Società Medico Chirurgica di Ferrara

Ferrara, 29 marzo 2019

Uso ed abuso di sostanze psicotrope nei giovani
Quali strategie a Ferrara

Comprendere il fenomeno droga: tra vecchie e nuove sostanze

Paolo Frisoni

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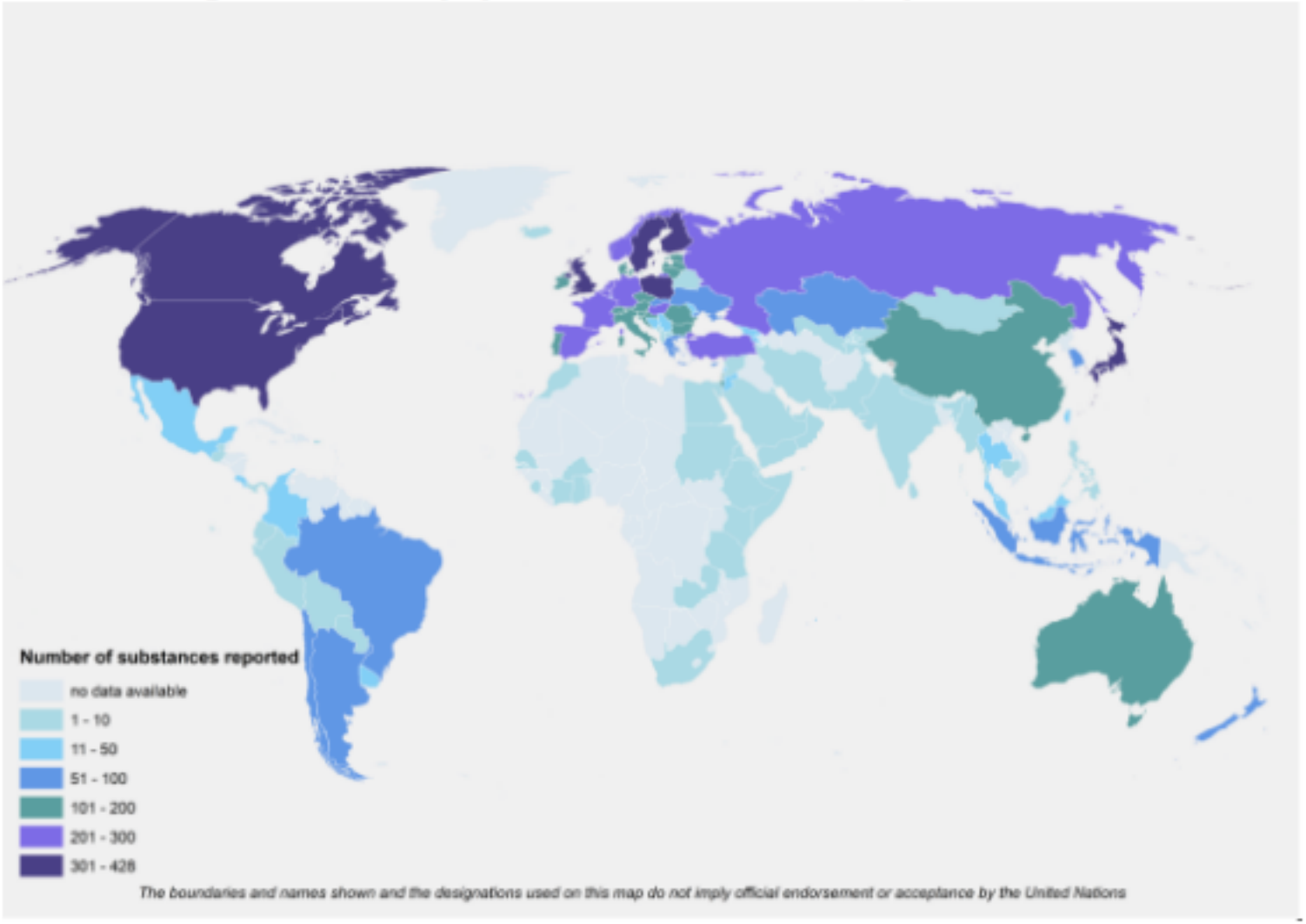
FERRARIAE UNIVERSITAS · 13 91 · EX LABORE FRUCTUS

NPS (Novel psychoactive substances)

- Lo United Nations Office on Drugs and Crime (UNODC) definisce le NPS come "*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*".

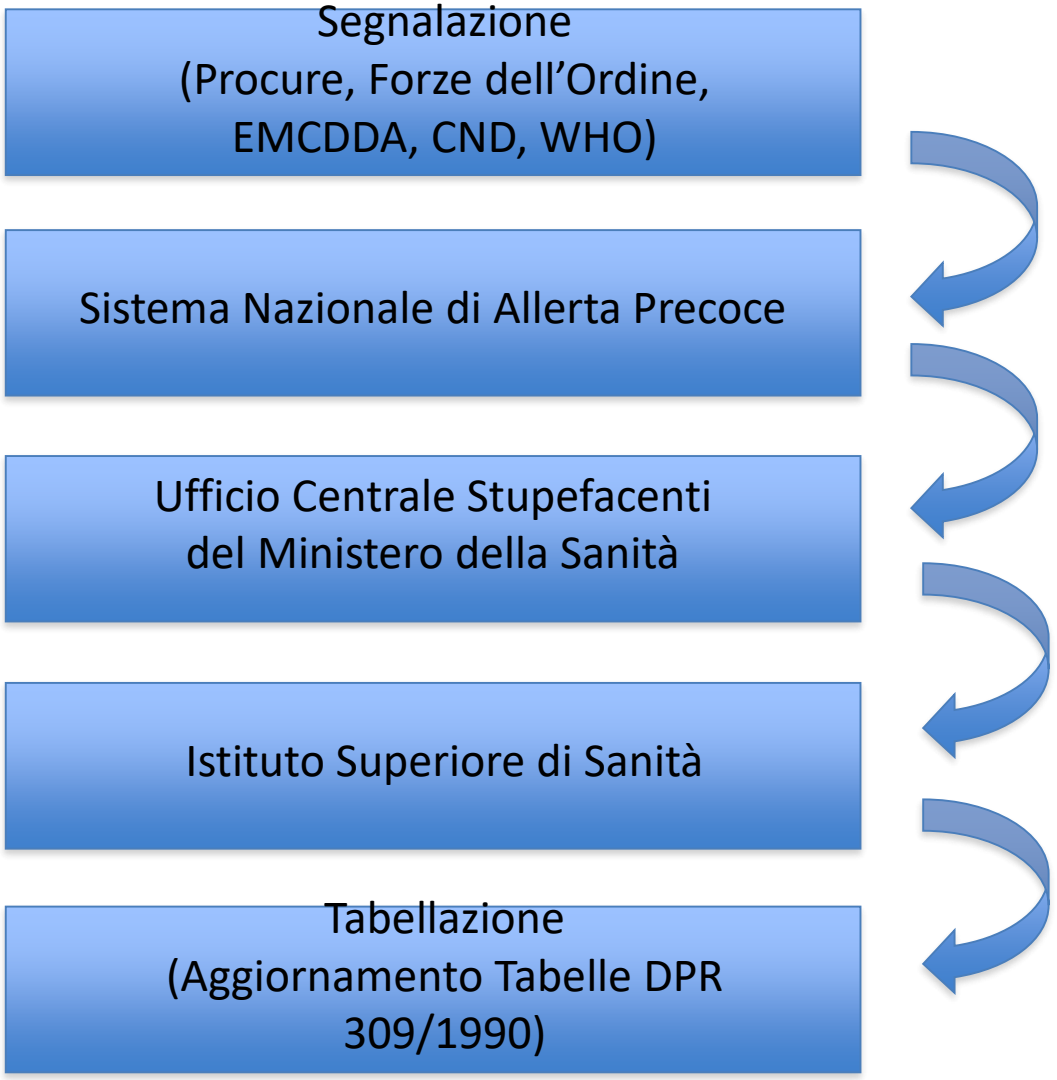
Global emergence of new psychoactive substances, up to December 2018:



