I-SEE
European Project
on New Psychoactive Substance

Co-funded by the Prevention of and Fight against Crime Programme of the European Union
JUST/2013/ISEC/DRUGS/AG/6426

STUDY VISIT TO ITALY

December 14th – 18th 2015

Wednesday, 16th December – Pavia

Poison Control Center "S. Maugeri"

Dr Carlo Alessandro Locatelli

In the morning the delegates visited the Pavia Poison Control Center "S. Maugeri". Dr Locatelli explained the activities of the center and its structure. Great relevance was given to the NPS issue, highlighting their collaboration with the National Early Warning System (NEWS) program. Moreover, several clinical cases were also described.

Policlino San Matteo

Dr Pietro Papa

Dr Papa presented the Policlinico San Matteo and its laboratories.

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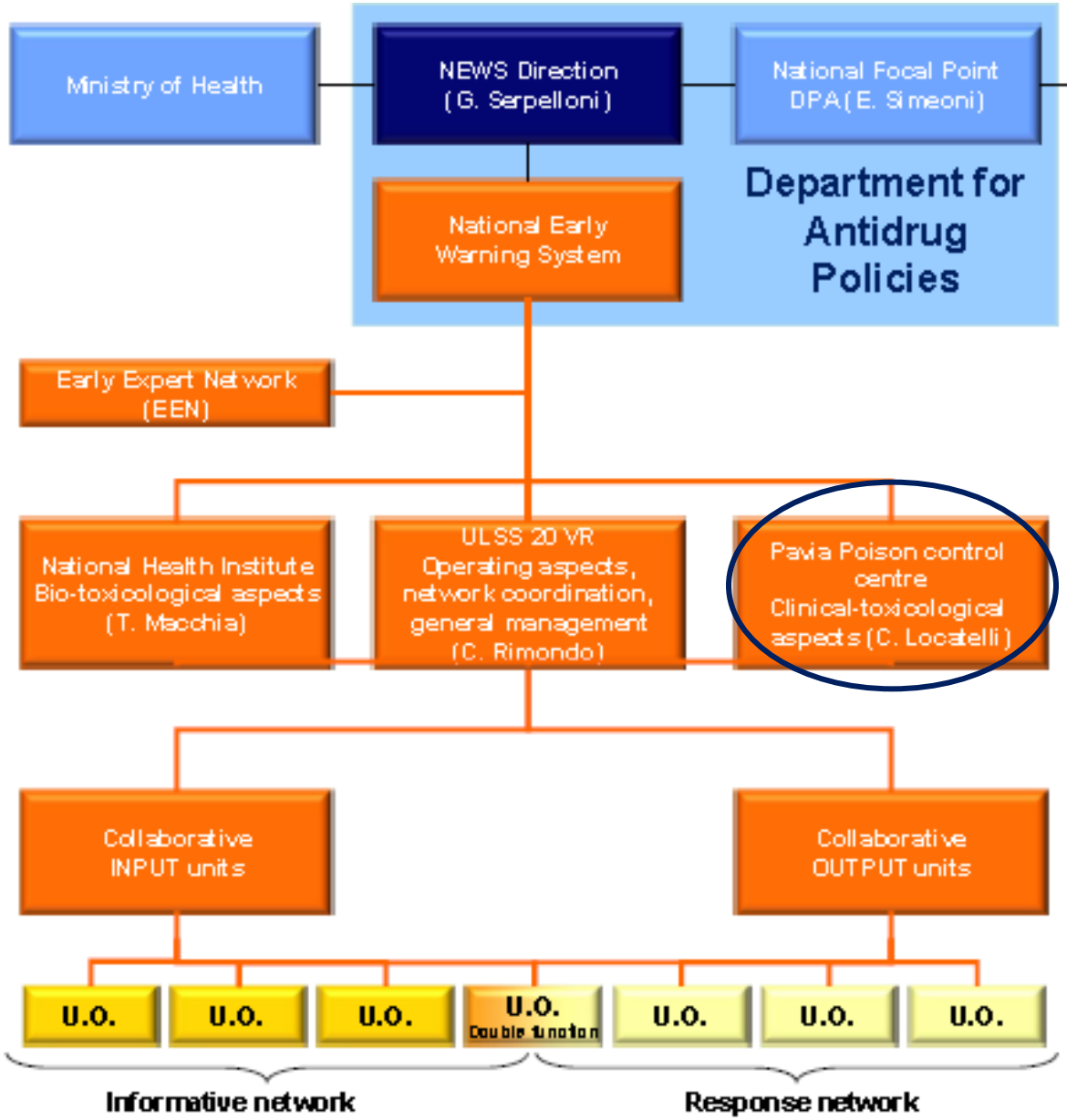
Poison Control Centres and Tox Labs clinical-toxicological network in Italy NPS intoxications - examples

Carlo Locatelli M.D.

- Pavia Poison Control Centre - National Toxicology Information Centre, Pavia
- National Early Warning System

The Italian NEWS

NATIONAL EARLY WARNING SYSTEM



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

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

Accordo, ai sensi dell'articolo 4 del decreto legislativo 28 agosto 1997, n. 281, tra il Governo, le Regioni e le Province autonome di Trento e di Bolzano concernente la definizione di attività ed i requisiti basilari di funzionamento dei Centri Antiveleni.

Rep. Atti n. 56/CSR del 28 febbraio 2008

LA CONFERENZA PERMANENTE PER I RAPPORTI TRA LO STATO, LE REGIONI E LE PROVINCE AUTONOME DI TRENTO E BOLZANO

Nella odierna seduta del 28 febbraio 2008:

VISTI gli articoli 2, comma 1, lettera b) e 4 del decreto legislativo 28 agosto 1997 n. 281 che attribuiscono a questa Conferenza la facoltà di promuovere e sancire accordi tra il Governo e le Regioni e le Province autonome, in attuazione del principio di leale collaborazione, al fine di coordinare l'esercizio delle rispettive competenze e svolgere attività di interesse comune;

VISTO il decreto legislativo 14 marzo 2003, n. 65, ed in particolare l'articolo 15 e l'allegato XI, che indicano alcune caratteristiche operative minime dei Centri Antiveleni in Italia per l'accesso alla Banca Dati Preparati Pericolosi dell'Istituto Superiore di Sanità;

VISTO il capitolo 5, paragrafo 5.8 del Piano Sanitario Nazionale 2006-2008, nella parte in cui sottolinea l'importanza di sistemi di sorveglianza sindromica che utilizzano dati prediagnostici tali da indicare gli stadi precoci di situazioni emergenziali, da attivare prioritariamente nei servizi assistenziali di emergenza quali Pronto Soccorso e Centri Antiveleni;

CONSIDERATO che i Centri Antiveleni svolgono funzioni specifiche, non riconducibili ad altre strutture operative;

RITENUTO necessario, ai fini di un corretto funzionamento della rete dei Centri Antiveleni, pervenire ad un accordo per la definizione delle attività assicurate dai Centri Antiveleni, dei requisiti basilari per il loro funzionamento e delle modalità di raccordo per la costituzione della rete;

CONSIDERATO che il Ministero della salute ha attivato, nel gennaio 2007, un gruppo misto Regioni – Ministero al fine di poter pervenire ad un Accordo, da perfezionarsi in questa Conferenza, concernente il funzionamento dei Centri antiveleni ed il loro inserimento nella rete di sorveglianza sindromica come strutture specialistiche che svolgono funzioni non riconducibili ad altre strutture operative del Servizio Sanitario Nazionale;

CONSIDERATO che il predetto gruppo ha elaborato i seguenti documenti:
- Centri antiveleni (CAV);
- Definizione di un set minimo di dati condiviso dai Centri antiveleni (CAV);
- Sindromi tossicologiche da agenti chimici;

Presidenza del Consiglio dei Ministri
CONFERENZA PERMANENTE PER I RAPPORTI TRA LO STATO, LE REGIONI E LE PROVINCIE AUTONOME DI TRENTO E BOLZANO

VISTA la nota del 19 luglio 2007, con la quale il Ministero della salute ha trasmesso la proposta di Accordo in oggetto concernente l'approvazione dei citati elaborati;

VISTA la lettera in data 16 novembre 2007, con la quale il Ministero della salute ha trasmesso la definitiva proposta di Accordo in oggetto modificata, rispetto alla precedente versione, con il recepimento delle osservazioni formulate in proposito dal Ministero dell'economia e delle finanze;

VISTA la nota in data 19 febbraio 2008, con la quale la Regione Toscana, Coordinatrice interregionale in sanità, ha comunicato il proprio assenso tecnico;

ACQUISITO, nel corso dell'odierna seduta, l'assenso del Governo e dei Presidenti delle Regioni e delle Province autonome,

SANCISCE ACCORDO

tra il Governo, le Regioni e le Province autonome di Trento e di Bolzano nei termini di seguito riportati:

Art. 1

Si approvano, ai fini della definizione delle regole per il funzionamento dei Centri Antiveleni, anche per il loro riconoscimento nelle sedi istituzionalmente competenti, i documenti di cui agli allegati 1, 2 e 3, parti integranti del presente Accordo, concernenti rispettivamente:
- Centri Antiveleni (CAV): funzioni, ruolo, obiettivi ed attività;
- Definizione di un set minimo di dati condiviso dai CAV;
- Sindromi tossicologiche da agenti chimici o più brevemente "sindromi chimiche" da includere nel pannello delle sindromi da sottoporre a sorveglianza da parte dei CAV.

