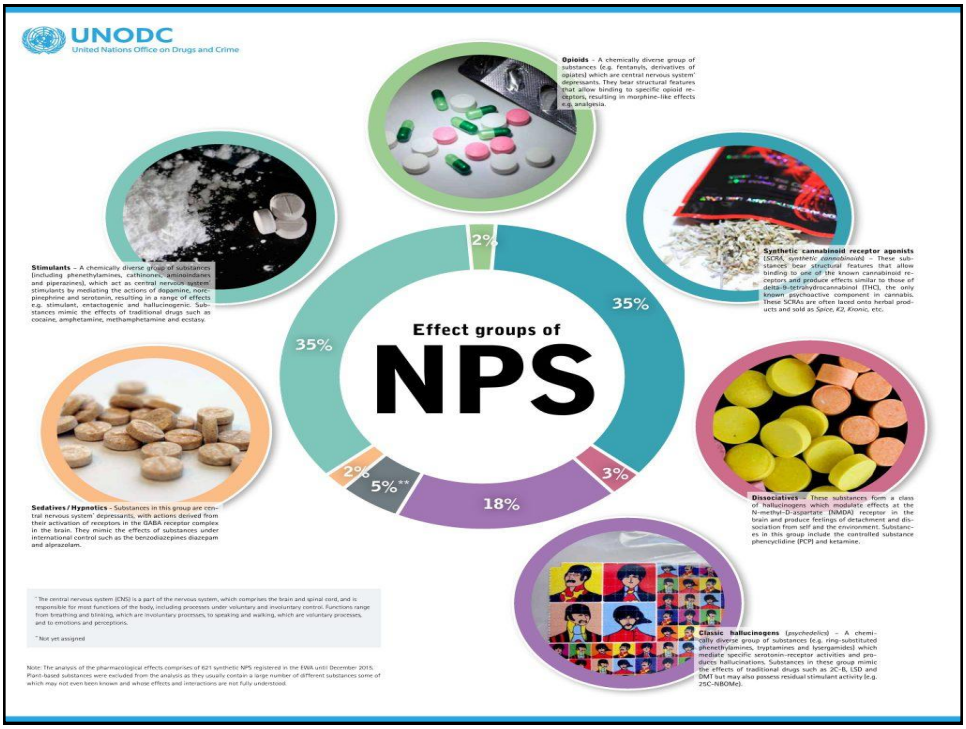
Nuove sostanze psicoattive: la nuova frontiera delle dipendenze