Source: UNODC Early Warning Advisory on NPS, 2019.

Al dicembre 2018 sono state segnalate 888 sostanze

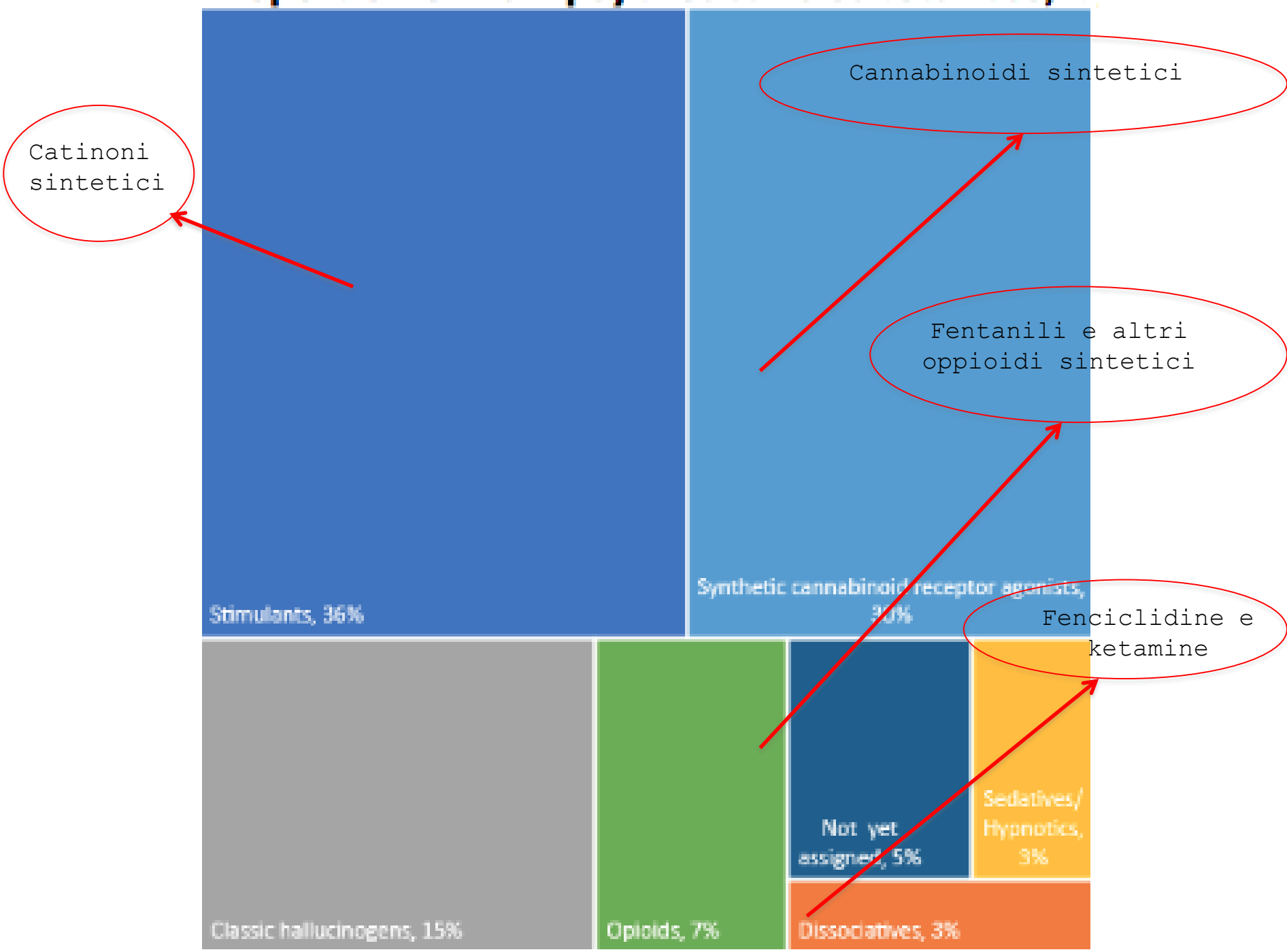
Iter per la tabellazione delle NPS in Italia



NPS (Novel psychoactive substances)

Principalmente sintetiche (derivate da stupefacenti noti, prodotti farmaceutici o piante):

- oppioidi sintetici;
- cannabinoidi sintetici;
- catinoni sintetici;
- fenetilammine;
- piperazine;
- ketamina e analoghi;
- analoghi della fenciclidina;
- altre (aminoindani, triptamine, benzofurani, GHB, GBL, Z-drugs…)


Catinoni sintetici
Cannabinoidi sintetici
Fentanili e altri oppioidi sintetici
Fenciclidine e ketamine
Stimulants, 36%
Synthetic cannabinoid receptor agonists, 30%
Classic hallucinogens, 15%
Opioids, 7%
Not yet assigned, 5%
Sedatives/ Hypnotics, 3%
Dissociatives, 3%

Oppioidi sintetici

Morbidity and Mortality Weekly Report

Opioid Overdose Outbreak — West Virginia, August 2016

Joel Massey, MD[1,2]; Michael Kilkenny, MD[3]; Samantha Batdorf, MPH[2]; Sarah K. Sanders, PhD[2]; Debra Ellison[3]; John Halpin, MD[4]; R. Matthew Gladden, PhD[4]; Danae Bixler, MD[2]; Loretta Haddy, PhD[2]; Rahul Gupta, MD[2]

Ontario, Canada:

J Forensic Sci, January 2018, Vol. 63, No. 1
doi: 10.1111/1556-4029.13517
Available online at: onlinelibrary.wiley.com

Community-Based Response to Fentanyl C
San Francisco, 2015

Christopher Rowe · Eliza Wheeler ·
T. Stephen Jones · Clement Yeh · Phillip O. Coffin

TOXICOLOGY; PATHOLOGY/BIOLOGY

Teri L. Martin[1,*], Kare
[1]Toxicology Section, Ce
[2]Office of the Chief Cor

Jessica B. Dwyer,[1] M.D.; Jennifer Janssen,[1] M.S.; Todd M. Luckasevic,[1] D.O.; and Karl E. Williams,[1] M.D.

