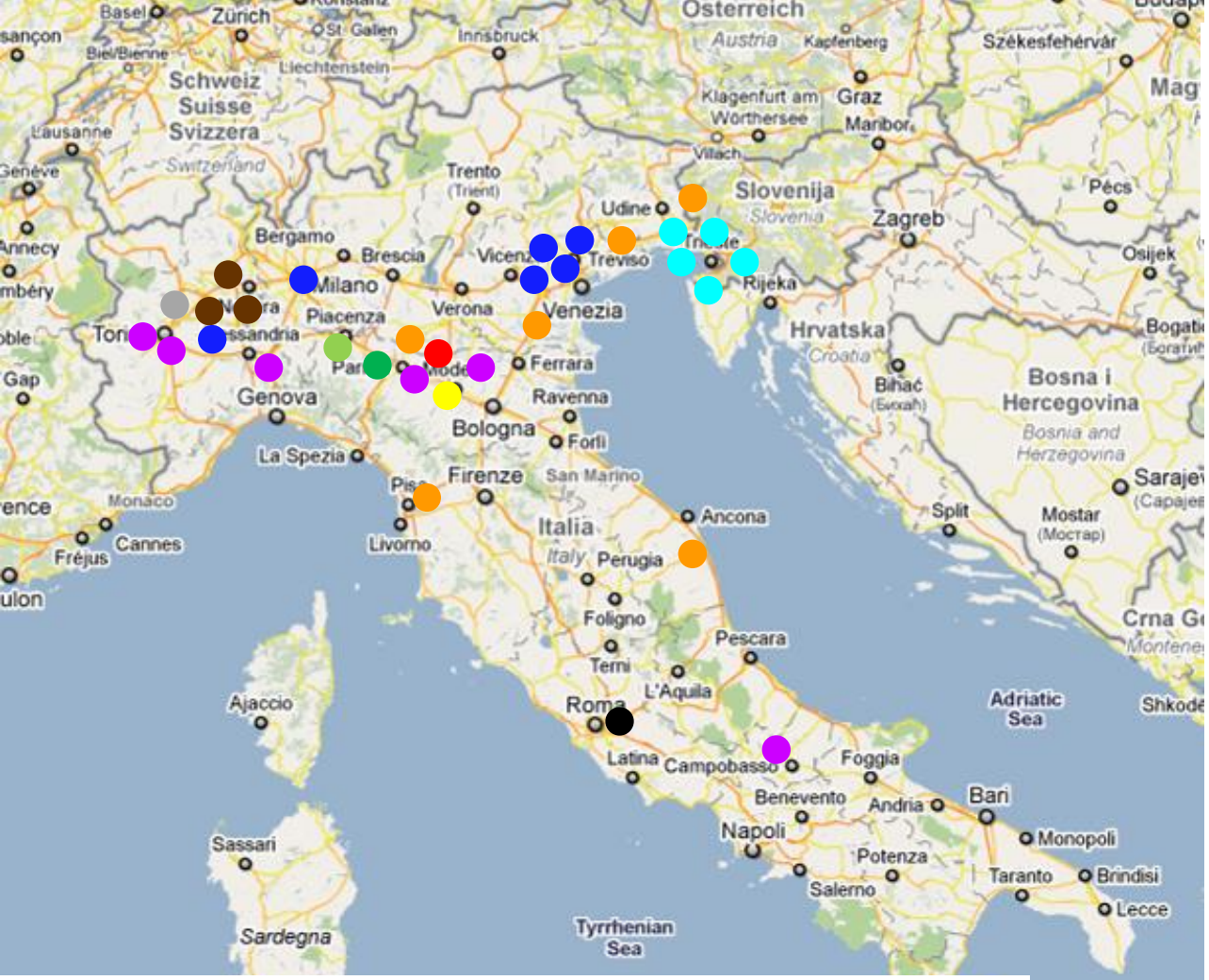
Results
Clinical manifestations of «sentinel» cases (n= 604) at EDs admission





Age range: 14-55 y-o

- ✓ 14-21 years 22/33 66,6%
- ✓ 22-35 years 8/33 24,4%
- ✓ 36-55 years 3/33 9%

Clinical and/or lab-confirmed cases (Jan 2010- 29 Feb 2012)

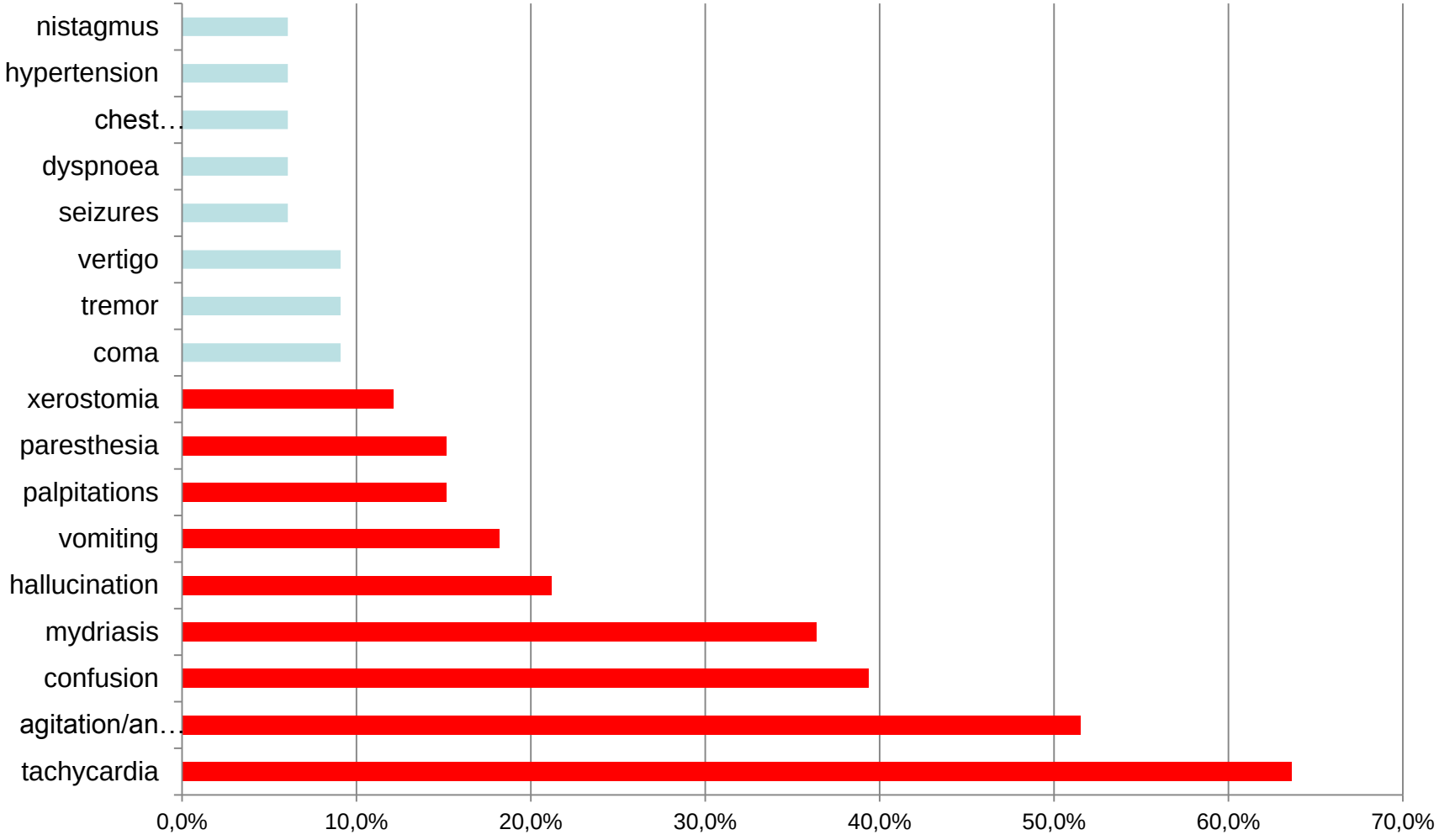
33 cases

PRODUCT'S NAME

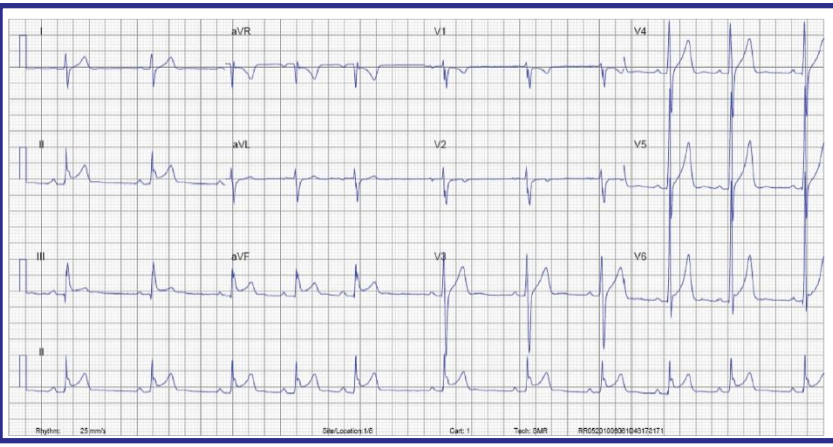
- 6 n-Joy (JWH-018)
- 1 Spice
- 3 Forest Green (JWH-122; JWH-250)
- 6 Jungle Mistic Incense (JWH-122)
- 6 Bonzai (JWH-122; JWH-018)
- 1 Genie
- 1 Orange Oxana
- 1 Amnesia
- 1 Atomic bomb (JWH-018)
- 1 Ocean Burst Red (JWH-122; JWH-018; JWH-073)
- 6 Generic herbal blend (JWH-122; JWH-018; JWH-073)