Dr Maurizio Coppola

Torino, 19.02.2019



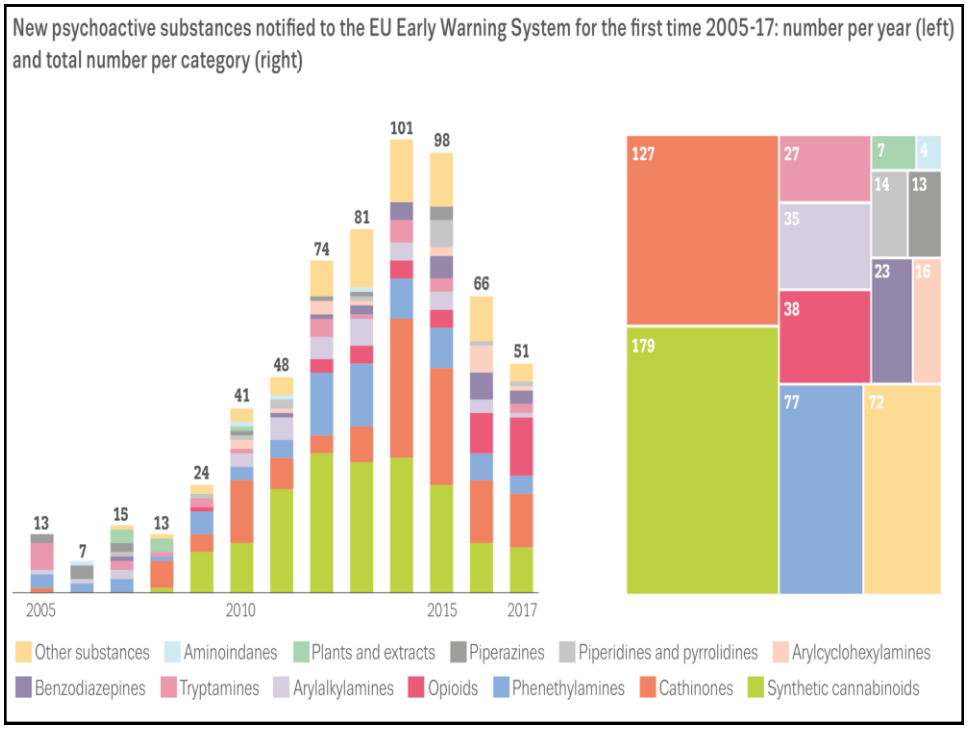
Definizione

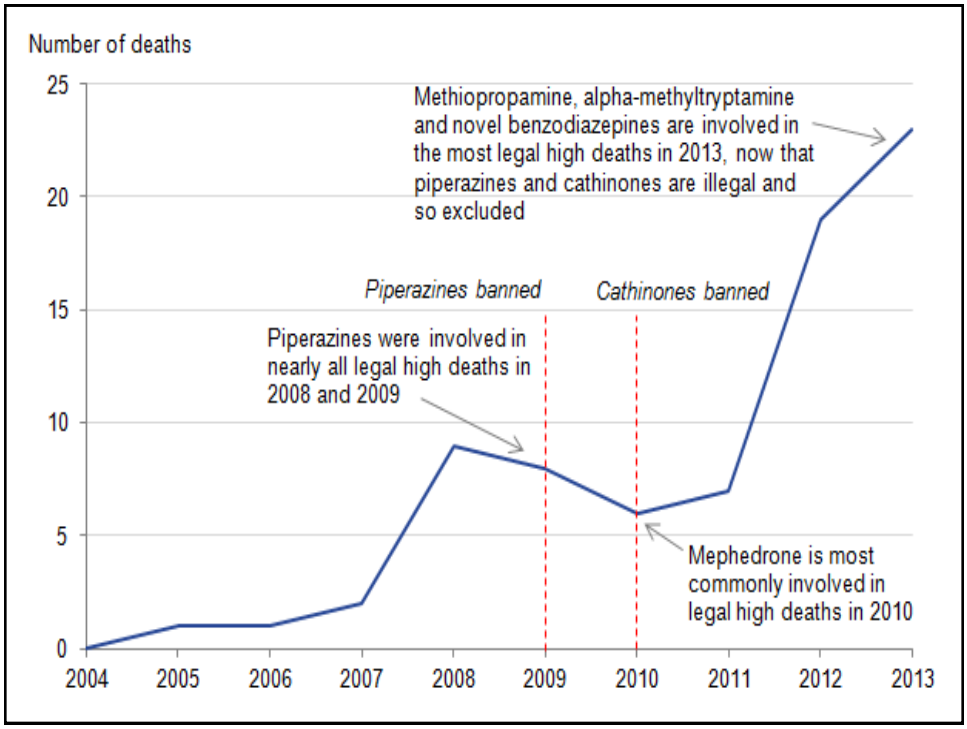
- Le nuove sostanze psicoattive, anche definite legal highs, smart drugs, designer drugs, chemical research, sono un gruppo eterogeneo di sostanze psicoattive, di nuova sintesi o di nuova immissione sul mercato delle droghe d'abuso, capace di mimare gli effetti delle droghe tradizionali, ma che differentemente da queste, sfugge al controllo dalla legislazione internazionale.
  - EMCDDA, 2013