Report of Increasing Overdose Deaths that include Acetyl Fentanyl in Multiple Counties of the Southwestern Region of the Commonwealth of Pennsylvania in 2015–2016*

Contents lists available at ScienceDirect
Drug and Alcohol Dependence
journal homepage: www.elsevier.com/locate/drugalcdep

Full length article

Post-mortem review of fentany
drug users in Southern Bavaria

Inga Sinicina[a,*], Hans Sachs[b], Wolfgang
[a] Department of Legal Medicine, Ludwig Maximilians University, Nus
[b] Forensic Toxicological Centre, Bayerstr. 53, 80335 Munich, Germa

Contents lists available at ScienceDirect
Preventive Medicine
journal homepage: www.elsevier.com/locate/ypmed

RESEARCH LETTER

Changes in Synthetic Opioid Involvement in Drug Overdose Deaths in the United States, 2010-2016

Drug overdose deaths are at unprecedented levels in the United States.[1] Prescription opioids have been the most common drug

Short Communication

The 'fentanyl epidemi
on opioid-related mor

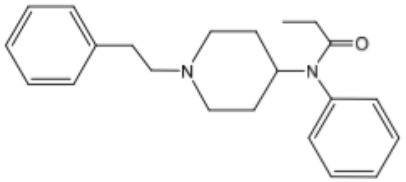
Benedikt Fischer[a,b,c,d,e,*], Le
[a] Institute for Mental Health Policy Research, Ce
[b] Department of Psychiatry, University of Toront
[c] Institute of Medical Science (IMS), University o
[d] Centre for Criminology & Sociolegal Studies, Un
[e] Department of Psychiatry, Federal University of
[f] Dalla Lana School of Public Health, University
[g] Institut für Klinische Psychologie und Psychothe

Morbidity and Mortality Weekly Report

Deaths Involving Fentanyl, Fentanyl Analogs, and U-47700 — 10 States, July–December 2016

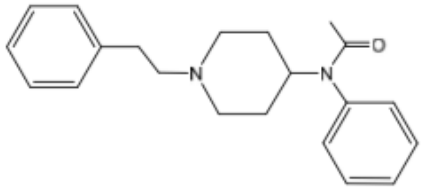
Julie K. O'Donnell, PhD[1]; John Halpin, MD[1]; Christine L. Mattson, PhD[1]; Bruce A. Goldberger, PhD[2]; R. Matthew Gladden, PhD[1]

volvement in drug overdose deaths.



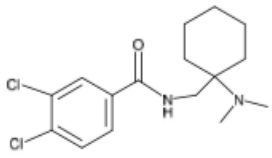
Fentanyl

Oppioidi sintetici

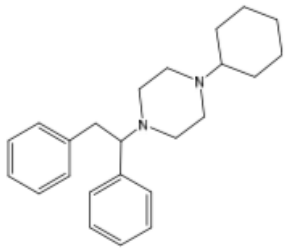


Acetylfentanyl

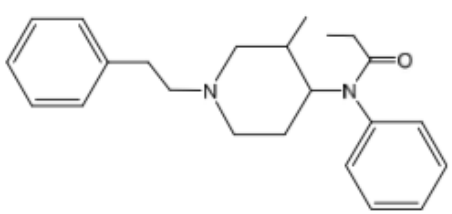
- Agonisti recettori oppioidi μ, δ, κ nel S.N.C. e S.N.P. (maggiore specificità per recettori μ rispetto all'eroina)
- Blocco rilascio di neurotrasmettitori presinaptico; azione su recettore μ accoppiato a prot. G diminuisce cAMP intracellullare; efflusso di K+ dal neurone post-sinaptico → iperpolarizzazione e refrattarietà al'eccitazione