Art. 2

Dall'attuazione del presente Accordo non devono derivare nuovi o maggiori oneri a carico della finanza pubblica.
I Centri Antiveleni provvedono alle attività previste dal presente Accordo con le risorse umane, finanziarie e strumentali disponibili a legislazione vigente.

IL SEGRETARIO
Avv. Giuseppe Busia

IL PRESIDENTE
On.le Prof. Linda Lanzillotta

Pavia Poison Control Centre - National Toxicology Information Centre

Personnel involved in the NEWS activities

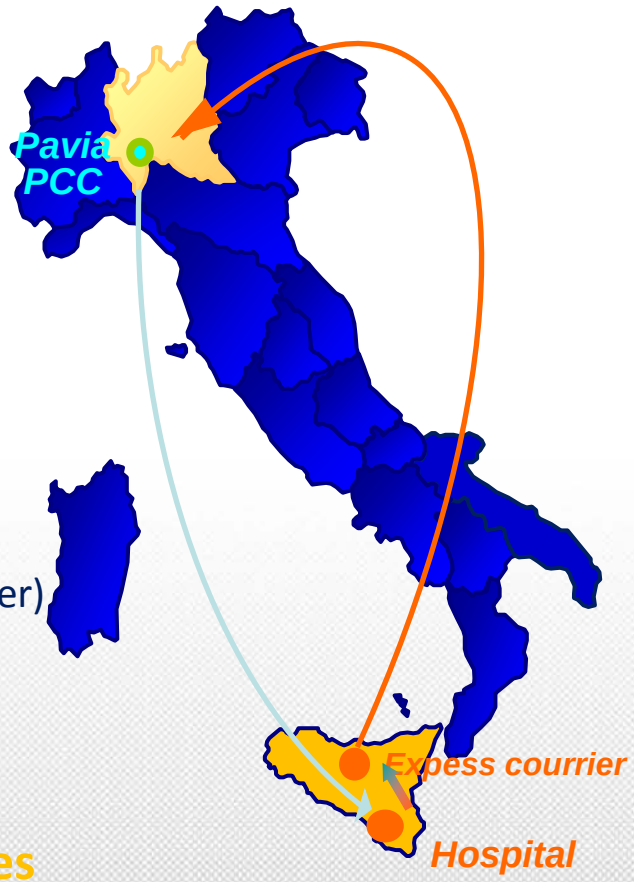
- **medical doctors → n. 7 / 9**
  - 24/24, 7/7 front-office → diagnosis and treatment (WHO, 1997)
    - Identification/selection of atypical/sentinel cases
- **pharmacists → n. 3**
- **computer technician: n. 1**
- **administrative: n. 1**

- **1st level Laboratory of analytical toxicology (emergency screenings and research activity)**
  - biologists: n. 2
  - laboratory technicians: 2
- **associated 2nd level Laboratory of clinical-analytical toxicology, IRCCS S. Matteo Hospital, Pavia (emergency activity)**
  - biologists: n. 5

Pavia Poison Control Centre - National Toxicology Information Centre

Procedures for the NEWS activities

- **internal data-base of cases**
- **clinical activity**
  - diagnosis / treatment
  - → complete follow-up
- **blood-urine samples collection**
  - hospital-to-hospital contact and agreement
  - transport
    - emergency action for severe intoxications (118, other)
    - delayed 1-2 days (courier)
  - stocking and PCC → laboratory transportation
- **Laboratory → analytical procedures and activities**



NPS → trend in EU

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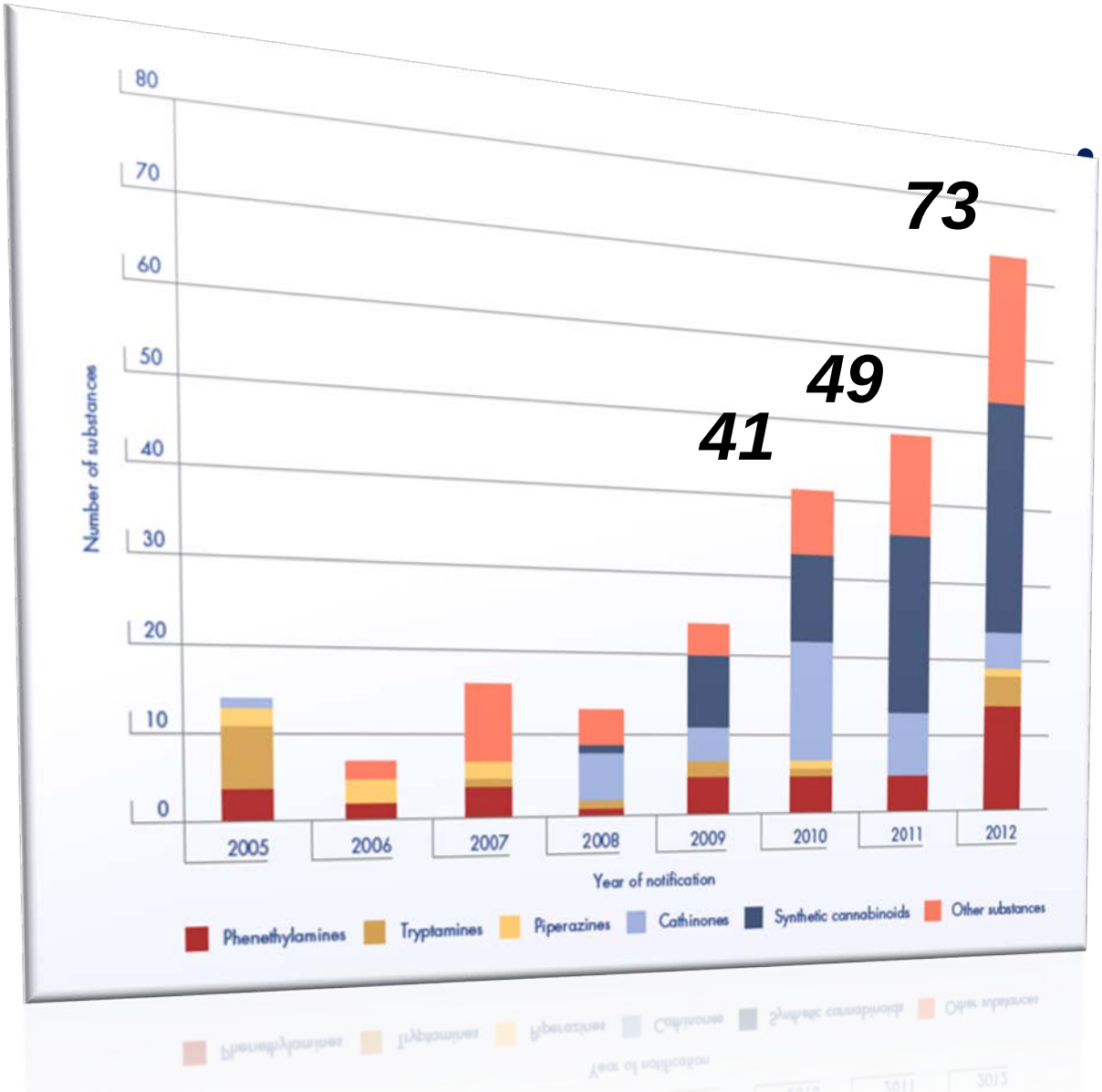

> 540 NSP detected by the EU Early Warning System (EWS) until Dec 2015

EMCDDA, 2015

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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

NPS medical relevance (?)

