Ferrara, 13 gennaio 2023
Società Medico Chirurgica di Ferrara
Nuove frontiere in Medicina Intensiva

Sfide emergenti in tossicologia clinica

Presidenza del Consiglio dei Ministri
Dipartimento Politiche Antidroga
National Early Warning System

Ministero della Salute
Difesa Civile - Scorta Nazionale Antidoti
Centro di Riferimento Nazionale

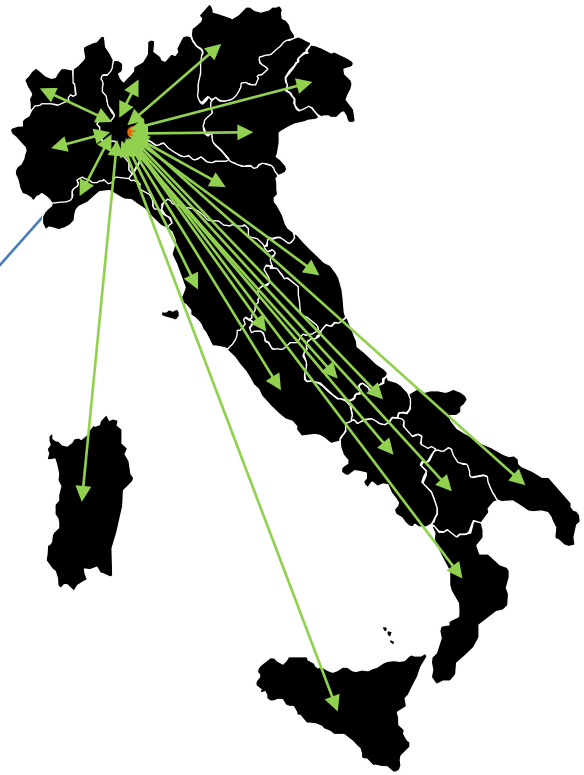
Presidenza del Consiglio dei Ministri
Dipartimento della Protezione Civile
Centro di Competenza

Carlo A. Locatelli
Centro Antiveleni di Pavia e Centro Nazionale di informazione Tossicologica, Laboratori di Tossicologia Clinica e Sperimentale, Servizio di Tossicologia
Ospedale Istituto Scientifico di Pavia, IRCCS Fondazione Maugeri, Pavia
Coordinamento clinico-tossicologico, Sistema Nazionale di Allerta Rapida per le droghe (DPA-PCM)
Scorta Nazionale Antidoti e Farmaci (Ministero della Salute-Difesa Civile)

Funzioni dei Centri Antiveleni - CAV

front/back-office

- consulenza specialistica a distanza
- cura degli intossicati
- documentazione
- prevenzione
- tossico- e farmaco-vigilanza
- antidoti
- formazione
- diagnostica analitica di tipo tossicologico
- ricerca tossicologica ed epidemiologica



Presidenza del Consiglio dei Ministri
Dipartimento Politiche Antidroga
National Early Warning System

Presidenza del Consiglio dei Ministri
Dipartimento della Protezione Civile
Centro di Competenza

Ministero della Salute
Scorta Nazionale Antidoti
Centro di riferimento nazionale

WHO, Poison Contol Centres, 1951
WHO – IPCS, 1980 and 1985
European Resolution (90/C 329/03 CEE)
WHO, Poison Control Centres Guideline, 1997 and 2021
International Health Regulations, 2015
Accordo Stato-Regioni 28.02.2008
LEA, 2017

CENTRO ANTIVELENI PAVIA
CAV
CNIT
CENTRO NAZIONALE INFORMAZIONE TOSSICOLOGICA

Centro Antiveleni di Pavia

Centro Nazionale di Informazione Tossicologica

- consulenza specialistica 24/24, 7/7
  - SSN / SSR (attività / funzioni → Accordo Stato-Regioni 2008 / LEA 2017)
  - unico riferimento formale (Amministrazioni dello Stato) nel Paese per
    1. Sostanze d'abuso – NEWS / SNAP coordinamento nazionale aspetti clinico-tossicologici (Dipartimento Politiche Antidroga - Presidenza del Consiglio dei Ministri)
    2. Emergenze chimiche (Dipartimento Protezione Civile - PCM)
    3. NBCR (Difesa civile – Ministero della Salute)

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

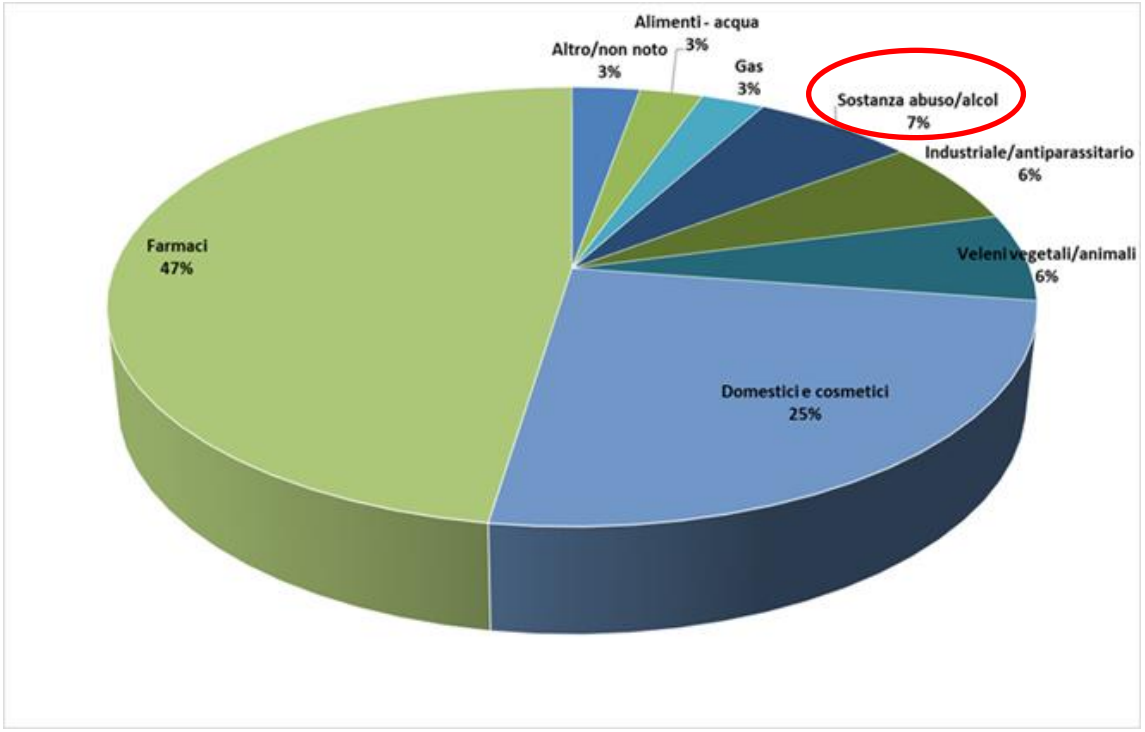
National Antidotes Stockpile
Ministry of Health - Civil Defense Advisory Centre

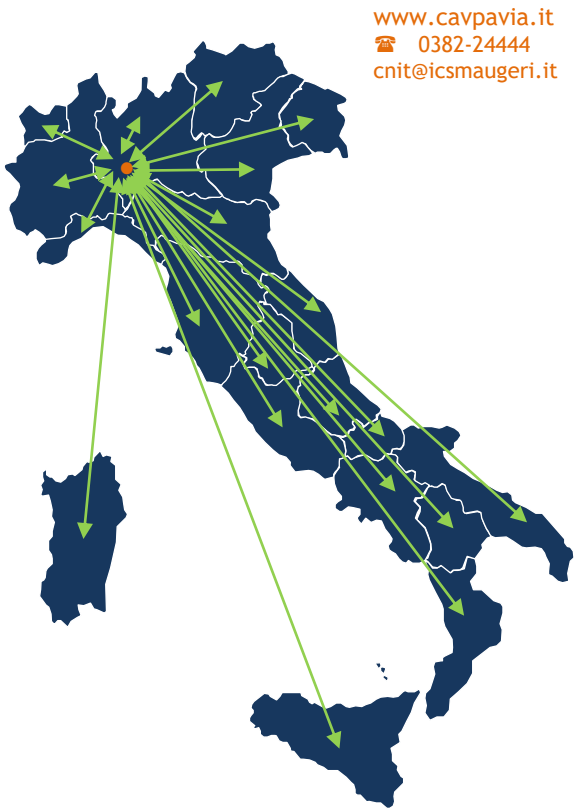
Presidency of the Ministry Council
Dipartimento della Protezione Civile
Reference Centre

- alta specializzazione e organizzazione (problematiche tossicologiche maggiori / ricerca / formazione / gestione emergenze / …)
  - personale specializzato / formazione e addestramento specifici
  - degenza / ambulatori
  - laboratori analitico-tossicologici di II livello (rifermento nazionale per urgenze)
  - Integrazione operativa a livello nazionale (laboratori diagnostici, antidoti, ….)

CENTRO ANTIVELENI PAVIA
CAV
CNIT
CENTRO NAZIONALE INFORMAZIONE TOSSICOLOGICA

- Perimetro CAV → modello a basso costo e ad alta efficienza
  - 92.229 consulenze specialistiche nel 2021 [52.217 pazienti in urgenza]





www.cavpavia.it
☎ 0382-24444
cnit@icsmaugeri.it

  - > 40.000 consulenze per H, circa 1/3 in TI

- Osservatorio unico sul SSN / Paese / ricerca → casistiche cliniche
  - Diagnosi (clinica + LabTox) e trattamenti/ADR/ET/nuovi rischi/ ….
  - → criticità (livello nazionale)

PEROSSIDO DI IDROGENO H_2O_2 : Prodotti

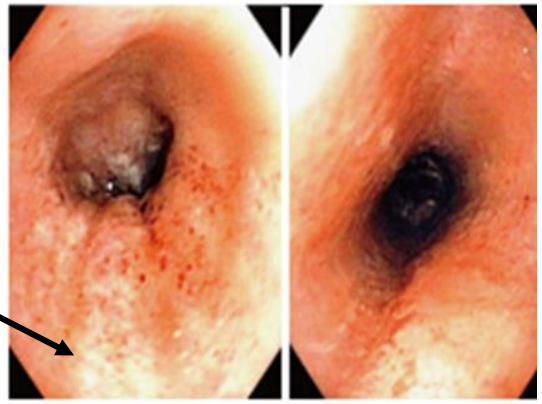
- Disinfettante e antisettico cutaneo
- Sbiancante e smacchiante
- Tinture per capelli

PEROSSIDO DI IDROGENO: Lesione caustica

→ Lesioni caustiche

Organo maggiormente colpito: stomaco.

La lesione caratteristica dell'ingestione di H_2O_2 è lo ***snow-white sign***



Martin JV et al. World J Clin Cases, 2017.

Classificazione delle lesioni da caustico →***score di Zargar***

Grade	Definition
0	Normal examination
1	Edema and hyperemia of the mucosa
2A	Superficial ulcerations, exudates, whitish membranes, blisters, erosions, hemorrhages and friability
2B	Grade 2A plus deep discrete or circumferential ulceration
3A	Small, scattered areas of necrosis
3B	Extensive necrosis

EGDS entro 12 ore / 24 ore → gravità ed estensione lesioni
La lesione caratteristica dell'ingestione di H_2O_2 è lo ***snow-white sign***

TC con classificazione di danno di parete (grado 1: aspetto normale; Grado 2: edema di parete e dei tessuti molli con aumentato enhancement di parete; grado 3: necrosi trans murale con assente enhancement di parete).

→ Embolismo gassoso sistemico
→ Embolismo gassoso portale

PEROSSIDO DI IDROGENO: Embolismo gassoso cerebrale

Cerebral Air Gas Embolism -→ Stroke Ischemico secondario a embolismo gassoso

Complicanza legata ad ingestione di H_2O_2 > 35%

Diagnosi :
Relazione tra ingestione di H_2O_2 e comparsa di sintomatologia neurologica.

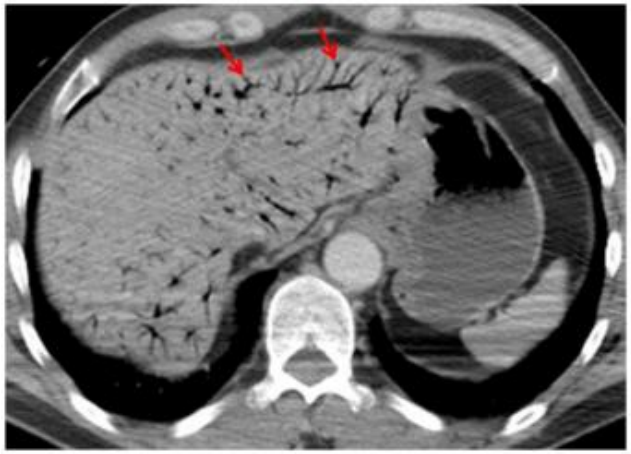
TC encefalo smc → bolle nella circolazione intracranica
RM → multiple aree di ischemia cerebrale

Trattamento: Terapia Iperbarica

Ashdown BC et al. AJR Am J Roentgenol, 1998;

Byrne B et al. J Emerg Med, 2014;

PEROSSIDO DI IDROGENO: Embolismo gassoso venoso portale



Youssef EW et al. J Radiol Case Rep, 2018.

Differential	CT findings
Portal vein gas	Branching air densities following portal vein distribution and more peripheral in location.
Pneumobilia	Branching air densities with more central distribution.

Aria a livello del Sistema Venoso Portale

≠

Aerobilia o Pneumobilia

2 Abboud B et al. World J Gastroenterol, 2009

intentional ingestion of sodium nitrite: an increasing problem

Background and Objective

Sodium nitrite:
- Inorganic salt
- Used in food industry as a preserving agent

→ In overdose methemoglobinemia

Intentional use

Objective

Emerging problem as method of suicide

- Cheap and easily available on the web
- Web forum and online communities with recommendations to commit suicide

To evaluate the trend of sodium nitrite poisoning in the last 6 years

- Retrospective observational study (2016-2021)
- Patients included → all sodium/potassium nitrite poisoning referred to Pavia Poison Centre

Case series → 9 cases

Case n.	Year	Gender	Age	Consumption modality	Clinical Manifestations at ED-admission	MetHb (%) at ED-admission	Methylene blue administered dose	Outcome
1	2019	M	-	Suicide	Cardiac arrest	-	-	Death before ED admission
2	2021	M	18	Suicide	Cardiac arrest	-	-	Death before ED admission
3	2021	F	56	Homicide	Dyspnea, Cyanosis, Lactic acidosis	72.2	2 mg/kg	Improvement
4	2021	M	-	Homicide	Cardiac arrest	-	-	Death before ED admission
5	2021	M	21	Suicide	Syncope, Hypotension, Lactic acidosis	79.6	2 mg/kg	Improvement
6	2021	M	49	Suicide	Syncope, Cyanosis, Hypotension, Tachycardia, Lactic acidosis	Not performed	1 mg/kg	Improvement
7	2021	M	29	Suicide	Asymptomatic	0.5	-	No clinical manifestations
8	2021	M	42	Suicide	Coma, Cyanosis, Syncope, Tremors	30	1 mg/kg	Improvement
9	2021	M	33	Suicide	Cyanosis	64	1.5 mg/kg	Improvement

- ✓ Increasing trend in 2021, especially in young people
- ✓ Fatal if not recognized
  - ✓ a prompt administration of methylene blue is life saving → it should be available in every ED
- ✓ Perform ABG with met-Hb in case of syncope/hypotension/peripheral cyanosis
- ✓ Nitrite blood concentration level is not available in emergency setting
  - ✓ It can be performed by forensic labs in order to confirm the clinical diagnosis
- ✓ PCC → a crucial role in syndromic surveillance and in spreading the alert

Allerta 2021
per aumento TS da sodio nitrito acquistato nel web

Istituti Clinici Scientifici Maugeri

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Responsabile: Dr. Carlo A. Locatelli
Tel. Centro Antiveleni 0382-24444 - Tel. Segreteria 0382-26261 - Fax 0382-592799 - e-mail cav@icsmaugeri.it

Alla c.a. Ministero della Salute
Direzione Generale Prevenzione

Ministero della Salute
Direzione generale Alimenti

e p.c. Assessorato Sanità Regione Lombardia
Assessorato Regionale Regione Liguria
Assessorato Sanità Regione Emilia-Romagna
Assessorato Sanità Regione Veneto
Assessorato Sanità Regione Lazio
Assessorato Regionale Regione Campania
Assessorato Regionale Regione Puglia

Oggetto: due allerte su **intossicazioni gravi da agenti metaemogliobinizzanti** con accesso al sistema d'urgenza

Si segnalano **due differenti emergenze** identificate dal Centro Antiveleni di Pavia nel territorio nazionale, **entrambe relative ad agenti metaemoglobinizzanti** (riportate di seguito in sequenza temporale):

- allerta 1: casi di gravi intossicazioni acute (alcune ad esito letale) da somministrazione volontaria di nitriti a scopo lesivo/autolesivo
- allerta 2: casi di intossicazioni acute gravi correlate ad assunzione di alimenti, verificatesi nella presente settimana.

Allerta 1

Nell'arco di 4 mesi del 2021 (febbraio-aprile) sono stati identificati n. 6 casi di suicidio/tentato suicidio/somministrazione a terzi a scopo lesivo (indagini in corso) che hanno causato grave metaemoglobinemia, in alcuni casi letale:

a. il Centro Antiveleni di Pavia ha identificato n. 6 casi di intossicazioni acute gravi con elevata metaemoglobinemia che hanno fatto accesso a strutture ospedaliere nelle città di Genova, Varese, Bologna, Bassano del Grappa, Roma (1 ulteriore caso sospetto a seguito di richiesta da parte di Carabinieri potrebbe essere accaduto a Piacenza)
b. il servizio di Medicina legale dell'Azienda Ospedaliera Universitaria Integrata di Verona (Prof. Franco Tagliaro) (a) ha già segnalato all'Autorità Giudiziaria altri 2 casi di decesso da nitriti/nitrati avvenuti in precedenza, ed (b) è riuscito a confermare mediante tecnica analitica separativa (elettroforesi capillare) l'elevata presenza di nitrati e nitriti anche in alcuni dei casi di intossicazione acuta con metaemoglobinemia identificati dal Centro Antiveleni di Pavia

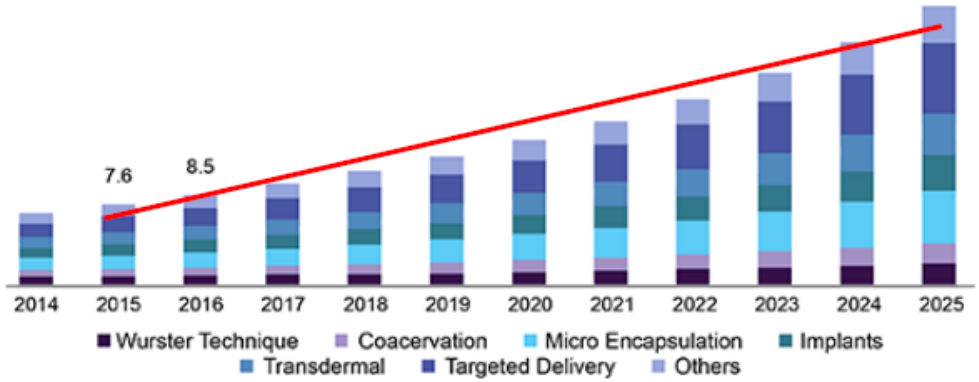
The «jungle» of the definitions

There is no industry standard for these abbreviations, and confusion and misreading have sometimes caused also prescribing errors ….

CD	controlled delivery
CR	controlled release
DR	delayed release
ER	***extended release***
IR	immediate release
LA	long-acting
LAR	long-acting release
MR	modified release
PR	prolonged release
SA	sustained action
SR	sustained release
TR	timed release
XL	***extended release***
XR	***extended release***
XT	***extended release***

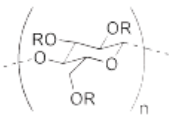
Europe controlled release drug delivey market size, by technology - 2014-2025 (USD Billion)

www.grandviewresearch.com



BRAND	MECHANIS of RELEASE	OTHER INGREDIENTS	BEZOAR
SEROQUEL XR® 50 mg (Astrazeneca) *quetiapine fumarate*	EXTENDED (double matrix: hydrophobic quetiapine micro-matrix surrounded by swellable/gelling matrix)	Matrix core composition: microcrystalline cellulose, sodium citrate, HPMC (hypromellose), magnesium stearate, lactose monohydrate Film coating: HPMC (hypromellose), PEG 400, titanium dioxide, red iron oxide	YES
TEGRETOL RETARD® 200 mg (Novartis Healthcare) *carbamazepine*	EXTENDED (erodible matrix: carbamazepine erodible matrix particles surrounded by immediate-disintegrating coating)	Colloidal silicon dioxide, ethylcellulose (contains: cetyl alchol, sodium lauril sulfate), microcrystalline cellulose, polyacrylate (ethyl acrylate/methyl methacrylate copolymer), magnesium stearate, croscarmellose sodium, talc, HPMC (hypromellose), polyoxyl hydrogenated castor oil, red and yellow iron oxide, titanium dioxide	NO
PINEX RETARD® 500 mg (Actavis Nordic) *paracetamol*	EXTENDED (swellable/gelling matrix)	Magnesium stearate, HPMC (hypromellose), povidone, talc, Eudragit RS 100 (ethylacrylate, methylmethacrylate, methacrylic acid ester), ethanol	YES
ISOPTIN RETARD® 240 mg (BGP Products AB Solna) *verapamil hydrochloride*	EXTENDED (swellable rigid matrix)	Matrix core composition: microcrystalline cellulose, sodium alginate, povidone, magnesium stearate, purified water Coating layer: HPMC (hypromellose), PEG 400, PEG 6000, talc, titanium dioxide, Sicopharm green lake (contains: aluminum hydroxide, water, quinoline yellow, indigotine), Hoechst wax E	YES
PANODIL® 500 mg (GSK Consumer Healthcare) *paracetamol*	IMMEDIATE	Corn starch, pregelatinized starch, povidone, potassium sorbate, talc, stearic acid, HPMC (hypromellose), triacetin, carnauba wax	NO

HPMC (hydroxypropyl methylcellulose, hypromellose)



R = H or CH_3 or $CH_2CH(OH)CH_3$

- polymer with pH-dependent solubility and gelling properties (temperature related) in aqueous solution → viscosant/gelling/swellable agent
- the viscosity is directly related to the HPMC concentration (quantity) in the mass and to the concentration of the methoxy group (OR) (degree of substitution): the higher the concentration is, the more viscous the mass is
- depending on the concentration and type/degree of substitution, it functions as **controlled release agent** to delay the release of a medicinal compound into the digestive tract. It is also used as **component of tablet coatings**

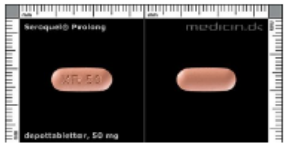
Pharmacopeial specifications for hypromellose

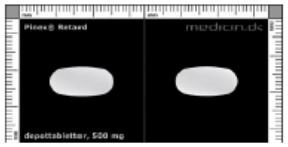
Type	Methoxy content USP	Methoxy content Eur. Ph	Hydroxypropoxy content USP	Hydroxypropoxy content Eur. Ph
1828	16.5-20.0%	16.5-20.0%	23.0-32.0%	23.0-32.0%
2208	19.0-24.0%	19.0-24.0%	4.0-12.0%	4.0-12.0%
2906	27.0-30.0%	27.0-30.0%	4.0-7.5%	4.0-7.5%
2910	28.0-30%	28.0-30%	7.0-12.0%	7.0-12.0%

Methods

5 pharmaceutical preparations were selected

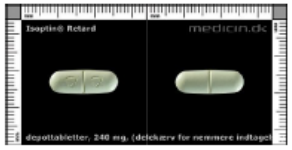
- *4 extended release preparations*
  - Quetiapine: SeroquelVR XR 50 mg, AstraZeneca. Lot. no: 18922; size 6.5" 16.2 mm
  - Paracetamol: PinexVR Retard 500 mg, Actavis Nordic. Lot. no: 166829; size 8" 17 mm
  - Verapamil: IsoptinVR Retard 240 mg, BGP. Lot. no: 1047229; size 10" 10 mm
  - Carbamazepine: TegretolVR Retard 200 mg, Novartis. Lot. no: T188301; size 5.6" 12.1 mm





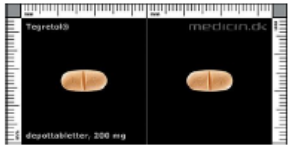
Mono-depot

drug embedded within a hydrogel polymer coating material that swelled on hydration forming a gel layer through which the drug diffuses for release or dissolution into surrounding fluid



Mono-depot

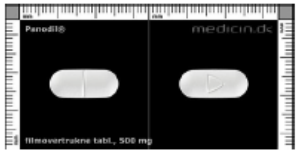
tablet swells and is subsequently eroded



Poly-depot

poly-depot, or micro-spheres packed within a water-soluble coating material

- *1 immediate release paracetamol*
  - Paracetamol: PanodilVR 500 mg, GlaxoSmithKline. Lot. no: Y75U; size 7.3 " 17.5 mm



Tablet coated with a polymer (different) from the ER paracetamol preparation

Hoegberg LCG et al. Clin Toxicol (Phila). Epub 2018 Oct 11.

