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

Tuesday, 15th December – Florence

Department of Emergency – Medical Toxicology, University of Florence

Prof. Guido Mannaioni

Prof. Mannaioni presented the organization and the activities of the Clinical Toxicology Unit of Careggi Hospital. During the visit, clinical cases related to NPS were discussed and the tasks of the Poison Control Center of Florence were also described. An interesting debate followed the visit with a broad exchange of knowledge and experiences among all the participants.

UNIVERSITÀ
DEGLI STUDI
FIRENZE
NEUROFARBA
DIPARTIMENTO DI NEUROSCIENZE,
PSICOLOGIA, AREA DEL FARMACO
E SALUTE DEL BAMBINO

Azienda
Ospedaliero
Universitaria
Careggi

Medical Toxicology Unit: organization, activities and clinical cases related to NPS

Guido Mannaioni

Department of Neuroscience, Psychology, Drug Research and Child Health
(NEUROFARBA),
Section of Pharmacology and Toxicology,
Università degli Studi di Firenze
and
SOD Tossicologia Medica
Azienda Ospedaliero Universitaria Careggi

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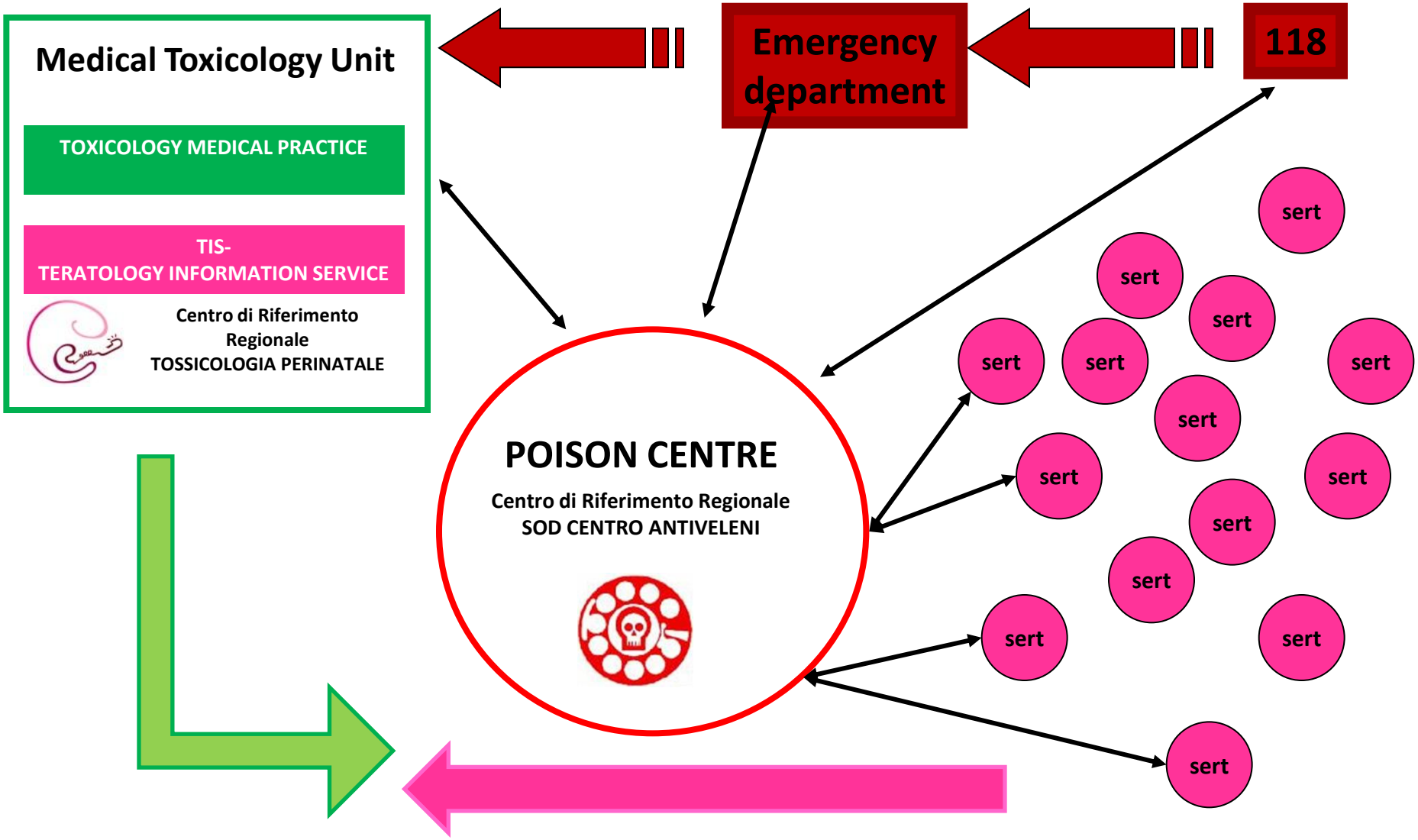
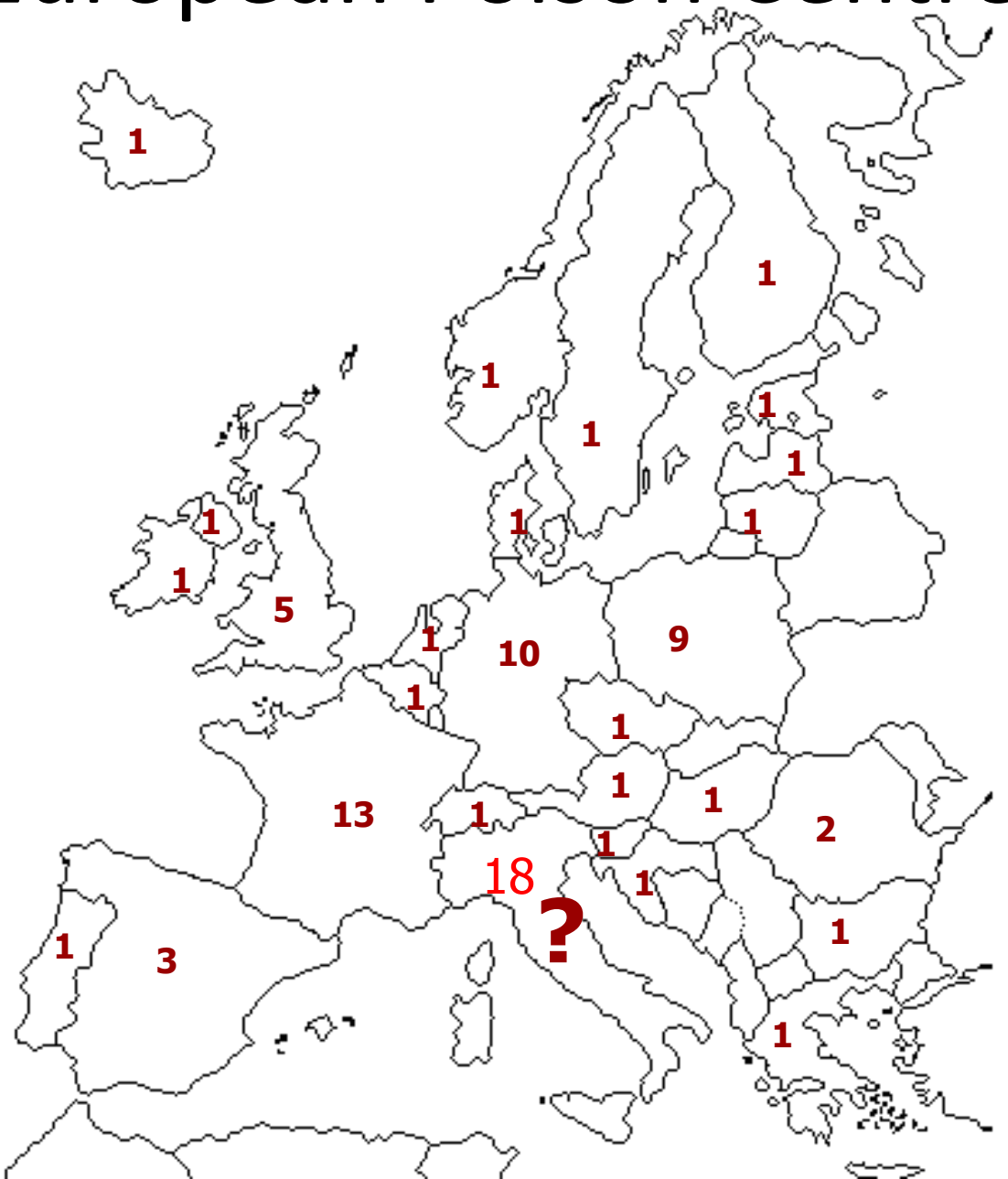
Azienda Ospedaliero Universitaria Careggi - Firenze