Source: Italian National Early Warning System

Manifestazioni cliniche principali (n = 33)*



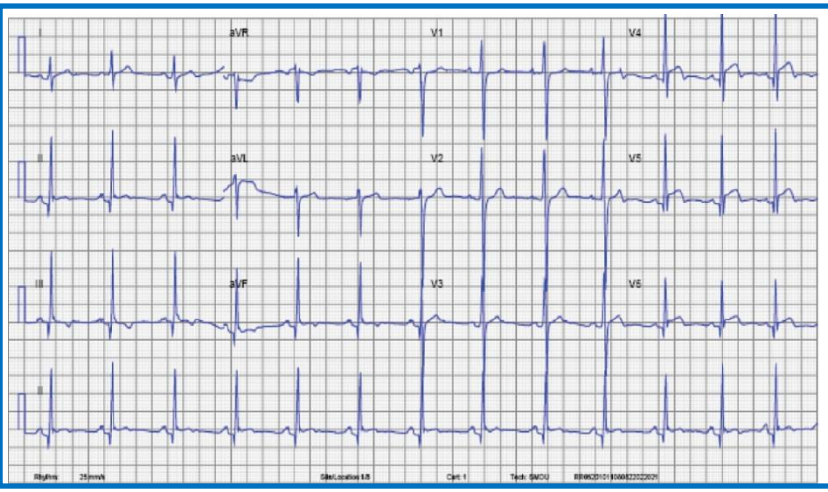
* other symptoms (frequency < 4%): syncope, hypertonia, clonus, choreoathetosis, aphasia, diplopia, hypotension



M, 16 attività sportiva non agonistica
In PS per dolore toracico (da 3 giorni)
ECG elevazione ST derivazioni inferolaterale – TN 3 (vn <0.4 ng/ml)
Ecocardiografia : nella norma

Dopo 24 ore: peggioramento clinico e stumentale (ECG); aumento della TN 25
Coronarografia : nella norma

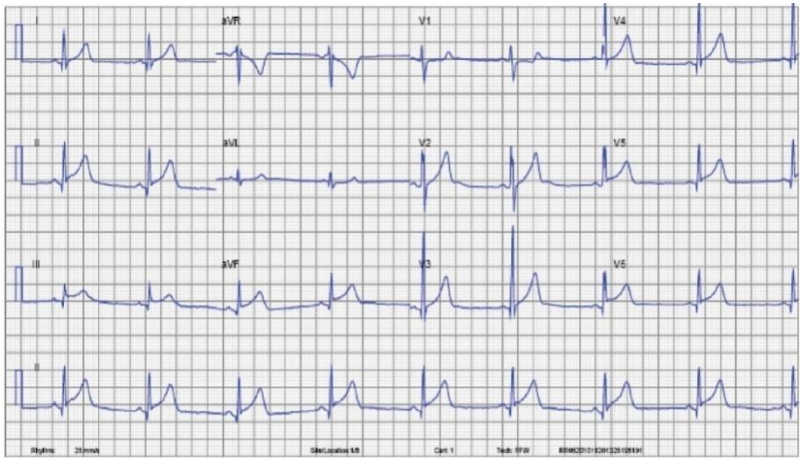
Assunzione K2 → 24 ore prima dell'esordio dei sintomi
Marijuana → 3 settimane prima



M, 16
In PS per dolore toracico (da 1 settimana): "fastidio al cuore", episodi di durata di 30 minuti
ECG elevazione ST derivazioni inferolaterale – TN 11.6
Ecocardiografia : nella norma

Coronarografia : nella norma

Assunzione K2 → 3 gg prima dell'esordio dei sintomi
Marijuana → 2 settimane prima



M, 16
In PS per dolore toracico (da 3 giorni): retrosternale, episodico, episodi di durata di 1-2 ore
ECG elevazione ST derivazioni inferolaterale – TN 7
Ecocardiografia : nella norma

Dopo 24 ore: peggioramento ECG e aumento della TN 12

Assunzione K2 → 7 gg prima dell'esordio dei sintomi

Negatività urinaria per: JWH-018 e -073

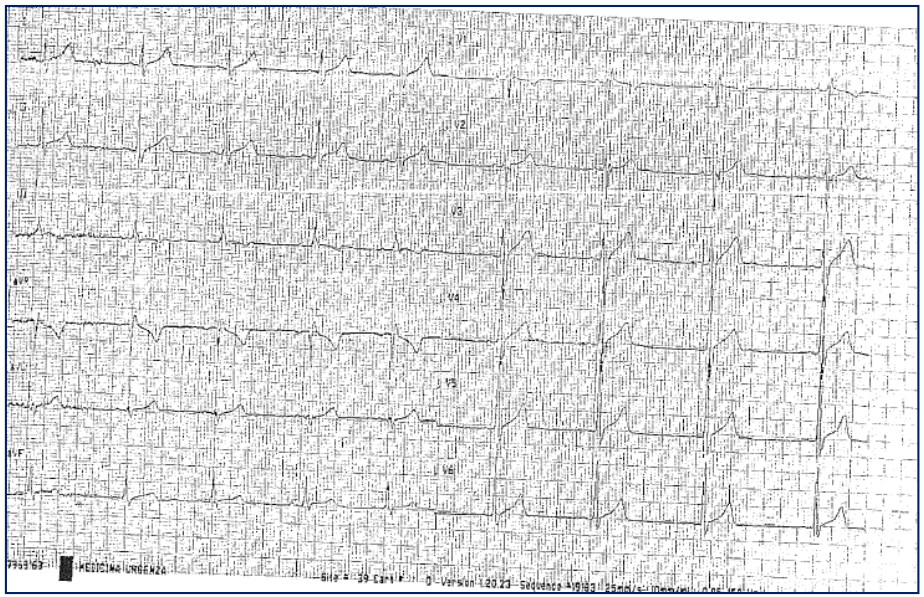
Mir et al., 2011

Bonzai

M, 19 → in PS alle 21.38
Assunzione nel pomeriggio di *Bonzai*

Dopo l'assunzione ha presentato:
malessere generale, nausea e vomito e allucinazioni

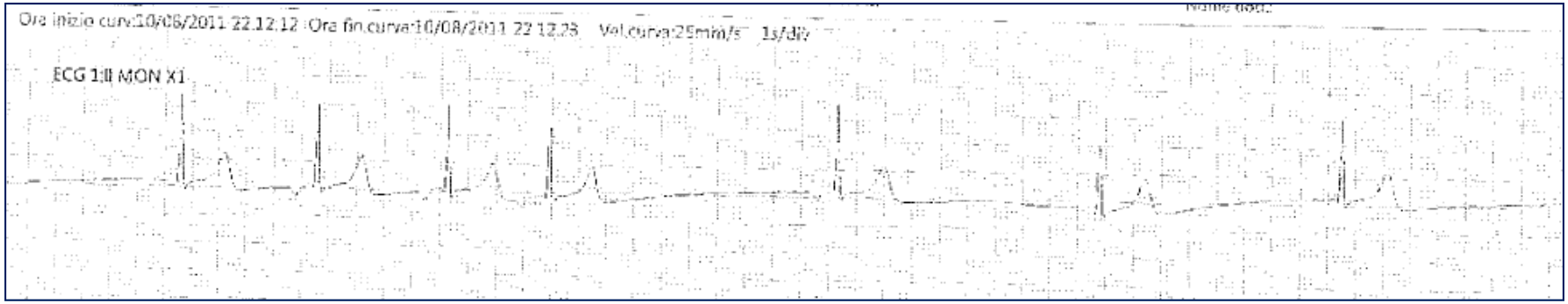
In PS: paziente amnesico rispetto al consumo del prodotto.