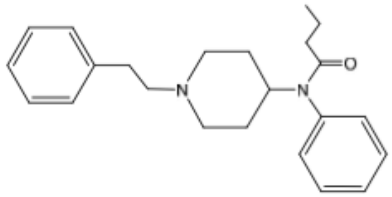
AH-7921



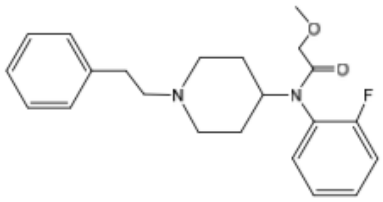
MT-45



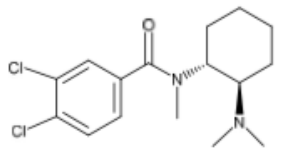
3-Methylfentanyl



Butyrylfentanyl

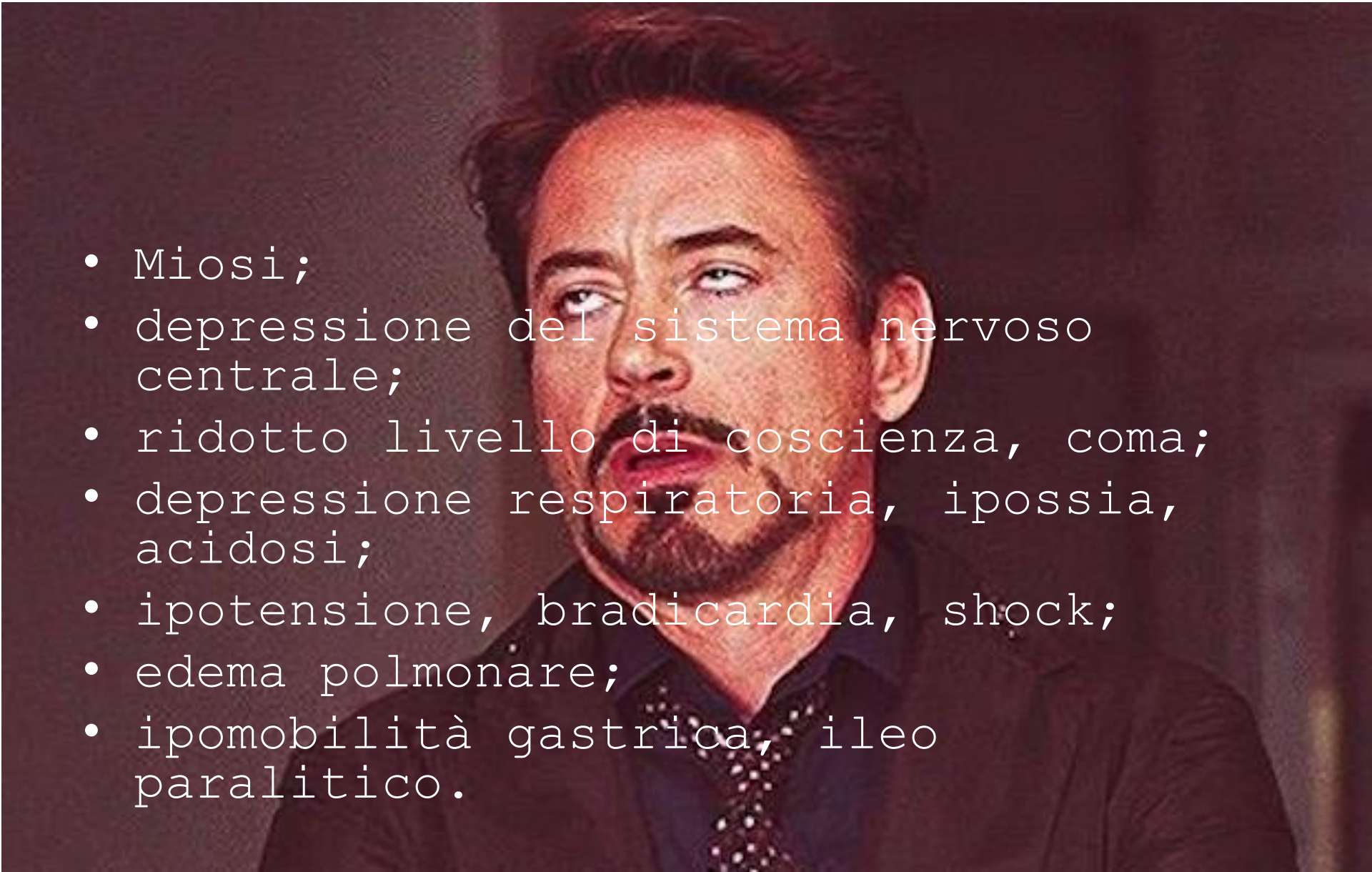


Ocfentanil



U-47700

Oppioidi sintetici



- Miosi;
- depressione del sistema nervoso centrale;
- ridotto livello di coscienza, coma;
- depressione respiratoria, ipossia, acidosi;
- ipotensione, bradicardia, shock;
- edema polmonare;
- ipomobilità gastrica, ileo paralitico.

Table 1. Lethal concentrations data reported in the literature.

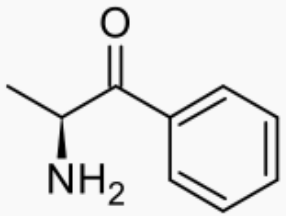
	Potency Ratio to Morphine [14]	Administration Route Associated with Overdose	Blood Concentration (ng/mL)	Other Concentrations (Site, ng/mL)
Acetylfentanyl [53,58,80,88]	15.7	Nasal, intravenous	153–260 247.5–285 (heart)	Liver 100–2400 ng/g; urine 2.6–2720 ng/mL; stomach content 880 ng/mL; vitreous humor 131–240 ng/mL.
Alpha-Methylfentanyl [89]	56.9	Intravenous	3.1	liver 78 ng/g; bile 6.4 ng/mL.
Butyrylfentanyl [59,71]	1.5–7.0	Nasal, rectal, intravenous, sublingual	66–99 ng/mL; 39–220 ng/mL (heart)	liver 41–57 ng/g; kidney 160 ng/g, muscle 100 ng/g; vitreous humor 32 ng/mL; bile 260 ng/mL; urine 64 ng/mL; gastric contents 590 ng/mL; brain 93 ng/g.
Carfentanil [90]	10,000		0.11–0.88	
4-Fluorobutyrfentanyl [91]	Unknown	By smoking	91–112	urine, 200–414 ng/mL; liver, 411–902 ng/g; kidney 136–197 ng/g.
Furanylfentanyl [49,60]	Unknown	Nasal, intravenous	0.43–26	
3-Methylfentanyl [83,92]	48.5–7000	Intravenous	0.3–1.9	
Ocfentanil [62,93]	90	Nasal, by smoking	9.1–15.3; 23.3–27.9 (heart)	vitreous humor 12.5 ng/mL; urine 6.0 ng/mL; bile 13.7 ng/mL; liver 31.2 ng/g; kidney 51.2 ng/g; brain 37.9 ng/g; nasal swabs 2999 ng/swab.
AH-7921 [5,44,64,66]	Unknown	Oral, nasal, by smoking, intravenous	330–6600 480–3900 (heart)	urine 760–6000 ng/mL; bile 17,000 ng/mL; liver 530–26,000 ng/g; kidney 7200 ng/g; brain, 7700 ng/g; vitreous humor 190 ng/mL; stomach content, 40 µg/mL.
U-47700 [5,49,94,95]	7.5	Oral, nasal, intrarectal, smoking, intravenous	59–525 1347 (heart)	Urine 360–1393 ng/mL; liver 430–1700 ng/g; kidney 270 ng/g; lung 320 ng/g; brain 97 ng/g.
MT-45 [5,66,96]	Unknown	Oral, nasal, intrarectal, intravenous	520–660 1300 (heart)	Urine 370 ng/mL; vitreous humor 260 ng/mL; gastric content 49 µg/mL; liver 24 µg/g.
Fentanyl [70,82,86,87,97,98]	100	Oral, transdermal, nasal, intravenous	0.5–383	Urine 2.9–895 ng/mL; gastric content 31.6–745 µg/mL; liver 5.8–613 µg/g.

Frisoni P. et al. ***Novel Synthetic Opioids: The Pathologist's Point of View*** Brain Sci. 2018, 8, 170

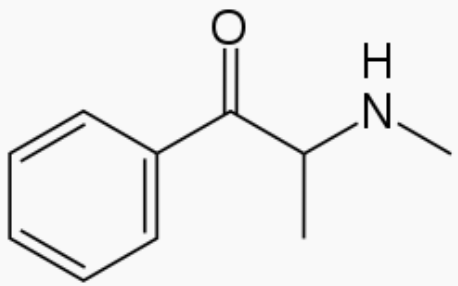
Oppioidi sintetici

- Alcuni approvati per uso farmaceutico (fentanyl, sufentanyl, alfentanyl)
- Composti con elevata potenza
- Diffusi (anche in Italia)
- Elevato numero di decessi riportati
- Spesso venduti come eroina, miscelati ad eroina o presenti come sostanze di taglio o contaminanti in altre preparazioni (es. cocaina)
- Numerose molecole, poco conosciute, mancanza di standard analitici → possono sfuggire alle indagini tossicologiche di routine
- Reperti aspecifici alle comuni indagini medico-legali