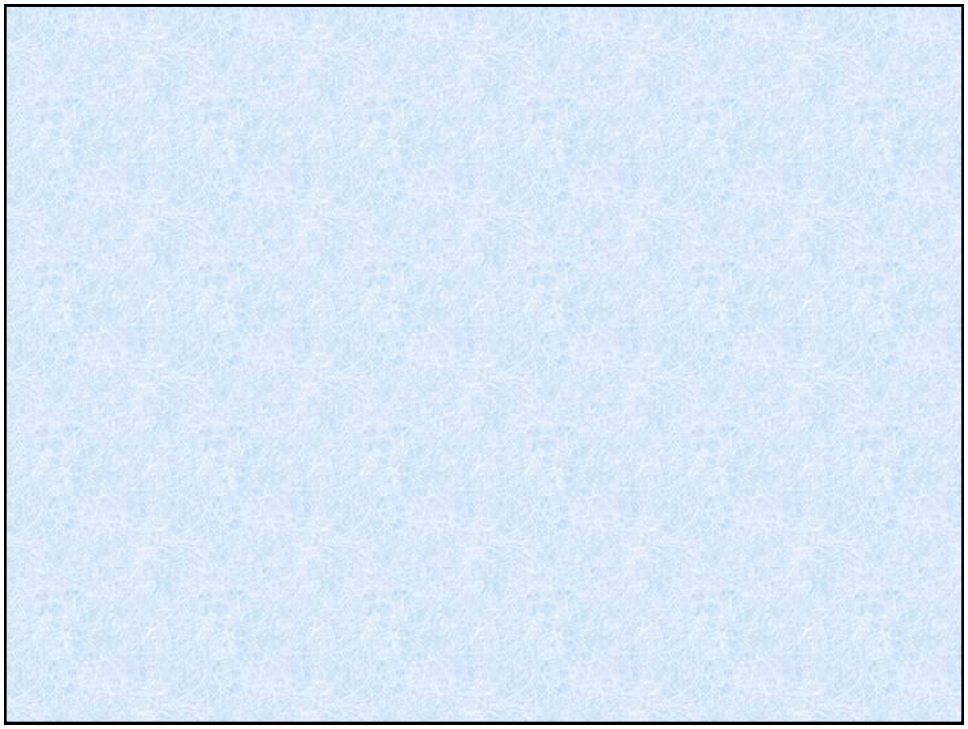
Epidemiologia

- Tra il 2005-2017 sono state segnalate 803 NPS per la prima volta attraverso l'Early Warning System
- Tra il 2008-2017 sono state segnalate 803 NPS in 102 Paesi facenti parte dell'UNODC
- Il 19% dei Paesi ha identificato più di 100 NPS sul proprio territorio
- Lo studio Flash Eurobarometer (14-24 aa) del 2014 ha evidenziato che la prevalenza media lifetime di uso di NPS è dell'8% (0% in Polonia / 9.7% in Irlanda) conto il 3% del 2011
  - UNODC, 2018; EMCDDA, 2018


GLOBAL EMERGENCE OF NEW PSYCHOACTIVE SUBSTANCES
UP TO JULY 2012
Number of countries and territories
Yes
No


New psychoactive substances notified to the EU Early Warning System for the first time 2005-17: number per year (left) and total number per category (right)
13
7
15
13
24
41
48
74
81
101
98
66
51
2005
2010
2015
2017
127
27
7
4
14
13
35
23
16
38
179
77
72
Other substances
Aminoindanes
Plants and extracts
Piperazines
Piperidines and pyrrolidines
Arylcyclohexylamines
Benzodiazepines
Tryptamines
Arylalkylamines
Opioids
Phenethylamines
Cathinones
Synthetic cannabinoids


Number of deaths
25
20
15
10
5
0
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
Methiopropamine, alpha-methyltryptamine and novel benzodiazepines are involved in the most legal high deaths in 2013, now that piperazines and cathinones are illegal and so excluded
Piperazines banned
Cathinones banned
Piperazines were involved in nearly all legal high deaths in 2008 and 2009
Mephedrone is most commonly involved in legal high deaths in 2010