- Epidemiological data
  - EMCDDA
  - NEWS
  - ….
- Seizures / analytical identification
- Health effects → clinical effects
  - acute / chronic intoxications acute / death
  - addiction / tolerance / withdrawal
  - short / medium / long term heath concerns

Tossicological data on NPS

scientific literature

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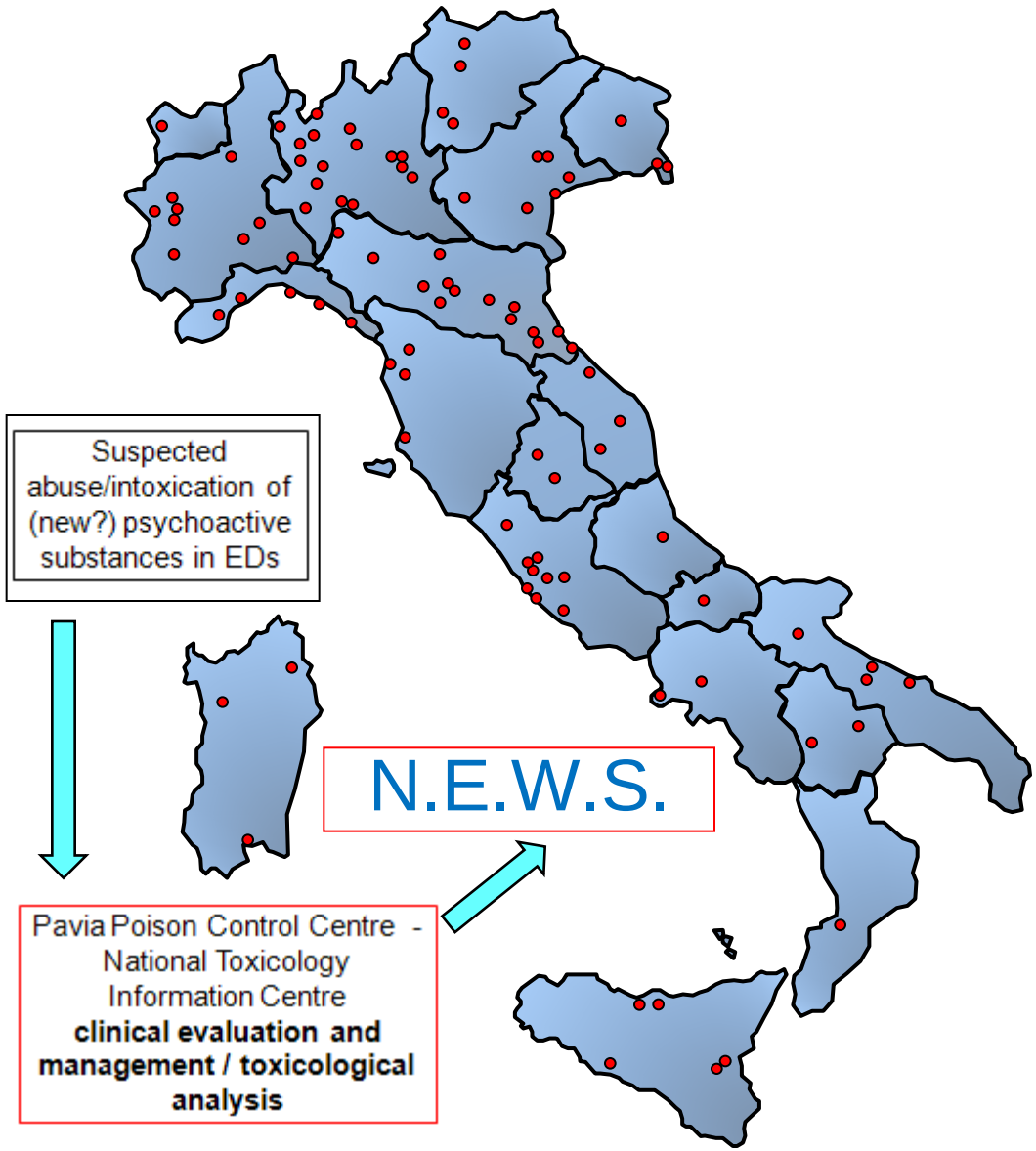
anni	Synthetic cannabinoid(s)	Synthetic cathinon(s)	Benzofury - APB	Methoxetamine
1969-2003	158	56	-	-
2004-2009	204	31	-	-
2010	51	17	-	-
2011	74	24	-	1
2012	107	51	-	11
2013 (September)	32	14	1	6
Tot human (pre-clinical)	594 (739)	180 (244)	1 (1)	18 (7)

Network of EDs (n. 234)



Pavia PCC and EDs network

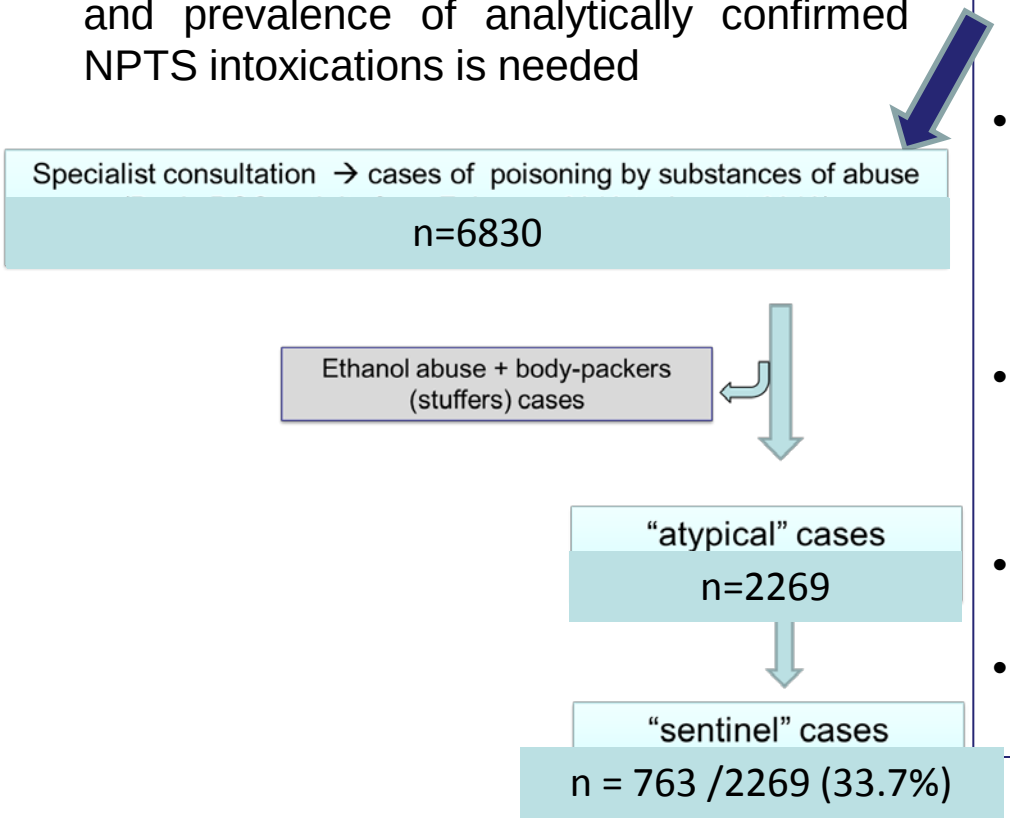
Detection, collection/evaluation of "new drugs" of abuse (NPSs) poisonings as national point of view

- 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 useful in the emergency setting
- post-acute consequences
- ……

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

Background

- prevalence and severity of patients admitted to the EDs for ***new psychoactive and toxic substances*** (NPTS) is insufficiently known
  - →diagnosis and clinical management ?
- "standard" toxicological screening results in most cases negative or positive to alcohol or to the "old" substances of abuse
- an improved evaluation of clinical features and prevalence of analytically confirmed NPTS intoxications is needed



Study methods – data until 04/2014

- February 2010 to April 2014, Italian EDs network referring to the Pavia Poison Control Centre (PPC)
- all consecutive cases due to suspected / confirmed substances of abuse poisoning were evaluate (n = 6830)
- Inclusion criteria: all cases presenting (i) history for NPTS or (ii) atypical-clinical pictures were assessed for: demographics, history, acute clinical manifestations, evolution and toxico-analytical investigations.
- Exclusion criteria: ethanol, cocaine, opiates, cannabis, ecstasy, amphetamine and methamphetamine were defined "old drugs": poisoning due solely these substances
- body-packers, cases not evaluated in EDs/ICUs, or traumatic, or with medic-legal implications
- Inclusion or exclusion criteria were applied prospectively by PPC clinical toxicologists
- In selected ("sentinel") cases a second level lab investigation was performed

Clinical pictures and management priorities in EDs

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- 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

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- 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
- ……

Impossibile visualizzare l'immagine.