Catinone



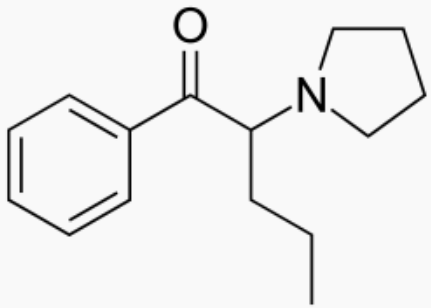
Metcatinone



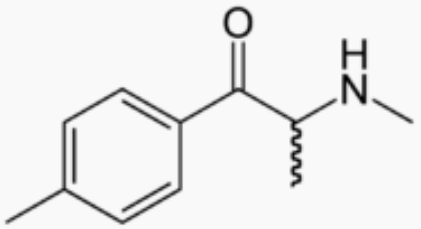
Catinoni sintetici

- Molecole simili al khat, estratto dalla *Catha edulis*
- Inibitori del reuptake delle monoammine (serotonina, dopamina, noradrenalina) e/o releaser delle monoammine
- Sovrastimolazione del sistema simpatico

Alfa-Pirolidinopentiofenone



Mefedrone



Catinoni sintetici

- Psicostimolanti, euforizzanti
- Allucinogeni
- Sintomi da sovrastimolazione simpatica (tremori, insonnia, agitazione psicomotoria, ipertermia maligna)
- Aumentano la contrattilità miocardica, la pressione arteriosa e la frequenza cardiaca
- Rabdomiolisi

Catinoni sintetici

- Ampia diffusione
- Facile reperibilità ("sali da bagno")
- Associati a decessi ed episodi penalmente rilevanti (aggressioni, excited delirium syndrome…)
- Numerose molecole (terza classe più numerosa), poco conosciute, mancanza di standard analitici → possono sfuggire alle indagini tossicologiche di routine
- Reperti aspecifici (o assenti) alle comuni indagini medico-legali

Cannabinoidi sintetici

Int J Legal Med
DOI 10.1007/s00414-013-0864-1

CASE REPORT

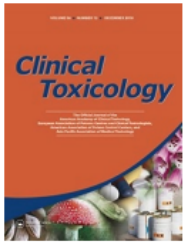
Driving under the influence of synthetic cannabinoids ("Spice"): a case series

Frank Musshoff · Burkhard Madea · Gerhard Kernbach-Wighton · Wolfgang Bicker · Stefan Kneisel · Melanie Hutter · Volker Auwärter

Contents lists available at ScienceDirect
Accident Analysis and Prevention
journal homepage: www.elsevier.com/locate/aap

Prevalence of synthetic cannabinoids in blood samples from Norwegian drivers suspected of impaired driving during a seven weeks period

Silja Skogstad Tuv*, Hege Krabseth, Ritva Karinen, Kirsten M. Olsen, Elisabeth L. Øiestad, Vigdis Vindenes



Taylor & Francis
Clinical Toxicology
ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

Forensic Science International
Available online 21 February 2019
In Press, Corrected Proof

Fatal intoxication with new synthetic cannabinoids AMB-FUBINACA and EMB-FUBINACA

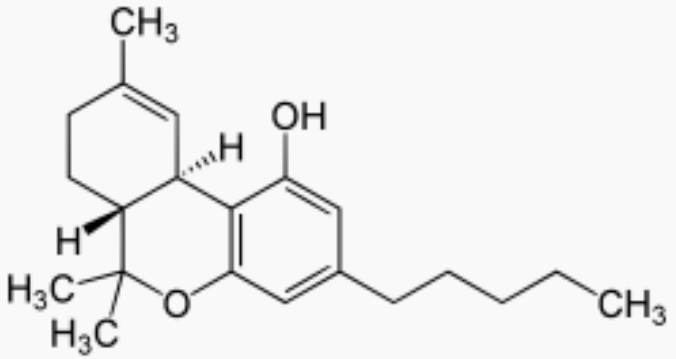
Piotr Adamowicz, Ewa Meissner & Marta Maślanka

Case Report

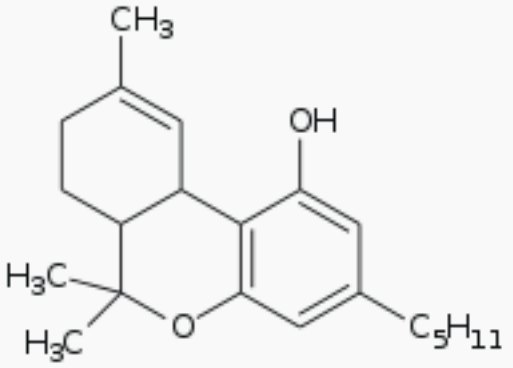
A case of 5F-ADB / FUB-AMB abuse: Drug-induced or drug-related death?

Ivo D. Ivanov [a, b], Silviya Stoykova [a, b], Elka Ivanova [c], Aleksandrina Vlahova [d], Nikola Burdzhiev [e], Ivayla Pantcheva [a], Vasil N. Atanasov [a, b]