Dopo 24 ore:
bradicardia (frequenza variabile tra 39 e 42 bpm) con alcuni battiti ectopici.

Dopo 72 ore:
asintomatico ma con persistenza di alterazioni all'ECG (frequenza cardiaca media di 55 bpm, con valori minimi di 37 bpm, ritmo atriale ectopico con BAV 2°grado).

→ JWH-122
→ (negativo per : JWH-018; JWH-250; JWH-200; JWH-073; AM-694; WIN 55212)



Letters to the Editor

Psychiatric Sequelae of Spice, K2, and Synthetic Cannabinoid Receptor Agonists

TO THE EDITOR: Spice and K2 are among the plethora of herbal smoking blends available at smoke shops and via the internet. These otherwise inert herbal mixes are adulterated with synthetic cannabinoid receptor agonists, which are responsible for their psychoactive effects. Users may manifest a variety of neuropsychiatric symptoms.[1] Here, we describe the case of a patient using these products who presented with symptoms of psychosis.

Mr. A was a 20-year-old honors college student who presented to the emergency department with severe anxiety and paranoia. Work-up was negative for any acute medical problem and urine toxicology screening was negative. Psychiatric consultation was requested to evaluate for new onset psychosis.

Examination revealed a healthy appearing man who was anxious, tachycardic, and diaphoretic, with halting speech and avoidant eye contact. He described a gradual increase in anxiety over the previous 6 months, acutely worse over the last 2 weeks with development of paranoia and both auditory and visual hallucinations. He noted that this acute exacerbation of his symptoms coincided with his new daily habit of smoking marijuana (that had started 3 weeks prior to his Emergency Department presentation), which he had hoped would assuage his anxiety, but Δ^9-tetrahydrocannabinol (THC) was not detected in his urine. On further questioning, he clarified that he had actually been smoking Spice purchased from a local smoke shop.

It was unclear if Mr. A was experiencing a drug-induced psychosis or exacerbation of a nascent primary psychosis. He declined voluntary psychiatric admission. He was counseled to stop smoking Spice; immediate outpatient psychiatric follow-up was arranged.

Synthetic cannabinoid receptor agonists, such as JWH-018 and HU-210, have become popular alternatives to marijuana since they can be obtained legally in many parts of the United States and via the internet (although a number of jurisdictions have recently passed legislation outlawing their sale).[1] JWH-018 (the active agent in Spice) is a potent agonist of cannabinoid receptor 1 (CB_1), whereas THC is postulated to only be a weak agonist.[2] While little information exists on the association between synthetic cannabinoids and psychosis, there are data to suggest that cannabis use is associated with the development or worsening of psychosis.[3] Given similar receptor activity and possible greater potency, it is plausible that synthetic cannabinoids may also be associated with psychosis.

Unlike marijuana, synthetic cannabinoids are not detected by conventional urine drug tests,[1] thus clinicians should familiarize themselves with the names of these products available in their area and ask patients specifically about their use. Anecdotal reports of hypokalemia associated with the use of these substances may provide an objective diagnostic clue.[1] In this case, Mr. A admitted to using marijuana despite a negative urine drug screen, prompting a more detailed discussion about the type of "marijuana" he was smoking. Unfortunately, other patients may not be quite so forthcoming.

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References

1. Vearrier D, Osterhoudt C: A teenage with agitation: higher than she should have climbed. Pediatr Emerg Care 2010; 26: 462–465
2. Atwood BK, Huffman J, Straiker A, et al: JWH018, a common constituent of 'spice' herbal blends, is a potent and efficacious cannabinoid CB1 receptor agonist. Br J Pharmacol 2010; 160:585–593
3. Every-Palmer S. Warning: Legal synthetic cannabinoid-receptor agonists such as JWH-018 may precipitate psychosis in vulnerable individuals. Addiction 2010; 105:1859–1860

Products containing synthetic cannabinoids and psychosis

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DOI: 10.1177/0004867411433974

To the Editor

In June 2011, products containing synthetic cannabinoids were banned in Western Australia (Sydney Morning Herald, 2011; Daily Telegraph, 2011). Elsewhere, they are sold in tobacco shops and are widely available (Sydney Morning Herald, 2011; Daily Telegraph, 2011). These products are most commonly known as 'kronic' or 'kronic black' in Western Sydney, but are also known as 'spice', 'K2', 'purple haze', 'kaos', 'dream', and 'voodoo'. Often these products are sold as mixtures of herbs and they are of particular relevance to Australian mining communities where they are not detected by urine drug testing (Sydney Morning Herald, 2011). There have been several case reports published internationally associating these products with psychosis (Muller et al., 2010; Johnson et al., 2011; Schneir et al., 2011; Simmons et al., 2011).

Although these products are reported to have been available in Australia for the last 2 years (Daily Telegraph, 2011), only in recent months has the problem of synthetic cannabis products and psychosis been recognized in patients presenting to Nepean hospital, Sydney. In these cases, psychosis has been associated with more agitation than would be expected from cannabis alone. This has been reported in case reports (Muller et al., 2010; Schneir et al., 2011; Simmons et al., 2011) and has been hypothesized to be related to differences in its chemical structure and in particular the absence of cannabidiol (CBD) which in itself is presumed to have antipsychotic potency (Every-Palmer, 2011).

Synthetic cannabinoid products are associated with psychosis, more prominent agitation, and are not detected by routine drug testing. Clinicians should consider screening for synthetic cannabinoid use when interviewing patients presenting with psychosis or agitation.

Ischemic stroke after use of the synthetic marijuana "spice"

Melissa J. Freeman, MD
David Z. Rose, MD
Martin A. Myers, MD
Clifton L. Gooch, MD
Andrea C. Bozeman, MS, ARNP-C
W. Scott Burgin, MD

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ABSTRACT

Objectives: To report and associate acute cerebral infarctions in 2 young, previously healthy siblings with use of the street drug known as "spice" (a synthetic marijuana product, also known as "K2"), which they independently smoked before experiencing acute embolic-appearing ischemic strokes.

Methods: We present history, physical examination, laboratory data, cerebrovascular imaging, echocardiogram, ECG, and hospital course of these patients.

Results: We found that in both siblings spice was obtained from the same source. The drug was found to contain the schedule I synthetic cannabinoid JWH-018. Full stroke workup was unrevealing of a stroke etiology; urine drug screen was positive for marijuana.

Conclusions: We found that our 2 patients who smoked the street drug spice had a temporal association with symptoms of acute cerebral infarction. This association may be confounded by contaminants in the product consumed (i.e., marijuana or an unidentified toxin) or by an unknown genetic mechanism. The imaging of both patients suggests an embolic etiology, which is consistent with reports of serious adverse cardiac events with spice use, including tachyarrhythmias and myocardial infarctions. *Neurology*® 2013;81:2090–2093

NATIONAL EARLY WARNING SYSTEM

Severity of poisonings

Substance Abuse and Mental Health Services Administration
SAMHSA
Behavioral Health is Essential to Health
Prevention Works • People Recover
Treatment is Effective

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SAMHSA News Release

Date: 12/4/2012 9:00 AM
Media Contact: SAMHSA Press Office
Telephone: 240-276-2130

First-of-its-kind report finds that street forms of "synthetic marijuana" products linked to thousands of hospital emergency departments visits each year

Young people, particularly males, most often involved

3 deaths may be tied to synthetic marijuana in Colorado

By **Jacque Wilson**, CNN
September 7, 2013 -- Updated 1550 GMT (2350 HKT)

Smoking synthetic marijuana may damage kidneys

Cathy Payne, USA TODAY *7:11 p.m. EST February 14, 2013*

Synthetic Marijuana Use During Pregnancy Can Cause Symptoms of Preeclampsia and Eclampsia

FILED UNDER **HEALTH & WELLNESS**, **SUBSTANCE ABUSE** BY LENA BUTLER

Like 2 +1 Tweet

Journal of Analytical Toxicology 2013;37:534–541
doi:10.1093/jat/bkt068 Advance Access publication August 22, 2013

Special Issue

Toxicological Findings of Synthetic Cannabinoids in Recreational Users

Robert Kronstrand[1,2*], Markus Roman[1], Mikael Andersson[1] and Arne Eklund[1]