Dipartimento DEA

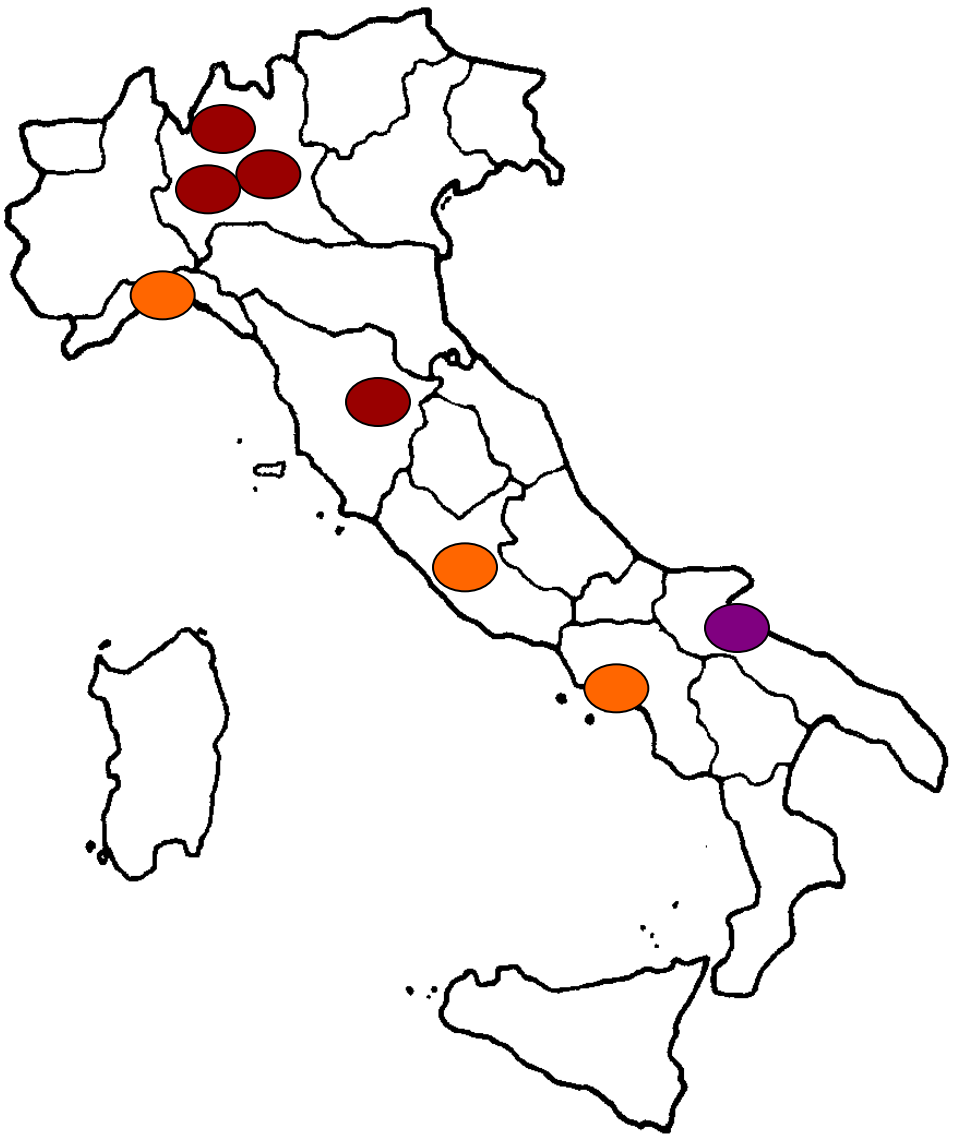


European Poison Centres



Italian Poison Centres

BERGAMO
BOLOGNA
CATANIA
CESENA
CHIETI
FIRENZE
LA SPEZIA
GENOVA
GENOVA S.M.
LECCE
MILANO
NAPOLI
PAVIA
PORDENONE
REGGIO C.
ROMA U.S.
ROMA U.C.S.C.
TORINO
TRIESTE



- **BERGAMO**
  - *AO Ospedali Riuniti*
- **MILANO**
  - *Niguarda*
- **PAVIA**
  - *IRCCS Fondazione Maugeri*
- **GENOVA**
  - *IRCCS Gaslini*
- **FIRENZE**
  - *AOU Careggi*
- **ROMA**
  - *U.C.S.C. Gemelli*
- **NAPOLI**
  - *AO Cardarelli*

FOGGIA

AOU Ospedali Riuniti

What is a poison?

"All things are poison and nothing is without poison; only the dose makes a thing not a poison… Solely the dose determines that a thing is not a poison."

«Dosis facit venenum»

Phillipp Theophrast von Hohenheim
Paracelsus (1493-1541)

What does a toxicologist do?

- ***Treat the poison?***
- ***Treat the patient not the poison?***
- ***Treat the patient and the poison !***