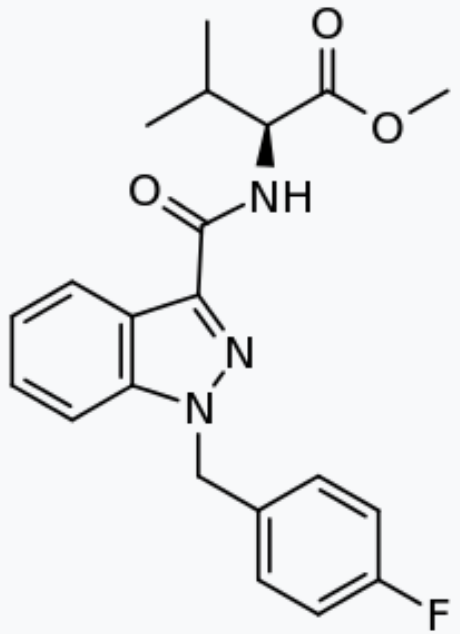
Delta-9-tetraidrocannabinolo



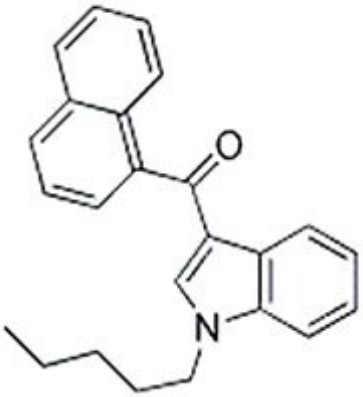
Dronabinol



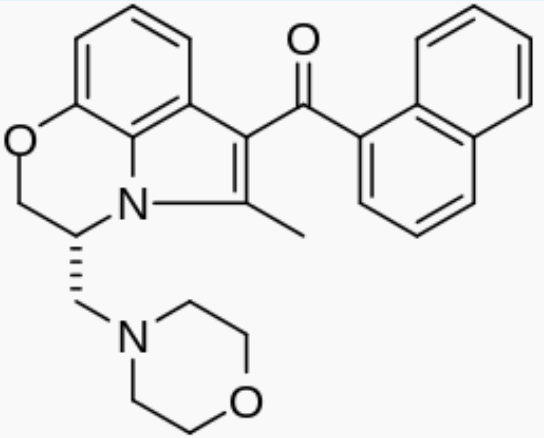
AMB-FUBINACA



JWH-018



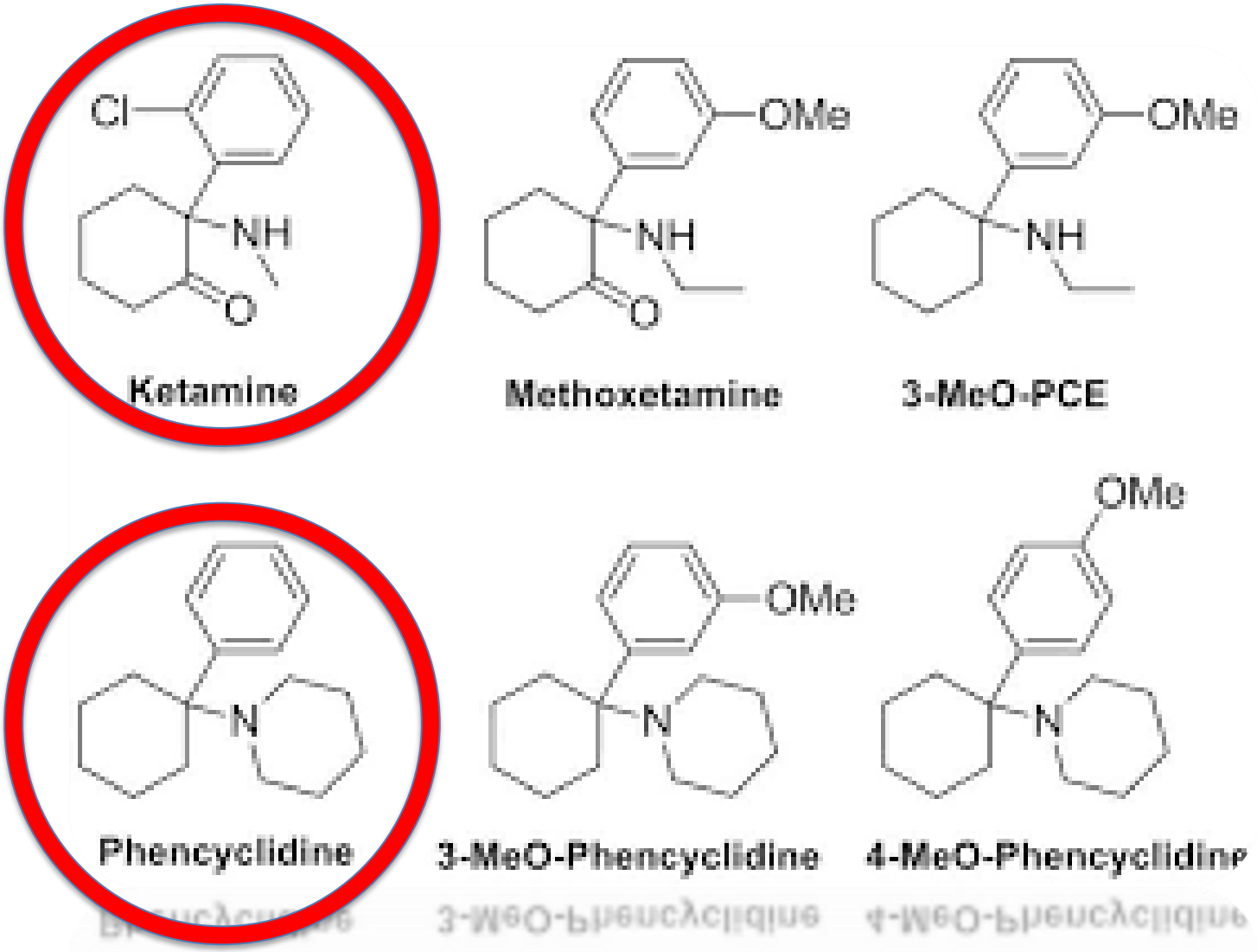
WIN 55,212-2



Cannabinoidi sintetici

- Agonisti recettori per i cannabinoidi CB1 e CB2 (recettori accoppiati a prot. G)
- inibizione presinaptica del rilascio di neurotrasmettitori(dopamina, glutammato) /inibizione del reuptake
- effetti tipici dei cannabinoidi tradizionali: euforia, rilassamento, percezione spazio-temporale alterata; alterazioni uditive, olfattive e visive, ansia, disorientamento, stanchezza, stimolazione dell'appetito, iperemia congiuntivale
- gravi effetti indesiderati: psicosi, depressione respiratoria, arresto cardiaco, nefrotossicità, iperemesi, rabdomiolisi, ipertermia, convulsioni, ischemia cerebrale.

Anestetici dissociativi



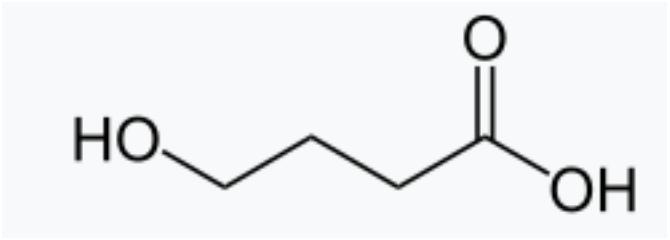
Anestetici dissociativi

- Antagonisti recettore NMDA
- interazioni con sistema colinergico e oppioide
- inibitori del reuptake di DA, NA e 5-HT
- legano i recettori D1 e D2, e il 5-HT2A

(metossietamina, ketamina).

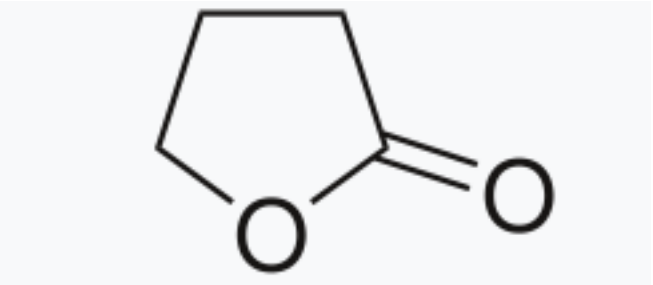
- Percezione temporale e spaziale alterata
- Allucinazioni
- Effetti dissociativi
- Intenso distacco dalla realtà
- Delirio
- Amnesia
- Catatonia
- Aumento dell'aggressività (metossietamina)
- Depressione respiratoria (ketamina)
- Aumento della pressione arteriosa
- Aumento di gittata e frequenza cardiaca

"Droghe da stupro"



GHB (acido γ-idrossibutirrico)