Patients selection in the emergency setting

inclusion criteria

- subjects known/unknown as “abuser”
- subjects that refer a “recreational” use (frequent/occasional) of one/some new/undetermined/unknown substances (synthetic, natural) or “products”
- subjects that report the use of substances that are at present unidentifiable in EDs (independently from the positivity/negativity of common drugs testing)
- severe health effects due to
  - co-assumption of new and/or classical substances
  - new cutting substances

Patients selection in the emergency setting

inclusion criteria/method: → clinical picture

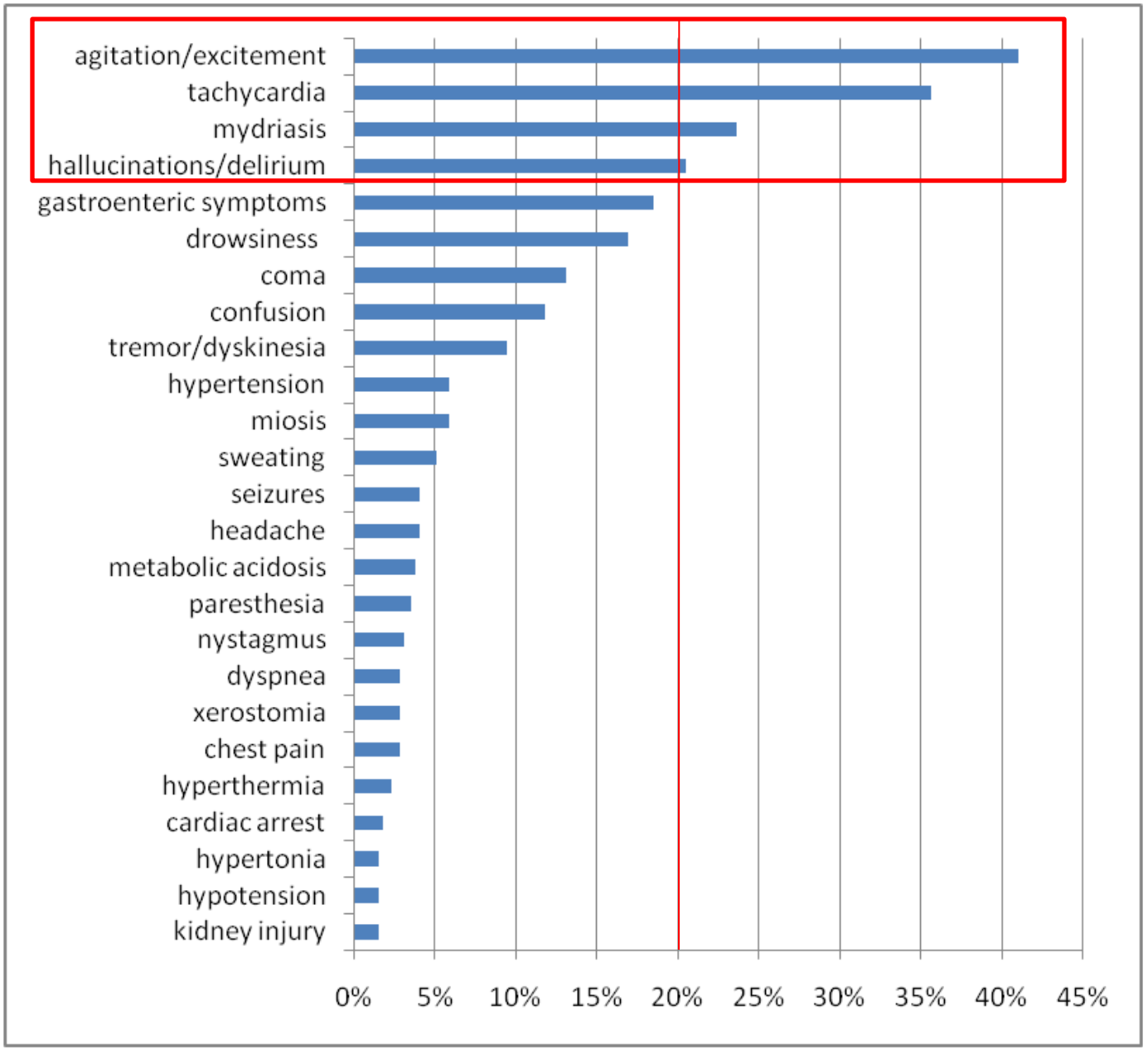
- “atypical” cases
  - suspected use of new substances
  - unusual clinical presentation

- “sentinel” cases
  - ascertained use of new substances of abuse, *or*
  - clinical effects do not correlate to the referred substances and/or to urine rapid detection of the classical* substances, *or*
  - severe clinical effects very likely related to new or still unknown substances (stimulants / excitants / hallucinogenic), even if unsuspected in the history

  - * classical substances
    - cocaine
    - opiates (e.g.. heroin, methadone)
    - cannabis
    - amphetamines / methamphetamines