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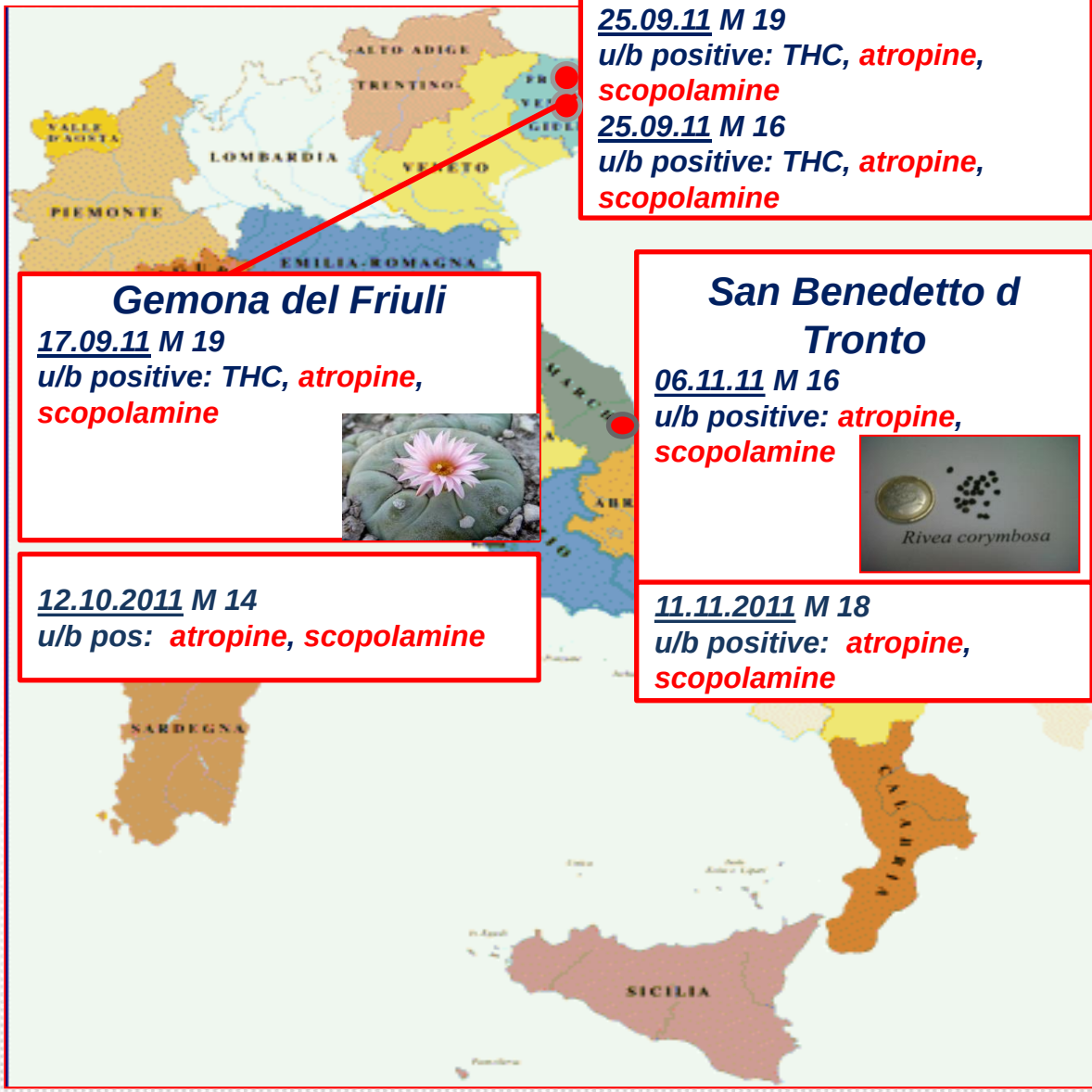
[2]Division of Drug Research, Linköping University, Linköping, Sweden

In recent years, several synthetic cannabinoid compounds have become popular recreational drugs of abuse because of their psychoactive properties. This paper presents toxicological findings of synthetic cannabinoids in whole blood from some cases of severe intoxication including quantitative data from recreational users and a fatal intoxication. Samples were analyzed by liquid chromatography–tandem mass spectrometry in a scheduled multiple reaction mode after a basic liquid extraction. Twenty-nine synthetic cannabinoids were included in the method. In our data set of ~3000 cases, 28% were found positive for one or more synthetic cannabinoid(s). The most common finding was AM-2201. Most of the analytes had median concentrations of <0.5 ng/g in agreement with other published data. The emerging drugs MAM-2201 (n = 151) and UR-144 (n = 181) had mean (median) concentrations of 1.04 (0.37) and 1.26 (0.34), respectively. The toxicity of the synthetic cannabinoids seems to be worse than that of natural cannabis, probably owing to the higher potency and perhaps also to the presence of several different cannabinoids in the smoked incense and the difficulties of proper dosing. The acute toxic effects may under certain circumstances contribute to death.

Anticholinergic poisoning cases reported to NEWS

- young people
- geographical and temporal distribution
- symptomatology → a "toxidrome"
- antidotic treatment → physostigmine



Tolmezzo
***25.09.11* M 19**
u/b positive: THC, atropine, scopolamine
***25.09.11* M 16**
u/b positive: THC, atropine, scopolamine

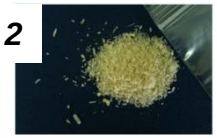
Gemona del Friuli
***17.09.11* M 19**
u/b positive: THC, atropine, scopolamine

***12.10.2011* M 14**
u/b pos: atropine, scopolamine

San Benedetto d Tronto
***06.11.11* M 16**
u/b positive: atropine, scopolamine

***11.11.2011* M 18**
u/b positive: atropine, scopolamine

Identified cathinones and related formulations (seizures)



Dec, 2011
Milan
Pentedrone (1)
Methylone (2)
4-MEC (3)
Mephedrone (4)

Dec, 2010
Bolzano
Flephedrone
Mephedrone
MDPV

March, 2010
Treviso
Mephedrone

March, 2010
Padova
Mephedrone

March, 2010
Modena
Mephedrone

March, 2011
Milan
3-FMC

July, 2010
Venice
Mephedrone (50%)

November, 2011
Venice
α-PVP, 4-MEC

Agugust , 2010
Treviso
Mephedrone (45%)
4-MEC+MDPV
MDPV+4-FA
4-MEC+MDPV+4-FA
Cocaine+MDPV
Cocaine+MDPV+4-MEC
Methylone

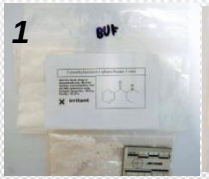
June, 2010
Val di Susa
Butylone and Methylone

Sept, 2010
Rome
Pentedrone
Pyrovalerone
Dipipanone

March, 2011
Vicenza
Butylone

February, 2011
Rome
Butylone

Dec, 2011
Naples
Buphedrone (1)
N-ethylcathinone



January and June, 2010
Catania - Mephedrone and Caffeine

August, 2011
Verona
Butylone

Cathinons: acute poisoning cases in 2010-2012

anno	Sesso, età	sostanza dichiarata	Esami Tossicologici (sangue=S e urine=U)	Altre positività e negatività agli esami tossicologici (sangue=S e urine=U)
2010	M, 36	GHB Mefedrone (fertilizzante)	non eseguiti	non eseguiti
2011	M, 20	3 capsule bianche	**Butilone e MDPV (U)**	**THC: positivo (U)** LSD, atropina, scopolamina, mefedrone: negativo (U)
2011	M, 18	cannabis	**4-MEC (U)**	Ketamina, atropina, scopolamina, mefedrone, levamisolo: negativi (U) cannabinoidi sintetici: negativi (S)
2011	M, 24	concime (droga sintetica)	**Butilone (U)**	Ketamina, atropina, scopolamina, mefedrone, levamisolo: negativi (U) cannabinoidi sintetici: negativi (S)
2012	M, 37	6-APB (Benzofuria)	**4-MEC e** 6-APB (prodotto) 4-MEC negativo (U e S)	**6-APB: positivo (S e U)** THC, cocaina, metadone, oppiacei, amfetamine, MDMA: negativo (U). Alcolemia: negativo
2012	M, 34	mefedrone	**4-MEC (U e S)**	Ketamina, atropina, scopolamina, levamisolo, mefedrone, butilone, metossietamina, APB (isomeri), 4-FA, MDAI: negativo (U)
2012	M, 25	Ketamina, ecstasy, cocaina, popper	**Mefedrone (U)** **pentedrone (U)**	**Ketamina/norketamina, levamisolo, cocaina, amfetamine, ecstasy in urina: positivi (U)** Atropina, scopolamina, butilone, 4-MEC, PMA, PMMA, metossietamina, APB (isomeri), 4-FA, MDAI: negativo (U)
2012	M, 38	MDMA, Energy, Crystal, mefre	**MDPV (U e S)**	Ketamina, atropina, scopolamina, levamisolo, mefedrone, butilone, 4-MEC, metossietamina, APB (isomeri), 4-FA, MDAI: negativo (U)