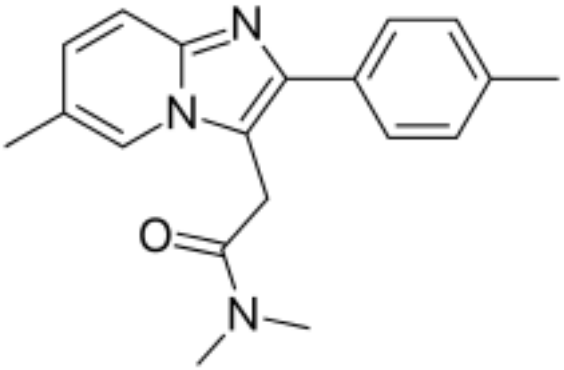
- normalmente presente in vari organi
- agisce su un proprio recettore e sui recettori per il GABA. Sedativo centrale.
- liquido incolore e inodore
- A basse dosi: euforia, benessere, rilassatezza, aumento della sensazione tattile e del desiderio sessuale
- Ad alte dosi: amnesia, depressione respiratoria, coma
- Effetto rapido (5-20 min.) e breve durata (1-4 h)
- Metabolizzato velocemente (< 8 h nel sangue; urine < 12 h,)



GBL (γ-Butirrolattone)

- reattivo chimico (facile reperibilità)
- profarmaco del GHB

"Droghe da stupro"



"Z-DRUGS"

- zolpidem, zopiclone, zaleplon
- nonbenzodiazepine
- effetti sovrapponibili
- frequente associazione ad alcool
- metabolismo veloce (rintracciabile nelle prime 36 h)

Ricerca su NPS, perché?

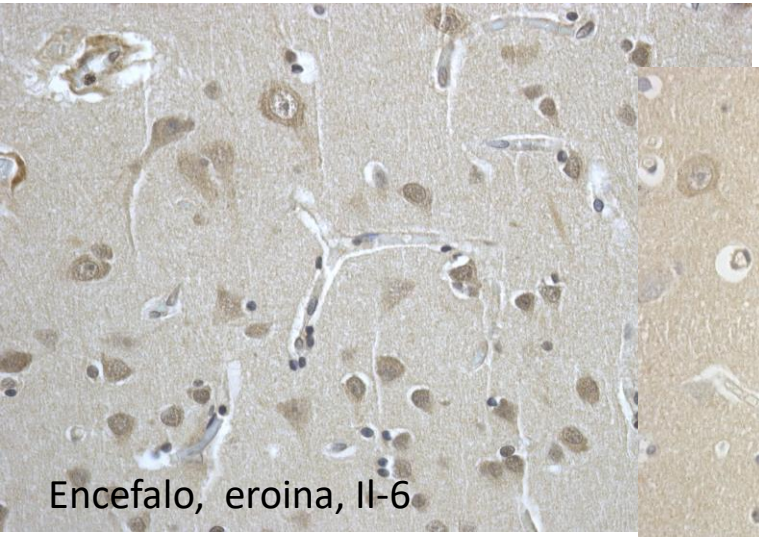
- Emergenza sociale
- Effetti simili o maggiori rispetto alle corrispondenti sostanze “tradizionali”
- Dati farmacocinetici, farmacodinamici e clinici scarsi o inesistenti
- Poliassunzione
- Ognuna delle classi principali è associata a uno o più decessi riportati

NPS in campo forense

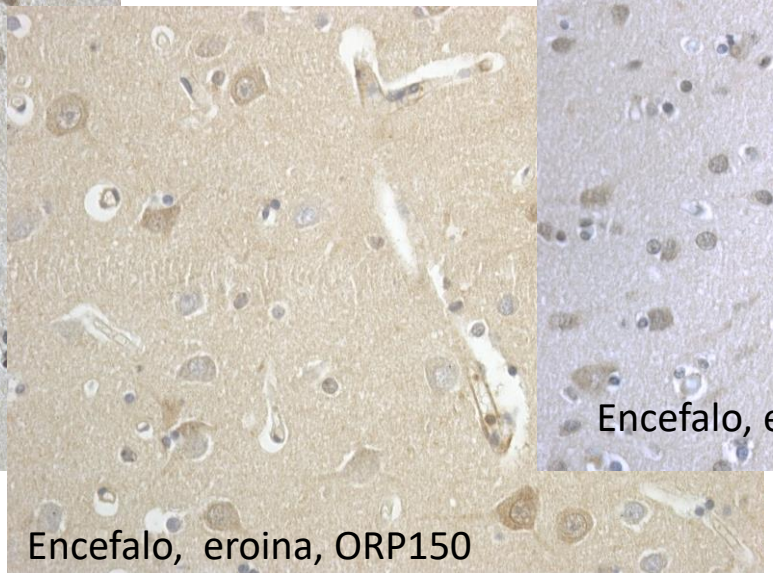
- L'autopsia e le indagini istologiche forniscono dati aspecifici
- Sfuggono alle indagini tossicologiche di routine
- un approccio immunoistochimico?

Possibili bersagli – oppioidi sintetici

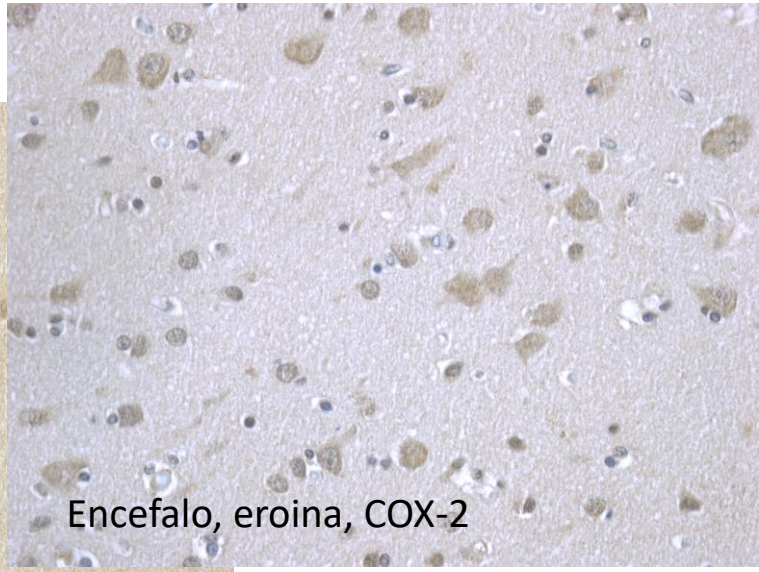
- Encefalo
- Markers di infiammazione (Il-6, Il-15, COX-2)
- Markers di ipossia/stess ossidativo (Oxygen-regulated protein 150, HSP-70)