Methods

In vitro assay

- Each test drug was placed in three identical 2 L glass beakers

Glass I	Glass II	Glass III
2 tablets - Ther. dose	30 tablets - Overdose wrapped in 30 cm diameter mesh bag	30 tablets - Overdose individually wrapped in 7.5 cm diameter mesh bag
		
	interaction between tablets in nylon mesh bag completely immersed in SGF	**NO interaction between tablets**

- All bags were completely immersed in SGF and the amount of drug released was quantified at
  - 0.5, 1, 2, 4, 8, 12, 24, 48 hours

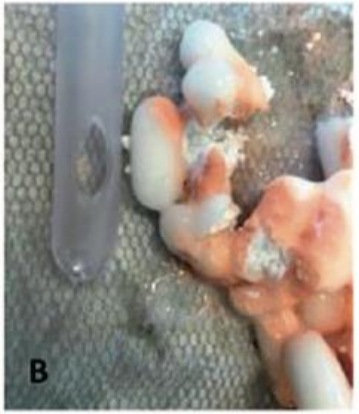
Hoegberg LCG et al. Clin Toxicol (Phila). Epub 2018 Oct 11.

Results
Quetiapine/Seroquel VR XR 50 mg

Generic name/ pharmaceutical	Observations (time, hours) 30 min	4 h	8 h	24 h	48 h	Additional comments
Quetiapine/Seroquel® XR 50 mg, 30 separated tablets	Intact tablets	Intact tablets	Intact tablets	Intact tablets	Complete disintegration	
Quetiapine/Seroquel® XR 50 mg, 30 collected tablets	Intact tablets	Pharmacobezoar formed	Pharmacobezoar	Pharmacobezoar	Complete disintegration	Strong sticky pharmacobezoar, solid for up to 24 h
Quetiapine/Seroquel® XR 50 mg, 2 collected tablets	Intact tablets	Intact tablets	Intact tablets	Intact tablets	Complete disintegration	

Visual inspection:

pharmacobezoar (30 tablets collected) in one bag after incubation in SGF for 4 h (A); compared to a 30F orogastric lavage tube (B)

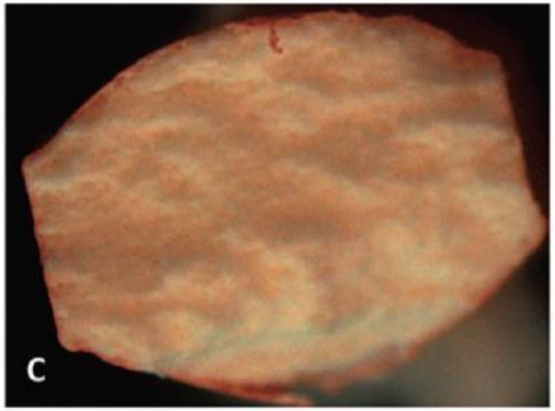


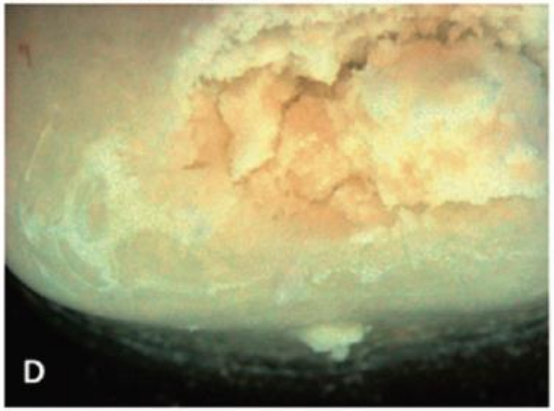
Hoegberg LCG et al. Clin Toxicol (Phila). Epub 2018 Oct 11.

Results
Quetiapine/Seroquel VR XR 50 mg

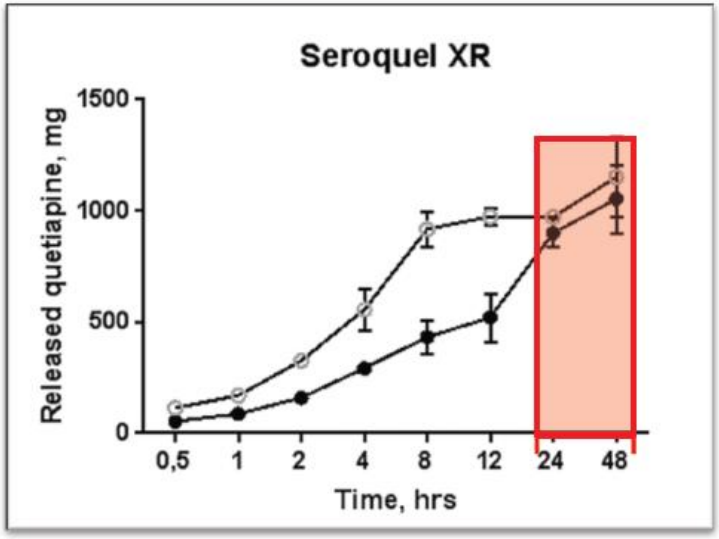
polymer film coating material (dry section)

polymer film coating material swelled in contact with SGF forming a diffusion controlled gel-layer surrounding





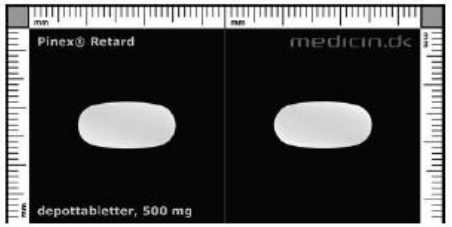
Light microscopy of one tablet (at 4 h in SGF) (D).



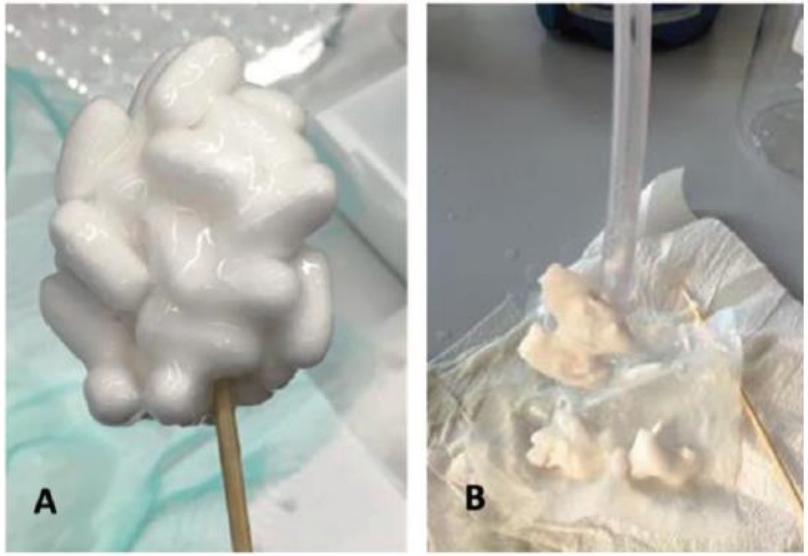
Dissolution profile:
released quetiapine *vs* time for 30 tablets in separate bags (open circles), and 30 tablets collected in one bag (closed circles).

Hoegberg LCG et al. Clin Toxicol (Phila). Epub 2018 Oct 11.

Results
Paracetamol/Pinex VR retard 500 mg



Generic name/ pharmaceutical	Observations (time, hours) 30 min	4 h	8 h	24 h	48 h	Additional comments
Paracetamol/Pinex® Retard 500 mg, 30 separated tablets	Intact tablets	Intact tablets	Intact tablets	Intact tablets	Eroded to smaller tablets	
Paracetamol/Pinex® Retard 500 mg, 30 collected tablets	Intact tablets	Pharmacobezoar formed	Pharmacobezoar	Pharmacobezoar	Pharmacobezoar partly disintegrated	Strong sticky pharmacobezoar
Paracetamol/Pinex® Retard 500 mg, 2 collected tablets	Complete tablet disintegration	–	–	–	–	

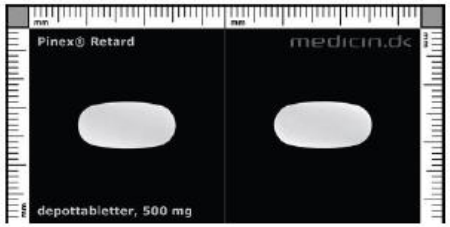


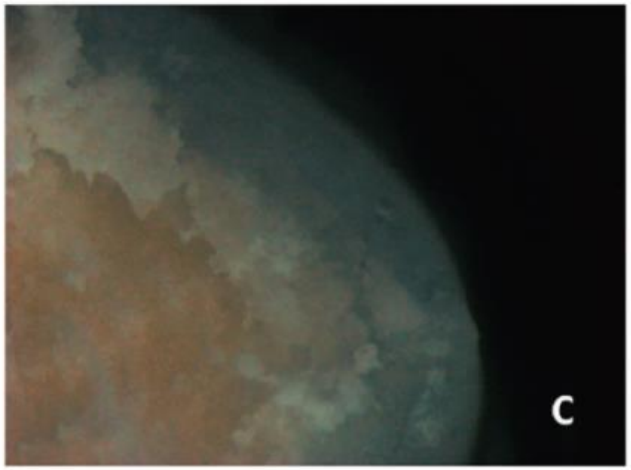
Visual inspection:

pharmacobezoar formation (30 tablets in one bag) after incubation in SGF for 8 h (A); compared to a 30F orogastric lavage tube (B)

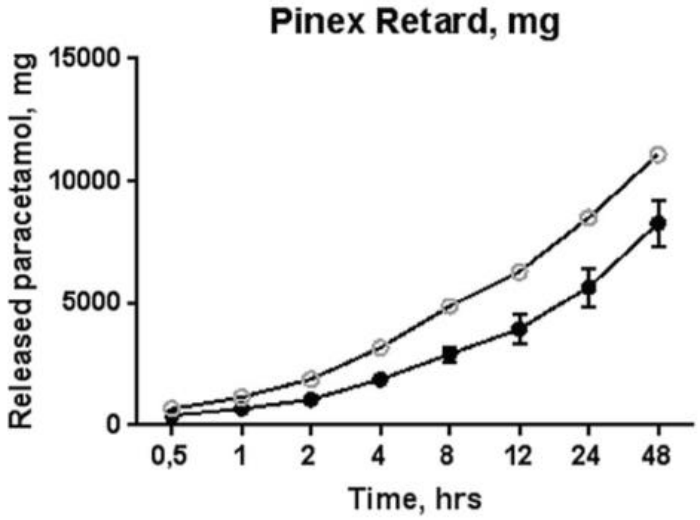
Hoegberg LCG et al. Clin Toxicol (Phila). Epub 2018 Oct 11.

Results
Paracetamol/Pinex VR retard 500 mg





Light microscopy:
polymer film coating material swelled in contact with SGF forming a diffusion controlled gel-layer surrounding the tablet, photo at 4 h (C).



Dissolution profile:
released paracetamol *vs* time for 30 tablets in separate bags (open circles), and 30 tablets collected in one bag (closed circles).

Hoegberg LCG et al. Clin Toxicol (Phila). Epub 2018 Oct 11.

Results
Verapamil/Isoptin VR retard 240 mg

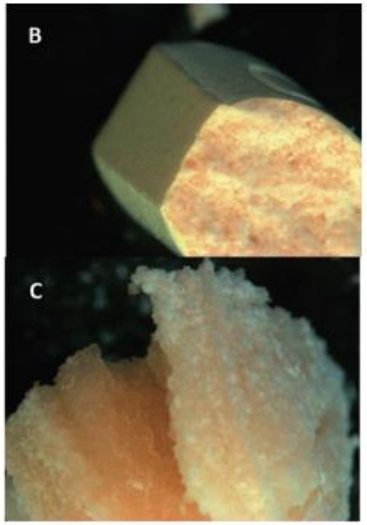
Generic name/ pharmaceutical	Observations (time, hours) 30 min	4 h	8 h	24 h	48 h	Additional comments
Verapamil/Isoptin® Retard 240 mg, 30 separated tablets	Swelled, intact tablets	Swelled, intact tablets	Swelled, intact tablets	Swelled, intact tablets	Swelled, intact tablets	
Verapamil/Isoptin® Retard 240 mg, 30 collected tablets	Swelled	Pharmacobezoar formed	Pharmacobezoar	Pharmacobezoar	Pharmacobezoar of sticking swelled tablets	Strong pharmacobezoar, but outer tablets tended to break off
Verapamil/Isoptin® Retard 240 mg, 2 collected tablets	Swelled, intact tablets	Swelled, intact tablets	Swelled, intact tablets	Swelled, intact tablets	Swelled, intact tablets	

Visual inspection:

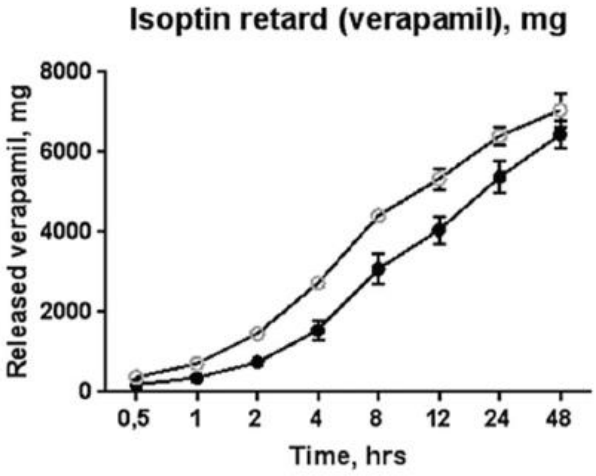
30 tablets collected in one bag after incubation in SGF for 48 h

Hoegberg LCG et al. Clin Toxicol (Phila). Epub 2018 Oct 11.

Results
Verapamil/Isoptin VR retard 240 mg



Light microscopy:
polymer film coating material in the dry section (B) and a tablet turning its inside out in contact with SGF forming a rigid and slow-releasing matrix, photo at 4 h (C).



Dissolution profile:
released verapamil *vs* time for 30 tablets in separate bags (open circles), and 30 tablets collected in one bag (closed circles).

Hoegberg LCG et al. Clin Toxicol (Phila). Epub 2018 Oct 11.

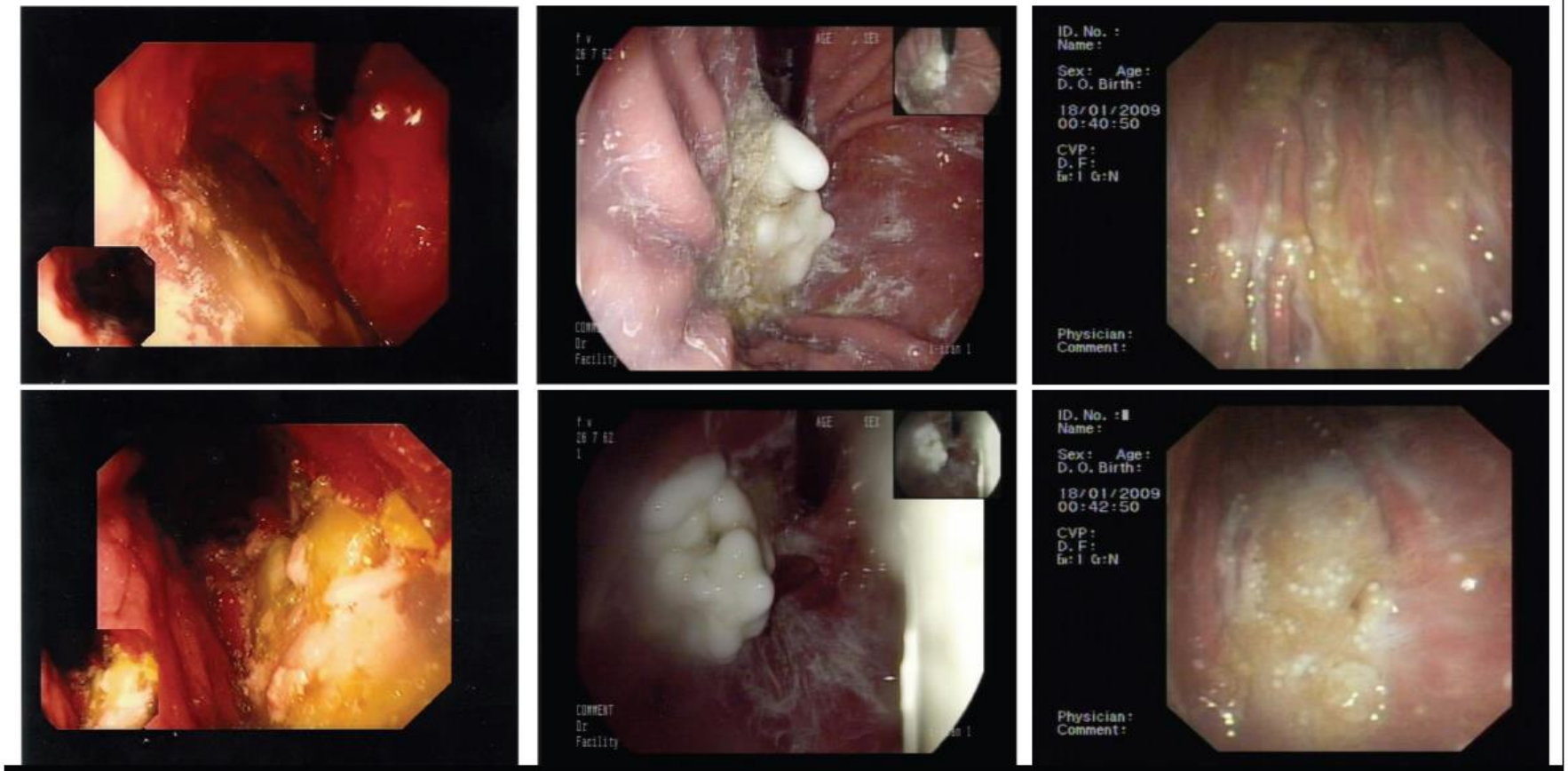
Discussion

- present study simulated massive overdose and development of pharmacobezoar of 30 extended release tablets

- *in vitro* model showed
  - reproducible results with low intra-series and inter-day variation
  - seems to be useful to study pharmacobezoar formation/disintegration of pharmaceuticals.

- materials in the mono-depot formulations is the most probable cause of pharmacobezoar formation
  - ✓ hydroxypropylmethylcellulose (HPMC)
    - ✓ quetiapine/SeroquelVR XR 50 mg
    - ✓ paracetamol/PinexVR Retard 500mg tablets,
  - ✓ sodium alginate :
    - ✓ verapamil/IsoptinVR Retard 240 mg tablets
  - ✓ polyacrylate (eudragit) :
    - ✓ paracetamol/Pinex Retard 500 mg tablets

Hoegberg LCG et al. Clin Toxicol (Phila). Epub 2018 Oct 11.