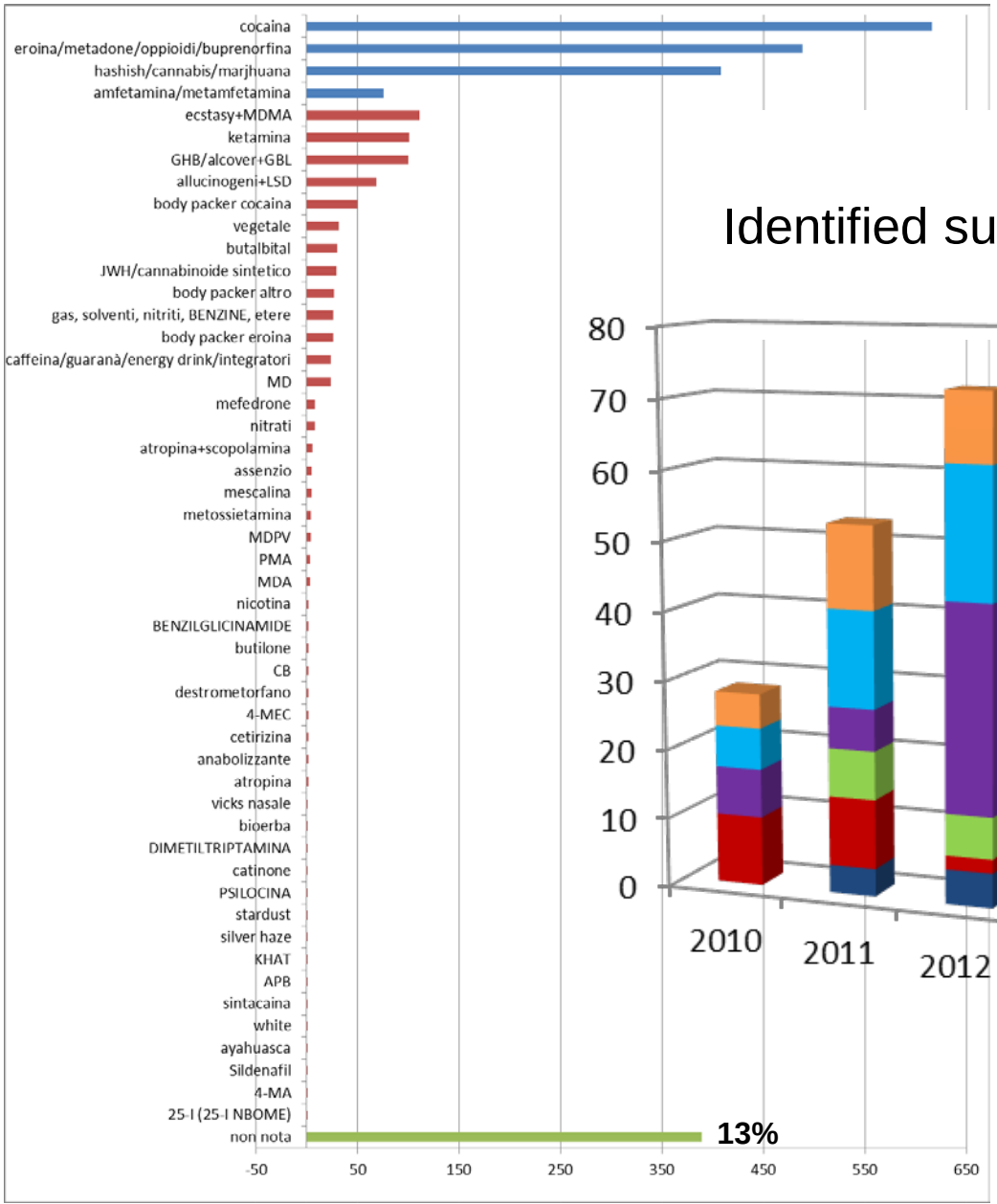
Results

Clinical manifestations of «sentinel» cases (n= 763) at EDs admission

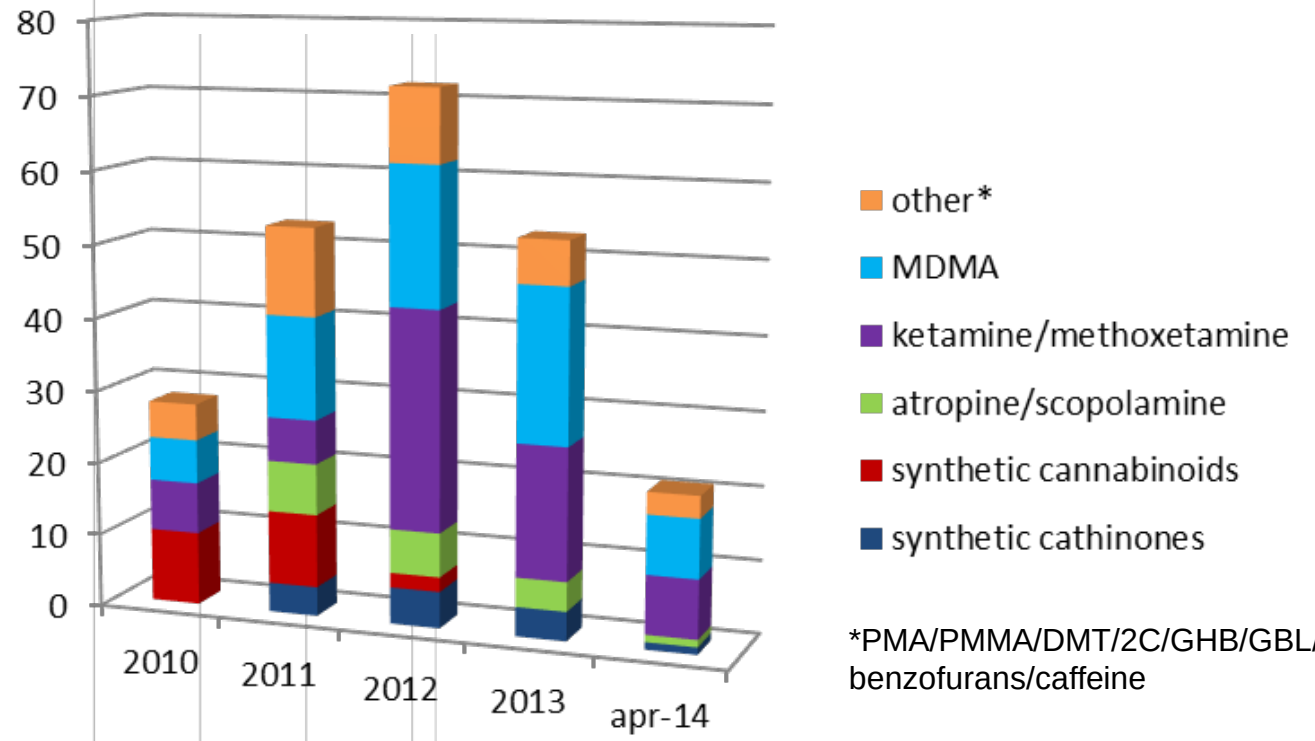


Results

Declared substances (n=2269 unusual cases)



Identified substances → 763 sentinel cases



*PMA/PMMA/DMT/2C/GHB/GBL/benzofurans/caffeine

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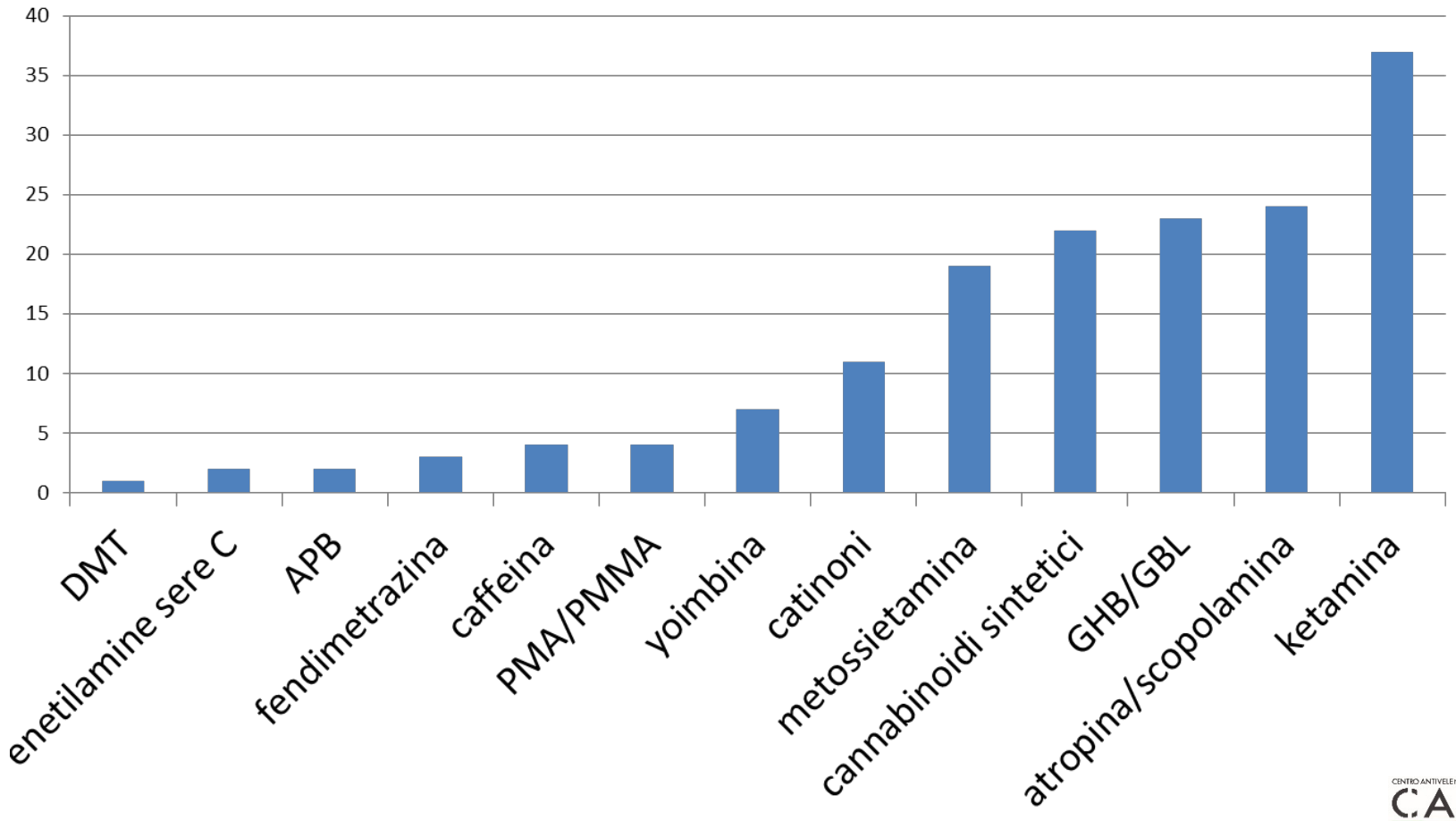
identified substances → 763 "sentinel" cases of NPS poisoning in Italy



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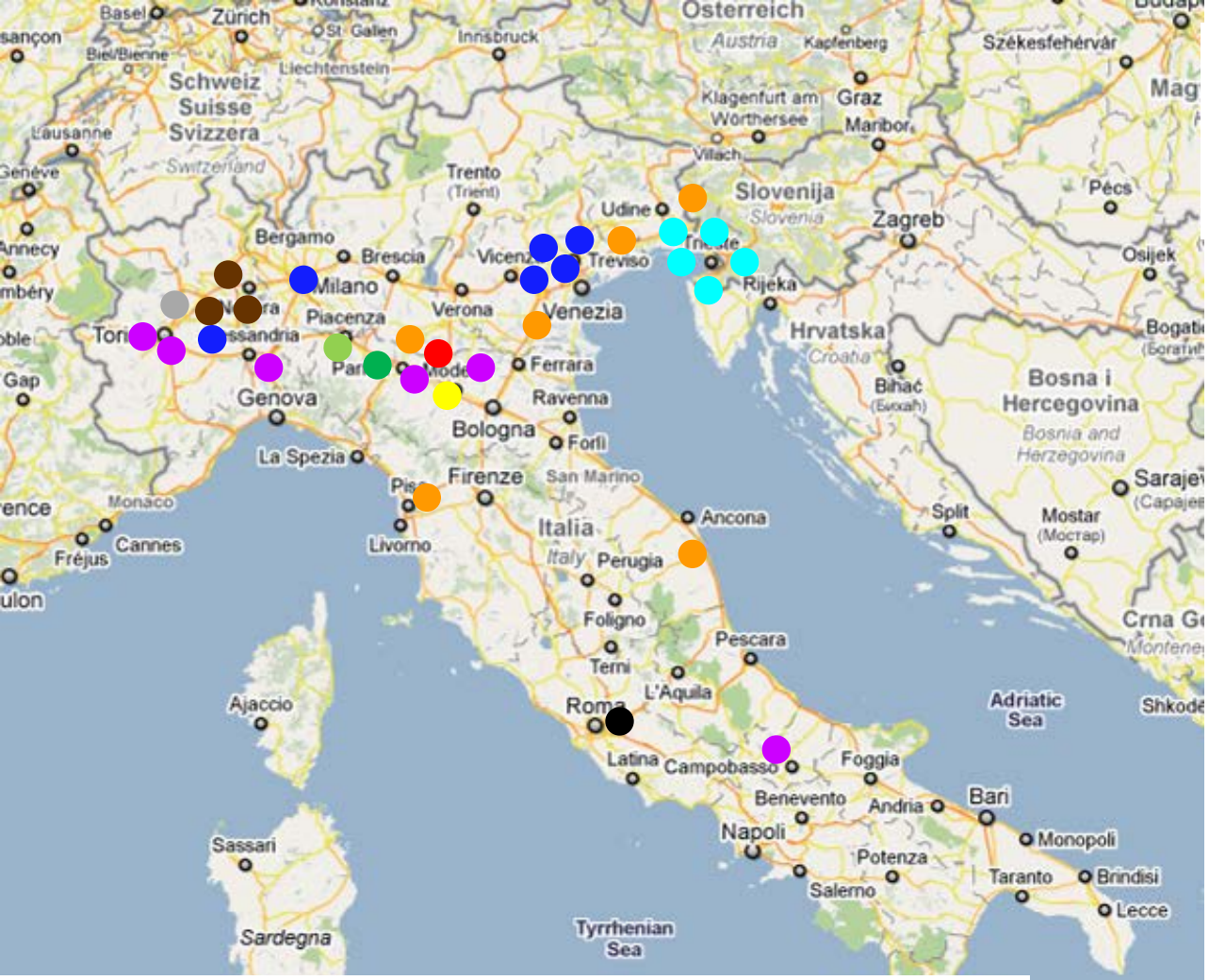