Forensic Science International 210 (2011) 195–200

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New designer drug of abuse: 3,4-Methylenedioxypyrovalerone (MDPV). Findings from apprehended drivers in Finland

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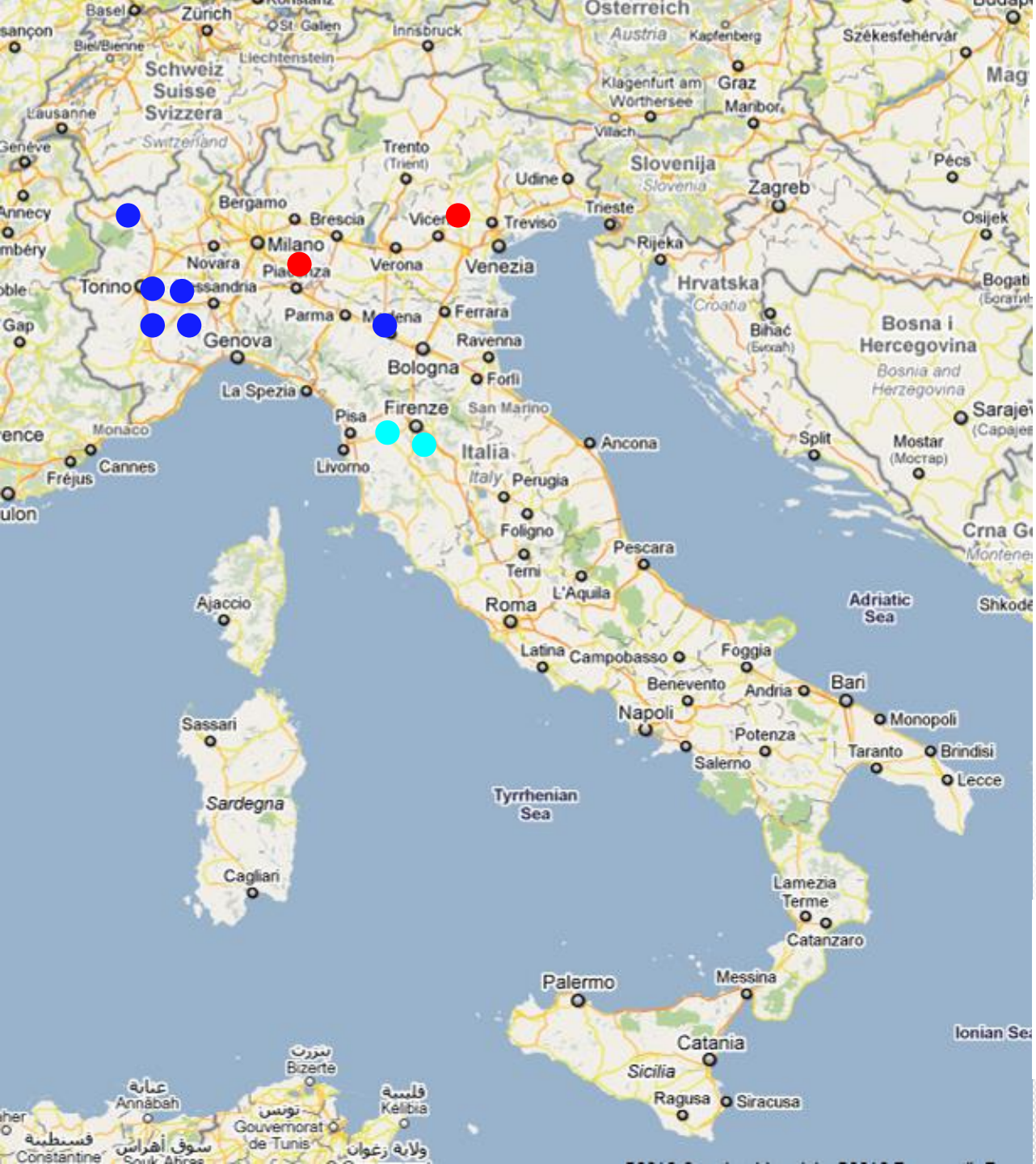
A B S T R A C T

Starting in 2008 a new designer drug, 3,4-methylenedioxypyrovalerone (MDPV) appeared among users of illegal drugs in Finland. Since then there have been several seizures of MDPV by police and customs and it has been connected to many crimes of different types. In this study the incidence and impact of the use of MDPV in drivers suspected of being under the influence of drugs (DUID) in Finland was assessed.

Since autumn 2009, blood samples from drivers suspected of DUID in Finland have been analysed for the presence of MDPV. A new LC–MS/MS method for the determination of MDPV in serum was established. In order to assess the impact of MDPV on driving performance, drug and alcohol findings of positive MDPV cases were compared with data from the clinical examination carried out while the suspect was under arrest. In a period of one year there were 259 positive MDPV cases from apprehended drivers (5.7% of all confirmed DUID cases). In 80% of the cases in which MDPV was found, amphetamine was also present. Benzodiazepines were also frequently found together with MDPV, which was to be expected since in Finland, in our experience, stimulants are very often used together with benzodiazepines.

In most cases it remained unclear whether the observed psycho-physical achievement deficiency was induced by MDPV because the concentrations of other drugs, especially other stimulants, were often high. However, in some subjects, MDPV, or MDPV in combination with other substances was the most probable cause of the impairment. The concentrations of MDPV varied from 0.016 mg/L to over 8.000 mg/L.

Little is known about the pharmacology of MDPV. However, based on our findings it is clear that MDPV has a serious impact on traffic safety in Finland.



Clinical survey in the emergency setting for fentanyls (Jan 2007- Aug 2012)

10 cases

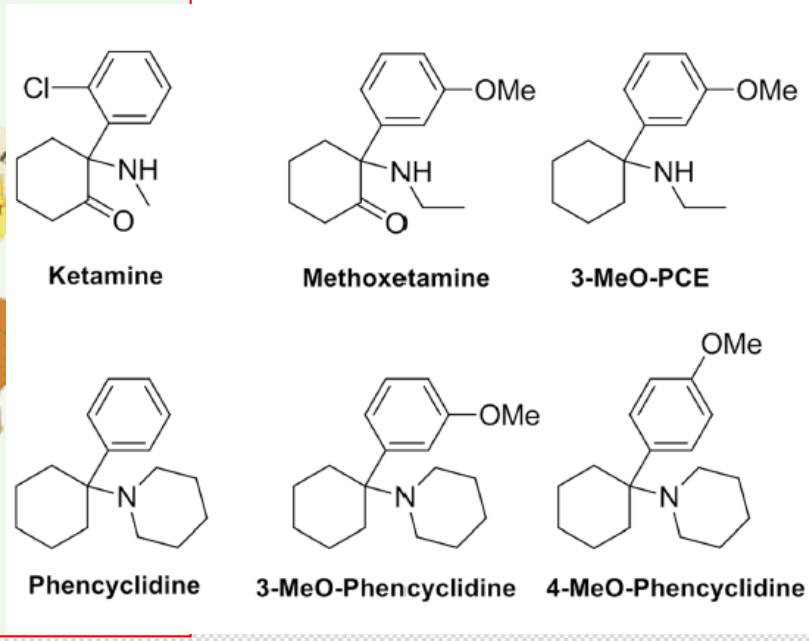
- **6 “White” or “China white”**
- **2 medications**
- **2 medications (transdermal)**

Age: 20-49 years

Male / female → 8/2

Source: Italian National Early Warning System

MXE (methoxetamine) abuse: case series in Italy



12 MXE confirmed intoxications in 1 year

(Feb 2012 – Feb 2013)