New formulations, slow release preparations and GI decontamination

Pavia PCC cases

PAVIA PCC OPERATIVE NATIONAL SYSTEMS FOR ANTIDOTE STOSKPILING

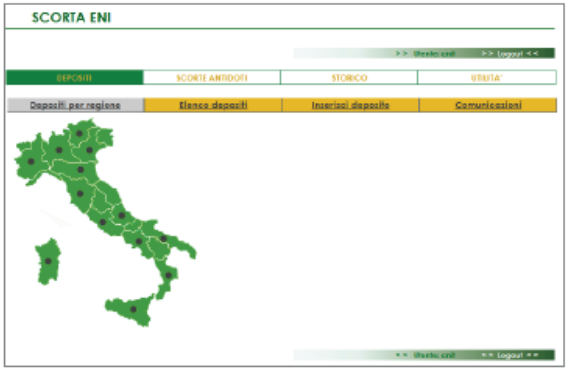
NHS HOSPITALS

System involving the National Hospitals Public network

GOVERNATIVE

System relate to the Scorta Nazionale Antidoti

INDUSTRIES OCCUPATIONAL SETTING



System concerning pharmaceutical and chemical industries

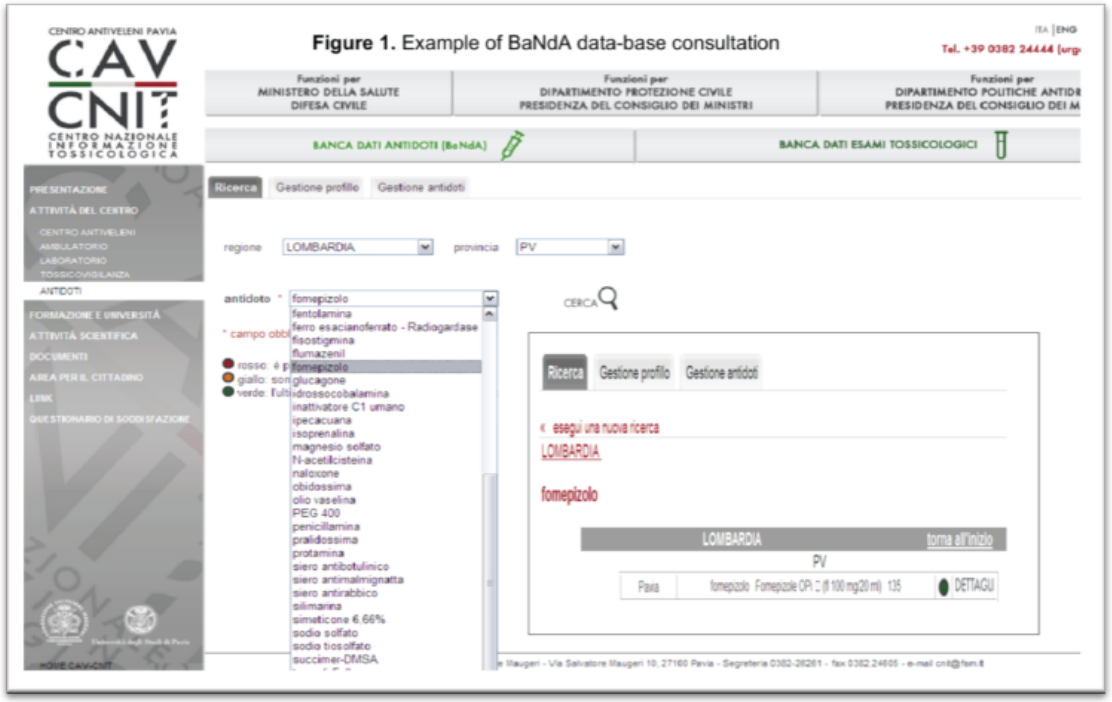
NHS Hospitals model

National data-base of antidotes - BaNda

- first national, free and constantly up-dated data-base (since 2003) aimed:
  - to create a network of antidotes availability throughout the NHS
  - to provide prompt and easy access to antidotes in the nearby hospitals or regions (avoiding expensive transport)
  - to optimize antidote stockpiles (especially for expensive and rare-use ones) making turn-over easier with saving of resources

- BaNdA involves
  - more than 430 services (PCCs, EDs, Intensive Care Units, Hospital Pharmacies)
  - corresponding to 40% of Italian hospitals with emergency services

- BaNda is currently accessed by approximately 100 emergency services monthly.



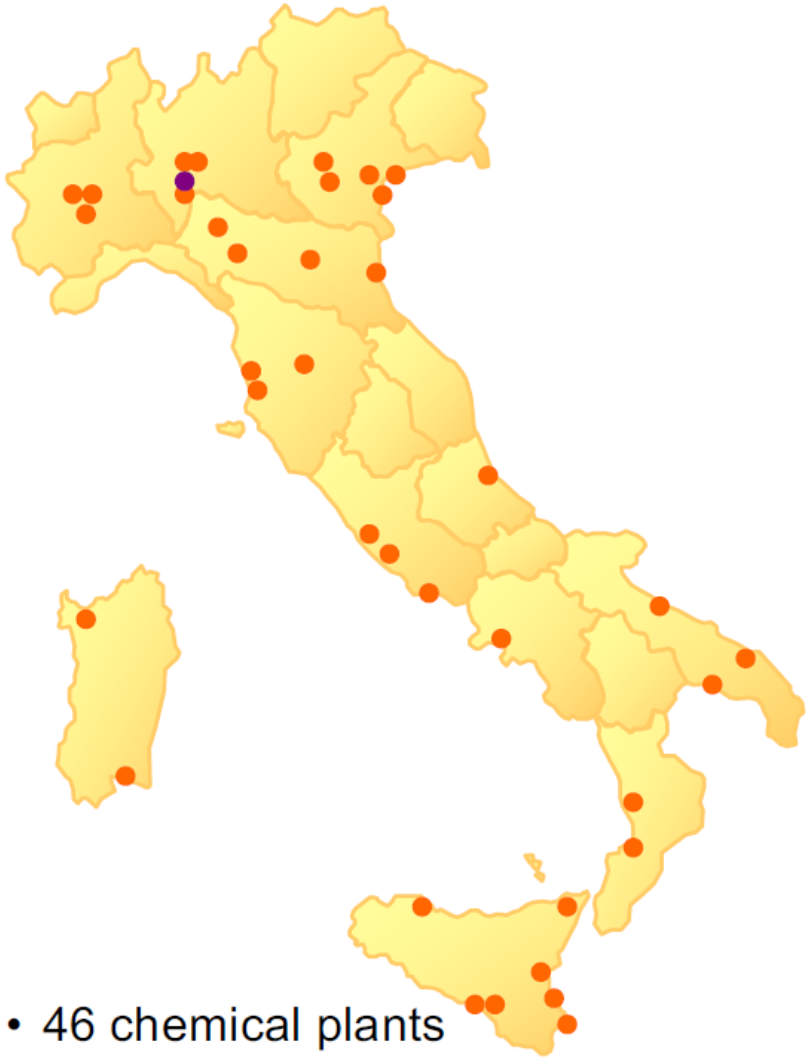
INDUSTRIES model

Chemical plant-network for *in situ* antidotes availability (from 1996)

accidental / occupational poisonings

activated charcoal	160	bottles
amyl nitrite	7680	vials
calcium disodium edetate	300	vials
calcium gel	1200	tubes
ethanol 10 ml	1000	vials
hydroxocobalamin	103	kits
methylene blue	1000	vials
oxygen	160	cylinders
PEG 400	50	bottles
penicillamine	16	bottles
simethicone	160	bottles
sodium thiosulfate	900	vials

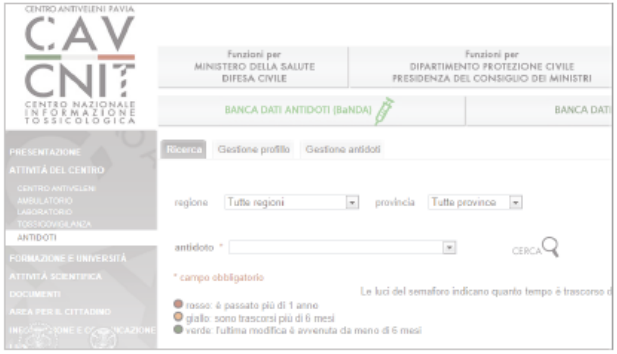
(Example from 12 petro-chemical plants)



- 46 chemical plants
- *ad hoc* operating procedures

PAVIA PCC OPERATIVE NATIONAL SYSTEMS FOR ANTIDOTE STOSKPILING

NHS HOSPITALS

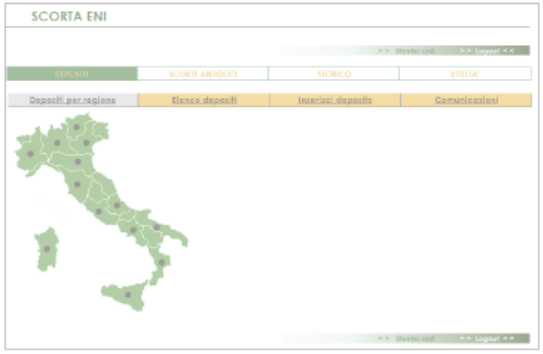


System relate to the National Hospitals Public network

GOVERNATIVE

System relate to the Scorta Nazionale Antidoti

INDUSTRIES OCCUPATIONAL SETTING



System concerning pharmaceutical and chemical industries

Charged by the Ministry of Health, the Pavia Poison Control Centre (PPCC) is the clinical unit responsible for:

- ✓ Diagnostic-therapeutic specialist consultation for non-conventional attacks
- ✓ SNA operational management (e.g. upgrade, distribution planning)
- ✓ Continuous training of the Italian National Health System (NHS)

INTANGIBLE NATIONAL ANTIDOTES STOCKPILE
for
Terrorists Chemical and Radio-Nuclear Events
CBRN Emergencies

National organization of SNA: regional ● and national ● stockpiles are located in hospitals and in State's deposits respectively

GOVERNATIVE model

Ministero della Salute

Scorta Nazionale Antidoti

every antidote is identified by:

- **numeric code**
- **colour code**
  - **chelators**
  - **cyanide**
  - **organophosphates**
  - **botulinum antitoxin**
  - **miscellanea**

Strategic National Antidote Stockpiles (SNA)

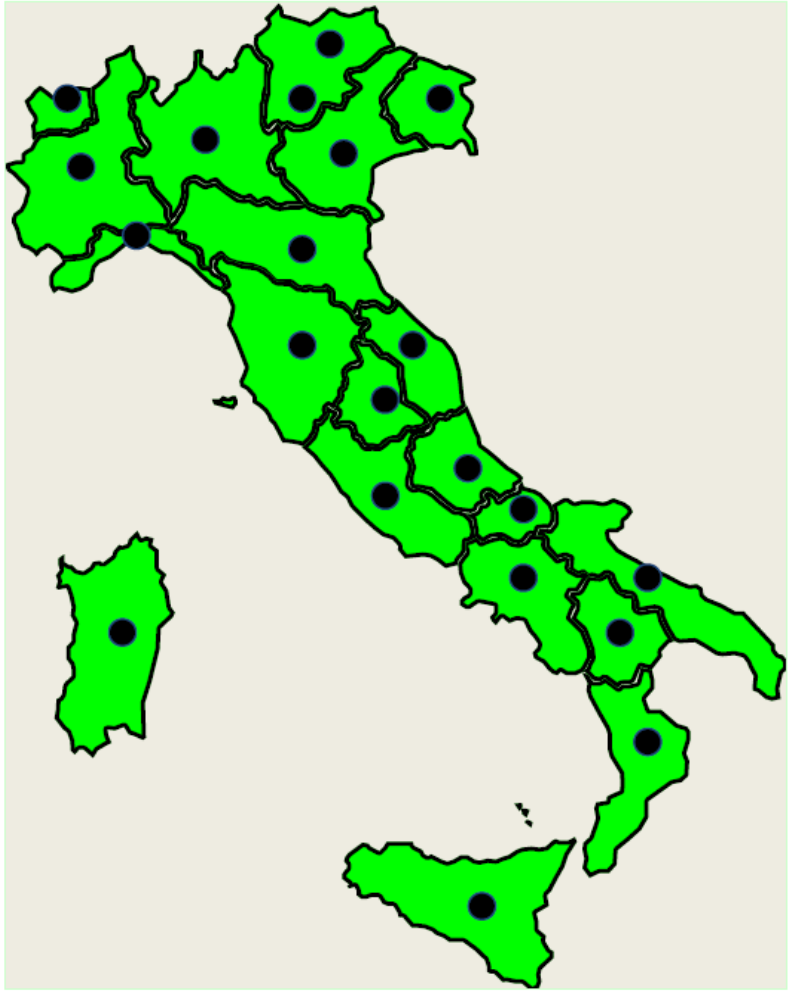
GOVERNATIVE model

20 regional stockpiles (SNA R…)

- AMYLE NITRITE
- SODIUM THIOSULPHATE

- ATROPINE
- PRALIDOXIME

- N-ACETYLCISTEINE
- METHILENE BLUE
- NALOXONE
- PHYSOSTIGMINE



Strategic National Antidote Stockpiles (SNA)

GOVERNATIVE model

13 national stockpiles

- HYDROXOCABALAMIN
- AMYLE NITRITE
- SODIUM THIOSULPHATE

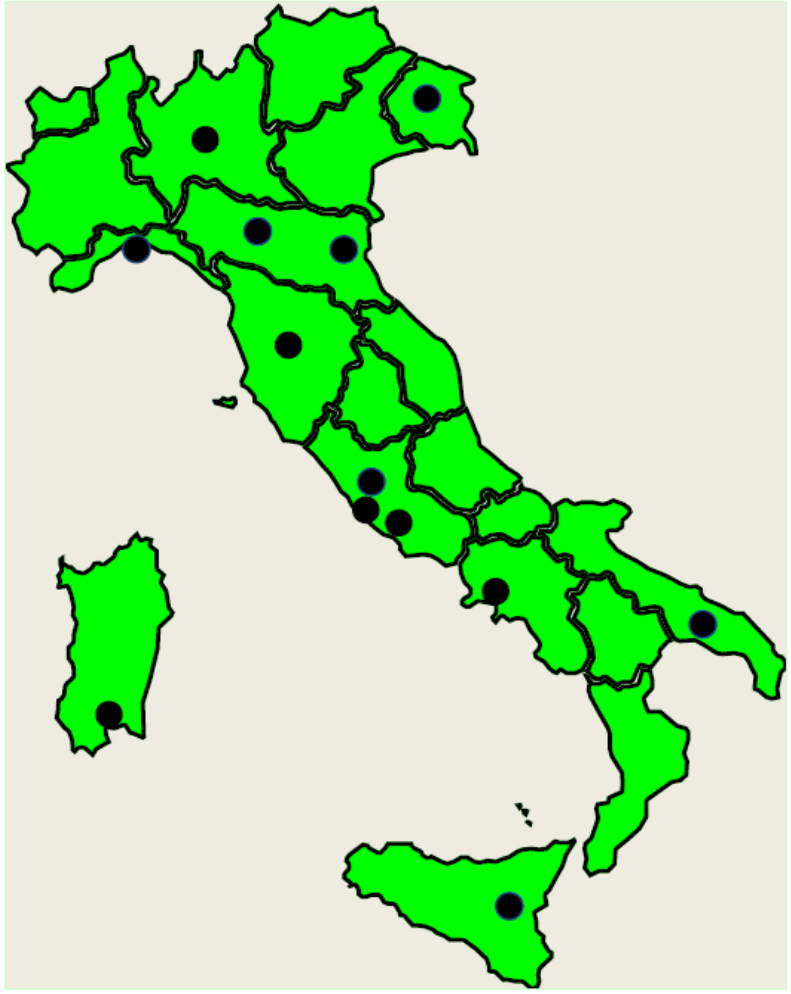
- ATROPINE
- PRALIDOXIME

- N-ACETYLCISTEINE
- METHILENE BLUE
- NALOXONE
- PHYSOSTIGMINE

- DMSA
- DMPS (os, ev)
- Ca-DTPA
- PRUSSIAN BLUE

- POTASSIUM IODIDE

- BOTULINUM ANTITOXN



Extraordinary Mobilization from SNA to NHS

Studied period: 2008-2018

→ For each EM authorized/made we have evaluated:

a) Cause of the extraordinary request

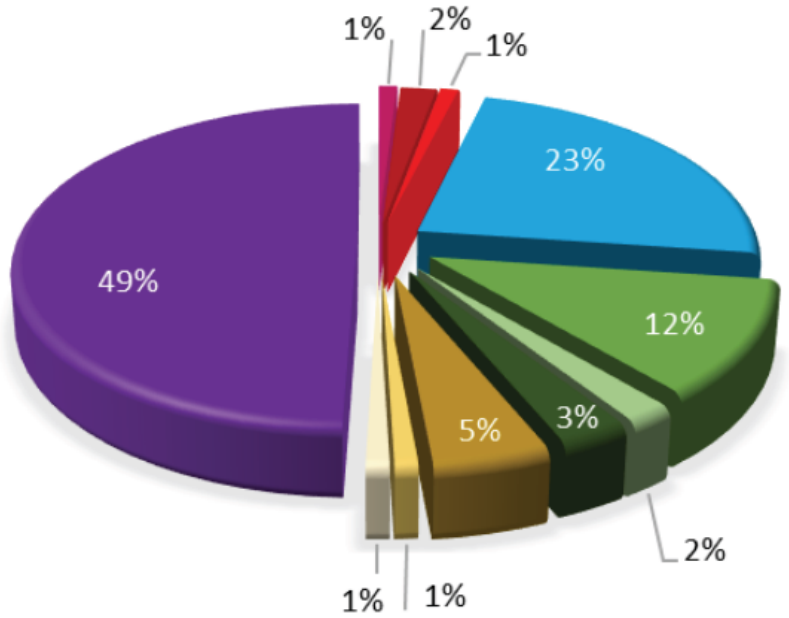
CLINICAL INDICATIONS

ANTIDOTES AVAILABILITY/SHORTAGE in the NHS hospital

b) SNA stockpile involved

Total performed SNA-EM (2008-2018): 101

Total nr. of patients: 138



Antidote (nr. of cases)

- Amyl nitrite (1)
- Hydroxocobalamin (2)
- Sodium thiosulphate (1)

→ Cyanide (fire smoke inhaletion)

- Pralidoxime (24)

→ Organophosphates

- Prussian blue (12)
- DMPS (2)
- DMSA (3)

→ Metals (Pb, Hg, As, Tl)

- Physostigmine (5)
- Methylene blue (1)
- N-acetylcysteine (1)

→ Various indication

- Botulism antitoxin (51)

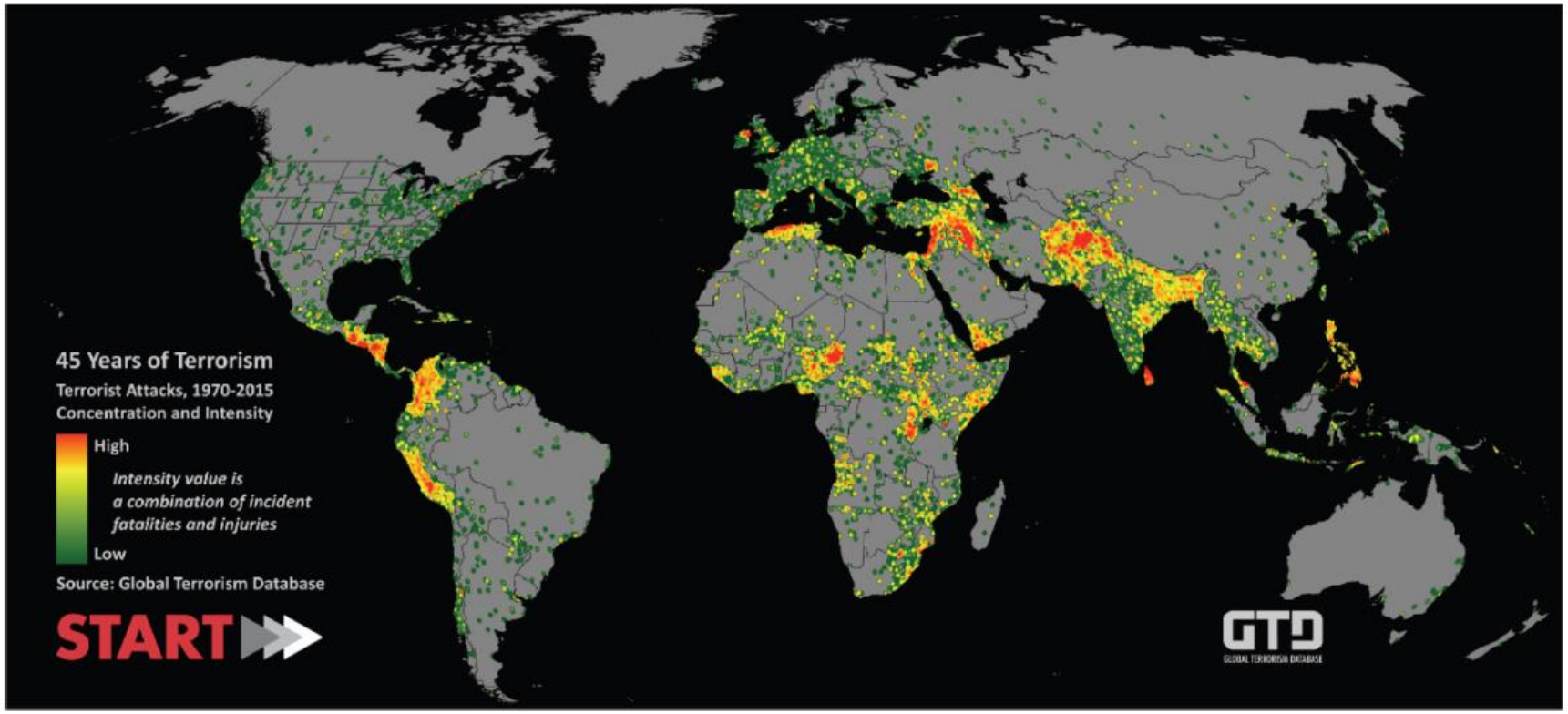
→ Botulism

"unusual Antidotes"
some examples

- Human Rabies Immunoglobulins (HRIG)
  - 60 doses of HRIG mobilized from BaNdA (2013-2018)
  - 21 patients treated for suspected imported Rabies
- Diphtheria Antitoxin
  - 2 case treated with DAT (1 not confirmed; 1 confirmed *Clostridium Ulcerans*)
- *Lactrodectus Mactans* Antivenin (available, never used)

- *<u>Antidote lacking (example)</u>*
  - Exotic animals
  - Glucarpidase
  - Uridine triacetate
  - Andexanet alfa

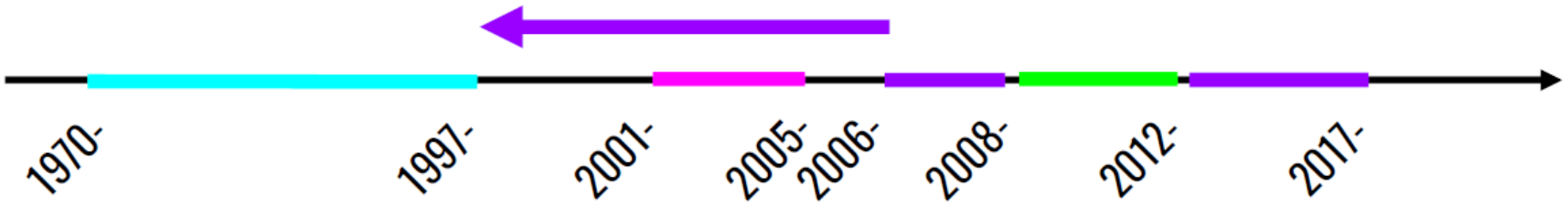
Global Terrorism Database



Global Terrorism Database

- Pinkerton Global Intelligence Services (PGIS)
- University of Maryland
- START
- Institute for the Study of Violent Groups (ISVG)

- Open source database
- >180,000 global terrorism events between 1970 and 2017
- Most comprehensive unclassified database on terrorist attacks worldwide
- Statistical data from credible media sources, which is updated as information becomes available
- Currently compiled by the National Consortium for the Study of Terrorism and Responses to Terrorism (START), a center of excellence of the US Department of Homeland Security, led by the University of Maryland
- Improved methodology in data collection since 2012
- Downloaded >89,000 times since 2007