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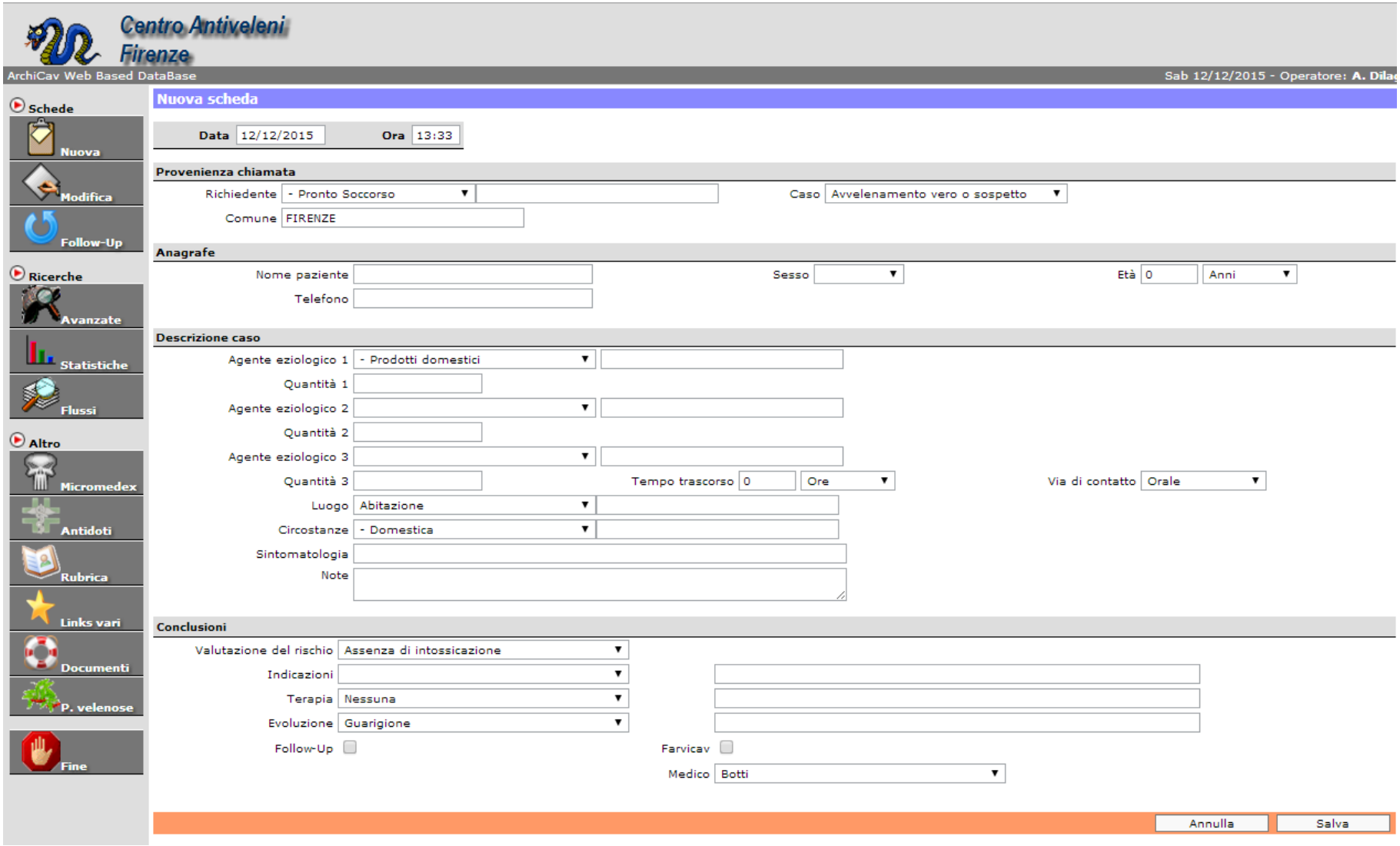
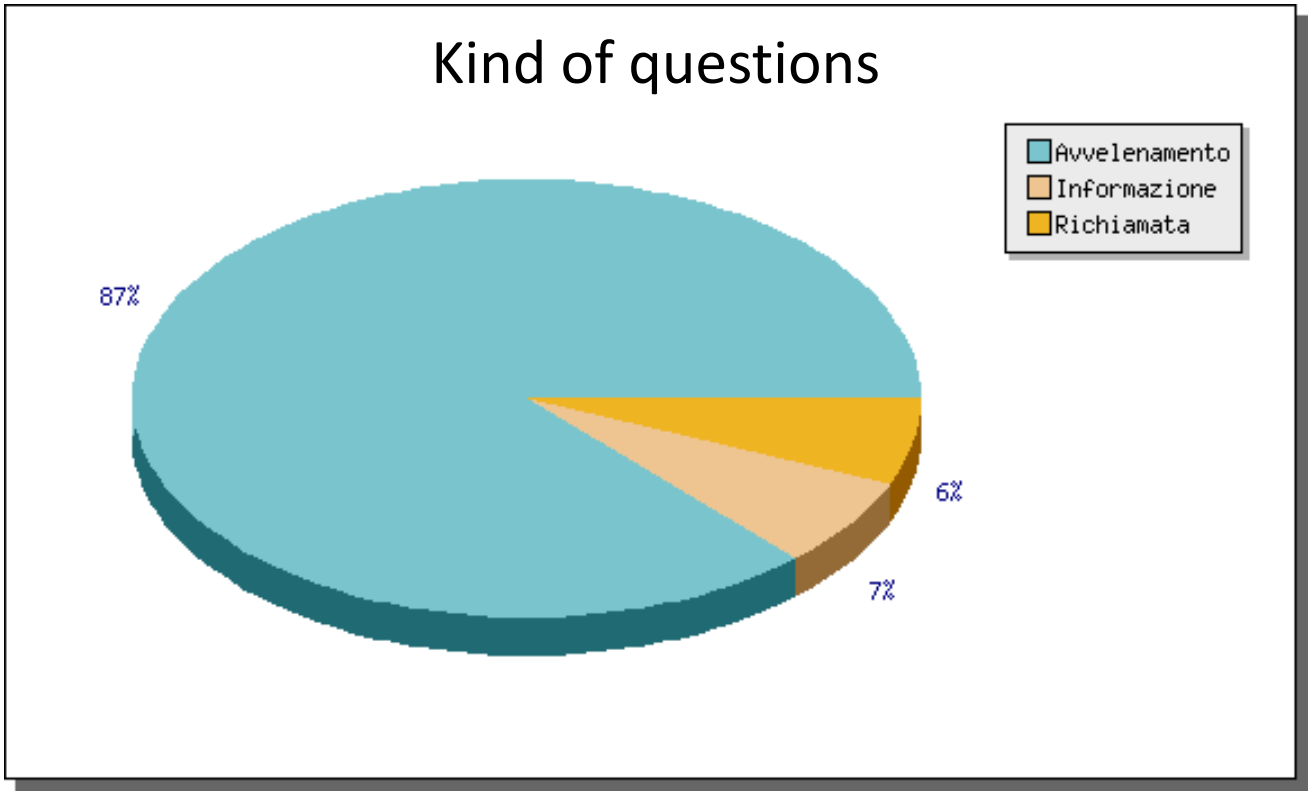
PRINCIPLES OF MANAGING THE ACUTELY POISONED PATIENT

- **Antidote** (only 3% of intoxications)
- **Basic life support**
  - **A -** airway
  - **B -** breathing
  - **C -** circulation
- **DeContamination**
  - **Gastric lavage**
  - Prevention of xenobiotic absorption with:
  1. **Activated charcoal**
  2. **Whole-bowel irrigation**
- **Depuration and Enhanced Elimination**
  1. **Multiple-dose activated charcoal**
  2. **Urinary alkalinization**
  3. **Extracorporeal drug removal**
- **Laboratory?**