Age, sex	Subtances	Clinical manifestations	treatment	Lab results (positivity)
27, M	Dextromethorphan, mxe	severe psychomotor agitation, hallucinations confusion, tachycardia (120 BPM)	benzodiazepines, valproic acid, haloperidol	**MXE** (product) and biological samples(167 mcg/ml urine, 0,2 mcg/ml serum). Methorphan urine
17, M	MDMA, 1 blue pill and ketamine	severe psychomotor agitation, hallucinations, mydriasis	fluids and benzodiazepine	**MXE** (198 ng/ml serum e 9000 ng/ml urine), ketamine/nork, MDMA, MDA, amphetamine, THC (urine)
24, M	Unknown	severe psychomotor agitation, hallucinations, mydriasis, tachycardia (150 BPM)	benzodiazepine, betablocker (metoprolole) e calcium channel blockers (diltiazem)	**MXE, APB**-isomers, levamisole, methadone, benzoilecgonine, ecsatsy (urine); ethanol (2,7 g/L)
38, M	Unknown and ethanol	severe psychomotor agitation, aggressive, mydriasis, hypertension (150/90 mmHg)	fluids	**MXE** (167 ng/ml serum e 7400 ng/ml urine), **APB**-isomers (164 ng/ml), amphetamine and MDMA urine
23, M	Ethanol, unknown (red liquid contained in 3 vials)	confusion, drowsiness, rhabdomyolysis (CPK 1400 U/L)	symptomatic	**MXE**, levamisole, benzoilecgonine, THC e opiates (urine)
23, M	THC and ketamine	coma, dyspnoea, (Sat O_2 90%)	naloxone 0.2 mg, fluids	**MXE**, ketamine and norketamine (urine)
22, M	THC and ketamine	severe psychomotor agitation and hallucinations, dissociative state, mydriasis	symptomatic	**MXE**, ketamine/norketamine (urine)
16, F	Ethanol and unknown	severe psychomotor agitation, confusion, amnesia	G/E decontamination, fluids	**MXE** e THC (urine)
17, F	unknown	severe psychomotor agitation, confusion hallucination and amnesia, miosis,	G/E decontamination, fluids	**MXE**, THC, ketamine, norketamine (urine)
23, M	ethanol and ketamine	drowsiness, tachycardia, vertical nistagmus, SatO_2 93%	G/E decontamination, fluids	**MXE**, benzoilecgonine, levamisole (urine)
22, F	ethanol, ketamine, heroin	drowsiness, hypertension	G/E decontamination, fluids, naloxone	**MXE**, benzoilecgonine, levamisole (urine)
18, F	Ketamine and LSD	tremors, chest pain, myalgia	benzodiazepines, fluids	**MXE** (urine)

MXE assumption has never been declared in the history

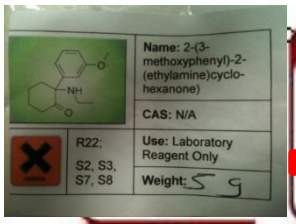
Chronic abuse of MXE and dextromethorphan (et al.....)

clinical course

period of hospitalization in ED and ICU **(red)** and in psychiatry **(blue)**

MXE
3-MeO-PCP
confirmed in urine samples

MXE in product and MXE and methorphan in biological samples



ICU
6 weeks

Coma (GCS 3)
Creatinine 4.03 mg/dL (anuric)
Mioglobine 35103 (< 105.7 ng/mL)
CPK 795.908 (<397 U/L)
ICU (3 weeks of CRRT)

MXE and methorphan in biological samples

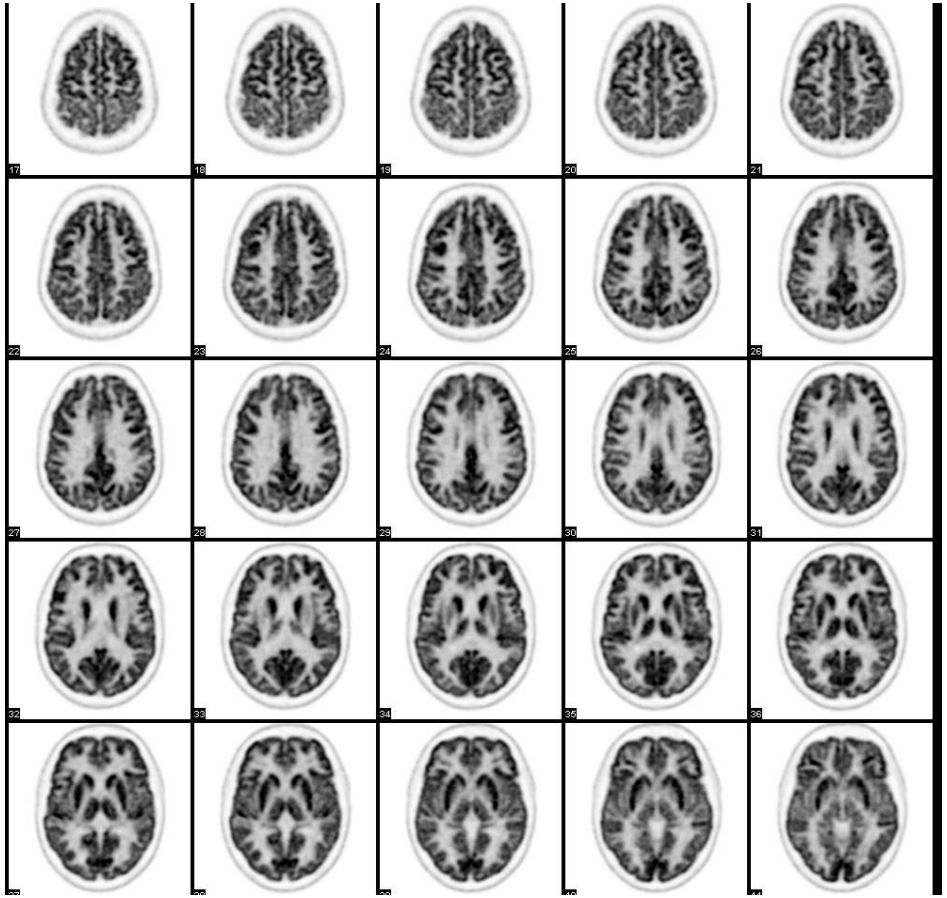
diprophylline

diprophylline
methylphenidate

Medical hystory of the patient: abuse of THC, MDMA and Ketamine.

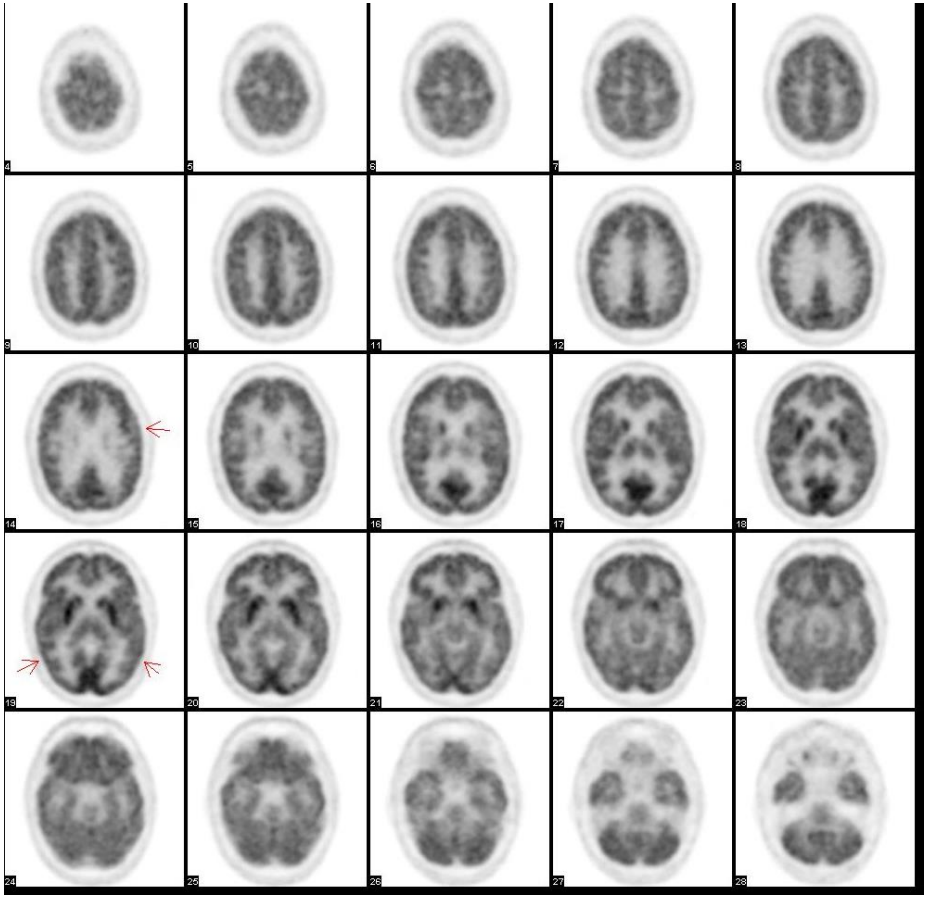
PET Cerebrale

Soggetto sano



omogenea distribuzione del 18F-FDG a carico della corteccia cerebrale, più marcato a carico dei nuclei della base e della corteccia occipitale.