CBRN Events

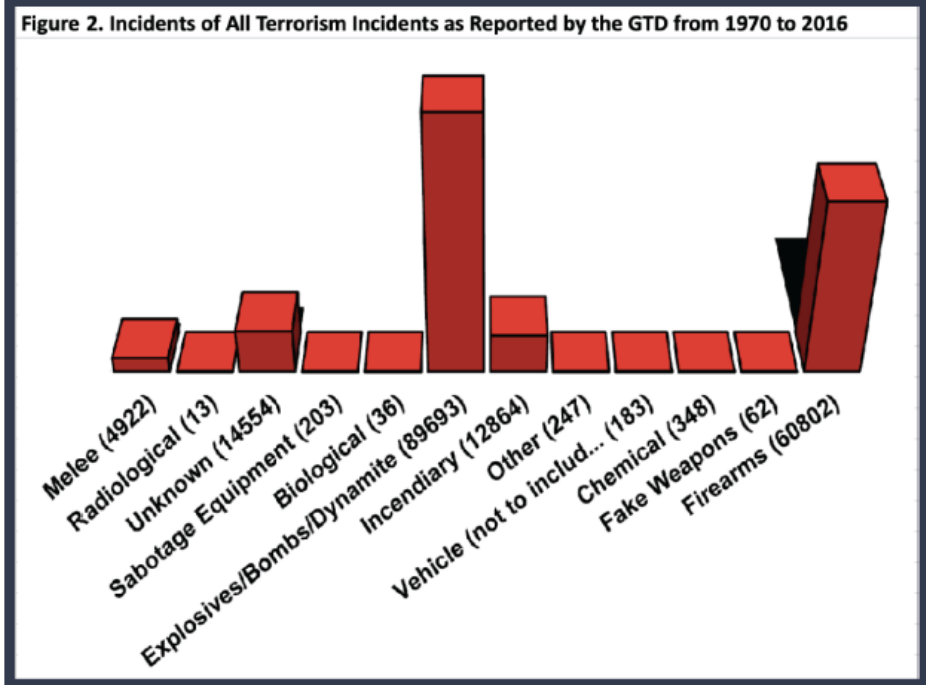
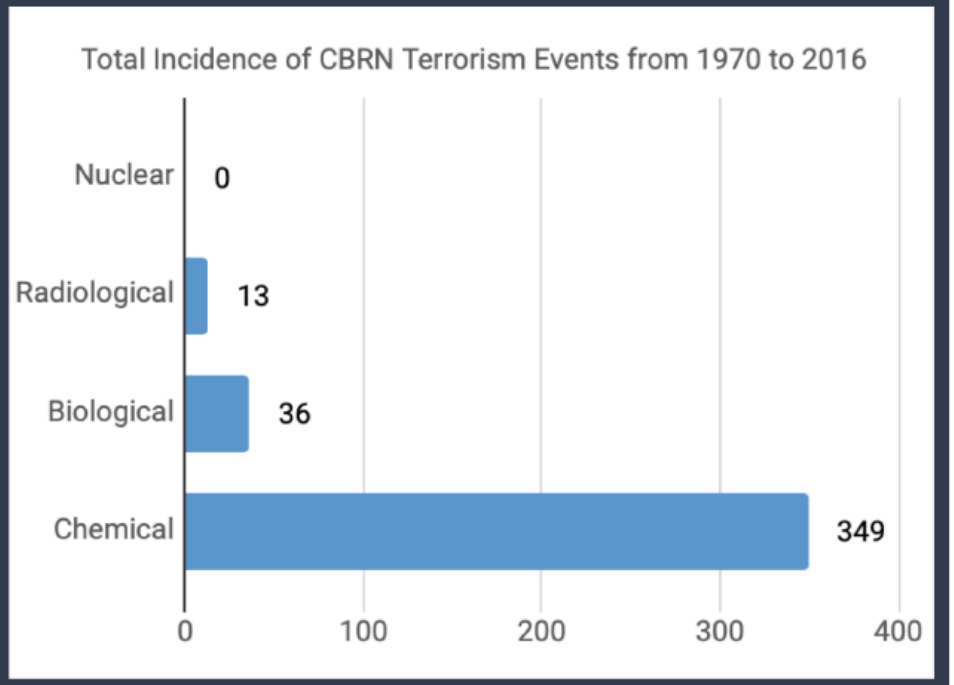
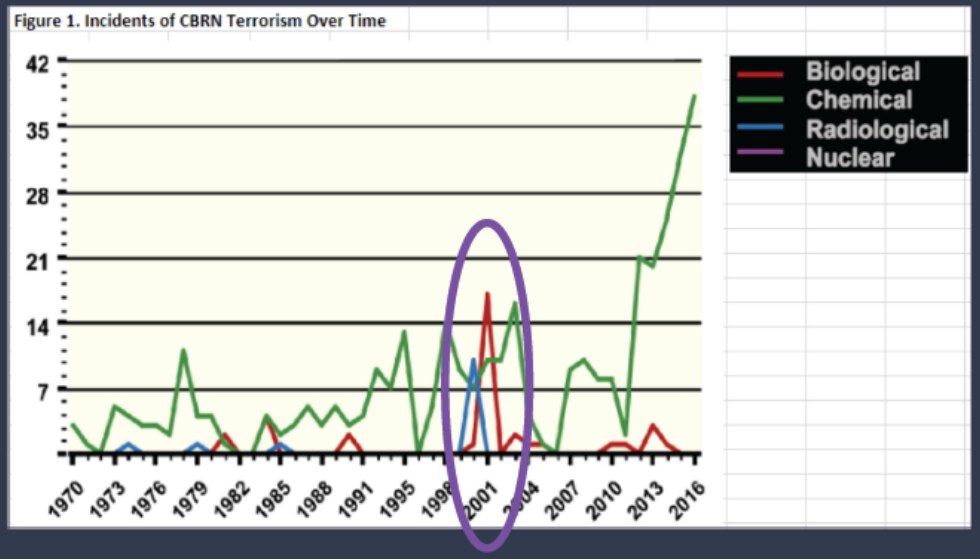


Figure 2. Incidents of All Terrorism Incidents as Reported by the GTD from 1970 to 2016
Melee (4922)
Radiological (13)
Unknown (14554)
Sabotage Equipment (203)
Biological (36)
Explosives/Bombs/Dynamite (89693)
Incendiary (12864)
Other (247)
Vehicle (not to includ... (183)
Chemical (348)
Fake Weapons (62)
Firearms (60802)


Total Incidence of CBRN Terrorism Events from 1970 to 2016
Nuclear
0
Radiological
13
Biological
36
Chemical
349
0
100
200
300
400

Incidence over Time



Mean Fatality and Mean Injury

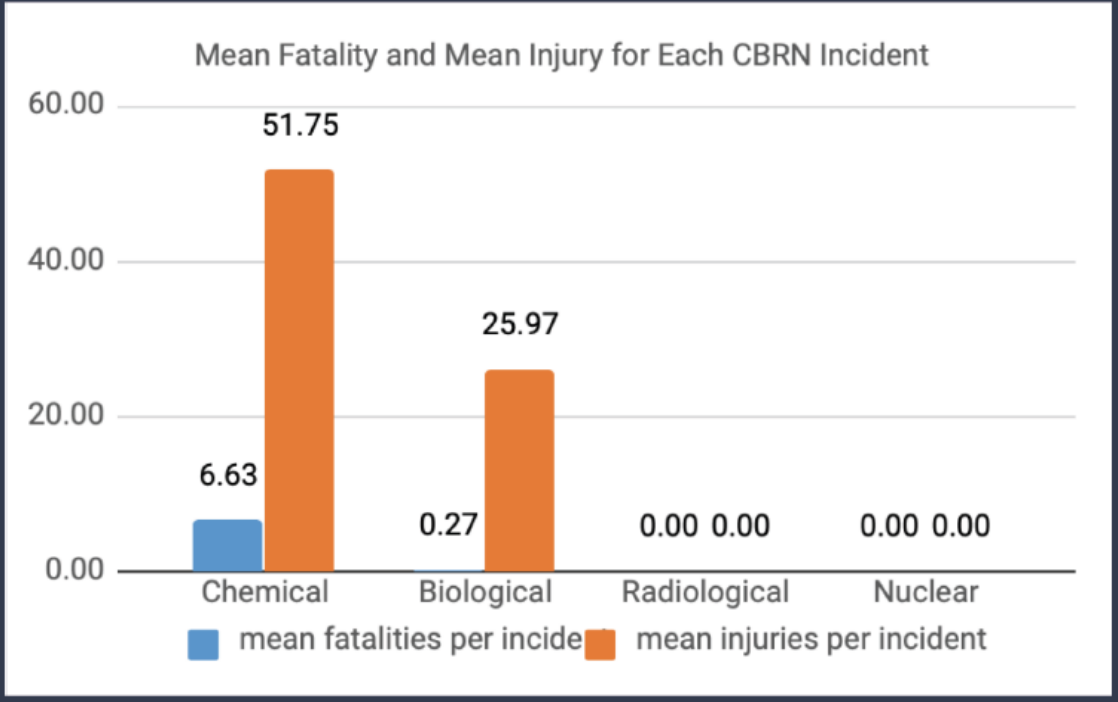


Figure 6. Frequencies of Various CBRN Incidents Across Different Regions

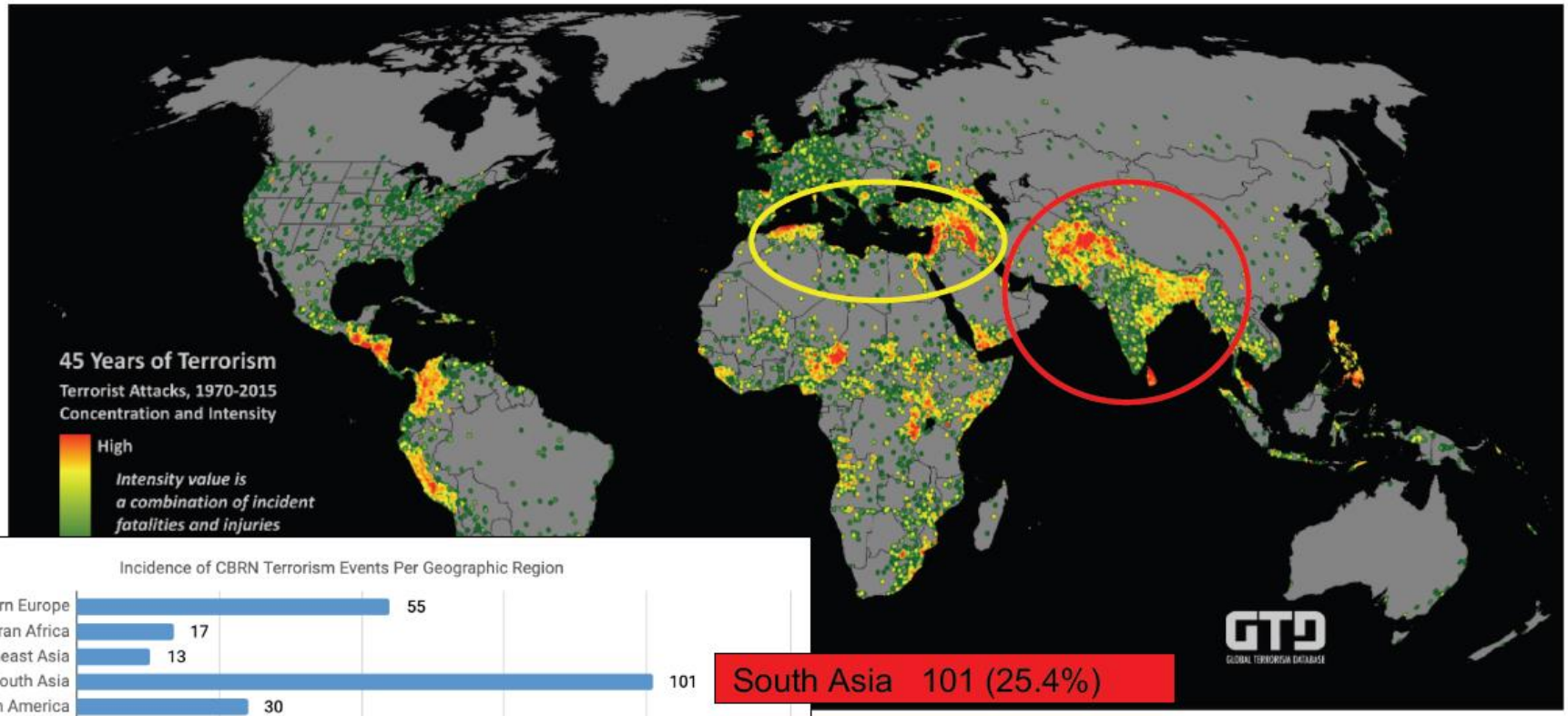
	Australia, Oceania	Central America, Carribean	Central Asia	East Asia	Eastern Eu	Middle East, North Africa	North America	South America	South Asia	Southeast Asia	Sub-Saharan Africa	Western Europe	Total
Chemical	11	2	2	19	13	68	29	28	99	13	14	51	349
Biological	0	0	0	2		1	24	2	2		3	2	36
Radiological	0	0	0	10	0	0	1	0	0	0	0	2	13
Nuclear	0	0	0	0	0	0	0	0	0	0	0	0	0
AGENT TOTAL	11	2	2	31	13	69	54	30	101	13	17	55	398
TOTAL PERCENTAGE	2.76%	0.50%	0.50%	7.79%	3.27%	17.34%	13.57%	7.54%	25.38%	3.27%	4.27%	13.82%	100.00%

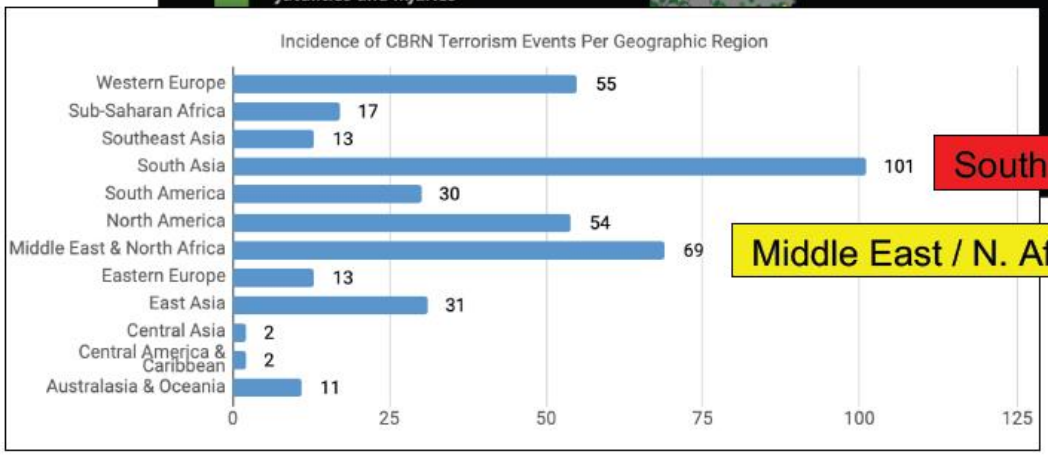
Middle East, North Africa — Algeria, Bahrain, Egypt, Iran, Iraq, Israel, Jordan, Kuwait, Lebanon, Libya, Morocco, North Yemen, Qatar, Saudi Arabia, South Yemen, Syria, Tunisia, Turkey, United Arab Emirates, West Bank and Gaza Strip, Western Sahara, Yemen

North America — Canada, Mexico, United States

South Asia — Afghanistan, Bangladesh, Bhutan, India, Maldives, Mauritius, Nepal, Pakistan, Sri Lanka

Western Europe — Andorra, Austria, Belgium, Cyprus, Denmark, Finland, France, Germany, Gibraltar, Greece, Iceland, Ireland, Italy, Luxembourg, Malta, Netherlands, Norway, Portugal, Spain, Sweden, Switzerland, United Kingdom, Vatican City, West Germany (FRG)



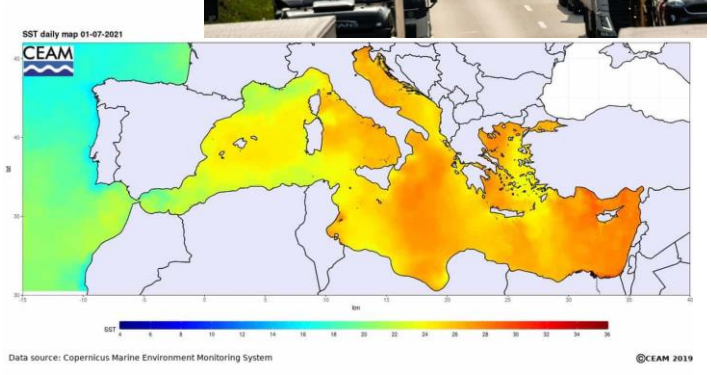


South Asia 101 (25.4%)

Middle East / N. Africa 69 (17.3%)

Fattori favorenti l'ingresso di nuove specie

- Trasporti intercontinentali
- Flussi migratori
- Rimozione barriere geografiche
- Riscaldamento globale
- Aree marine protette



Migrazione Lessepsiana

- Ferdinand de Lesseps: Console francese al Cairo, promotore del progetto Suez
- Canale di Suez: collegamento tra Oceano Indiano e Mar Mediterraneo

Condizioni favorenti:

- Vettori di trasporto
- Diminuzione salinità
- Uniformazione temperatura di superficie
- «Nile bloom»

Hermodice carunculata – Vermocane

Verme di fuoco barbuto

- Distribuzione anfiatlantica: Caraibi, Golfo del Messico e Mar Mediterraneo meridionale.
- Primo avvistamento Mediterraneo: XIX secolo, Mar di Levante, Egeo e Sicilia
- Casi CAV: 9
- Predatore vorace, in grado di adattare la sua dieta in condizione delle condizioni ambientali.
- Specie TERMOFILA: sotto i 19°C sospensione attività biologiche.
- CHETE calcaree che circondano l'animale; sensazione di bruciore al contatto con pelle.
- CARUNCULA organo sensoriale nella parte posteriore del prostomio.

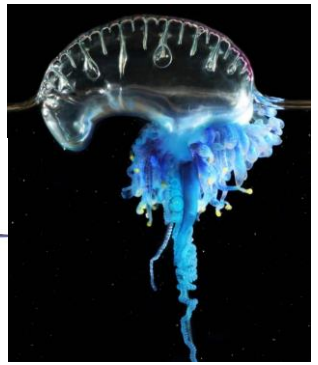
- Tossicità: Ipotesi cocktail di tossine
  - Inibitori proteasi, enzimi proteolitici lecitine C-type → disturbi emostasi e risposta infiammatoria
  - Fosfolipasi, metalloproteinasi M12 → necrosi locale
  - Peptidasi S10 e proteine CAP → prurito e reazioni anafilattiche.
  - Neurotossine → parestesie, numbness

Casi CAV Pavia

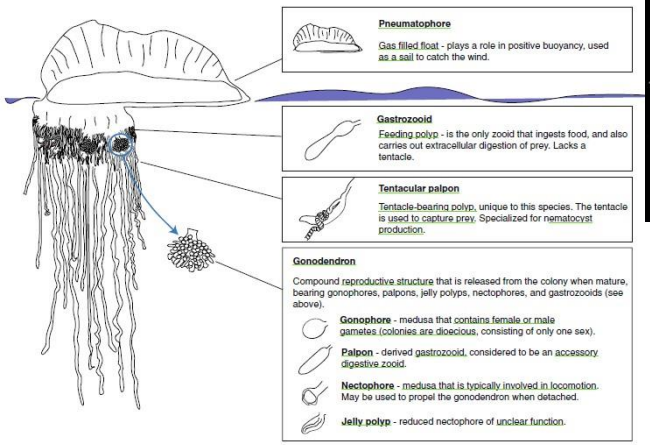
Terapia

- Rimozione meccanica delle chete;
- Immersione in acqua calda e aceto (discusso)
- Supporto

Physalia physalis – Caravella portoghese



- Origine: ubiquitaria in aree tropicali e subtropicali
- Via di ingresso: Oceano Atlantico
- Primo avvistamento: Costa atlantica Francia, 2008
- Casi CAV: 1 accertato, 1 sospetto



Sifonoforo composto da 4 tipologie di polipi.

- Pneumatoforo
- Dattilozoidi
- Gastrozoidi
- Gonozoidi

- Physalia-toxin, isolata dalle nematocisti
- Meccanismi di cardiotossicità e neurotossicità non noti.
- Sintomi locali: dolore, lesioni cutanee crostose.
- Complicanze sistemiche: GI, neurologiche, cardiologiche.

Terapia:

- Immediata decontaminazione → delicata rimozione tentacoli con acqua di mare

NO ACETO, NO AMMONIACA → aumentato rischio rottura nematocisti.

- Analgesia, anestesia locale.
- Terapia di supporto.
- Monitoraggio cardiaco.

Caso CAV Pavia

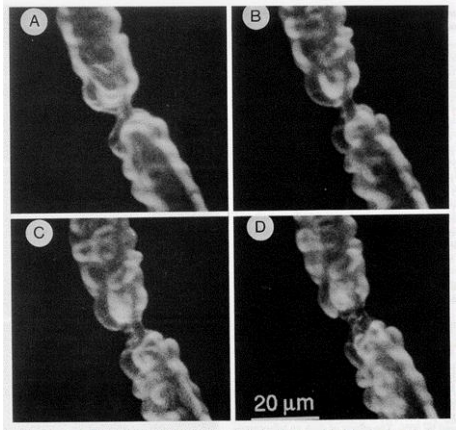
Ciguatossina

Diagnosi

- Anamnesi positiva per consumo di pesce a rischio per espozione a CTX
- Sintomi neurologici suggestivi per CTX, preceduti o accompagnati da sintomi GI
- Ricerca di ciguatossine su residui alimentari
- Quantitative sensory test (QST)

Terapia

- Non disponibile antidoto!
- Decontaminazione GI (se possibile)
- Terapia di supporto
- Mannitolo 1 g/kg ev, entro 72 ore da intossicazione



Ciguatera cronica

- Persistenza sintomatologia a 3-6 mesi dalla patologia acuta
- Ipotesi imbalance autoimmunitario → HLA fattore predittivo di cronicizzazione
- Trattamento: mannitolo 1 g/kg, 2-4 cicli di 5 giorni consecutivi.