Clinical and/or lab-confirmed cases (Jan 2010- 29 Feb 2012)

33 cases

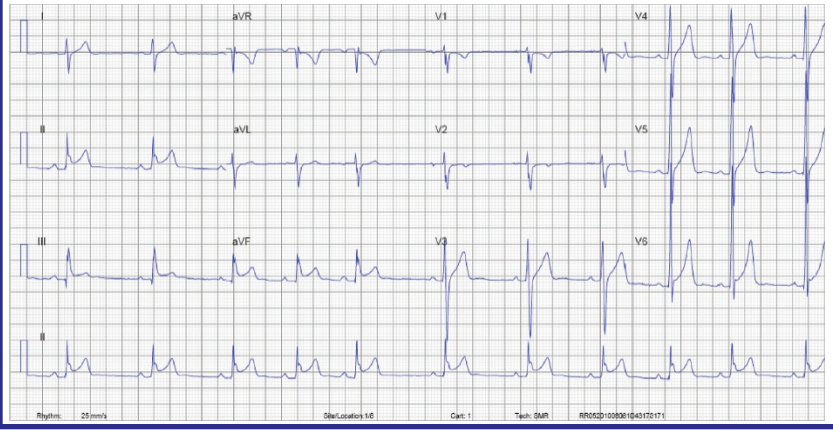
PRODUCT'S NAME

- 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)

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%

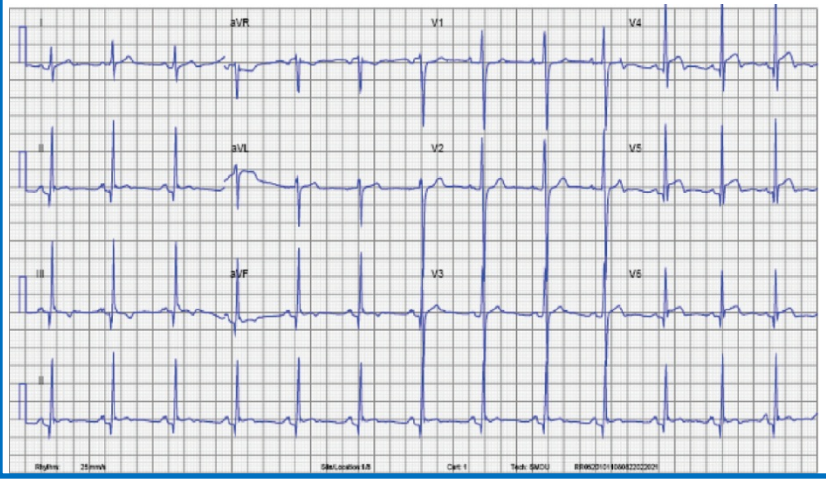
Source: Italian National Early Warning System



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

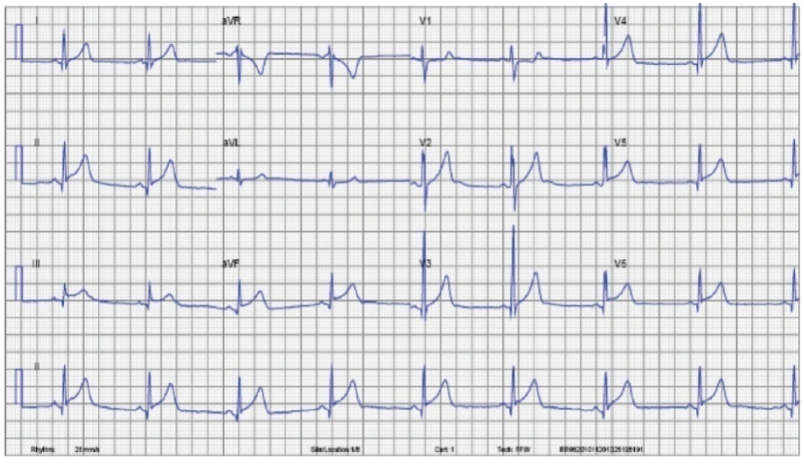
Assunzione K2 → 24 ore prima dell'esordio dei sintomi
Marijuana → 3 settimane prima



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

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.

Dawn M. Benford, MSN, PMHNP-BC
Jason P. Caplan, M.D.
Department of Psychiatry
St. Joseph's Hospital and Medical Center
Phoenix, AZ

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

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Products containing synthetic cannabinoids and psychosis

Vlasios Brakoulias

Discipline of Psychiatry, The University of Sydney and Nepean Hospital, Penrith, Australia

Corresponding author:
Vlasios Brakoulias, Discipline of Psychiatry, The University of Sydney and Nepean Hospital, Penrith, NSW 2751, Australia.
Email: vbrakoulias@bigpond.com

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

Correspondence to Dr. Burgin: wburgin@health.usf.edu

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

Severity of poisonings

NATIONAL EARLY WARNING SYSTEM

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

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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]

[1]Department of Forensic Genetics and Forensic Toxicology, National Board of Forensic Medicine, Linköping SE-58758, Sweden, and
[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.

PRESIDENZA DEL CONSIGLIO DEI MINISTRI
Dipartimento Politiche Antidroga

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

05/12/2013
Prot. EWS 278/13

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 – "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.

Clinical case: MAM-2201 intoxication after “synthacaine” consumption

ED admission:

- **Severe psychomotor agitation**
- Dry mouth
- Chest pain
- Severe dyspnoea
- tachycardia (150 bpm)
- hypertension (160/80 mmHg)

- CK (860 U/L; n.v. 24-195)
- glycaemia (160 mg/dL; n.v. 70 – 110)

- Treatment: fluids + diazepam (10 mg)