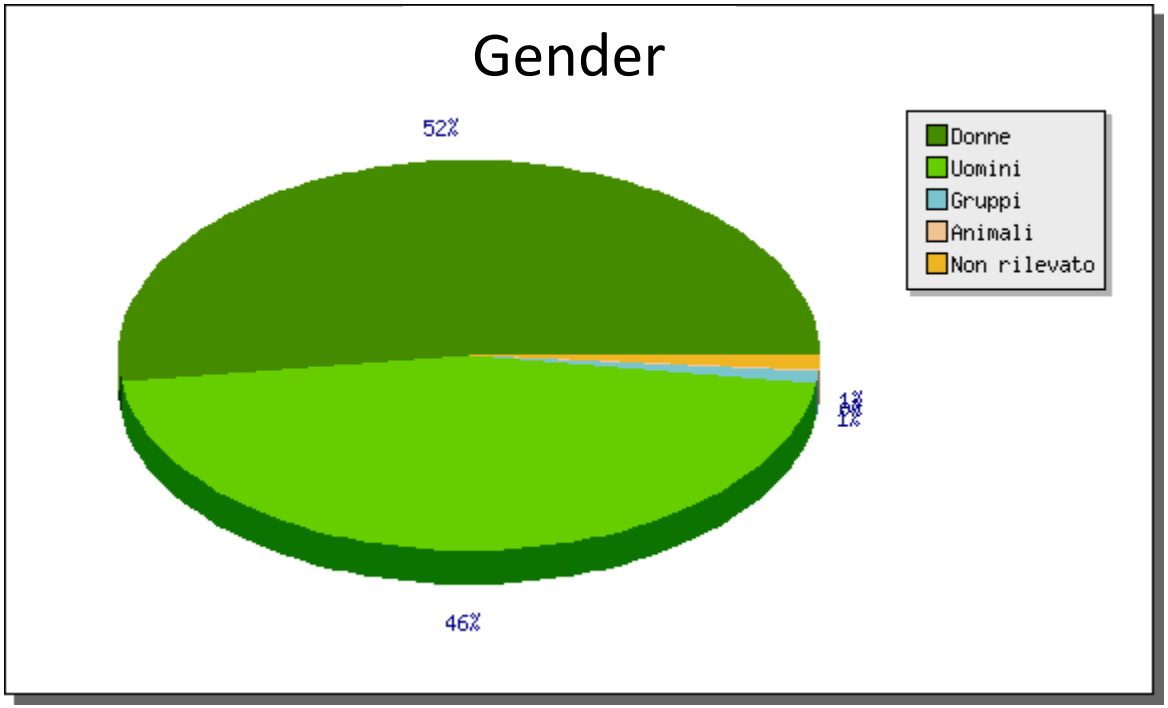
The Florence Poison Centre



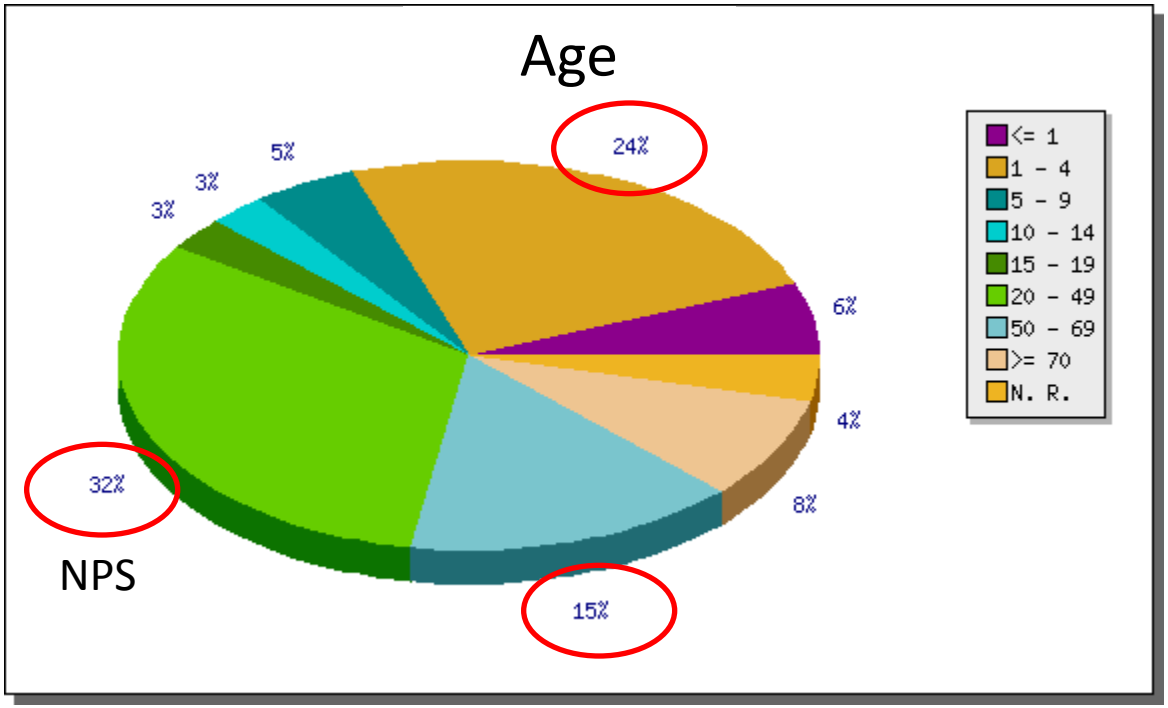
Florence Poison Centre: 4331 calls in 2014



Florence Poison Centre: 4331 calls in 2014



Florence Poison Centre: 4331 calls in 2014



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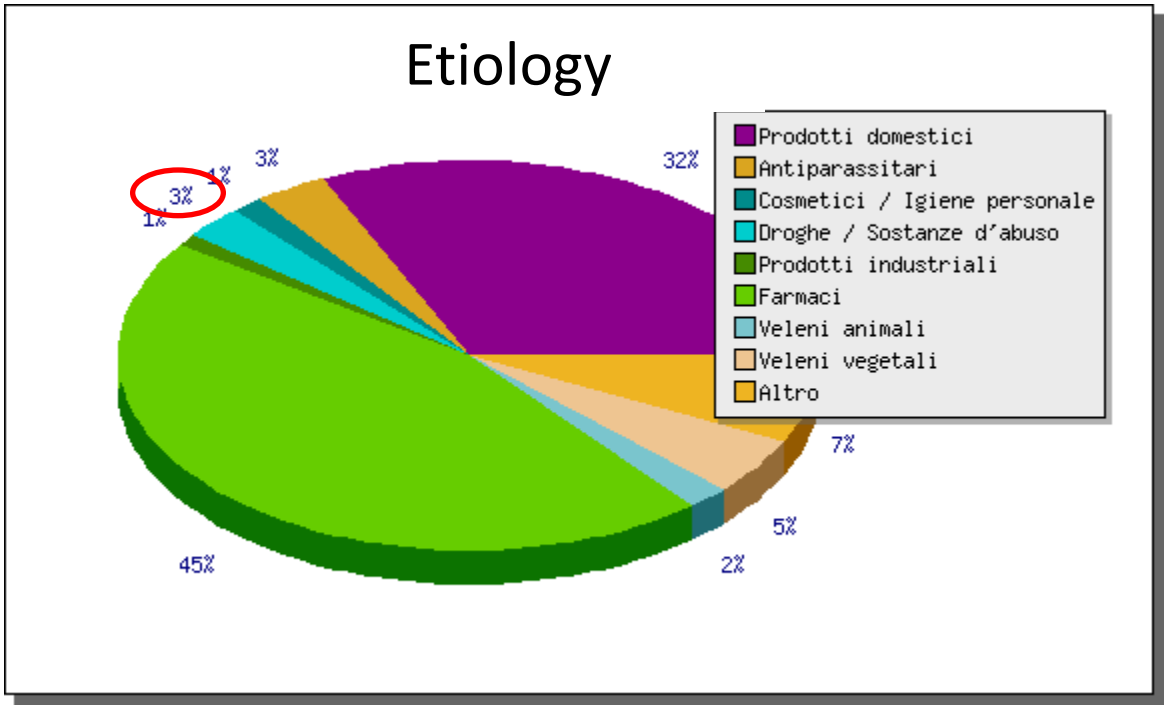

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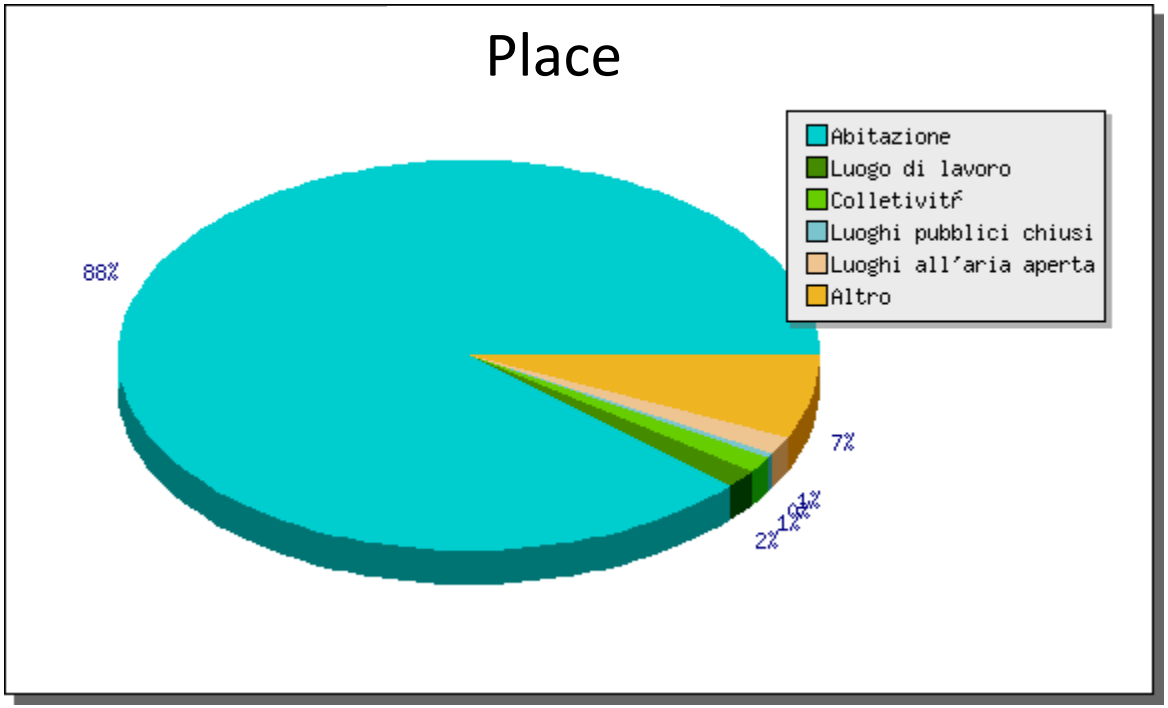
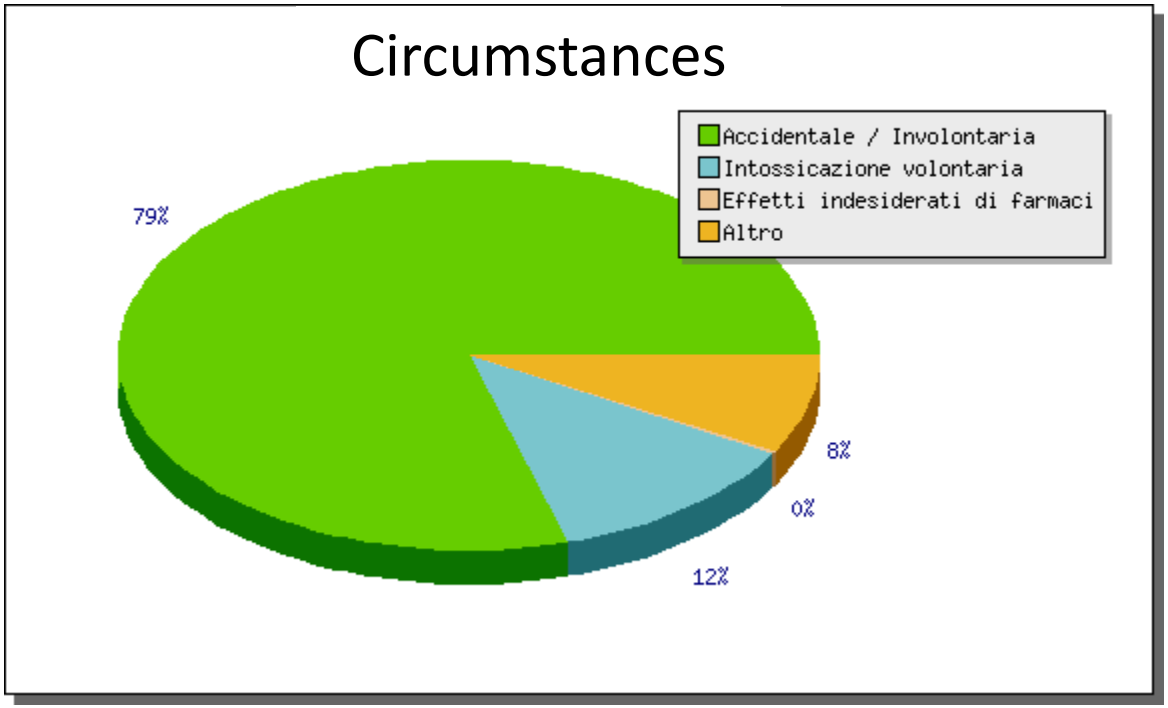