MANIFESTAZIONI CLINICHE →

- parestesia/disestesia
- allodinia
- prurito
- mialgia
- astenia severa

«Scorpioni di importazione»

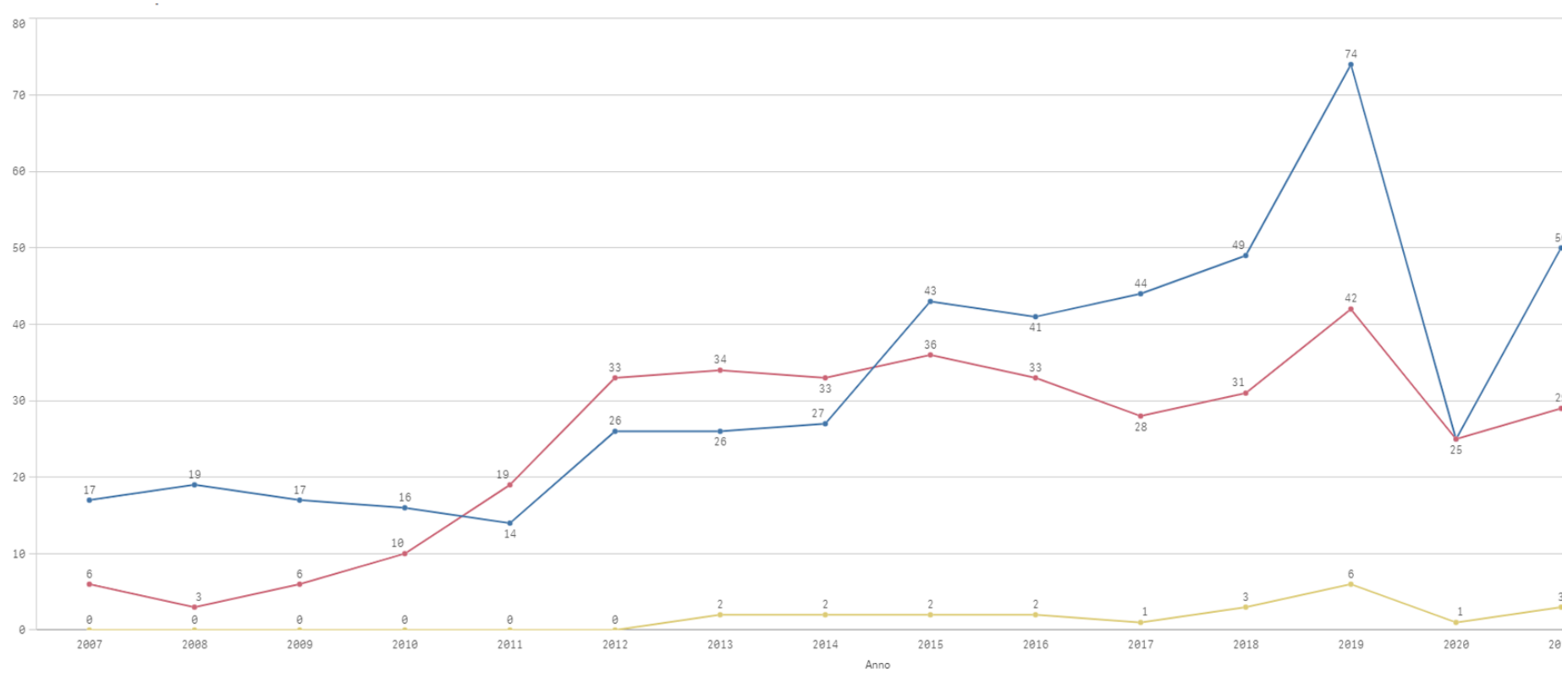
- Origine: Egitto, Cuba, Costa Rica, Grecia…
- Via di ingresso: valige di ignari viaggiatori
- Casi CAV: 4

Specie coinvolte

- Centruroides
- Tytius
- Buthus
- Non note…

Intossicazioni da sostanze d'abuso

2007-2021



Fasce di età

0-4	5-9	10-15
n = 520	n = 23	n = 394

confronto
16-18 → n = 883

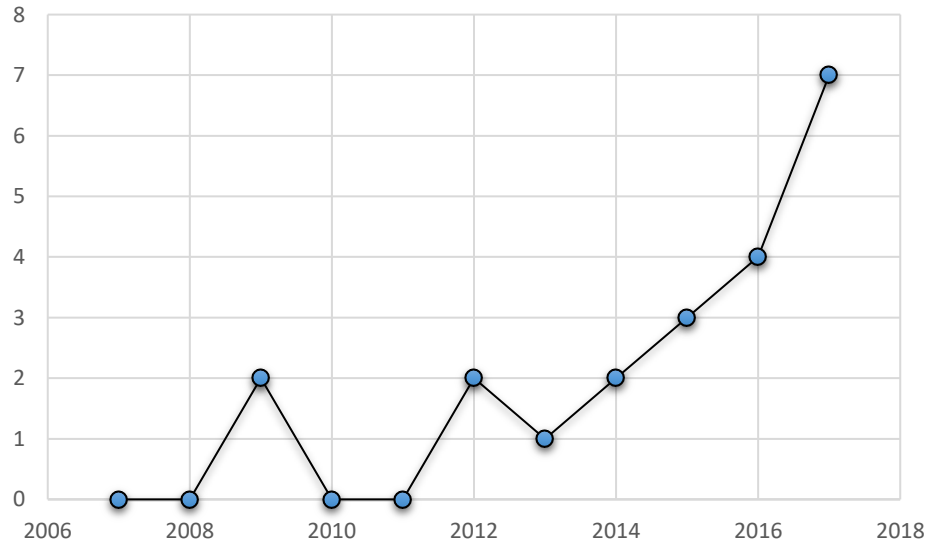
CENTRO ANTIVELENI PAVIA
CAV
CNIT
CENTRO NAZIONALE INFORMAZIONE TOSSICOLOGICA

Accidental THC ingestion in children

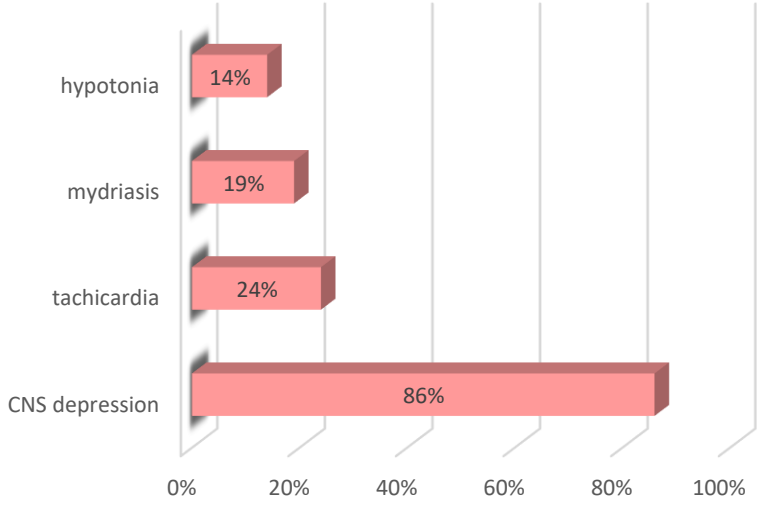
Pavia PCC case series: Jan 2007-May 2017

21 patients confirmed by urine detection

Median age: **1 year 10 months** (6 months – 6 y.o.)



Distribution of the cases during the analyzed period



Symptoms at the ED presentation

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ASSORTED GUMMY BEARS (1000MG PER BAG)

$80.00

Assorted Gummy Bears (1000mg per bag). 40 gummies per bag with 25mg of THC/gummies in each. These soft sweet and chewy delights are the perfect treats.

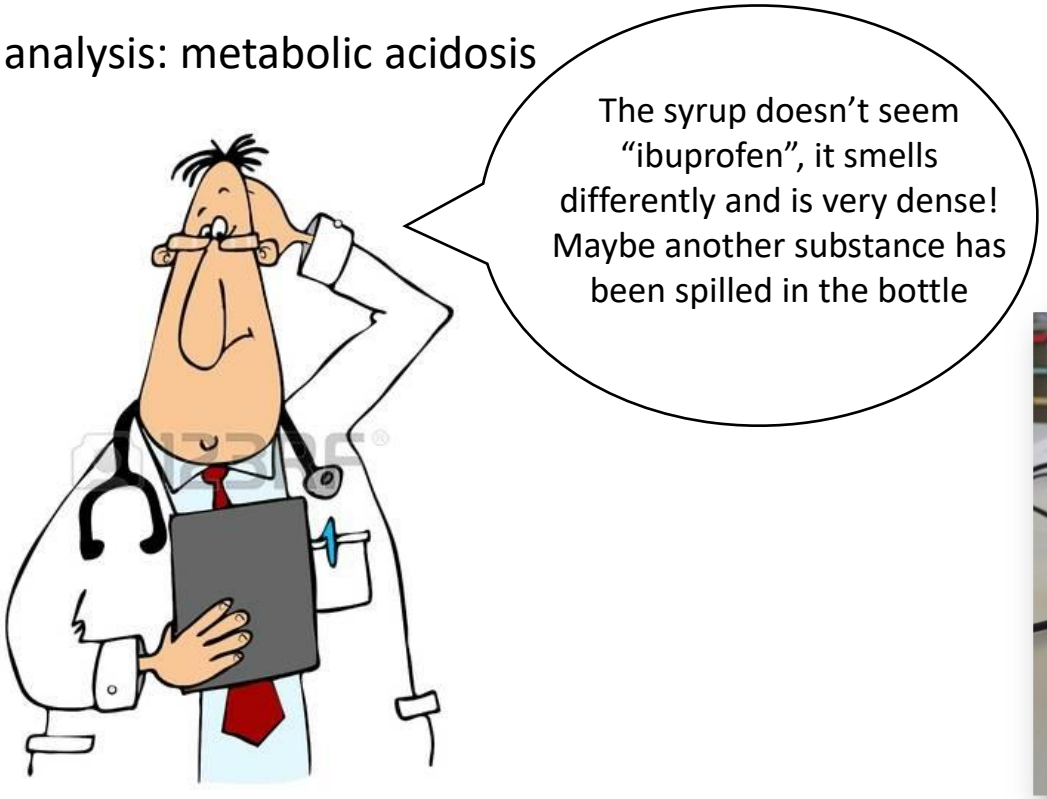
SOLD OUT

THC children ingestion
clinical case

- M - 1 y 8 months → He swallows something find in a «public garden» !? → He suddenly becomes somnolent
- ED admission (**20 minutes** after ingestion): **orotracheal intubation** + decontamination (GL + AC 7 g)
- First urinary screening: cocaine +++
- Hypertension, tachycardia, afinalistic chewing movements, diffused clonus
- analytical test on gastric lavage content cocaine and THC +++
- **24 hours** after admission: still intubated, slight troponin and CK increase
- **48 hours** after admission: extubated, laboratory values normalization.
- MR: no alterations → admitted to the paediatric unit
- ..further history: the baby probably took a piece of hashish mixed with cocaine while visiting his father (22 y.o.) in prison → A court order was made to turn the baby away from his family

Methadone
Clinical case

- F - 6 y.o. ; on holiday with her mother and aunt
- She's ill and her mother gives her a spoon of ibuprofen syrup
- 90 minutes later, ED clinical presentation: **CNS depression**, **miosis**, motor agitation, afinalistic chewing movements. She's thirsty.
- Blood gas analysis: metabolic acidosis



Methadone
Clinical case

- 2 hours after the ingestion: apnea, vomiting

  coma
  miosis
  apnoea

  naloxone 0,2 mg iv → partial resolution of the symptoms

- EKG: QTc prolongation (500 ms)

Urinary toxicological analysis: methadone +++

… further history revealed that the mother (a nurse) had taken the bottle away from the hospital ward where she worked

Italian methadone formulations (syrup)

1 mg/ml → 5 ml, 10 ml, 20 ml, 40 ml, 60 ml, 100 ml, 1000 ml

3 mg/ml → 20 ml

5 mg/ml → 5 ml, 10 ml, 20 ml, 60 ml, 500 ml, 1000 ml

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Binge drinking & NPS
Clinical case

- M, 16 y.o.

- ED admission: **psychomotor agitation**, **hallucinated**, alterning miosis-mydriasis.

- Blood alcohol level = 3 g/l
- Urinary toxicological screening = THC ++

- During the following hour he became more agitated and aggressive.
- Sedated with midazolam (40 mg) and propofol, than intubated → ICU admission

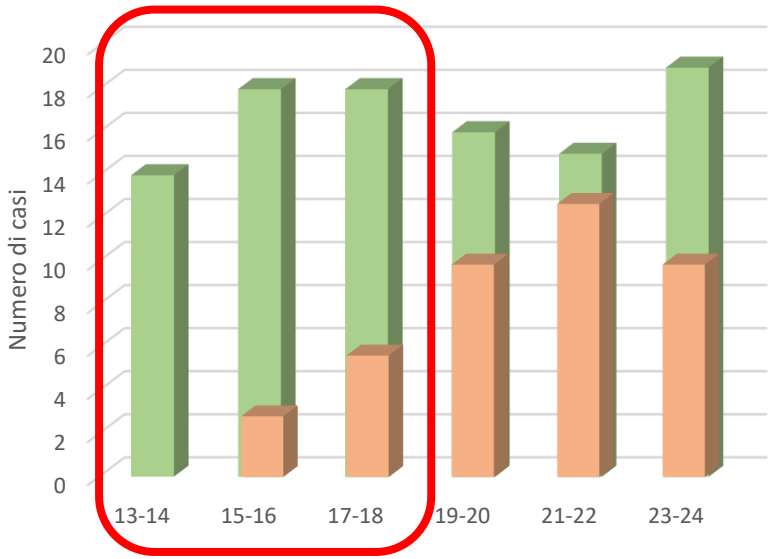
- Extubated and discharged from ICU 36 hours after ED admission

- **Second level blood analysis: JWH-073 +++**

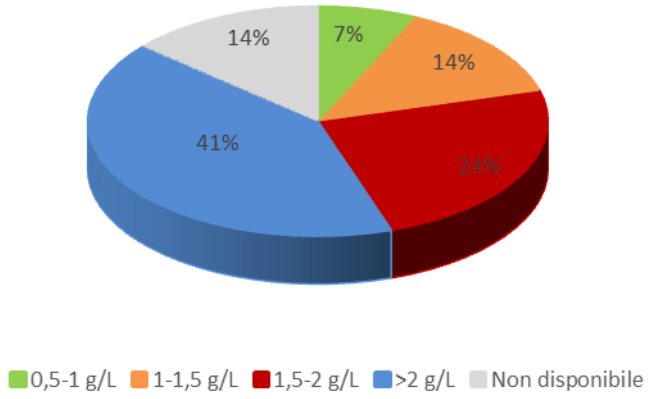
Binge drinking & NPS

Patients under 25 y.o. referred to Pavia PCC (Jan 2010- July 2015) with history of consumption of at least one NPS

Age distribution of alcohol + NPS abuse



Blood alcohol levels



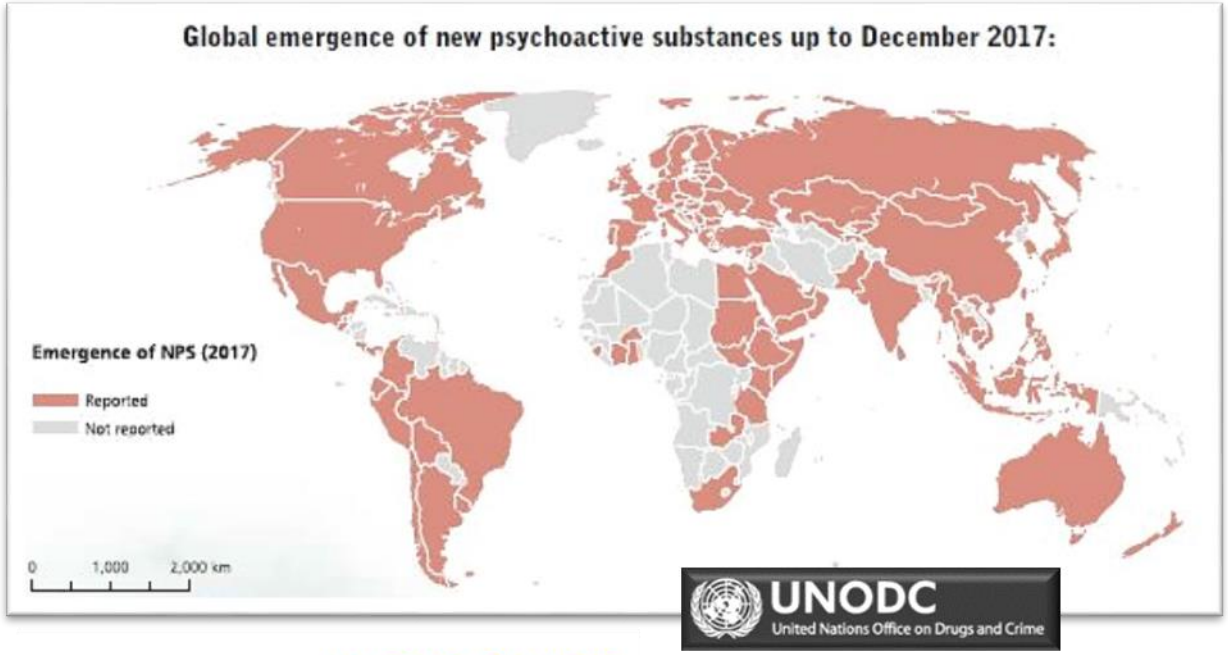
In **14%** of patients with acute alcohol intoxication at least 1 NPS was detected

New Psychoactive Substances - NPS

European Monitoring Centre for Drugs and Drug Addiction

di libera vendita

"a new **narcotic** or **psychotropic** drug, in pure form or in preparation, that is not controlled by the United Nations drug conventions, but which may pose a public health threat comparable to that posed by substances listed in these conventions"



UNODC-SMART:

More than 800 NPS have been reported to UNODC
from over 110 countries and territories from all regions of the world

New psychoactive substances

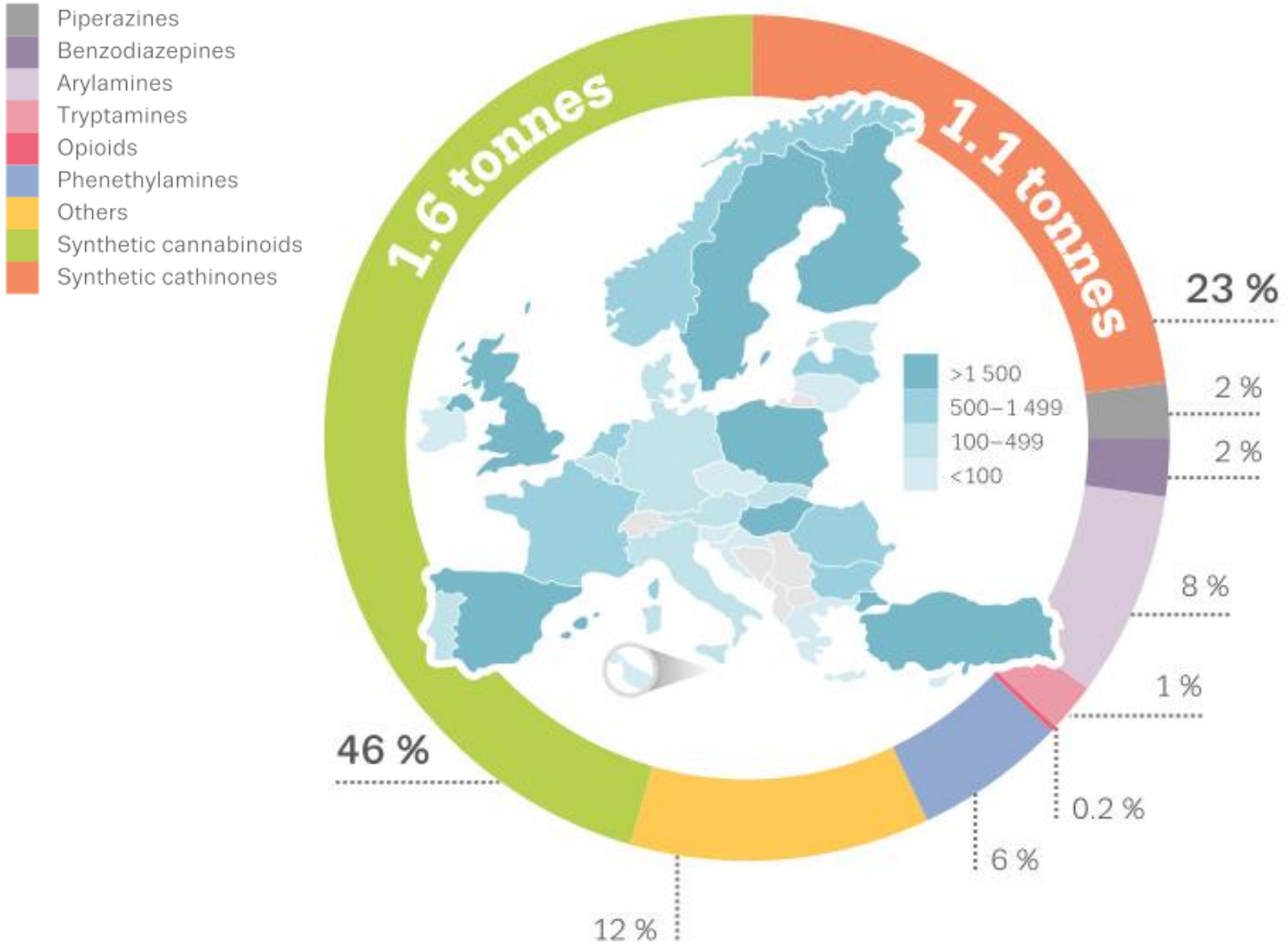
Table 1 Summary of the toxic effects of the treated groups of New Psychoactive Substances (NPS)

Chemical class	Principal mechanism of toxicity	Major toxic effects
Synthetic cannabinoids	CB1 and CB2 receptors agonists displaying higher affinity, efficacy and potency compared to 19-THC	Euphoria, anxiolytic, and antidepressant-like effects, paranoia, tachycardia, panic, convulsions, psychosis, visual/auditory hallucinations, vomiting, and seizures
Synthetic cathinones	Sympathomimetic drugs that act on serotonin, dopamine, and noradreline pathways	Agitation, restlessness, vertigo, abdominal pain, paranoia, rhabdomyolysis, convulsions, and death
Arylcyclohexylamines	Dissociative anesthetics that act as 5HT2A agonist and NMDA receptor antagonist and show high affinity for opioid receptors	Distort perceptions of sight and sound, dissociation from the environment and self without hallucinations
Phenethylamines	Serotoninergic receptor agonists that cause psychedelic effects and inhibit monoamine reuptake	Hypertension, vomiting, hyperthermia, convulsions, dissociation, hallucinations, respiratory deficits, liver and kidney failure, and death in case of overdose
Piperazines	Stimulants that promote the release of dopamine and noradrenaline and inhibit the uptake of monoamines	Hyperthermia, convulsions, and kidney failure; hallucinations and death have been reported at high doses
Tryptamines	5HT2A receptor agonists and serotonin reuptake inhibitors	Visual hallucinations, alterations in sensory perception, depersonalization

Locatelli CA et al. New Drugs of Abuse and Cardiovascular Function. In S. Govoni et al (eds): Brain and Heart Dynamics, Spriger Nature AG 2020, pag. 1-27

European Monitoring Centre
for Drugs and Drug Addiction

Number of NPS seizures and proportion of seizures by category of substance, 2013



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"purchasing on the web"

(May 14th, 2017)

	n. of website	(online)
• "buy cocaine (online)"	101,000	(7,920)
• "buy ecstasy (online)"	32,500	(4,220)
• "buy party pills (online)":	29,000	(9,740)
• "buy spice smoke (online)"	5,600	(1,040)
• "buy cannabinoids (online)"	3,780	(380)
– "buy herbal incense (online)"	80,700	(21,400)
– "buy K2 (online)"	48,500	(2,400)
• "buy cathinones (online)"	241	(8)
– "buy mephedrone (online)	48,700	(2,670)
• "buy ketamine (online)"	21,500	(4,370)
– "buy methoxetamine (online)"	3,800	(855)
• "buy research chemicals (online)"	124,000	(45,500)
• "buy magic mushrooms (online)":	16,800	(2,070)
• "buy fentanyl (online)"	67,900	(35,100)