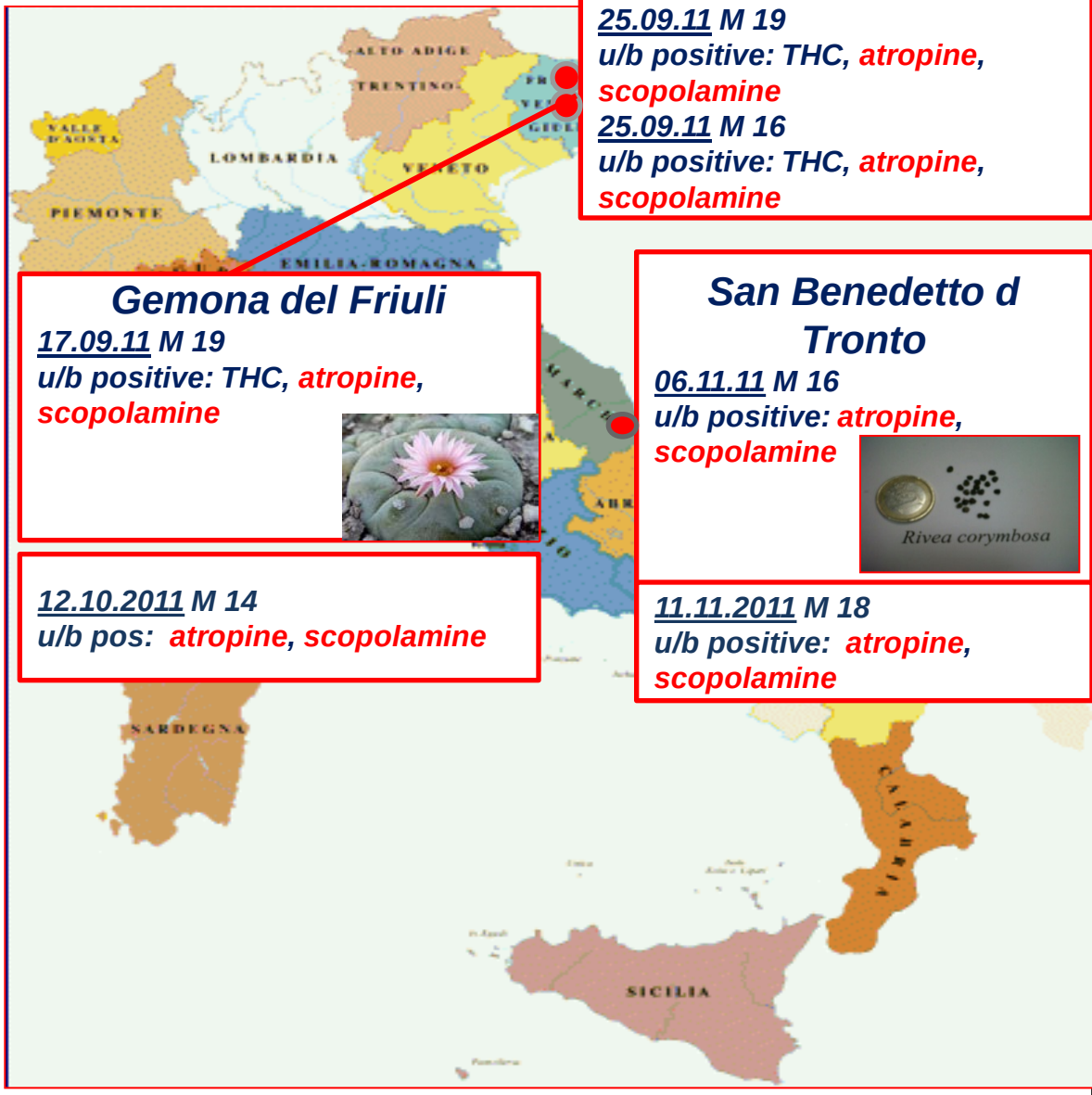
	powder	Urine	blood
	Results (methods; detection limits, LOD)		
Substances of abuse (opiates, cocaine, amphetamine, methadone, THC-COOH)	NEGATIVE (method GC-MS)	BENZOYLECGONINE (immunoassay)	BENZOYLECGONINE(137 ng/ml) (GC-MS; LOD Benzoylecgonine and cocaine 10 ng/ml)
Synthetic cannabinoids[a]	MAM-2201 (30% of the powder) (method GC-MS)	**POSITIVO (ELISA)**	**MAM-2201 (11 ng/ml) (LC-MS)**
Other NPS (including cathinones)*	NEGATIVE (method GC-MS)	NEGATIVE (GC-MS; LC-MS)	NEGATIVE (GC-MS; LC-MS)
Cutting substances	BENZOCAINE (20% of the powder) sugars (method GC-MS)	NEGATIVE (GC-MS; LOD Benzocaine 10ng/ml)	NEGATIVE (GC-MS; LOD Benzocaine 10 ng/ml)

[a] tested synthetic cannabinoids: AM694, WIN55212, WIN48,098; AM2201; AM2233; RCS4; RCS8; JWH-007; JWH-018; JWH-016, JWH-019; JWH-073;JWH-081; JWH-098; JWH 122; JWH-147; JWH-200; JWH-250; JWH-302; JWH-307; JWH-398; MAM-2201

Lonati D, Buscaglia E, Papa P, Valli A, Coccini T, Giampreti A, Petrolini VM, Vecchio S, Serpelloni G, Locatelli CA. MAM-2201 (Analytically Confirmed) Intoxication After "Synthacaine" Consumption. Ann Emerg Med. 2014

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

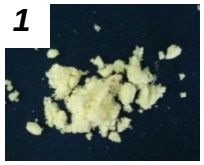
Gemona del Friuli
17.09.11 M 19
u/b positive: THC, atropine, scopolamine

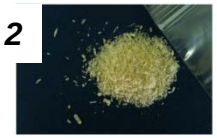
12.10.2011 M 14
u/b pos: atropine, scopolamine

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

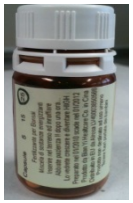
Agugust , 2010
Treviso
Mephedrone (45%)
4-MEC+MDPV
MDPV+4-FA
4-MEC+MDPV+4-FA
Cocaine+MDPV
Cocaine+MDPV+4-MEC
Methylone

June, 2010
Val di Susa
Butylone and Methylone

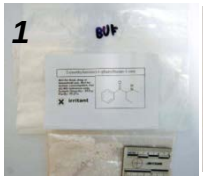
Sept, 2010
Rome
Pentedrone
Pyrovalerone
Dipipanone

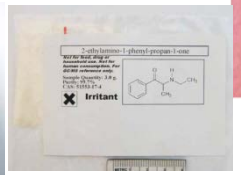
March, 2011
Vicenza
Butylone

February, 2011
Rome
Butylone



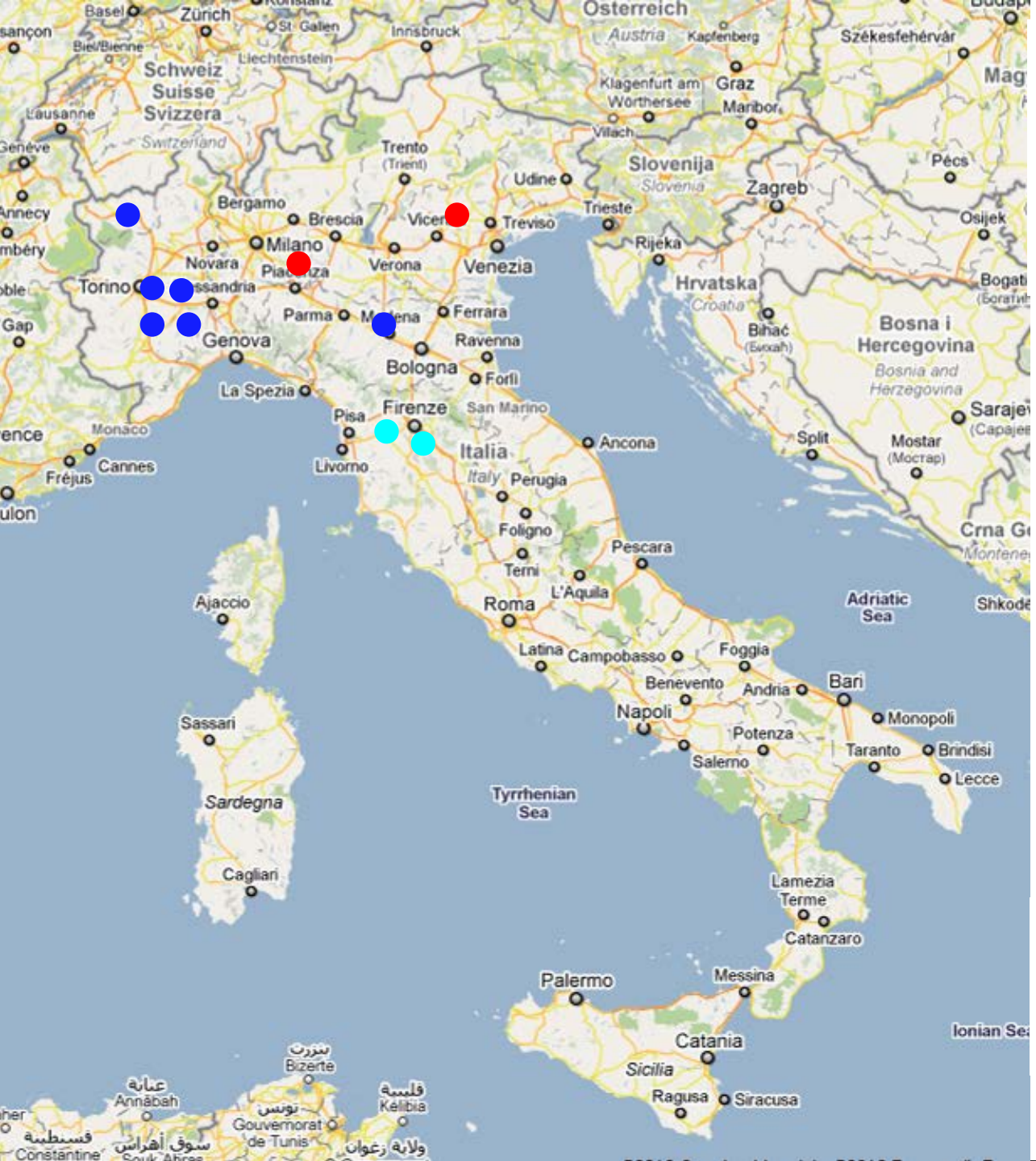
Dec, 2011
Naples
Buphedrone (1)
N-ethylcathinone





January and June, 2010
Catania - Mephedrone and Caffeine

August, 2011
Verona
Butylone



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

Patterns and trends in illicit use of fentanyls in Italy

Characteristic of the (at present) Italian available data

- Setting: emergency departments / Poison Control Centres
  - subjects known / unknown as “abuser”
  - subjects that refer a use (frequent / occasional) of street “white” (or China white) or medications
- Subjects
  - with severe health effects (→ acute poisonings) due to assumption of substances of abuse
  - that needed (asked to) help → MD !