Florence Poison Centre: 4331 calls in 2014

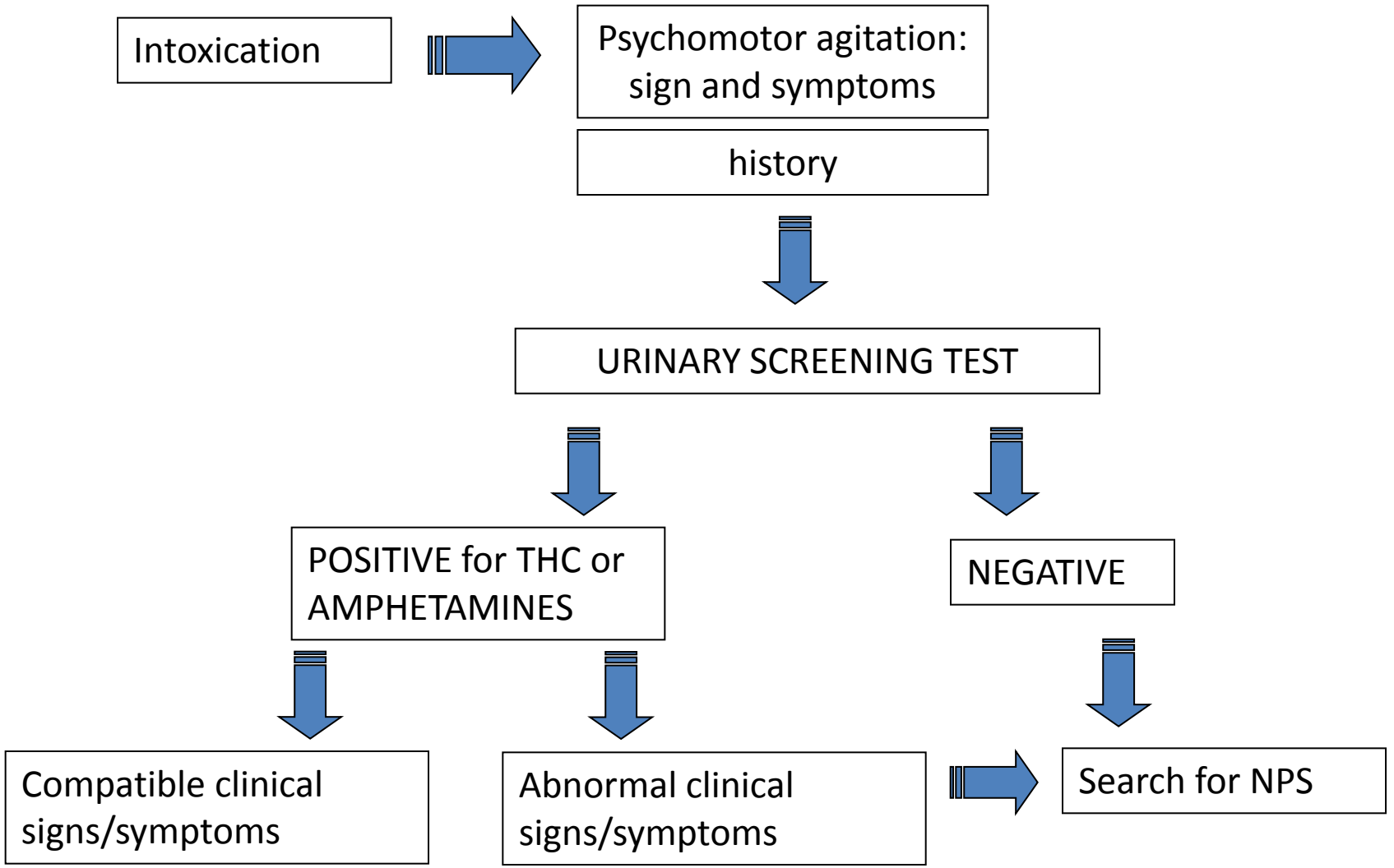


NPS - New psychoactive substances

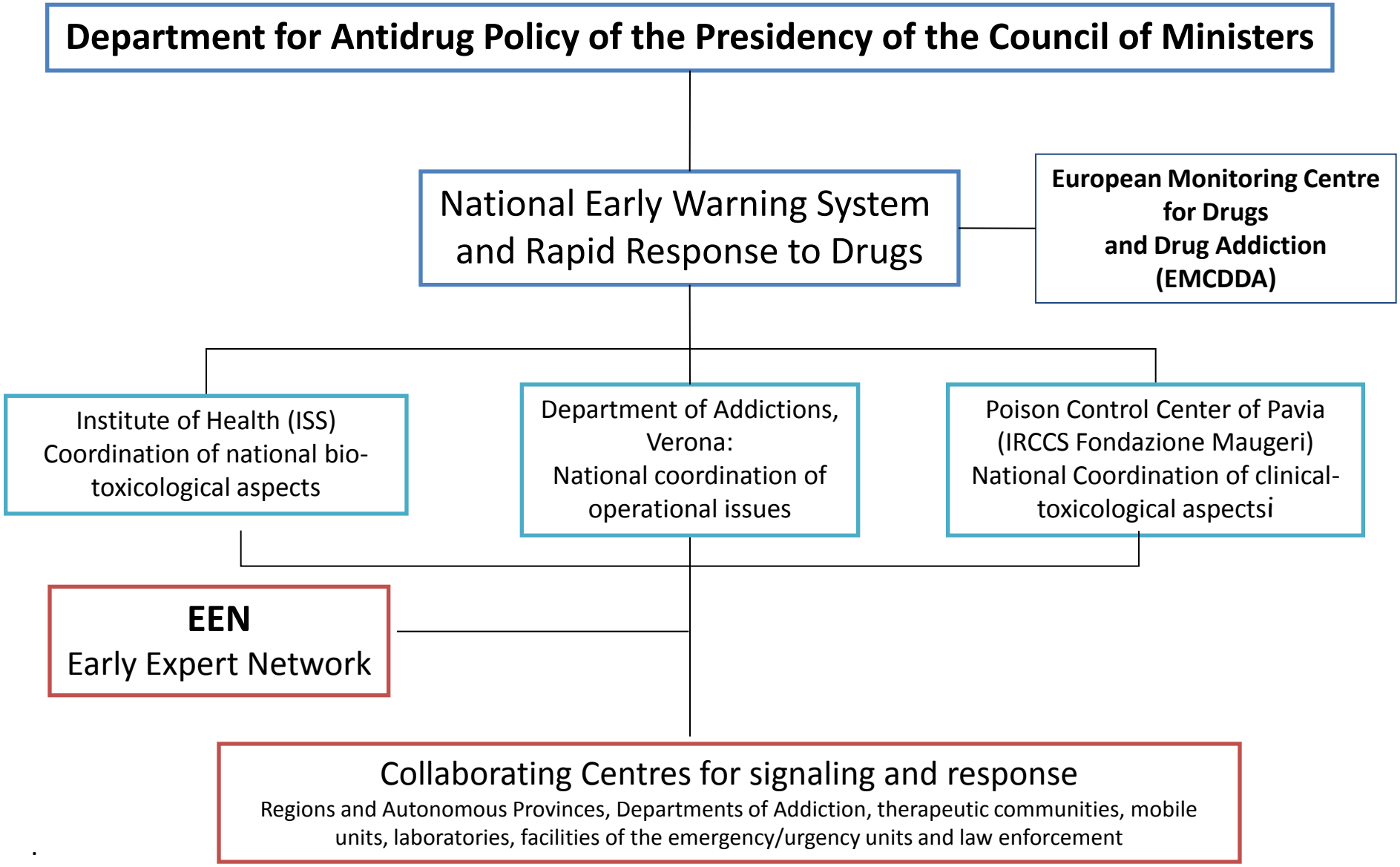
"new psychoactive substances (NPS)" which are defined as "substances of abuse, either in a pure form or a preparation, that are not controlled by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances, but which may pose a public health threat".