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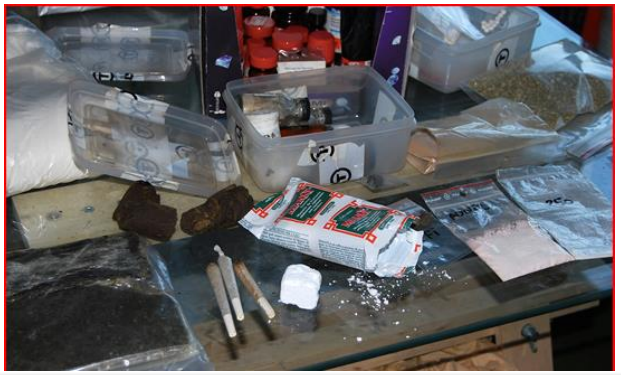
Produzione e trasformazione



Operazione
"Profumo di Droga"

Droghe legali _ il caso Tessier -Ashpool - Copia.mov

NEW PSYCHOACTIVE SUBSTANCES

52 first reported in 2020

880 being monitored

372 on the market each year

Seizures

Number

EU 22 230

EU + 2 41 100

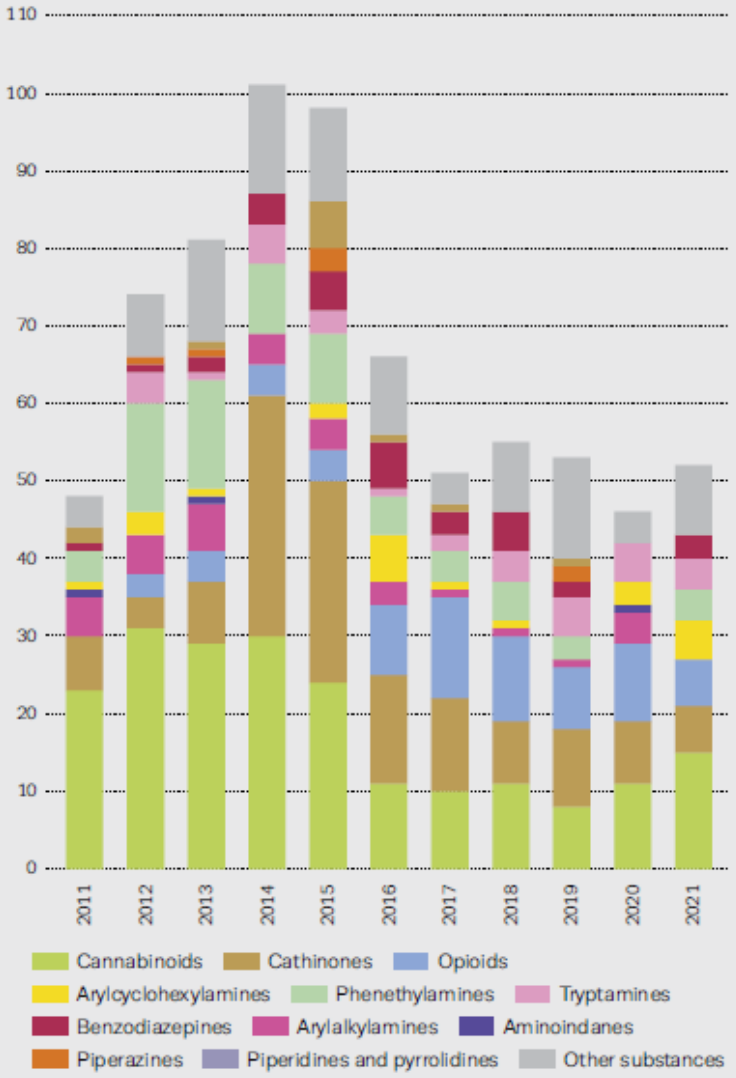
Quantity (tonnes)

EU 5.1

EU + 2 6.9

All physical forms measured in weight units — includes herbal material, powders, resins, others.

Number and categories of new psychoactive substances reported to the EU Early Warning System for the first time, 2011–21



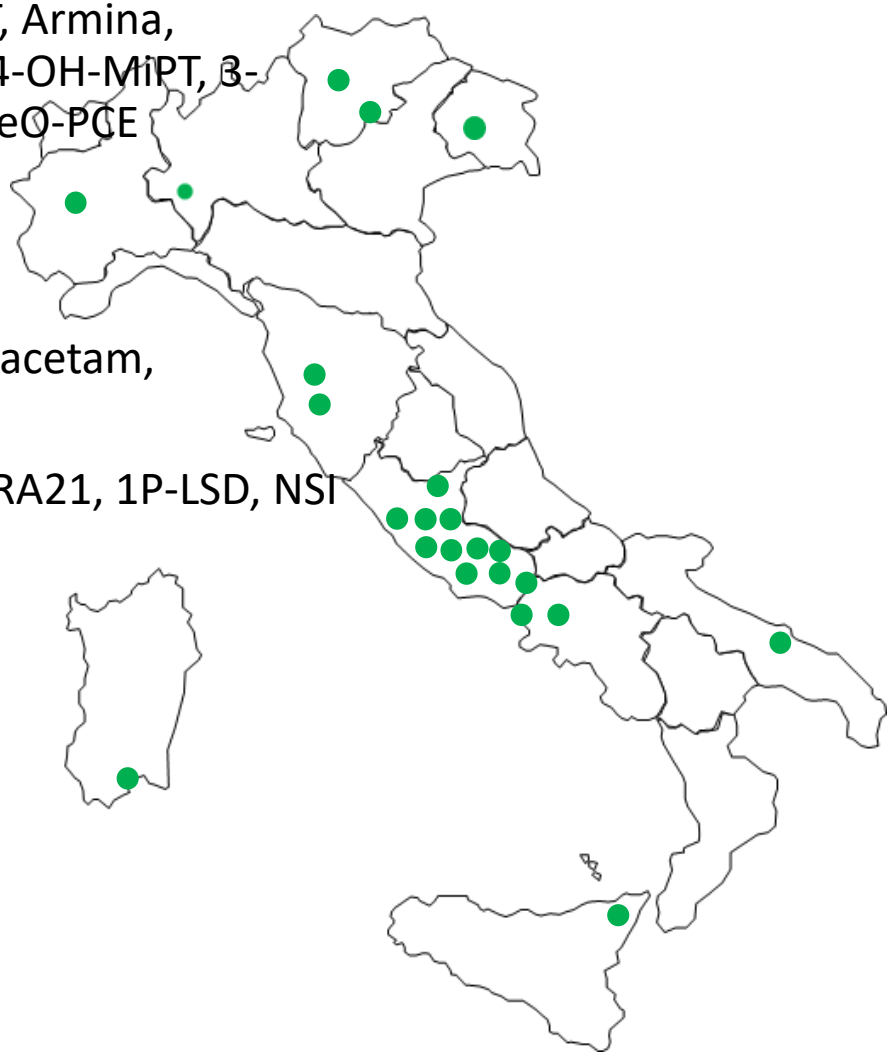
Continued on next page →

Segnalazioni FFO (sequestri) – SNAP, mese di ottobre

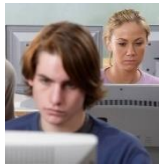
1. 4F-MDMB-BINACA (4F-ADB) + 4F-MDMB-BICA (4F-MDMB BINACA)
2. Etizolam + 4-HO-MiPT + 2-FDCK
3. Mefedrene + N-etilesedrone + Metallilescalina
4. Pirrolidinoesanofenone (α-PHP)
5. THC > 70%
6. Ketamina 60-65% + MDMA 37-77% + amfetamina 40,8%
7. Psychotria viridis
8. 3-Clorometcatinone (3-CMC)
9. Hashish + efedrina + meth
10. 2C-B-Fly + 4F-MPH + 1CP-LSD + clonazolam + 1PLSD + Flualrazolam
11. 1cP-LSD + 4-HO-MET + 5-MeO-DMT + O-PCE (descloro-N-etilketamina) + Etizolam
12. 2-FMA + MDMB-4en-PINACA
13. Oxiracetam + cardarina + 1cP-LSD + MK-2866/ostarina + Idra-21 + 1P-LSD + NSI-189 + NOOPEPT
14. Bromazolam + Etizolam + Flualprazolam [illegible]XPr
15. morfina, codeina, tebaina e papaverina ([illegible]iccat

Segnalazioni FFO (sequestri) – SNAP, mese di ottobre

16. LSD, psilocina, 3-MeO-PCP, Metallilescalina, 5-MeO-DMT, DMT, 5-MeO-DALT, salvia divinorum (Salvinorina A), 4-AcO-MET, 4-OH-MET, 4-Cl-alpha-PVP, 4-AcO-DMT, Armina, Armalina, Tetraidroarmina, 6-APB, 3-MMC, 4-OH-MiPT, 3-CMC, O-PCE, DPT, Ketamina, 3-OH-PCE, 3-MeO-PCE
17. MDPHP
18. α-PHiP, 3-MeO-PCE
19. 1P-LSD, 3-MMC, O-PCE, 3-MeO-PCP, Fenilpiracetam, Sintacaina
20. Piracetam, Cardarina, 1cP-LSD, Mk-2866, IDRA21, 1P-LSD, NSI 189, NOOPEPT
21. Isopropilfenidato, etizolam
22. Sintacaina-4-CMC
23. Delta-9-THC (Delta-9-tetraidrocannabinolo)
24. Caffeina, metamfetamina
25. 5F-EDMB-PICA
26. Eroina, 6-MAM
27. Flunitrazolam, di 4-AcO-MET, di 4-HO-DET
28. 2-FEA – 3-FEA



Il «giro» oggi



- Varietà dell'offerta
  - epocale per quantità
  - prezzi bassi
  - facilità di accesso
  - sperimentazione
- Spacciatore → in casa → web
  - marketing, promotion
  - fidelizzazione
  - falsa percezione di innocuità (← legalità)
  - indicazioni sull'uso (come ottenere/usare) → filmati dimostrativi
  - blog
    - → sistema di adescamento, raggiro
    - → «trial clinico» per lo sprovveduto

Priorità in cerca di soluzione

(salute)

- Diagnosi errate / non note
  - Errori terapeutici
  - NON appropriatezza
  - Problema «trasparente» nei DEA
    - Diagnosi analitica
  - NPS – sostanze classiche – farmaci contraffatti
- Nessuna informazione sui rischi
  - Scuola
  - Web / TV
- applicazione del CdS/omicidio stradale

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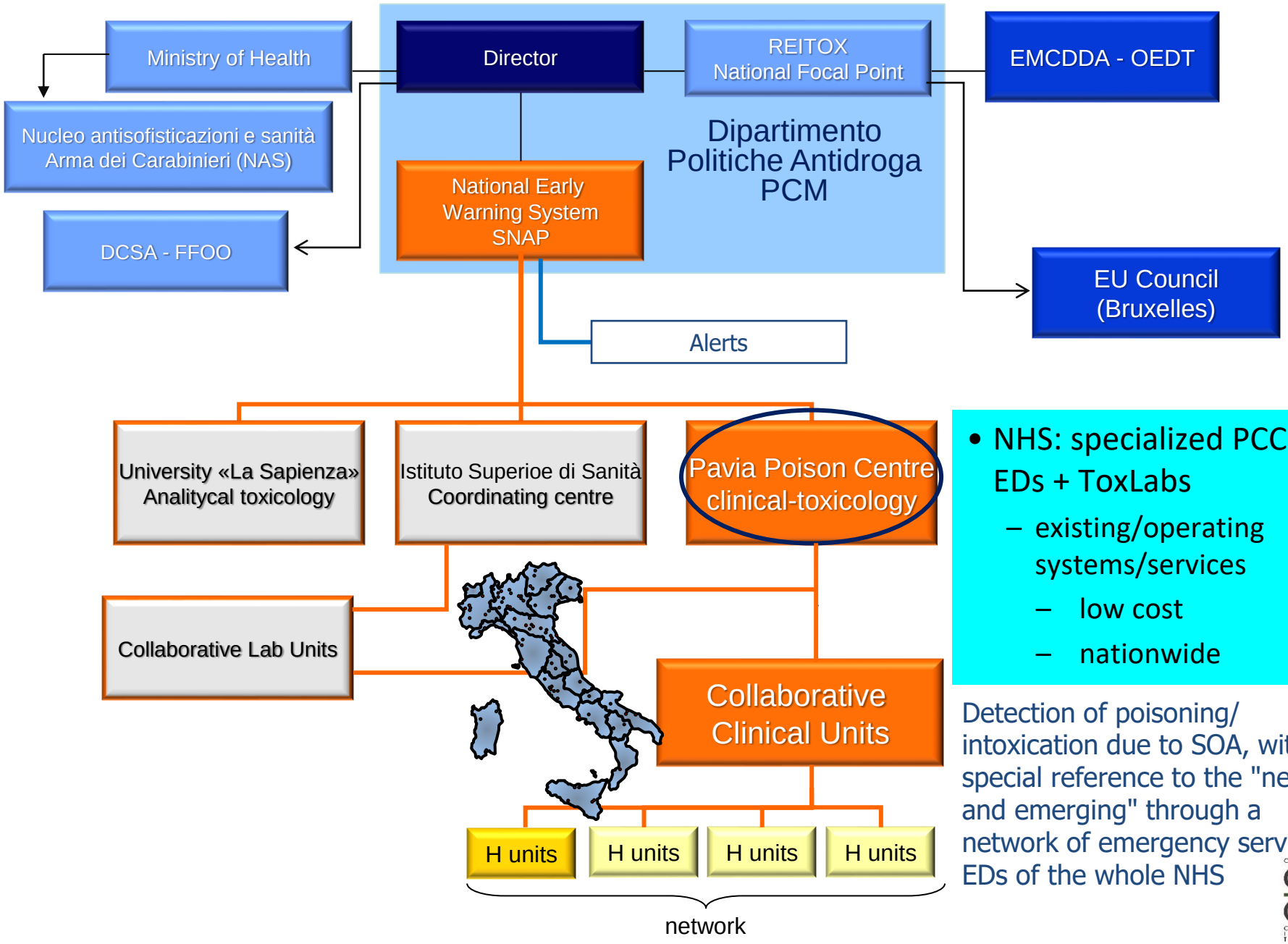
Clinical pictures and management priorities in ED

- clinical pictures
  - sympathomimetic / excitatory syndrome
  - agitated / aggressive / hallucinated patient in EDs
  - mixed syndromes / clinical effects
    - hallucination + agitation + violence + CNS depression + cardiovascular toxicity

- management priorities at admission (first hours):
  - stabilization, (decontamination), medications (antidotes ?)
  - specific toxicological diagnosis (clinical + analytical)
  - monitoring (clinical, instrumental, analytical)
  - choice of the appropriate hospital admission
    - observation / emergency medicine / ICU
    - psychiatric ward
    - other departments (paediatric ?)
  - transfer to less intensive Depts. / discharge

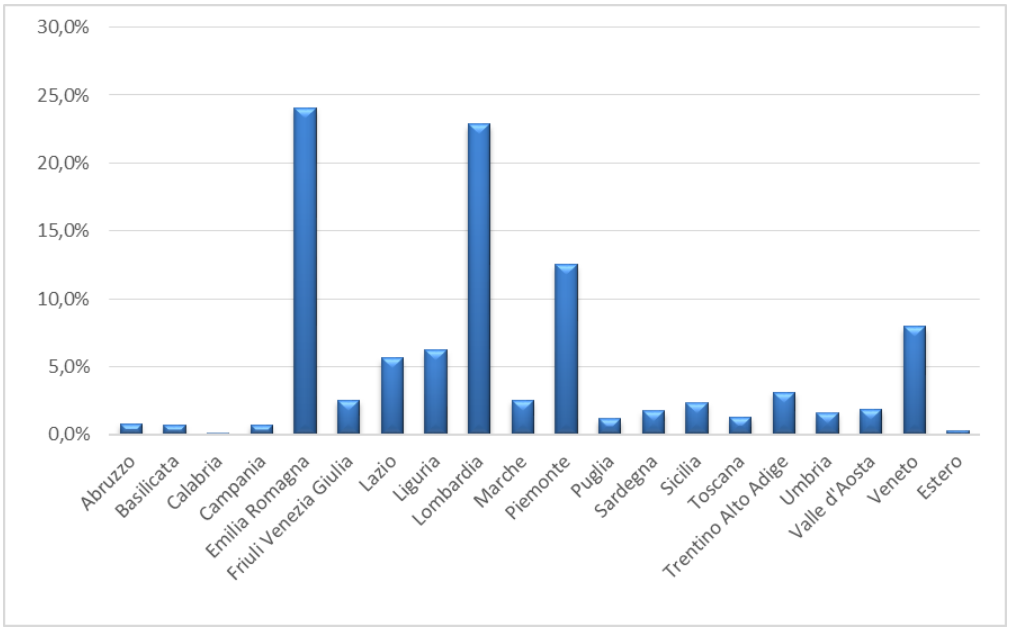
NEWS / SNAP - National Early Warning System
Operating System

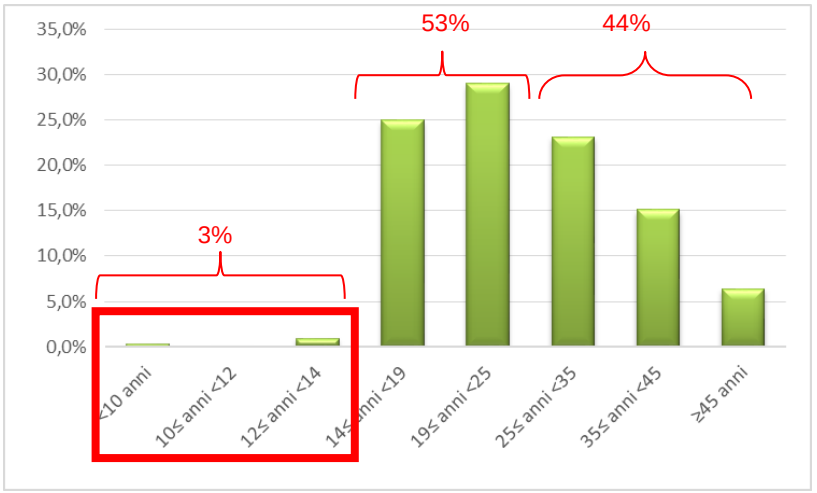


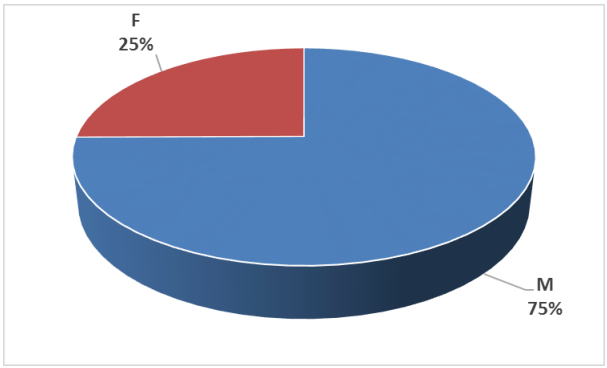
- NHS: specialized PCC + EDs + ToxLabs
  - existing/operating systems/services
    - low cost
    - nationwide

Detection of poisoning/ intoxication due to SOA, with special reference to the "new and emerging" through a network of emergency services/ EDs of the whole NHS

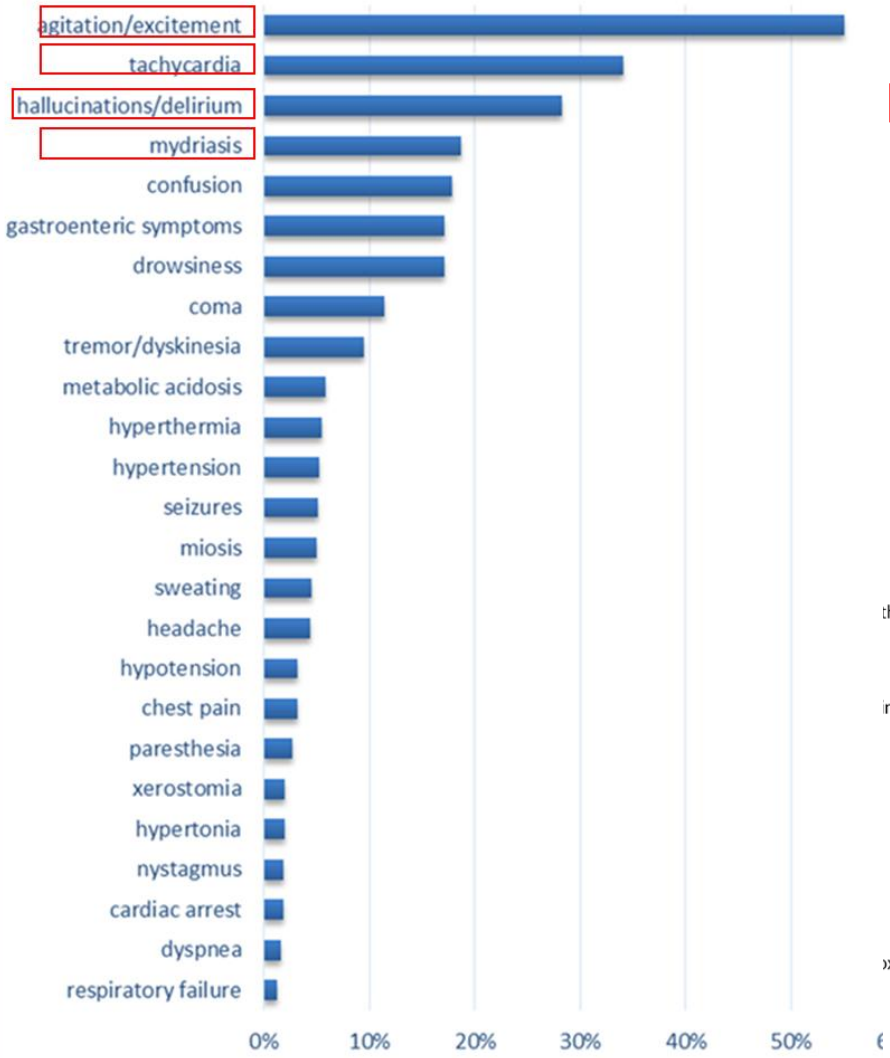
Sex, age, regional distribution (> 18,000 consultancies for SoA)
n. of cases of NPS studied (02/2010-12/2021) =2,265
(from 396 Hospitals in 258 cities)