Impossibile visualizzare l'immagine.

MXE (methoxetamine**) abuse: case series in Italy**

MXE
27 ys-old, man

History

abuse of:
- THC
- MDMA
- Ketamine

He stopped the abuse at the age of 18, scared of possible legal issues

He reported that it was the first intake of MXE, chosen exactly because it's legal.

ED evaluation after assumption of:
- MXE 1 g (sniffing)
- DXM 2 bottles (ingestion)

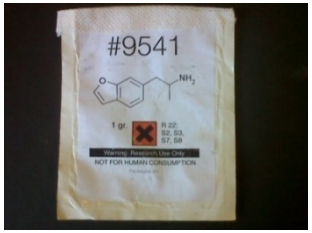
extremely agitated
confused-dreamlike state
disoriented
aggressive (physical restraints)
mydriatic
facial expression / yells
hallucinations

HR	120 bpm
BP	110/50 mmHg

Impossibile visualizzare l'immagine.

psychiatric ward (6 weeks)

- tested treatments
  - physical containment
  - Depakin 400 mg x 3, Serenase fl 2 mg x3, En 5 mg fl 2 mg x2, Clexane 4000
  - Depakin 400 mg x 3, En 5 mg fl 2 mg x2, Clexane 4000, Serenase fl 2 mg x3 → substitution at d 7 → Abilify 15 mg x2 + syptomatics
  - Talofen + en 2/5 mg x2, Abilify 15 mg x 2
  - Talofen gtt + En 2 mg, Abilify 15mg x2, Depakin 300 mg x2
  - Depakin 300 mg x2, Abilify 15 mg x2, Rivotril, Talofen, Ciproxin
  - Depakin 300 mg x2, Abilify 15 mg x2, Rivotril, Talofen



Clinical case

Saturday, 7:00 pm (May2012)

M, 40 yo, good social position, married

Hystory:

- Hypotiroidism
- ADHD
- HIV+ treated with: levotiroxine (75 mg/day), atazanavir (400 mg/day), lamivudine (600 mg/day), maraviroc (300 mg/day)

- volatile nitriles (2003-2004)
- GHB/GBL (2005)
- cocaine (2006)
- mephedrone, MDPV, 3,4-DMMC (2010)

Ed admission

- Severe psychomotor agitation
- confused
- Disoriented /hallucinations
- mydriasis
- profuse sweating
- tachycardia (167 bpm)
- hyperthermia (39.2°C)
- diffuse clonus

→ TI: meningoencephalitis

→ blood: APB 302 ng/ml

Actual daily assum ptionafter the intoxication: from Sept 2012 → 4-FA (15 mg/d)

2-C series Phenethylaminesrie (some seizures and intoxication cases – 2013)

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

2C-E
Ottobre 2013
Treviso

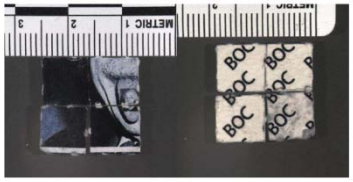
25I-NBOME; 25C-NBOME;
25H-NBOME
Ottobre 2013
Treviso

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

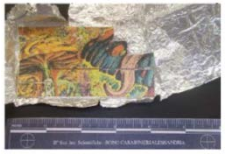


DOC
marzo2013
Firenze

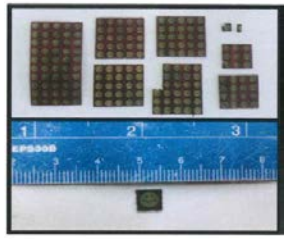
DOB - DOC
Marzo 2013
Ancona

2C-B
Aprile 2013
Perugia

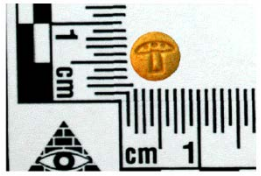
25I-NBOME
LSD
Giugno 2013
Casale Monferrato
52 fracobolli, 28 mg



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

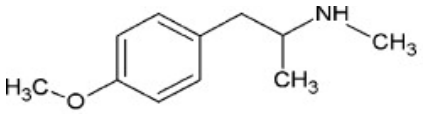


6-APDB
Agosto 2013
Reggio Calabria
0,143 gr

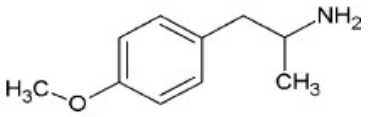


2C-B
Agosto 2013
Reggio Calabria
0,143 gr

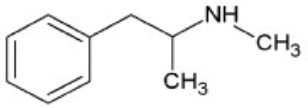
NATIONAL EARLY WARNING SYSTEM



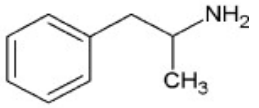
PMMA



PMA



Methamphetamine



Amphetamine

Acta Anaesthesiol Scand 2003; 47: 1298–1299
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ACTA ANAESTHESIOLOGICA SCANDINAVICA
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

Contents lists available at SciVerse ScienceDirect

Forensic Science International

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]

[a] *Division of Forensic Medicine and Drug Abuse Research (DFMDA), Norwegian Institute of Public Health (NIPH), P.O. Box 4404 Nydalen, N-0403 Oslo, Norway*
[b] *Section of Pathology, The Gade Institute, University of Bergen and Haukeland University Hospital, N-5021 Bergen, Norway*
[c] *Department of Pathology, University Hospital of Northern Norway, N-9038 Tromsø, Norway*
[d] *University of Oslo, The Medical Faculty, P.O. Box 1078 Blindern, N-0316 Oslo, Norway*

PMMA / PMA and MDMA acute intoxication

Saturday morning 5.00 am – August 2014 – 32 y-o, M

Rescued on a beach (00.30 am) with sevee psychomotor agitation, violence associated to mydriasis, tachyipnea, tachycarrdia180 bpm, hyperthermia, sweating – GCS 11.

ED: benzodiazepine → generalized muscular hypertonia, trismus and anisocoria (dx>sx), hypertermia (42°C)
Chemical parameters:

- creatinine 2.02
- myoglobin 316
- troponin 56

→ Sedation and curare → OT intubation and ventilation support
→ Cerebral CT scan: negative

Clinical evolution: metabolic acidosis, hypoglycaemia, hyperkalaemia → multiorgan failure, severe DIC. Death 30 hours after admission.

Toxicological screening (urine): positive to amphetamine, ecstasy, cocaine, THC and negative to opioids and benzodiazepine. Blood ethanol negative.

NPS and treatments

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

- addiction
  - ?

- withdrawal
  - ?

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

NATIONAL EARLY WARNING SYSTEM

Clinical collection/survey of cases in the emergency setting

Limitation in the collection of data

- only a part of the Italian EDs (1/6) is involved as collaborative center
- compliance of all the emergency physicians working in the EDs of the network as collaborating centres
  - use of PCC only for special / severe cases
- incompleteness of data due to lack of knowledge of NPS-related
  - *prise en charge* in addiction treatment services and in psychiatric ward
  - deaths

NATIONAL EARLY WARNING SYSTEM

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 ? Treatments iin the post-acute phase ?

Conclusions

NATIONAL EARLY WARNING SYSTEM

Toxicovigilance on NPSTs → the Italian NEWS experience

- a National Early Warning System should include a specific network of one (or more) specialist PCC connected to emergency medical services (e.g. EDs, psychiatric wards, ICUs) and to clinical toxicology labs, ….
- this network can efficiently contribute to the increase of
  - the "perception" of this new health problem
  - the knowledge of new substances for abuse in the National Health System
  - developing clinical and lab responses in the emergency setting to the phenomenon
- Main general results of the toxicovigilance system
  - enhanced reporting of specific intoxications (non fatal and fatal) with analytical confirmation → medical action → care of patients
  - correct evaluation and demonstration of relationships between clinical effects (→ patients) and analytical data
  - prompt detection of sentinel cases / signal of toxicity → alerts on new emerging toxicological problems
  - unique collection of new / original information/data on clinical toxicology of NPS

CENTRO ANTIVELENI PAVIA CAV CNIT CENTRO NAZIONALE INFORMAZIONE TOSSICOLOGICA

NATIONAL EARLY WARNING SYSTEM

Pavia Poison Control Centre - National Toxicology Information Centre

Procedures: Scientific information / training for the NEWS activities

- Training courses
  - 1 day/year in the national clinical toxicology congress
  - 35-40 clinical toxicology training courses/year (comprehending NEWS activities) → emergency physicians
  - 5 training courses / meetings on new drugs of abuse and NEWS activities / year → emergency physicians

- printed / e-mailed information
  - Department of Antidrug Policies activities
    - NEWS Activity Report
    - Dronet / DrogaNEWS Newsletters
    - information/alerts

- Internal information procedure
- Internal training and up-to-date (weekly, 1-2 hours)

CENTRO ANTIVELENI PAVIA CAV CNIT CENTRO NAZIONALE INFORMAZIONE TOSSICOLOGICA