Encefalo, eroina, Il-6



Encefalo, eroina, ORP150

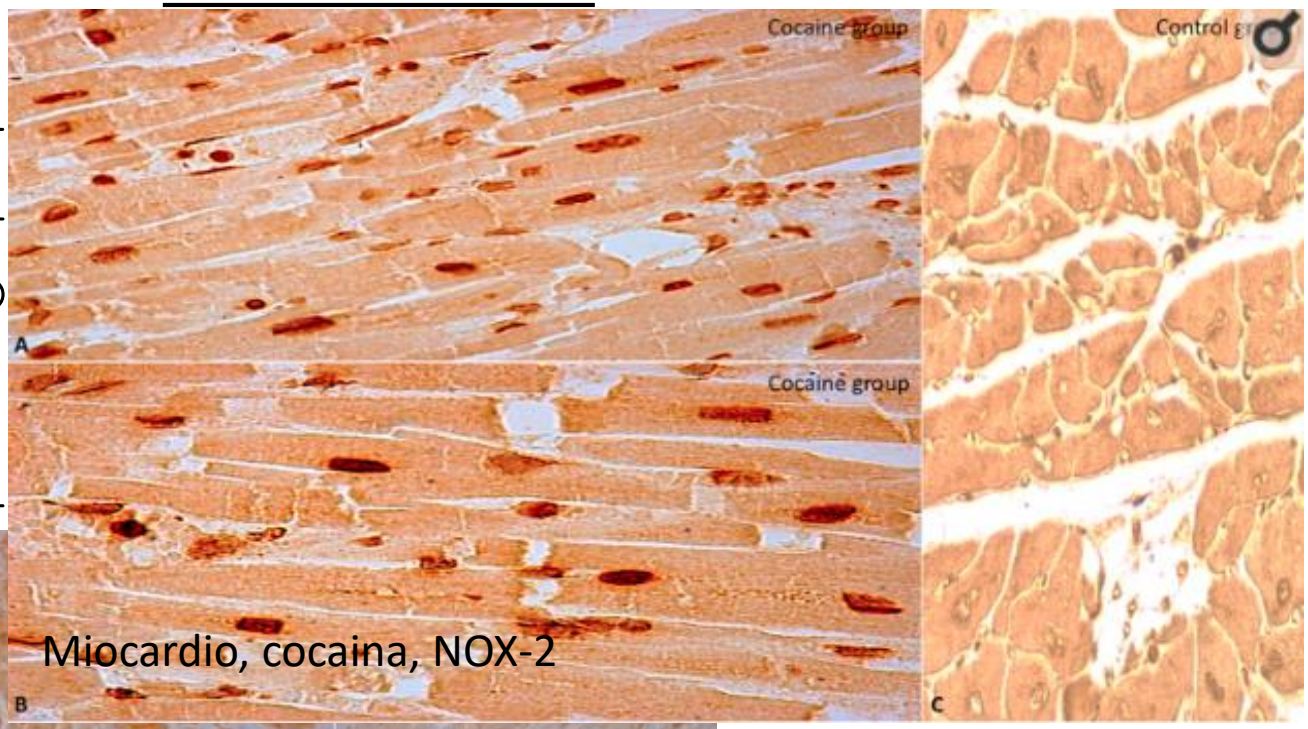


Encefalo, eroina, COX-2

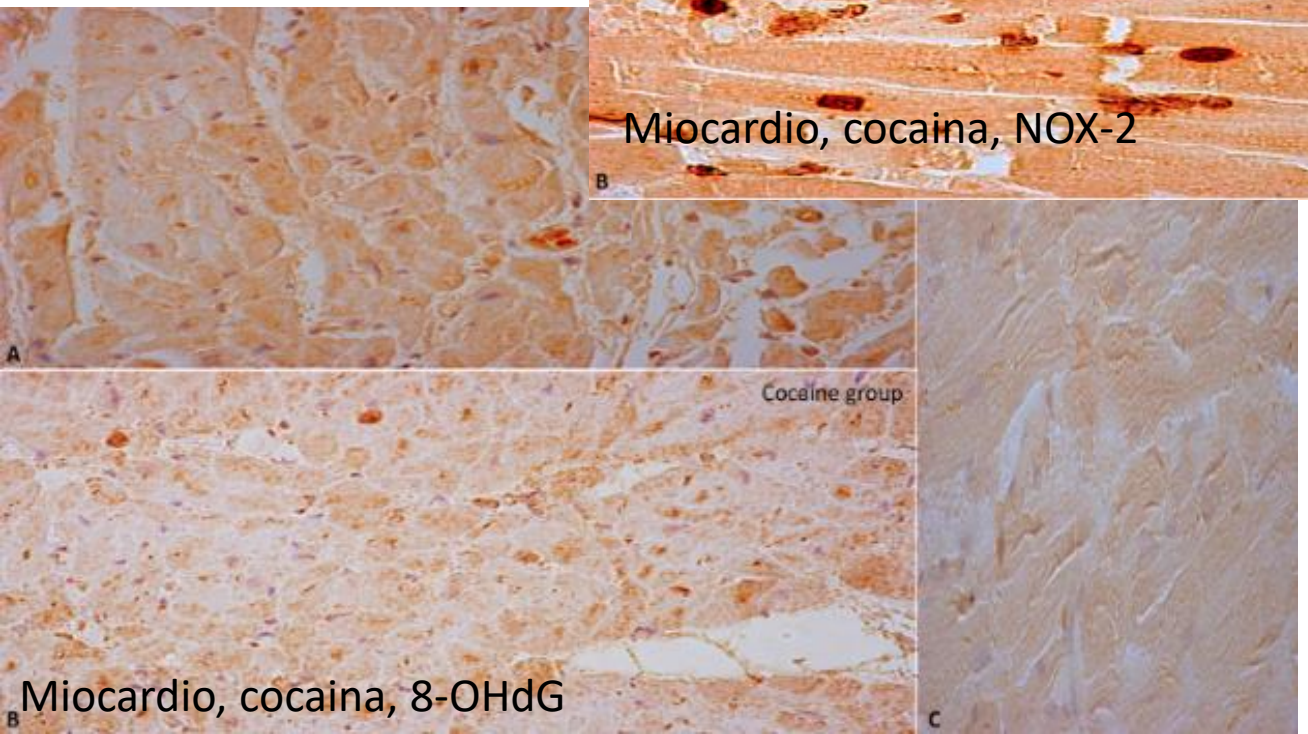
Neri M. et al. *Cytokines, Chaperones and Neuroinflammatory Responses in Heroin-Related Death: What Can We Learn from Different Patterns of Cellular Expression?* Int. J. Mol. Sci. 2013, 14, 19831-19845

Possibili bersagli – catinoni sintetici

- Cuore: ma
  OHdG) e n
  nitrotiro
- Encefalo:
  (SOD), va



Miocardio, cocaina, NOX-2



Miocardio, cocaina, 8-OHdG

Turillazzi et al. *Myocardial oxidative damage is induced by cardiac Fas-dependent and mitochondria-dependent apoptotic pathways in human cocaine-related overdose*. Sci Rep. 2017; 7: 44262

PRESIDENZA DEL CONSIGLIO DEI MINISTRI

Dipartimento Politiche Antidroga

SNAP

SISTEMA NAZIONALE ALLERTA PRECOCE

PROGETTO

"Effetti delle NPS: Sviluppo di una multicentrica di ricerca per il potenziamento informativo del Sistema di Allerta Precoce"
(Responsabile Scientifico M. Marti)

Grazie dell’attenzione!