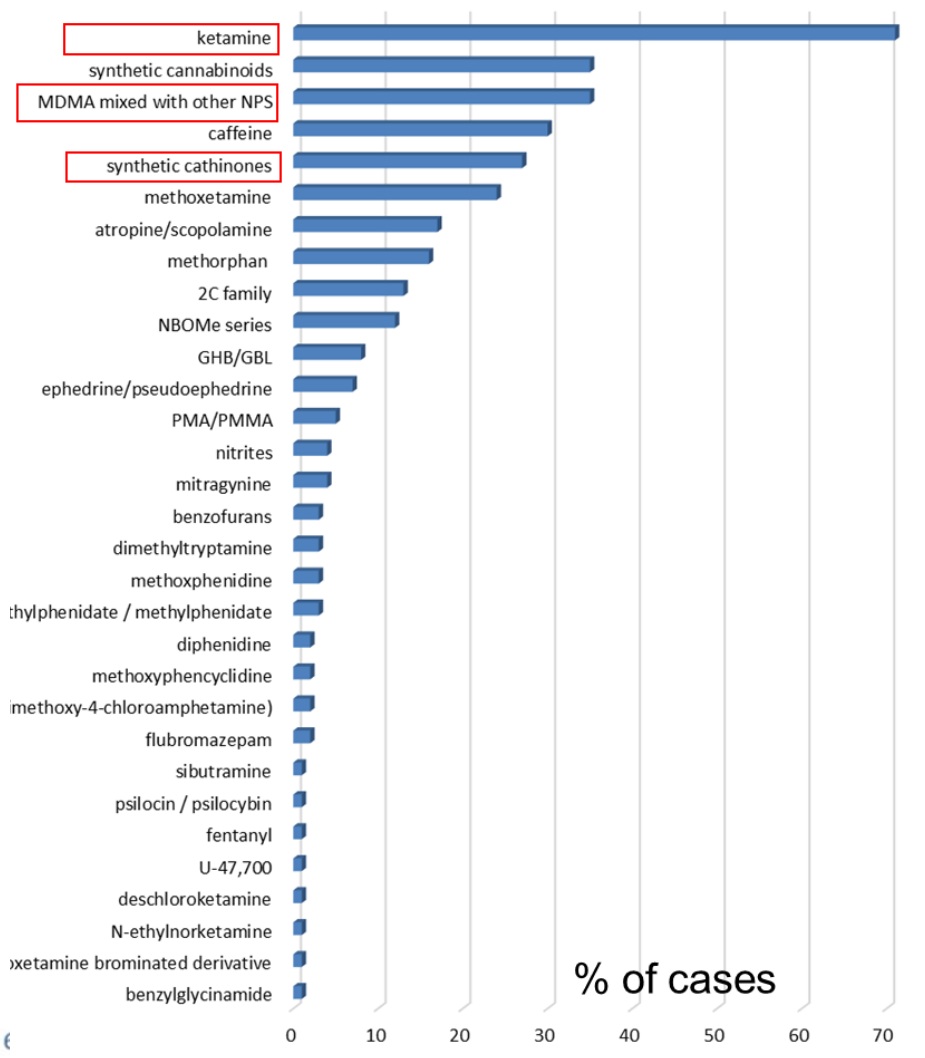




Clinical features
(n. of tested cases= 2,265 / > 25,000)



NPS analytically confirmed
February 2010 - 2021



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Methoxetamine Molecular Targets Profiled

Serotonin Receptors	5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{1E}, 5-HT_{2A}, 5-HT_{2B}, 5-HT_{2C}, 5-HT_3, 5-HT_5, 5-HT_6, 5-HT_7
Dopamine Receptors	D_1, D_2, D_3, D_4, D_5
Glutamate Receptors	NMDA Receptor (MK-801 binding site), $mGluR_5$
GABA Receptors	GABA-A, GABA-B, Benzodiazepine site on GABA-A, Peripheral Benzodiazepine Receptor
Biogenic Amine Transporters	SERT, NET, DAT
Adrenoceptors	α_{1A}, α_{1B}, α_{1D}, α_{2A}, α_{2B}, α_{2C}, β_1, β_2, β_3
Muscarinic Receptors	M_1, M_2, M_3, M_4, M_5
Cannabinoid	CB-1, CB-2
Nicotinic receptors	$\alpha_2\beta2$; $\alpha_2\beta4$; $\alpha_3\beta2$; $\alpha_3\beta4$; $\alpha_4\beta2$; $\alpha_4\beta2$ functional assays; $\alpha_4\beta4$
Opioid Receptors	MOR, KOR, DOR
Sigma Receptors	$Sigma_1$, $Sigma_2$
Histamine Receptors	H_1, H_2, H_3, H_4

doi:10.1371/journal.pone.0059334.t001

Representative pKi values for ketamine, PCP and analogues

Compound	NMDA pKi +/− SD (Ki, nM)	SERT pKi +/− SD (Ki, nM)	NET pKi +/− SD (Ki, nM)	$Sigma_1$ pKi +/− SD (Ki, nM)	$Sigma_2$ pKi +/− SD (Ki, nM)
Ketamine	6.18±0.07 (659)	–	–	–	–
Phencyclidine	7.23±0.07 (59)	5.65±0.05 (2234)	–	–	6.82±0.09 (136)
Methoxetamine	6.59±0.06 (259)	6.32±0.05 (481)	–	–	–
4-MeO-PCP	6.39±0.06 (404)	6.07±0.05 (844)	6.1±0.1 (713)	6.5±0.1 (296)	7.93±0.08 (143)
3-MeO-PCP	7.69±0.08 (20)	6.7±0.1 (216)	–	7.4±0.1 (42)	–
3-MeO-PCE	7.22±0.08 (61)	6.9±0.06 (115)	–	5.3±0.1 (4519)	6.31±0.1 (525)

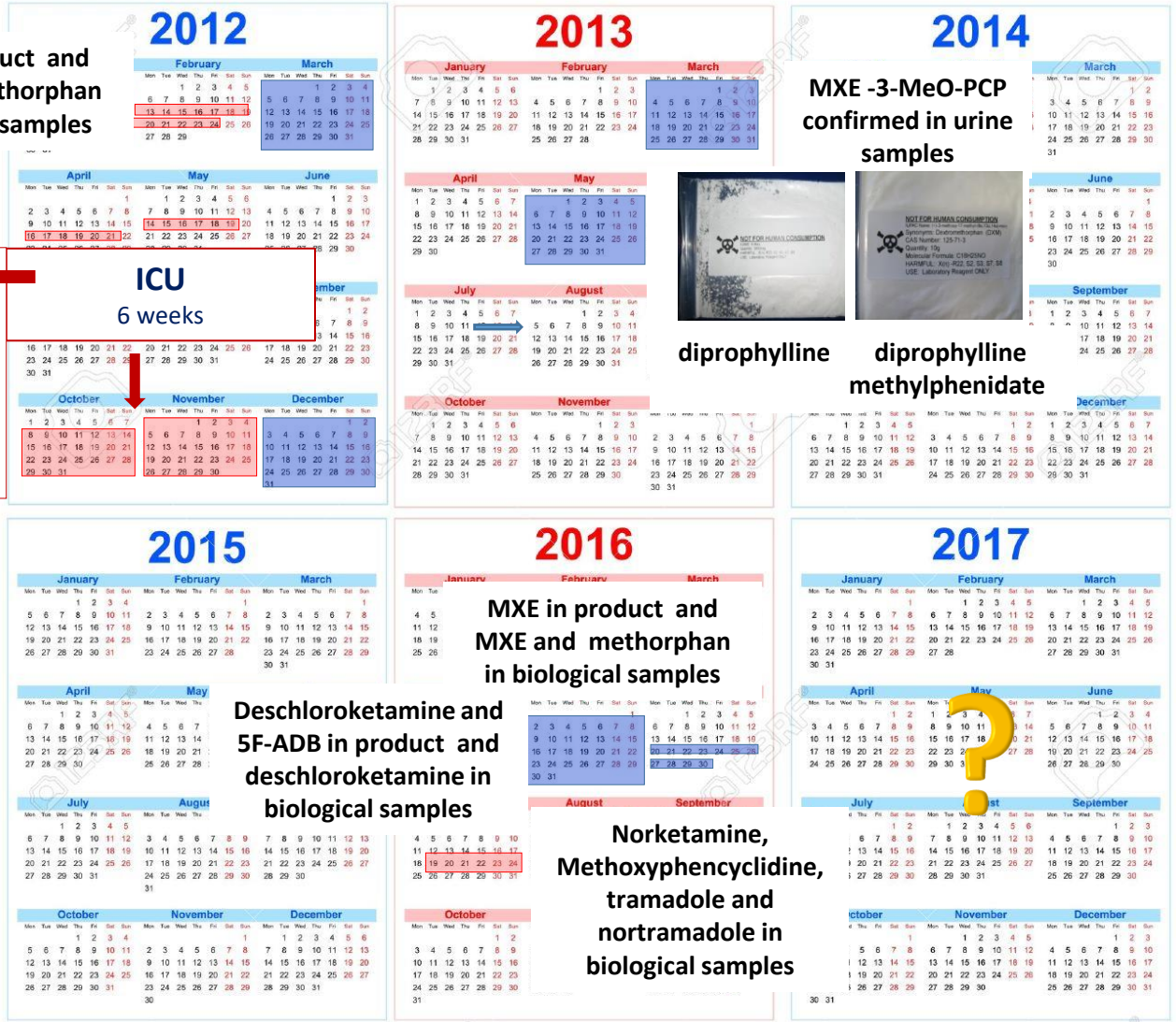
Open boxes with – indicate that compounds failed the Primary Screen criterion of >50% inhibition at 10 μM.
Abbreviations: NMDA (*N*-methyl-D-aspartate receptor); SERT (serotonin transporter); NET (norepinephrine transporter).
doi:10.1371/journal.pone.0059334.t002

Roth BL, et al. (2013) The Ketamine Analogue Methoxetamine and 3- and 4-Methoxy Analogues of Phencyclidine Are High Affinity and Selective Ligands for the Glutamate NMDA Receptor. PLOS ONE 8(3): e59334

Prolonged abuse of MXE and dextromethorphan

clinical course

M 27 → 32 yo with history of THC, MDMA and Ketamine abuse hospitalization in ED and ICU **(red)** and in psychiatry **(blue)**



Data della consulenza specialistica del CAV di Pavia: 11.04.2022 ore 23.27

Reparto: Pronto Soccorso **Ospedale**: Provincia di Perugia

Paziente: **anni**: 54 **sesso**: M **Sostanze dichiarate:** nessuna

Informazioni anamnestiche e descrizione evento

Paziente ritrovato a domicilio riverso al suolo (vomito, rilascio sfinterico, segni di puntura agli arti) in stato di coma nelle vicinanze di confezioni di farmaci (benzodiazepine) e anabolizzanti (boldenone, trenbolone, Tationil® - glutatione, Testoviron® - testosterone, Winstrol depot® - stanozololo) parzialmente utilizzati.

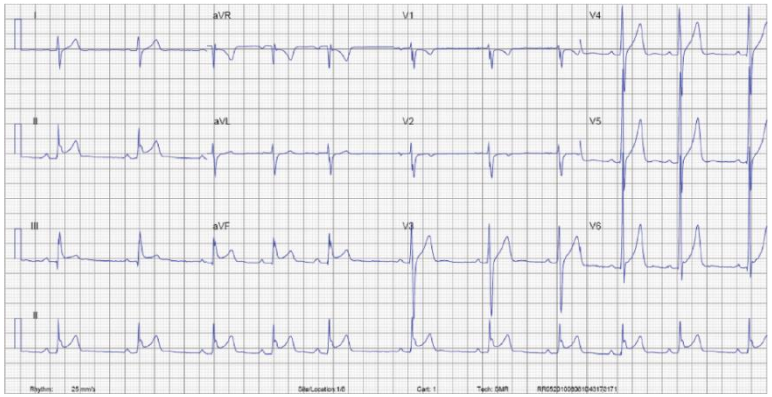
In PS è vigile, distonico, non collaborante, non responsivo agli stimoli verbali e dolorosi, iperteso (PA 220/110 mmHg), con sguardo fisso, movimenti spontanei afinalistici. I trattamenti effettuati sono stati: aspirazione delle vie aeree (rimozione di abbondanti secrezioni), decontaminazione gastrointestinale (CVA + catarsi), trattamento sintomatico. Il paziente è stato ricoverato in reparto di rianimazione (5 giorni) e poi in reparto psichiatrico per la prosecuzione delle cure.

I test tossicologici eseguiti in loco sono risultati positivi per amfetamine (negativi per benzodiazepine).

Analisi tossicologiche di secondo livello

Urina: **OXO-PCE (descloretilketamina)** (metodi GC-MS, LC-MS)

Valutazione finale complessiva (diagnosi) in relazione alla clinica (segni e sintomi) e alle positività/negatività riscontrate nei laboratori di II livello: intossicazione da OXO-PCE (descloretilketamina)



M, 16 non-competitive sporting activities
ED: chest pain (lasting 3 days)
EKG ST elevation (inferior-lateral) – TN 3 (n.v. <0.4 ng/ml)
normal echocardiography

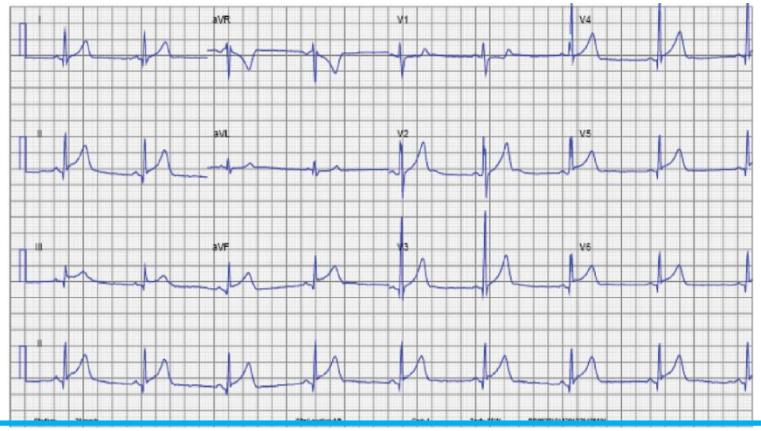
24 hrs later: clinical and EKG worsening; increase of TN to 25
coronary angiography : normal

Assumption of K2 → 24 hrs before the onset of symptoms
Marijuana → 3 weeks before

M, 16
ED: chest pain (lasting 7 days): heart "discomfort", 30 minutes episodes
EKG ST elevation (inferior-lateral) – TN 11.6
Normal echocardiography

coronary angiography : normal

Assumption of K2 → 3 days before the onset of symptoms
Marijuana → 2 weeks before



M, 16
ED: chest pain (lasting 3 days): retrosternal, episodic (1-2 hrs / episode)
EKG: ST elevation (inferior-lateral) – TN 7
normal echocardiography

24 hrs later: worsening of EKG and increase of TN to 12

Assumption K2 → 7 days before the onset of symptoms

Negativity (urine) for JWH-018 e -073

Mir et al, 2011

Ischemic stroke after use of the synthetic marijuana "spice"

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David Z. Rose, MD
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SCRA hazards

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

Selected Topics:
Toxicology

New hazards

REPEATED THROMBOSIS AFTER SYNTHETIC CANNABINOID USE

Amer Raheemullah, MD and Thomas N. Laurence, MD

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, Abstract—Background: Synthetic cannabinoids are swiftly gaining popularity and have earned a reputation of being relatively safer than other illicit drugs. However, there is a growing body of literature associating thromboembolic events with their use. Case Report: A 32-year-old woman presented on four separate occasions with a new thromboembolic event after smoking synthetic cannabinoids. She had no medical history, and over the span of 9 months she developed two kidney infarcts, pulmonary emboli, and an ischemic stroke. Each of these events occurred within 24 hours of smoking synthetic cannabinoids. During periods of abstinence, she remained free of thrombotic events. Why Should an Emergency Physician Be Aware of This?: This report shows that an association between thrombosis and the use of synthetic cannabinoids is reproducible and involves both venous and arterial thrombosis, suggesting activation of coagulation or inflammatory pathways. As the popularity of this drug continues to grow, we can expect to see a growing number of these cases. Synthetic cannabinoid use should be included in the differential diagnosis of young patients with no risk factors who present with venous or arterial thrombosis. Published by Elsevier Inc.

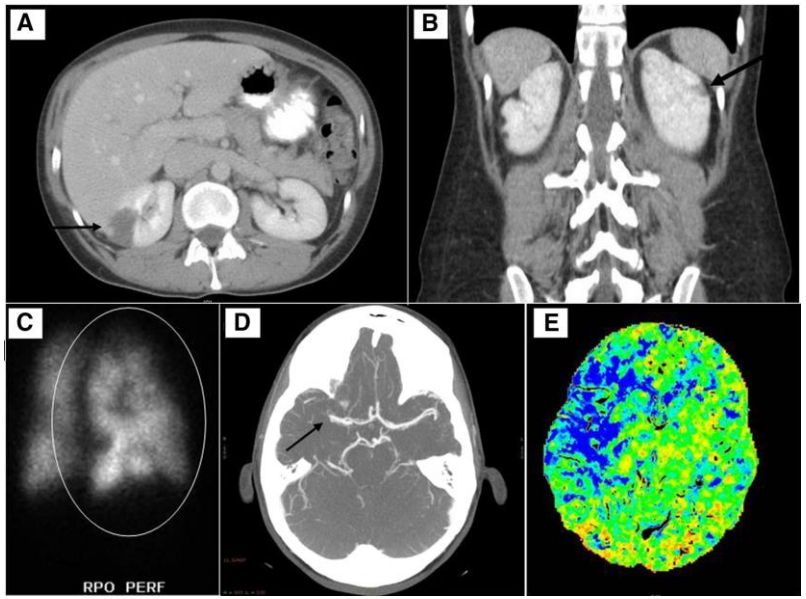

Figure 1. (A) An axial computed tomography scan showing a wedge-shaped infarct in the right kidney from the first thromboembolic event. (B) A coronal computed tomography scan showing a wedge-shaped infarct in the left kidney from the second thromboembolic event. (C) A ventilation-perfusion scan showing clear peripheral defects in the right lung from the third thromboembolic event. (D) An axial computed tomography scan showing occlusion of the right middle cerebral artery from the fourth thromboembolic event. (E) An axial computed tomography perfusion scan of the brain showing an elevated mean transit time (blue), consistent with ischemic penumbra in the territory of the right middle cerebral artery. (Color version of figure is available online.)

SC psychosis

Figure 3. AK-47 24 Karat Gold Foil Wrapper Containing Herbal Products Recovered from a Patient Involved in the Outbreak.
Also shown are three of the eight small blue bags containing aliquots of the agglutinated herbal material.

The NEW ENGLAND JOURNAL of MEDICINE
ORIGINAL ARTICLE

"Zombie" Outbreak Caused by the Synthetic Cannabinoid AMB-FUBINACA in New York

Axel J. Adams, B.S., Samuel D. Banister, Ph.D., Lisandro Irizarry, M.D., Iordan Trecki, Ph.D., Michael Schwartz, M.D., M.P.H., and Roy Gerona, Ph.D.

BACKGROUND

New psychoactive substances constitute a growing and dynamic class of abused drugs in the United States. On July 12, 2016, a synthetic cannabinoid caused mass intoxication of 33 persons in one New York City neighborhood, in an event described in the popular press as a "zombie" outbreak because of the appearance of the intoxicated persons.

METHODS

We obtained and tested serum, whole blood, and urine samples from 8 patients among the 18 who were transported to local hospitals; we also tested a sample of the herbal "incense" product "AK-47 24 Karat Gold," which was implicated in the outbreak. Samples were analyzed by means of liquid chromatography–quadrupole time-of-flight mass spectrometry.

RESULTS

The synthetic cannabinoid methyl 2-(1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamido)-3-methylbutanoate (AMB-FUBINACA, also known as MMB-FUBINACA or FUB-AMB) was identified in AK-47 24 Karat Gold at a mean (±SD) concentration of 16.0±3.9 mg per gram. The de-esterified acid metabolite was found in the serum or whole blood of all eight patients, with concentrations ranging from 77 to 636 ng per milliliter.

CONCLUSIONS

The potency of the synthetic cannabinoid identified in these analyses is consistent with strong depressant effects that account for the "zombielike" behavior reported in this mass intoxication. AMB-FUBINACA is an example of the emerging class of "ultrapotent" synthetic cannabinoids and poses a public health concern. Collaboration among clinical laboratory staff, health professionals, and law enforcement agencies facilitated the timely identification of the compound and allowed health authorities to take appropriate action.

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Catinoni sintetici

Table 18.16 Common name of representative compounds of psychostimulant NPS of the chemical group of synthetic cathinones (non-exhaustive list)

Pentedrone	bk-2C-B	4-Ethylethcathinone (4-EEC)
Mephedrone	2,4-DMEC	4-Fluoroethcathinone (4-FEC)
Methylone (bk-MDMA)	α-PHiP	2-Fluoromethcathinone (2-FMC)
MDPV 3,4-methylene-dioxypyrovalerone	MDPHP	3-Methylmethcathinone (3-MMC)
Butylone (bk-MBDB)	4-MeO-alpha-PVP	4-MMC
Flephedrone (4-FMC)	*N*-Ethylheptedrone	4-EMC
Mexedrone	4-Fluoropentedrone	α-PVP
Naphyrone	4-Fluorocathinone	3F-α-PVP
Buphedrone	4F-buphedrone	4F-α-PHiP
Pentylone	*N*-Butylpentylone	2-MEC
Ephylone	bk-PMMA	3-MEC
		3,4-DMMC

Locatelli CA et al. Neurotoxicological Emergencies. in G. Micieli et al (eds).: Decision Algorithms for Emergency Neurology. Spriger Nature AG 2021, pag. 545-608

Case zz

July. M, 36 y.o.