In recent years, the market for amphetamine-type stimulants (ATS) has been characterized by the appearance of several new substances, which often have chemical and/or pharmacological properties similar to internationally controlled substances. Their variety has never been as great as it is now.

Clinical decision algorithm for NPS detection



National Early Warning System (NEWS)



NUOVE SOSTANZE PSICOATTIVE (NPS)

Since 2009, european and italian collaborative centers reported to the **National Early Warning System 372** molecules:

110 synthetic cannabinoids

56 synthetic cathinones

82 phenethylamines

5 piperazines , 14 tryptamines , 5 ketamine and similar , 31 active ingredients drugs , fentanili 5 , 9 opioids , 8 similar azepanici , 3 analogs phencyclidine and other 44 molecules of various nature

NEWS_February 2009: *benzidamine*

Messaggio con priorità alta.

Da: Centro Anti Veleni

Inviato: lun 09/02/2009 12.02

A: allerta@dronet.org

Cc:

Oggetto: benzidamina

Allegati:

Visualizza come pagina Web

Ai soggetti della rete:

Si segnala il caso di una giovane donna (G.O. 34 anni, storia di poliabuso) giunta alla nostra osservazione per sindrome **disforico/allucinatoria**, a prevalente contenuto zooptico, **astenia, deficit della memoria recente** dopo assunzione **deliberata a scopo voluttuario** di alcune buste di Tantum Rosa (**benzidamina 500 mg**).
Il quadro sindromico è regredito con terapia sintomatica e di supporto. Lo screening tossicologico di laboratorio sui liquidi biologici è ha dato esito negativo per altre sostanze d'abuso.
L'impiego a scopo di "sballo" della benzidamina, facilmente reperibile e abuon mercato, ci era già noto per altre osservazioni (1995 e 1997) e segnalazioni da comunità carcerarie. Gli effetti osservati sono congrui con le caratteristiche della molecola. Rare segnalazioni in letteratura.

Cordiali saluti
Primo Botti

Dr. Primo Botti
Responsabile Centro Antiveleni Firenze
SOD di Tossicologia Medica

EUROPEAN ASSOCIATION OF POISON CENTRES AND CLINICAL TOXICOLOGISTS

Benzydamine: recreational misuse of a non recreational drug

Alessandra Pistelli, Cecilia Lanzi, Arianna Dilaghi, Maria Rita Quaranta, Maria Sili, Guido Mannaioni, Primo Botti

Toxicology Unit and Poison Centre
Azienda Ospedaliero-Universitaria Careggi AOUC, Firenze, Italy

Introduction

Benzydamine hydrochloride (fig.1) is an indolic non steroidal anti-inflammatory drug currently available only for local application: as mouthwash, vaginal douche, gel ointment (Anand et al., 2007). Being available over the counter this drug can be easily obtained and its recreational use has been described amongst street youth in developing countries (Mota et al., 2010).

Clinical signs or symptoms of unintentional ingestion are principally gastrointestinal with nausea, followed by vomiting and dizziness. Tremors, agitation, ataxia, convulsions and hallucination are described mainly in children (Ballesteros et al., 2005).

Case report

A 35 year old woman with a history of nutritional disorder and chronic ethanol abuse, detained in jail, was admitted to the Toxicology Unit of Florence University Hospital, due to hallucinatory confusional mental state in course of acute benzydamine intoxication.

The patient was taking the following medications:
4-hydroxybutyrric acid 22,5mg,
chlorpromazine 80mg,
lorazepam 1mg and delorazepam 1,25mg,
valproic acid 1,1g,
paroxetine 20mg,
lansoprazole 15mg.
Since two months the patient, while in custody, tried several self-injurious acts, through the ingestion of shampoo, perfume, alcohol and benzodiazepines.

On hospital admission the patient was confused, agitated with mild tachycardia (96 bpm) and hypertension (135/95 mmHg), with hallucinations (view of ants and insects) and muscle weakness.
Toxicologic screening was negative for alcohol and common drugs of abuse. An ECG was performed showing QT interval prolongation

The patient reported the abuse of 10 sachet for vaginal douche of Tantum rosa (benzydamine) 500 mg diluted in water with subsequent development of hallucination, asthenia and short-term memory loss.

Treatment was symptomatic (diazepam i.v. administered) and supportive. The hallucinations lasted for about six hours.
ECG was normal after 24 hours.
The patient was discharged in good health conditions after 6 days of hospedalization.

Pharmacology

- Benzydamine hydrochloride inhibits:
  - phagocyte degranulation and aggregation,
  - production of reactive oxygen species by phagocytes,
  - eukocyte adhesion to vascular endothelium.
- Following oral ingestion of 50mg benzydamine, peak plasma concentration of 1,5 µmol/L is obtained after 1,5h
- Gastrointestinal absorption is rapid and almost complete on account of its high solubility and low clearence.
- Protein binding capacity of benzydamine is less then 20%.
- Elimination half-life is about 13 hours

(Quane et al., 1998).

What to do:

- Monitoring vital parametres such heart rate, blood pressure, body temperature.
- Seizures and arrhythmias control (benzodiazepines, phenobarbital)
- Control of excitement, agitation and toxic psychosis (diazepam, haloperidol)
- Treatment of possible renal failure (following rabdomiolisis)

Conclusions

Benzydamine (fig.1) has structural similarity to dimethyltryptamine (fig.2) and for this reason could cause severe acute central nervous system impairment. Although the exact mechanism of benzydamine hallucination is still urknown, multiple pharmacological interactions could be hypothesized (Opaleye et al., 2009).
The presence of indazole (fig.3) could explain it being similar to the indole structure (fig.4) present in serotonin and in 5-hydoxyindole (fig.5), a recently described proconvulsant agent (Mannaioni et al., 2003) through the agonistic activation of the 5HT2A receptors, such as diethylamine in lysergic acid (LSD) and dimethyltryptamine in DMT.

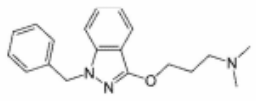


Figure 1. **Benzydamine hydrochloride**

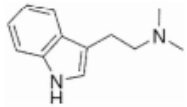


Figure 2. **Dimethyltryptamine**

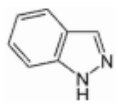


Figure 3. **Indazole**

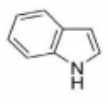


Figure 4. **Indole**

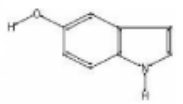
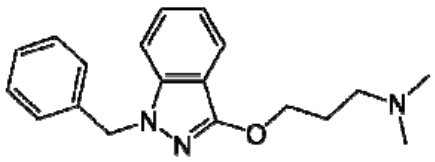


Figure 5. **5-hydroxyindole**

XXXI International Congress of the European Association of Poisons Centres and Clinical Toxicologists
24-27 May 2011, Dubrovnik, Croatia

Benzydamine: clinical use…

Benzydamine hydrochloride is an indolic non steroidal anti-inflammatory drug currently available only for local application: as mouthwash, vaginal douche or gel ointment (Anand et al.,2007).



…and recreational abuse!