Caso clinico



diffusa riduzione della fissazione del 18F-FDG a carico della corteccia cerebrale, più marcato a livello della corteccia temporo-parietale (vedi freccia). Appare conservata la captazione in corrispondenza dei nuclei della base e , in parte, della corteccia occipitale; tutto il resto è ridotto

Cases requiring differential diagnosis for meningoencephalitis or septicemia

sex, age	CNS	body temp (°C)	other signs and symptoms	treatment	invasive tests for diagnosis	substances	Lab result*
M, 33	Severe psychomotor agitation, seizure,	39	Miosis, 200 BPM, metabolic acidosis (pH 7.26; lactate 14), rhabdomyolysis (62300 U/l), AST 1724, LDH 5035 , renal impairment	fluids, urine alkalinisation, benzodiazepines, chlorpromazine	Cranial CT scan	Cocaine, other (?)	cocaine, levamisole
M, 30	confusion, severe psychomotor agitation	38	xerostomia, mydriasis, muscle rigidity, 140 BPM, rhabdomyolysis (3300 U/l)	fluids, benzodiazepines, orotracheal intubation	Cranial CT scan	unknown	atropine/ scopolamine
M, 40	confusion, severe psychomotor agitation	39.3	mydriasis, muscle rigidity, 140 BPM, metabolic acidosis, rhabdomyolysis (24000 U/l)	fluids, urine alkalinisation, benzodiazepines, orotracheal intubation, CRRT	Cranial CT scan	Meth (ice)	amph, caffeine (product assumed)
F, 21	Coma, seizure, severe psychomotor agitation, respiratory failure	39.1	tachycardia, metabolic acidosis	fluids, urine alkalinisation, benzodiazepines, orotracheal intubation	Cranial CT scan	unknown	THC (serum and urine)
M, 40	severe agitation, coma	39.2	mydriasis, profuse sweating, t167 BPM, diffuses clonuses, rhabdomyolysis (2592 U/l)	Fluids , intravenous midazolam , propofol , ceftriaxone and acyclovir	cranial-MRI and CT-scan, CSF analysis	Benzofury (APB, 4-MEC)	MDMA and amph (urine); APB-isomers

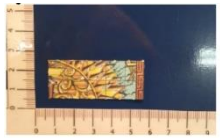
*lab analysis: JWH-200, JWH-073, JWH-302, JWH-250, JWH-007, JWH-081, JWH-098, JWH-398, JWH-147, JWH-016, JWH-018, JWH-307, JWH-122, JWH-019, AM-2233, AM-2201, AM-694, MAM-2201, WIN-55212, WIN-48,098, RCS4,RCS8 – ketamine, atropine/scopolamine, mephedrone, butylone, dimethylcathinone, dimethylmetcathinone, buphedrone, etcathinone, 4-fluormetcatinone, Pentedrone, Metedrone, Etilone, Pentilone, 1-naphyrone, MDPV, MXE, 4-MEC, 5-APB/6-APB, dimethyltriptiamine, 2-C-I, 2-C-T7, 2-C-B, DOB - 4-fluoroamfetamina, MDAI, PMMA-PMA.

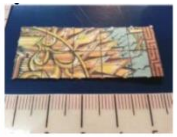
Fenetilaminedella serie 2C (sequestri – 2013. elenco non esaustivo - e casi di intossicazione acuta)

25I-NBOME
Maggio 2013
Lecco
14 francobolli (294 mg)

2C-E
Ottobre 2013
Treviso

25I-NBOME; 25C-NBOME;
25H-NBOME
Ottobre 2013
Treviso



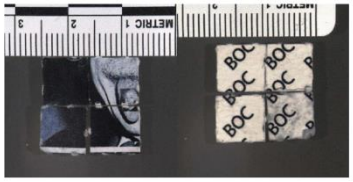


25I-NBOME
Maggio 2013
Venezia
"smile" colore giallo-arancio (20 mg)

25I-NBOME
LSD
Giugno 2013
Casale Monferrato
4 fracobolli, 20 mg

25C-NBOME
Ottobre 2013
Terlano

25I-NBOME; 25C-NBOME; 25H-NBOME
Settembre 2013
Savona

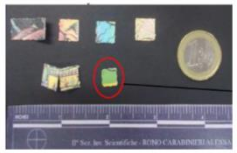


DOC
marzo2013
Firenze

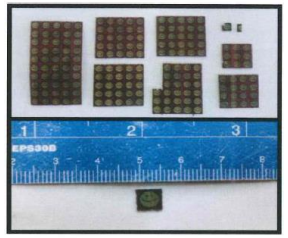
DOB - DOC
Marzo 2013
Ancona

2C-B
Aprile 2013
Perugia

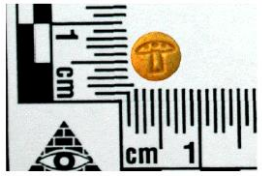
25I-NBOME
LSD
Giugno 2013
Casale Monferrato
52 fracobolli, 28 mg



25C-NBOME
25H-NBOME
Maggio 2013
Vibo Valentia
179 blotter art – 19-20 mg



6-APDB
Agosto 2013
Reggio Calabria
0,143 gr



2C-B
Agosto 2013
Reggio Calabria
0,143 gr

NATIONAL EARLY WARNING SYSTEM

PRESIDENZA DEL CONSIGLIO DEI MINISTRI
Dipartimento Politiche Antidroga

SISTEMA NAZIONALE DI ALLERTA PRECOCE
NATIONAL EARLY WARNING SYSTEM - N.E.W.S.

31/10/2013
Prot. EWS 277/13

Alla c.a.

Ministero della Salute - Direzione Generale Prevenzione
Ministero della Salute - Direzione Generale dei Dispositivi Medici, del Servizio Farmaceutico e della Sicurezza delle Cure
Agenzia Italiana del Farmaco
Assessorato Regionale alla Sanità
Assessorato Regionale alle Politiche Sociali
Referenti regionali per le Tossicodipendenze
Centri Collaborativi del Sistema Nazionale di Allerta Precoce
Servizi per le tossicodipendenze
Comunità terapeutiche
Unità mobili Croce Rossa Italiana
Unità di Emergenza Urgenza

Oggetto: Aggiornamento Allerta grado 3 “Segnalati casi di sequestro di prodotti contenenti la molecola 25I-NBOMe e segnalazione per la prima volta in Italia dell’identificazione delle fenetilammine 2C-C-NBOMe e 25H-NBOMe”.

1. Segnalazioni ricevute

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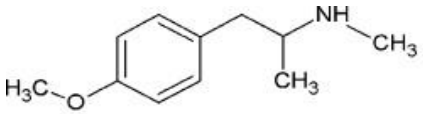
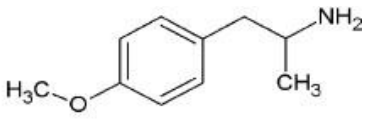
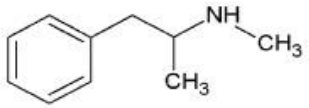


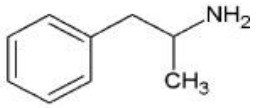
PMMA



PMA



Methamphetamine



Amphetamine

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ISSN 0001-5172

Case Report

Paramethoxyamphetamine (PMA) poisoning; a 'party drug' with lethal effects

S. REFSTAD
Department of Anaesthesiology and Intensive Care, Central Ho

Forensic Science International 219 (2012) 151–157

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journal homepage: www.elsevier.com/locate/forsciint

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

Merete Vevelstad [a,*], Elisabeth Leere Øiestad [a], Gerrit Middelkoop [a], Inger Hasvold [a], Peer Lilleng [b], Gerd Jorunn M. Delaveris [a], Tormod Eggen [c], Jørg Mørland [a,d], Marianne Arnestad [a]

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PMA-PMMA poisoning

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Caso 1 – 17 anni – Imperia agosto 2012	**Caso 2 – 16 anni – Treviso agosto 2012**	**Caso 3 – 17 anni – Pietra Ligure - settembre 2012**
soccorso all'interno di bosco nei pressi di un rave-party CLINICA • grave agitato • confuso • allucinato (riferiva di vedere insetti) • midriatico • tachicardico • etanolemia negativa • benzodiazepine Peridodo di ossrevazione: 12 ore	soccorso nei pressi discoteca CLINICA: • estremamente agitato • midriatico • modesta tachicardia (FC 105 bpm). • crisi epilettiche subentranti (stato di male generalizzato) → benzodiazepine poi con propofol → IOT • lieve innalzamento di troponina e mioglobina 48 ore di ricovero TI	CLINICA: • estremamente agitato • midriatico • FC 110 bpm dopo somministrazione di beta-bloccante • Stop beta-bloccante → trattamento con benzodiazepine Nota: screening positivo per AMF / MET come negli altri 2 casi

NPS and treatments

- acute effects
  - CNS: benzodiazepines, propofol, GA
  - cardiovascular: CCBs, vasodilators (nitroglycerin)
  - other: ……

- addiction
  - ?