History: found at beach in a coma

Clinical manifestations at ED admission:

- ✓ Coma, GCS 3
- ✓ Miosis
- ✓ HR 30 bpm
- ✓ Not responsive to flumazenil and naloxone administration
- ✓ Physical signs of violence, ecchymosis in genital region
- ✓ Ethanol blood level: 0 g/L
- ✓ Urinary toxicological screening: positive only for cannabis

Treatment:

- ✓ Orotracheal intubation and mechanical ventilation
- ✓ Atropine
- ✓ Biological samples collection at ED admission

Outcome:

- ✓ Patients extubated after 36 hrs
- ✓ When awake, he reported an history of physical violence after drink something

Toxicological test on biological fluids:

- ✓ urine GHB 297 mcg/ml, blood negative for NPS, GHB and other drugs

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Phenethylamines, piperazines, aminoindanes, benzofurans, pyrrolidines

Table 18.18 Representative compounds of NPS with predominant psychostimulant effects belonging to the chemical groups of the new phenethylamines/amphetamines, piperazines, aminoindanes, benzofurans and piperidine/pyrrolidines (non-exhaustive list)

Chemical group	Common names	
New amphetamine derivatives	PMMA	2-FMA
	PMA	2-PEA
	4-FMA	DMMA
	4-CA	DMA
	2-FA	Beta-Me-PEA2
	4-FA	Phenpromethamine
Piperazines	BZP	2C-B-BZP
	DBZP	TFMPP
	pCPP	pMeOPP
	mCPP	pFPP
Aminoindanes	1-Aminoindan	MMDAI
	2-Aminoindan	MDAT
	5-IAI	*N*-Methyl-2AI
	MDAI	
Benzofurans and benzodifurans or arylalkylamines	5-APB	6-APB
	5-APDB	6-APDB
	2C-B-Fly	Bromo-Dragonfly
Piperidines/pyrrolidines	2-DPMP	Isopropylphenidate
	Desoxy-D2PM	4-F-Methylpenidate (4F-MPH)
	Ethylphenidate	

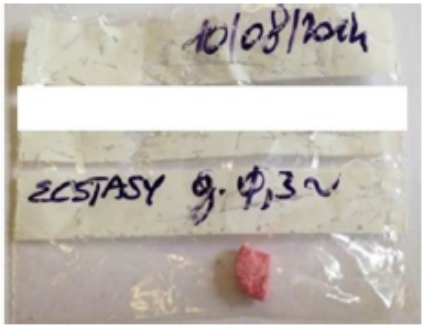
Locatelli CA et al. Neurotoxicological Emergencies. in G. Micieli et al (eds).: Decision Algorithms for Emergency Neurology. Spriger Nature AG 2021, pag. 545-608

Cases of analytically confirmed PMA/PMMA intoxications

N.	Age / sex	Declared substance (circumstances of assumption)	Clinical manifestations	Treatment and outcome	Immunoenzymatic urinary test	Second level urinary investigations
1	17 / M	Amphetamine and cannabis (rave party)	Agitation, tachycardia, mydriasis, sweating, hallucinations, confusion	Benzodiazepines; symptoms resolved after 12 hrs	Amphetamine, THC	PMMA/PMA, MDMA (*)
2	16 / M	MDMA (disco)	Agitation, tachycardia, mydriasis, seizures	Oro-tracheal intubation and respiratory support; clinical improvement after 48 hrs	Amphetamine, THC	PMMA/PMA (*)
3	17 / M	Unknown substances	Agitation, tachycardia, hallucinations	Benzodiazepines; symptoms resolved after 12 hrs	Amphetamine, THC	PMMA/PMA, MDMA (**)
4	23 / M	Unknow Substances	Agitation	Benzodiazepines; symptoms resolved after 12 hrs	Amphetamine, THC, cocaine	PMMA/PMA, MDMA, methoxietamine, ketamine, levamisole (**)
5	32 / M	Unknown substances (rave party)	Agitation, tachycardia, mydriasis, sweating, hypertonia, tremors, severe hyperthermia (42°C), metabolic acidosis, hypoglycemia, hyperkaliemia, multi-organ failure (MOF), severe disseminated intravascular coagulation (DIC)	Oro-tracheal intubation, respiratory support, hemodialysis; patient died in 20 hrs	Amphetamine, THC, cocaine	PMMA/PMA, MDMA/MDA, cocaine, levamisole, cocaethylene, tramadol (**)

LETHAL CASE

Analysis (GC-MS, LC-MS and LC-UV) of residual part of the tablet taken by the patient: PMMA 25 mg and MDMA 11 mg



Results of blood quantitative analysis:

substance	blood concentrations
PMMA	615 ng/mL
PMA	91 ng/mL
TRAMADOL	88 ng/mL
MDMA	192 ng/mL
MDA	< 20 ng/mL
COCAINE	28 ng/mL
BENZOYLECGONINE	529 ng/mL

(*) NPS tested: PMA/PMMA, MDMA, ketamine/metabolites, atropine, scopolamine, levamisole, mephedrone, butylone, 4-MEC, methoxetamine, 5/6 APB, 4-FA, MDAI.
(**) NPS tested: PMA/PMMA, MDMA, ketamine/metabolites, atropine, scopolamine, levamisole, mephedrone, butylone, 4-MEC, MDPV, dimethylcathinone, dimethylmethcathinone, buphedrone, ethcathinone, 4-fluoromethcathinone, pentedrone, methedrone, etylone, pentylone, 1-naphyrone, 4-FA, MDAI, 5/6 APB, DMT, 2C-I, 2C-B, 2C-E, 2C-T7, DOB.

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Fenetilamine ed NBOMe

Caso 1

Settembre 2017. M, 16 anni

- ✓ Ad una festa, bevuti alcolici e fumato cannabis «classica»
- ✓ In seguito usato «francobolli allucinogeni»
- ✓ Alcune ore dopo gli amici lo seguono, cercano di accompagnarlo a casa perché appariva «fuori di sé»
- ✓ Nonostante gli aiuti degli amici si è gettato in un fiume
- ✓ Il corpo è stato ritrovato circa 24 h dopo

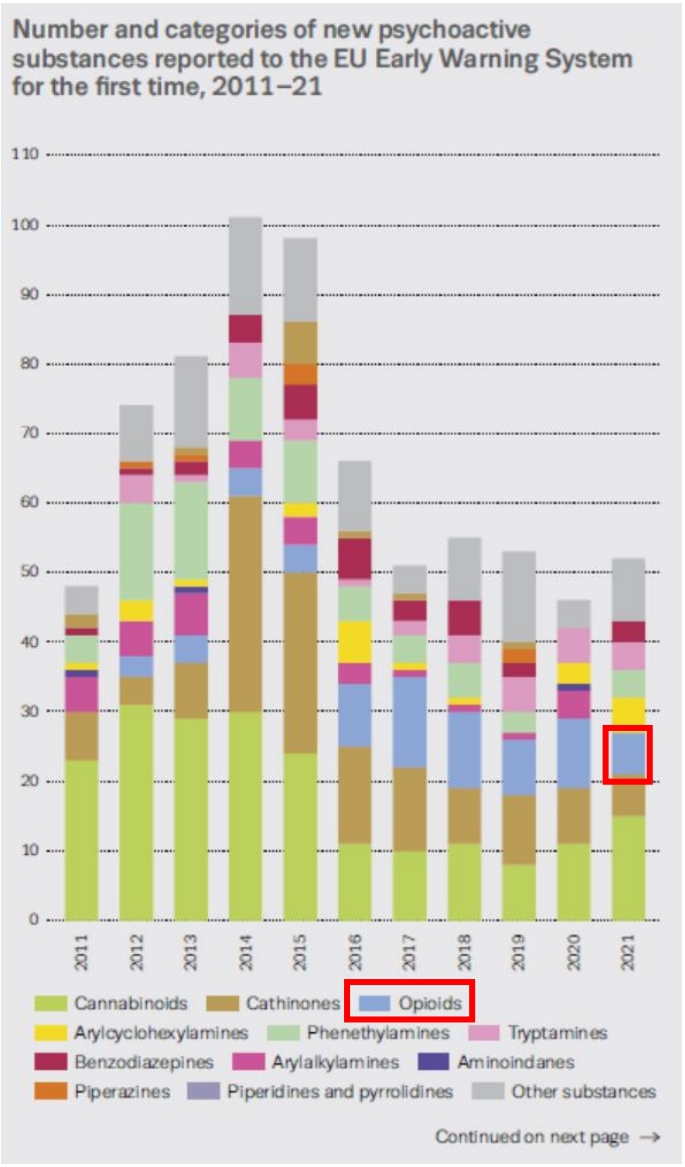
Analisi di secondo livello:

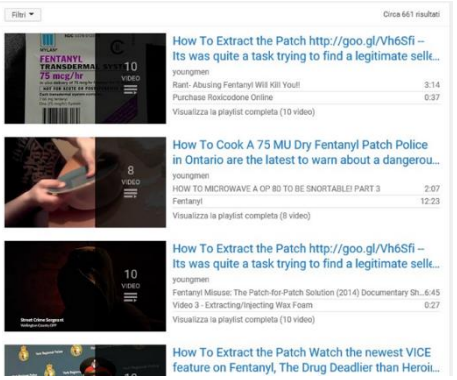
- ✓ Campioni biologici
  - → Sangue 25-C NBOMe, 25H-NBOMe, THC, THC-COOH
  - → Urina 25-C NBOMe, 25H-NBOMe, THC, THC-COOH
- ✓ Francobollo
  - → 25-C NBOMe, 25H-NBOMe

- ✓ allucinazioni non compatibili con uso solo di THC

European Monitoring Centre for Drugs and Drug Addiction

Nuovi oppioidi → fentanili → nitazeni
Principali problematiche sanitarie





- ✓ possono contenere
  - ✓ mix di differenti oppioidi
  - ✓ sostanze molto potenti
- ✓ maggiore gravità clinica rispetto alle “classiche” intox da oppioidi
- ✓ mancata corrispondenza tra quadro clinico e risultati analitici in urgenza
- ✓ Ridotta risposta alle normali dosi di antidoto
- ✓ Farmaci ≠ sostanze abuso
  - ✓ estrazione per bollitura da cerotti al fentanile
  - ✓ Prescrizioni illegali
- ✓ Più di 110.000 decessi (2021) in US, > 40% prescrizione (pain-killer)

Diagnostic difficulties for NPS in the emergency setting

- NPS use is frequent in “non addicted” (“recreational” use)
- incomplete / wrong history
- used to incapacitate (e.g. sexual assault)
- SoA deterction/analysis in EDs is frequently based only on the old “urine triage”)
  - NPS analytical identification → difficult/impossible (at the moment)
- Contemporary use of
  - old and detectable substances of abuse (e.g. THC)
  - several (more than one) NPS
  - medications (benzodiazepines, SSRI, CCBs, …)
  - ethanol

→ Incomplete/wrong diagnosis ! and treatments !?

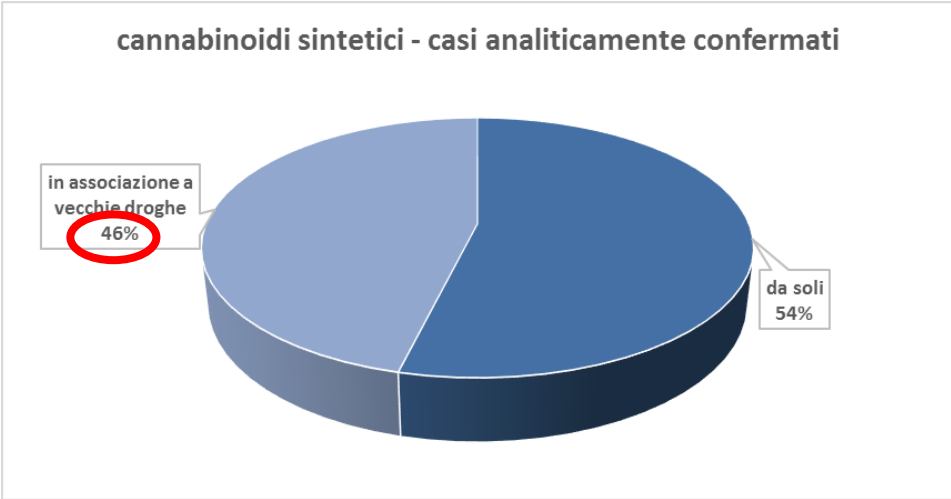
- trauma / accidents / surgical emergencies and NPS, …..

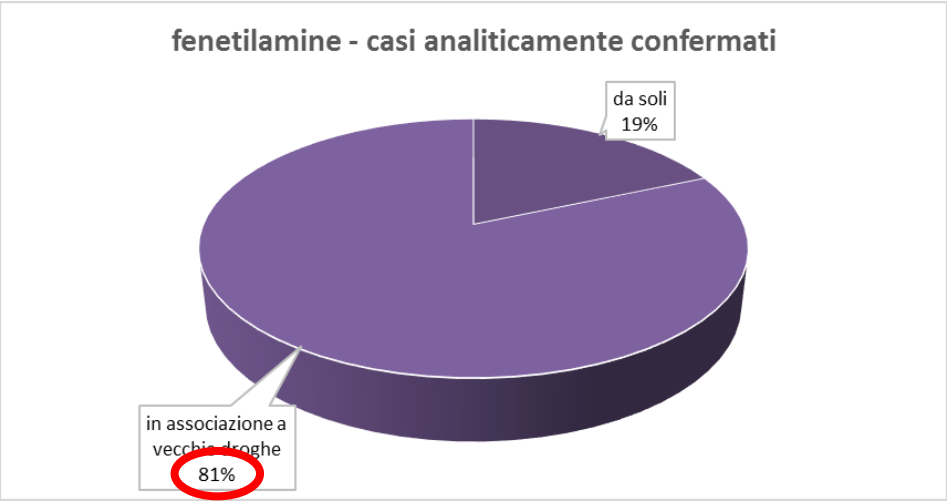
Triage urine

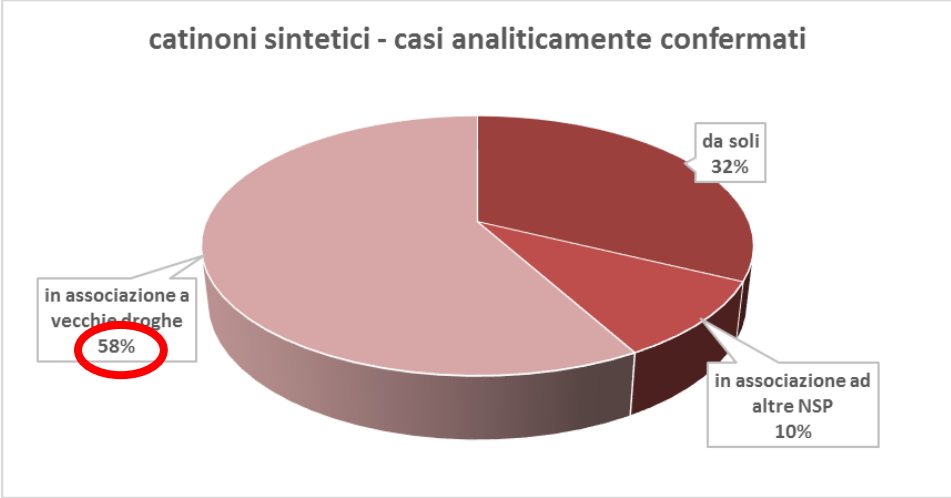
Sostanza		rilevabilità (giorni)
✓ oppioidi/morfina		2
✓ amfetamine		2
✓ cocaina (metaboliti)		2 - 5
✓ cannabinoidi/THC	uso moderato	5
	uso elevato	10
	cronico	20
✓ metadone		3
✓ ecstasy		0,5 - 1
✓ benzodiazepine	dose terapeutica	3
	dose sovraterapeutica	4 – 8
✓ ADT		3
✓ barbiturici		2

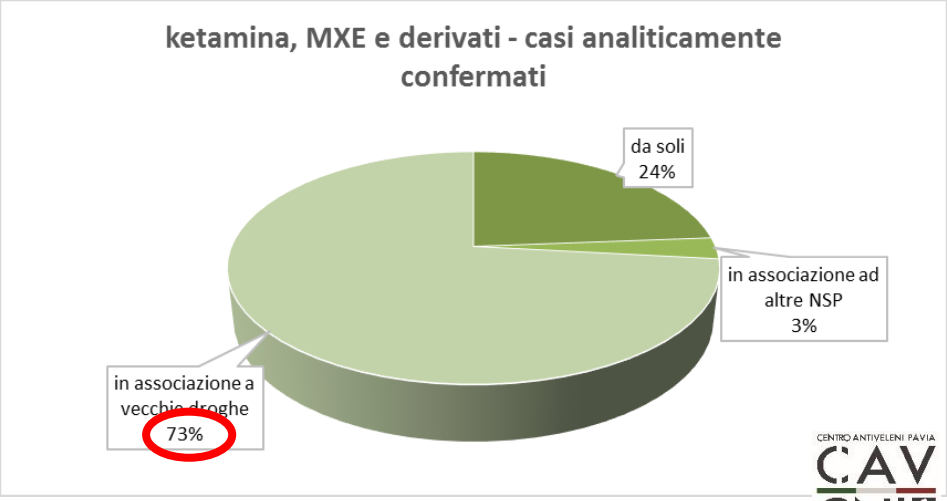
modificato da Carrigan et al, 2000

NSP e vecchie droghe (2010-2021)









Treatment NPS of severe clinical manifestations

Acute effects

- Agitation, psychosis, aggressivity → Benzodiazepines, Barbiturates, Physical containment
- Seizures → Benzodiazepines, barbiturates
- Hyperthermia → External cooling + [dantrolene]
- Cardiotoxicity → CCBs + vasodilators [beta-blockers?]

→ Propofol → ICU

~~Ketamine~~

Post-acute phase

- ✓ Haloperidol
- ✓ Olanzapine
- ✓ Dexmedetomidine (?)
- ✓ Valproate sodium

Prolonged/chronic effects

- ✓ Quetiapine?
- ✓ Olanzapine?
- ✓ Topiramate?
- ✓ Valproic acid ?
- ✓ Clozapine?
- ✓ Other?

Whitdrawal

Addiction

?

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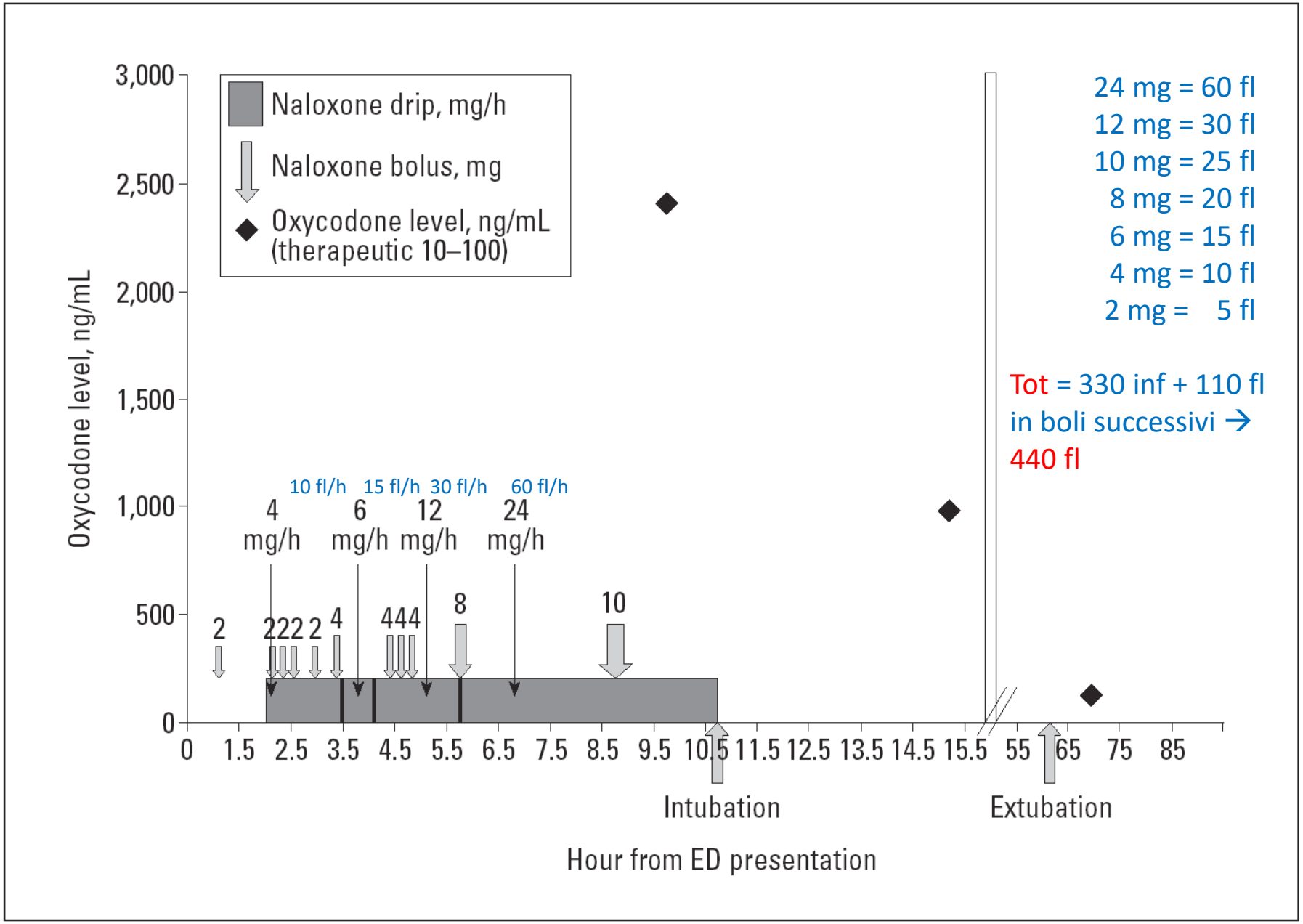

Schneir et al, Ann Emerg Med 2002

Unità di coordinamento
ISTITUTO SUPERIORE DI SANITÀ

Governo italiano
Dipartimento politiche antidroga
Presidenza del Consiglio dei Ministri

24/03/2022

Prot. S.N.A.P. 11/22

AD USO INTERNO DEI CENTRI COLLABORATIVI DEL S.N.A.P.

VIETATE LA DIVULGAZIONE E LA PUBBLICAZIONE SU WEB

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 (AIFA)
Assessorati Regionali alla Sanità
Assessorati Regionali 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: Allerta di grado 2

Identificazione di n.2 casi di intossicazione da scopolamina a seguito di fumo di farmaco a base di scopolamina n-butilbromuro

Supervisione tecnico scientifica della presente Comunicazione:
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E. Marinelli, A. Tini – Università Sapienza, Unità di Tossicologia Forense
F.P. Busardò – SOD Medicina Legale – Università Politecnica delle Marche
C. Locatelli, E. Buscaglia, G. Scaravaggi – ICS Maugeri IRCCS Istituto Scientifico di Pavia, Centro Antiveleni - Pavia

Supporto tecnico-informatico della presente Comunicazione:
Paolo Berretta, Michele Sciotti – Istituto Superiore di Sanità, Centro Nazionale Dipendenze e Doping – Roma
Marco Tallon – Istituto Superiore di Sanità, Servizio di Informatica – Roma

Fonte segnalazioni
Centro Antiveleni di Pavia in collaborazione con gli Ospedali del SSN, con il Laboratorio di Tossicologia Clinica Analitica dell'IRCCS Fondazione Policlinico San Matteo e con il Laboratorio di Tossicologia Clinica e Sperimentale del Centro Antiveleni di Pavia

Remarks

- over the past 30 years, such a rapid appearance of so many toxic and potent agents has never occurred
- the spread of the “NPS phenomenon” is not correctly quantifiable today
- severity of the intoxications → severe/permanent damage
- wrong perception of harmlessness
- the used substance is not perfectly known by intoxicated patients in 30-40% of cases
- identify the NPS-related poisoning
  - detection/analysis in EDs is based only on the limited “urine triage”
  - contemporary use of old (detectable) substances of abuse (e.g., THC) and/or NPS (more than one)
  - → risk management and appropriateness of care
  - an exceptional level of analytical support (ToxLabs) is needed (⍰ lack of analytical tests, at least in EDs (risk management) → Pavia PCC procedure
- Early Warning System → effective, operational, crucial, not expensive → networking among EDs/SerD/SPDC/Pediatric ward .. and a specialist PC

Percorso diagnostico-terapeutico e procedura NEWS / SNAP

1. Richiesta di consulenza clinico-tossicologica al CAV-CNIT (servizi d'urgenza/ospedalieri)
2. Diagnosi clinica e prima diagnosi sul tipo di NSP
3. Indicazioni su monitoraggio, trattamento in urgenza, tipo di ricovero, …..
4. Criteri di inclusione al programma NEWS
5. Prelievi di campioni biologici
6. Recupero campioni biologici (urgenza/corrieri)
7. Richiesta «clinicamente motivata» ai colleghi dei laboratori
8. Diagnosi definitiva con conferma analitica
9. dati disponibili per il NEWS