- Being available over the counter this drug can be easily obtained and its recreational use has been described amongst street youth in developing countries (Mota et al., 2010), especially in Brazil.

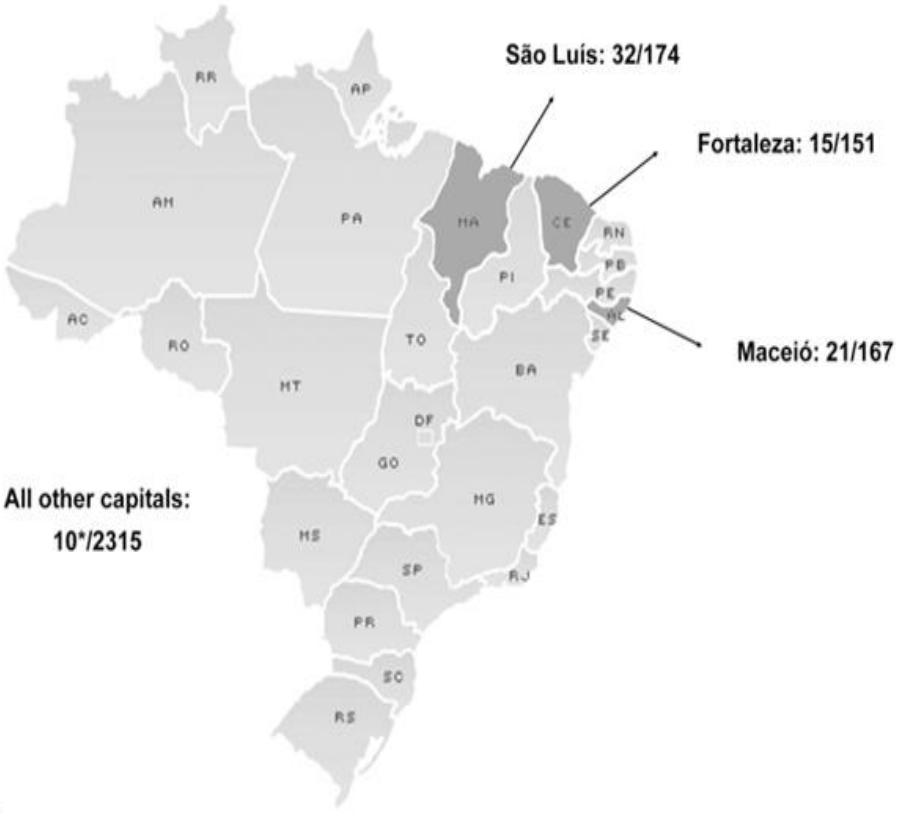


Figure 1 – Geographic distribution of 78 lifetime users of benzydamine among street youth, Brazil, 2003 *Goiânia and Teresina (n = 2); João Pessoa, Manaus, Porto Alegre, Rio de Janeiro, Salvador, São Paulo (n = 1)*

Benzydamine

has structural similarity

to dimethyltryptamine (DMT),

a natural occourring psychedelic

compound.

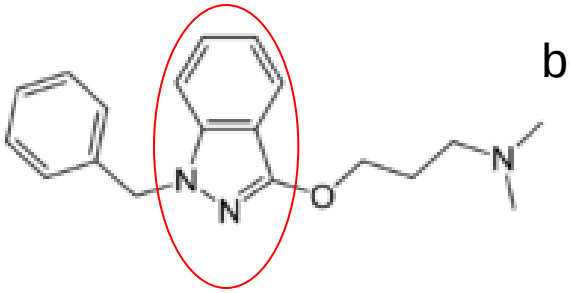
The presence of indazole nucleus makes

benzydamine similar to the indole

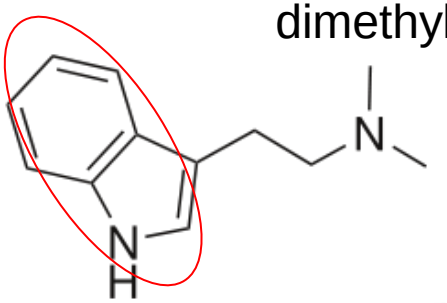
structure,

which is present in 5-hydroxyindole and

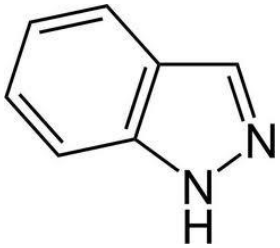
Serotonin.



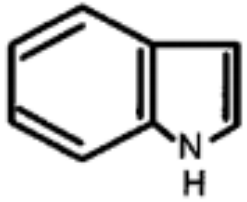
benzydamine



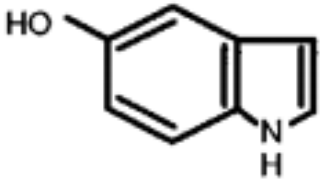
dimethyltryptamine



indazole



indole



5-OH indole

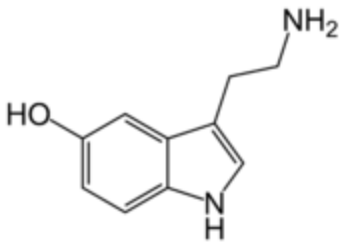
The exact mechanism of benzydamine hallucination is still unknow and multiple pharmacological interactions could be hypothesized.

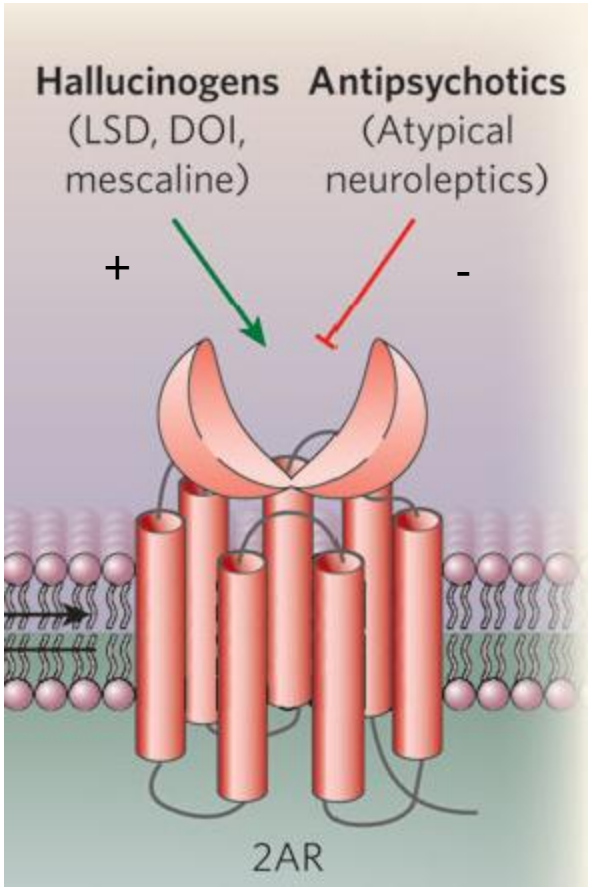
The structural similarity between benzydamine and serotonin may be translated into a serotoninergic action such as the agonistic activation of the **5HT2A receptors**.

Several indole compounds promote hallucination based on this mechanism, such as diethylamine in lisergic acid (LSD) and dimethyltriptamine (DMT).

DMT is the active principle in *ayahuasca*, a hallucinogenic tea used in religious rituals in Brazil. The main side effects reported with use of *ayahuasca*, wich are nausea and vomiting are similar to those of benzydamine use.

serotonina



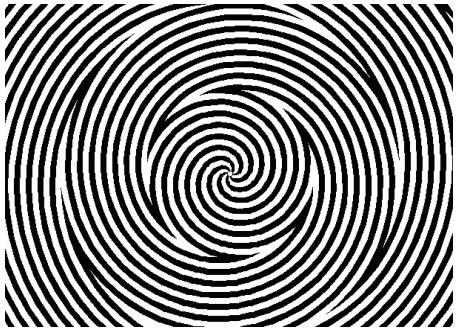


Clinical signs or symptoms of unintentional ingestion:

++ gastrointestinal with nausea,
followed by vomiting and dizziness
Tremors
Agitation
Ataxia
Convulsions
Hallucination
(Ballesteros et al., 2005).