- withdrawal
  - ?

- prolonged/chronic effects (medium / long term)
  - quetiapine?
  - topiramate ?
  - ?

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05/12/2013
Prot. EWS 278/13

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Oggetto: Aggiornamento Allerta grado 3 – "Registrati 2 nuovi casi di intossicazione acuta da cannabinoidi sintetici ed identificati, per la prima volta in Italia, i cannabinoidi sintetici AKB-48F, 5FUR-144, AKB48, 5F-PB22, STS-135 e MAM-2201"

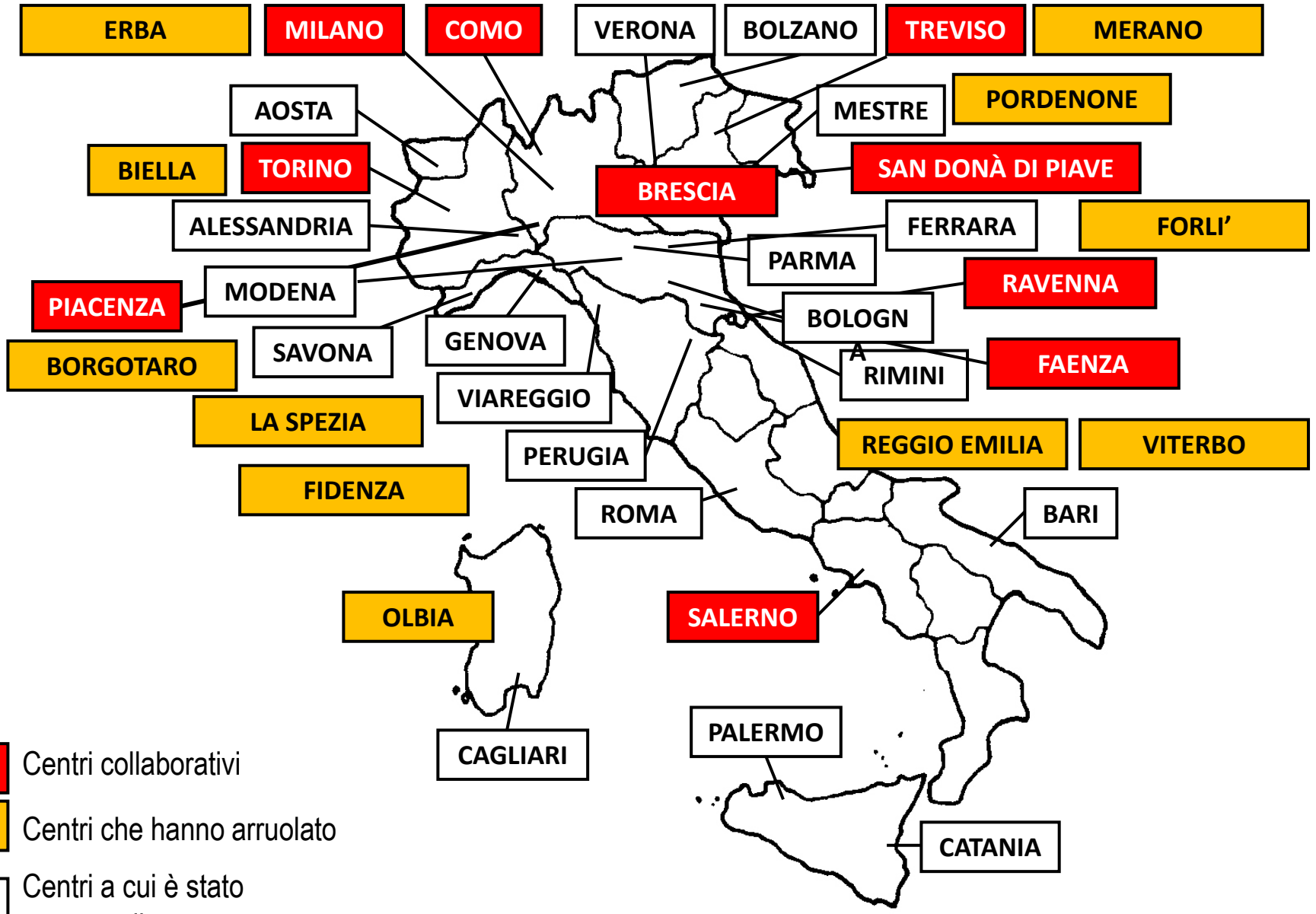
A seguito dell'attivazione della prima Allerta "Individuazione del cannabinoide sintetico JWH-018 in un prodotto denominato "n-Joy" acquistabile su Internet e negli smart shop" (Prot. EWS 84/10 del 26/02/2010) e dei successivi aggiornamenti, il Sistema Nazionale di Allerta Precoce ha ricevuto 10 nuove segnalazioni: 2 nuovi casi di intossicazione acuta da cannabinoidi sintetici registrati nell'area di Bologna e di Vipiteno, e casi di sequestro, con l'identificazione, per la prima volta in Italia, dei cannabinoidi sintetici AKB-48F, 5FUR-144, AKB-48, 5F-PB22, STS-135 e MAM-2201.

VARD - Violence and date Rape Drugs

Collaborative centres

- Dipartimento Politiche Antidroga – Presidenza del Consiglio dei Ministri
- *Tossicologia Forense - Università Cattolica del Sacro Cuore, Roma*
- *Centro Antiveleni - Centro Nazionale di Informazione Tossicologica, IRCCS Fondazione Maugeri e Università degli Studi, Pavia*
- > 130 cases enrolled (January 2013 - today)

PROGETTO VARD – CENTRI COLLABORATIVI



Allerte NEWS (Jan 2010 - Sep 2013)

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2010
- Eroina
- Eroina / Bacillus Anthracis
- N-Joy / JWH-018*
- N-Joy / JWH-073*
- Mefedrone
- MDPV
- Forest Green / JWH-250*
- Jungle Mistic Incense / JWH-122*

2011
- Ketamina*
- eroina con caffeina*
- decessi droga-correlati
- PMMA decessi
- decessi droga-correlati
- overdose non letali
- PMMA decessi
- JWH-210, JWH-019 *
- decessi droga-correlati
- eroina tipo “brown sugar” e “white” con metorfano, decessi

2012-settembre 2013:
- overdose da oppiacei
- cannabinoidi sintetici *
- overdose da oppiacei
- JWH-022, AM-2201 *
- Metossietamina *
- JWH-073
- 4-MEC, metilone, bufedrone
- Eroina/BacillusAnthracis
- 4-metilamfetamina decessi
- 6-APB *
- Eroina/Bacillus anthracis
- RCS-4, AM-2233, JWH-307 *
- 5-IT
- catinoni sintetici*
- Eroina/Bacillus anthracis
- PMA/PMMA *
- Metossietamina*
- 25I-NBOMe, 2C-B, 2C-H
- 2C-B, 2C-E*
- 4-MA
- Metossietamina*

** Casi identificati da CAV Pavia*

Conclusions

- patient history is frequently false / incorrect
  - the patients is uninformed about the substances used in more than 40-50% of the cases
- the same product may vary in the composition in a little period of time
- the knowledge of the substances available in a period of time in a specific region can help physicians in the diagnostic process
- co-assumption of more than two substances is frequent
- the severity of poisoning differs among the diverse cannabinoids/cathinons/other NPS
- the toxic effects (severity, duration) of several new substances are mostly unknown at this time
- the easy evaluation of the behavioural toxic effects may lead to underestimation of severe cardiovascular complications
- analytical tests usually available in EDs are insufficient to characterize the actual pattern of abuse → a need in emergency care
  - only in less than 10 % of our "sentinel" cases there is relation between reported substance and analytical results

Conclusions

- analytical tests usually available in EDs are insufficient to characterize the actual pattern of abuse → a need in emergency care
  - only in less than 10 % of our "sentinel" cases there is relation between reported substance and analytical results

- specifically organized PCC and clinical-toxicology Labs are the clinical services that more rapidly can
  - notice changes and news in this field → help EDs
  - correctly evaluate and demonstrate the relationships between the clinical effects and the analytical data (→ patients)
    - → several NPS → included in the Italian list of controlled substances in 2010-2013 thanks also to this activity
  - identify the analytical needs (e.g. point of care testing) for the emergency setting lined up the new trends of abuse
    - → stimulus for the industrial production of new methods/test/…

- NEWS: efficient and crucial system to detect/define/evaluate the medical aspecst of NPS