} Described mainly in children

Clinical signs or symptoms of intentional abuse:



++ hallucination
Nausea and vomiting
Hunger
Headache
Slowness and sadness
→ often in association with tobacco, alcohol or other drugs
(THC, cocaine, solvents)

NEWS_May 2009: *rupurut*

Italian Police reported that an intense trade of rupurut was present in young people during the weekend in order to manipulate alcohol breath test . Rupurut was sold in Slovenia and people from Udine and nearby cities used to cross the border in order to buy it.

Hydrotalcite is a layered double hydroxide of general formula $Mg_6Al_2CO_3(OH)_{16}\cdot 4(H_2O)$, whose name is derived from its resemblance with talc and its high water content.

Rupurt is an mild antiacid and an urban legend tells that it could alter alcohol breath test.

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

A mixed MDPV and benzodiazepine intoxication in a chronic drug abuser: Determination of MDPV metabolites by LC–HRMS and discussion of the case☆

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[a] Department of Health Sciences, Forensic Toxicology Unit, University of Firenze, Italy
[b] Forensic Toxicology and Antidoping, University Hospital of Padova, Italy
[c] Department of Health Sciences, University of Firenze, Italy

Highlights

- Two episodes of MDPV intoxication for the same subject are reported.
- Symptoms and self-reported manner of use are described.
- MDPV and its phase I and phase II metabolites were determined in urine.
- Several benzodiazepines were also found in urine.

Highlights

- Two episodes of MDPV intoxication for the same subject are reported.
- Symptoms and self-reported manner of use are described.

A 27-year-old man was found **irresponsive** in his apartment and was brought to the emergency department (ED) of a local hospital. When in ED, he rapidly recovered and self-reported to have recently injected some doses of MDPV that he had bought in the Internet. He left the hospital without medical cares. 15 days after, he was again admitted to the same ED due to **severe agitation**, **delirium** and **hallucinations**, and reported the use of ***MDPV*** and pharmaceutical drugs during the preceding week. He was sedated with diazepam and chlorpromazine

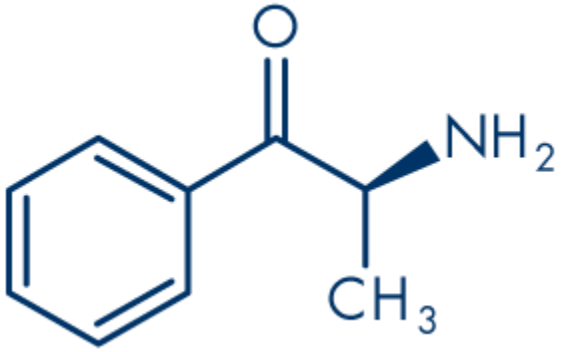
Highlights

- MDPV and its phase I and phase II metabolites were determined in urine.

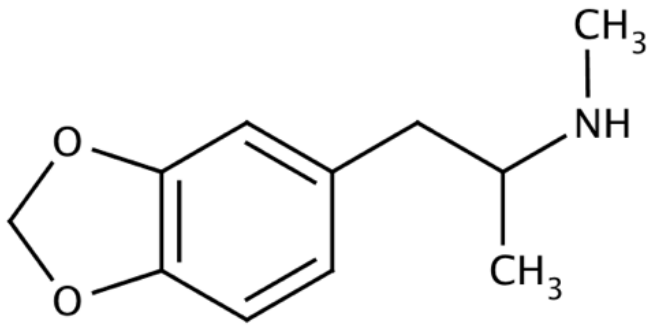
	Screening urinary tests					1st admission	2nd admission
Ecstasy (MDMA)			*mg/L*	*minimum: 0.150 borderline: 0.150-0.500 positive: > 0.500*		0,65	0,53

History and unusual clinical signs of acute MDMA poisoning → Liquid chromatography–high resolution multiple mass spectrometry (LC–HRMS/MS)

Highlights



MDPV



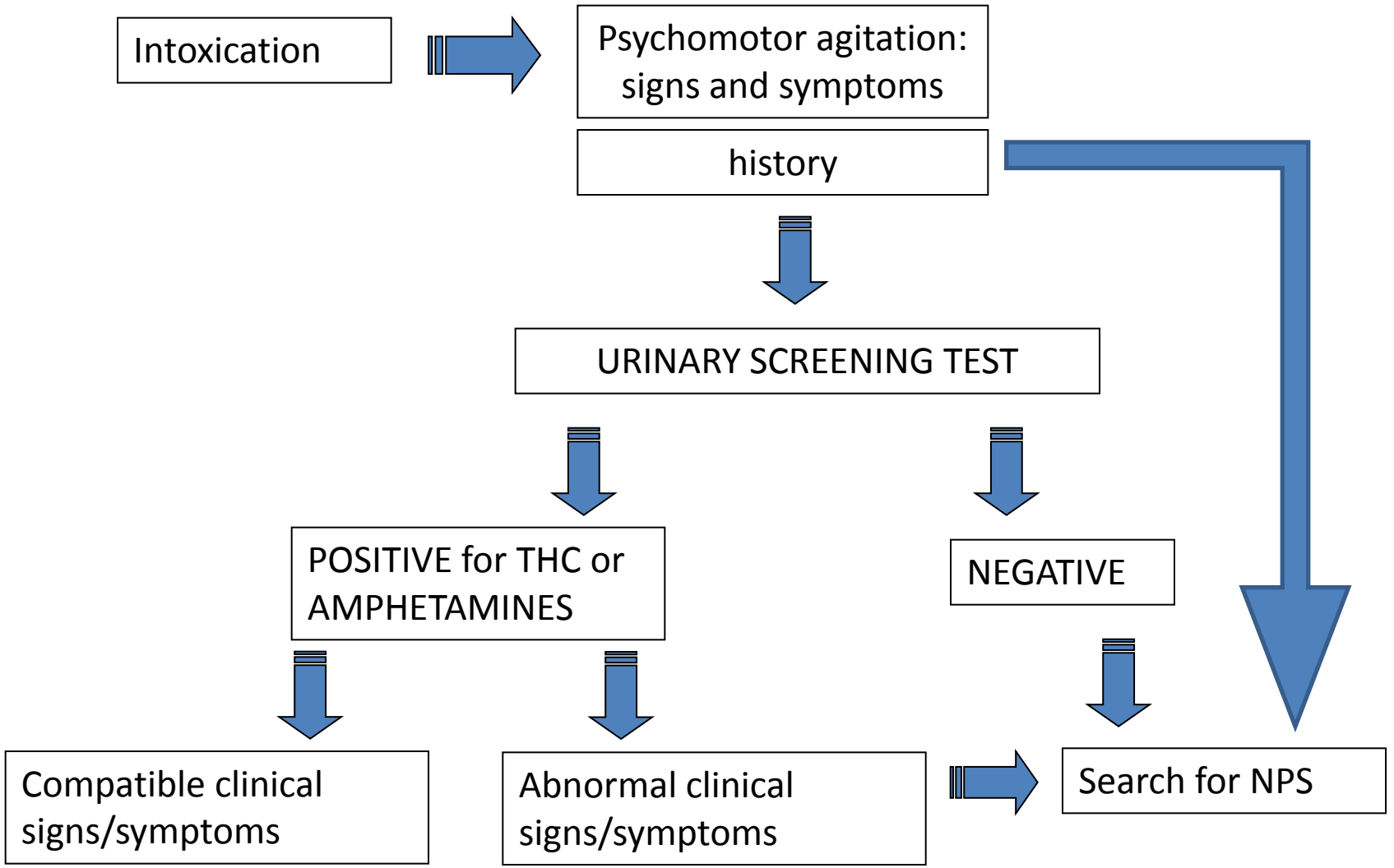
MDMA

MDPV shares structural similarity with MDMA, a known serotonergic agent, and has been reported to cause serotonin toxicity and, which may explains the vivid visual hallucinations seen in our patient. Other synthetic cathinones have been demonstrated to cause direct dopamine release and have significant effects on serotonergic receptors too,

Highlights

- weak point of the present case is the **lack of any blood samples** that would have been crucial to understand what and how much psychoactive substances were acting at patient's brain receptors at the moments when either loss of consciousness, hallucinations or psychotic effects were observed

Decision clinical algorithm for NPS detection



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TOXICOLOGY MEDICAL PRACTICE h 24

0039 055/7946238

POISON CENTRE h 24

0039 055/7947819

TIS- Teratology information Service h 9-20

0039 055/7946731 (patients)

0039 055/7946859 (physicians)