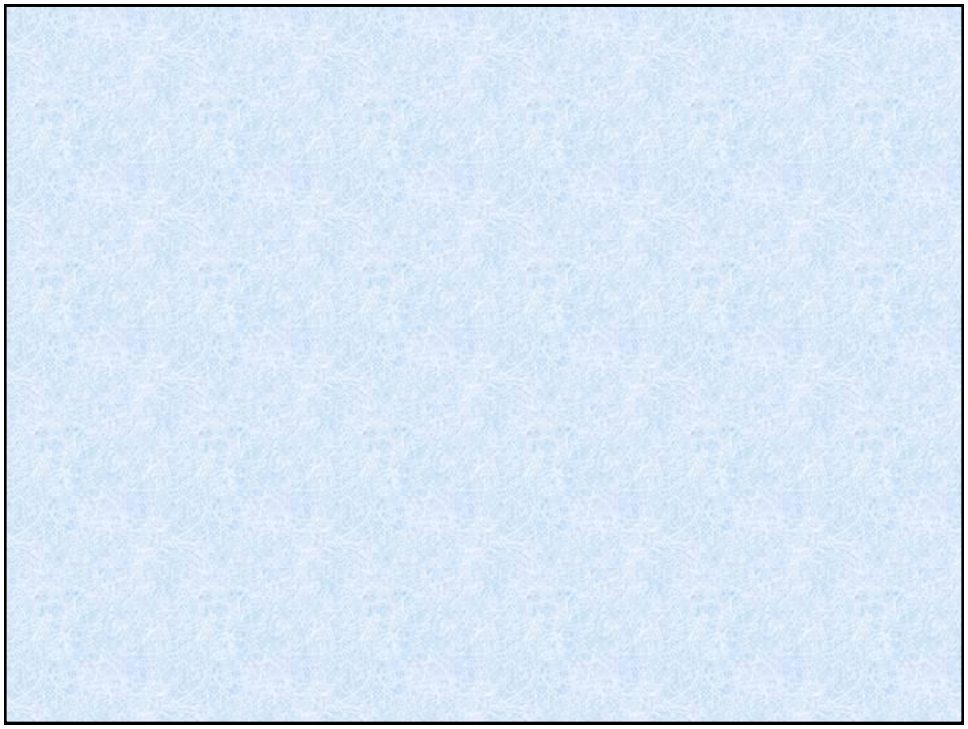
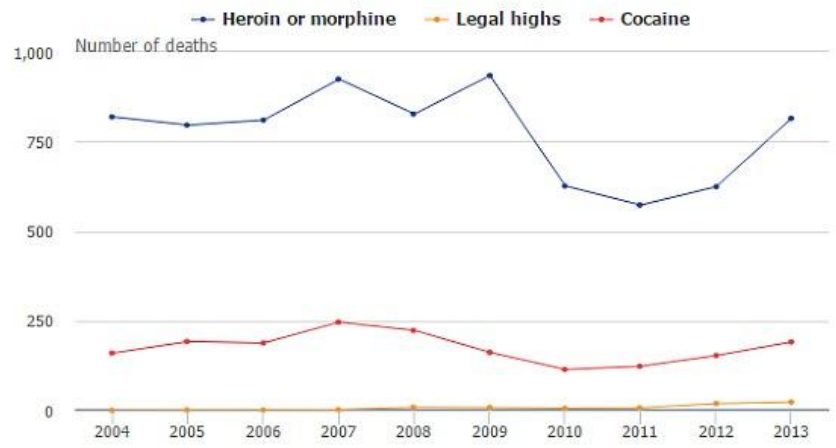
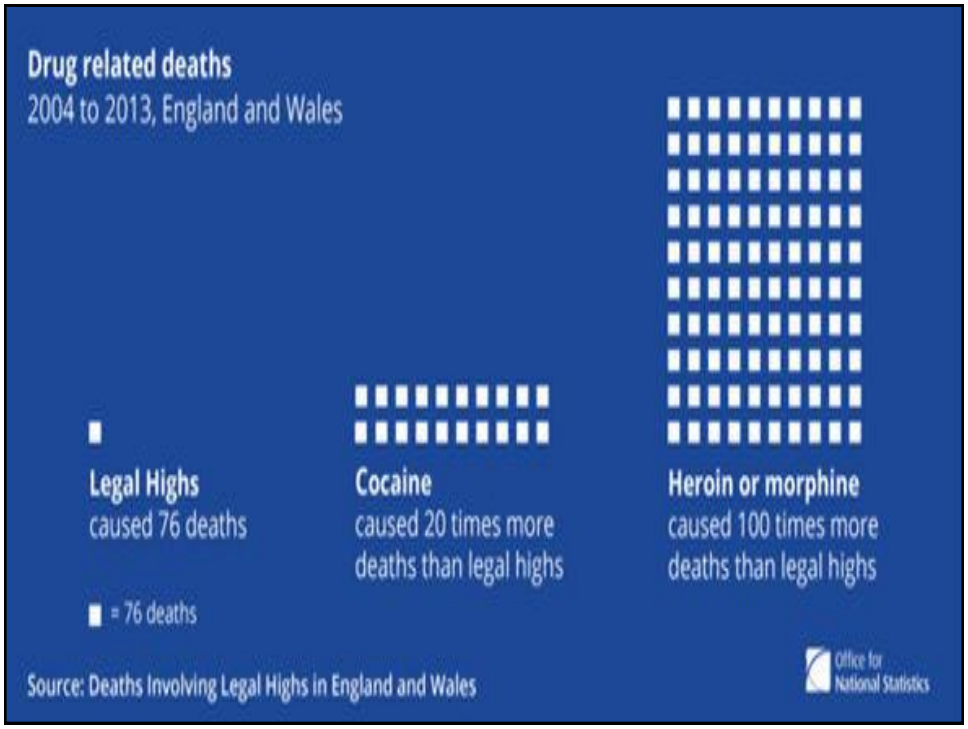


Figure 1: Number of deaths involving selected substances occurring between 2004 and 2013

England and Wales



Source: Office for National Statistics


Drug related deaths
2004 to 2013, England and Wales
Legal Highs
caused 76 deaths
Cocaine
caused 20 times more
deaths than legal highs
Heroin or morphine
caused 100 times more
deaths than legal highs
= 76 deaths
Source: Deaths Involving Legal Highs in England and Wales
Office for National Statistics

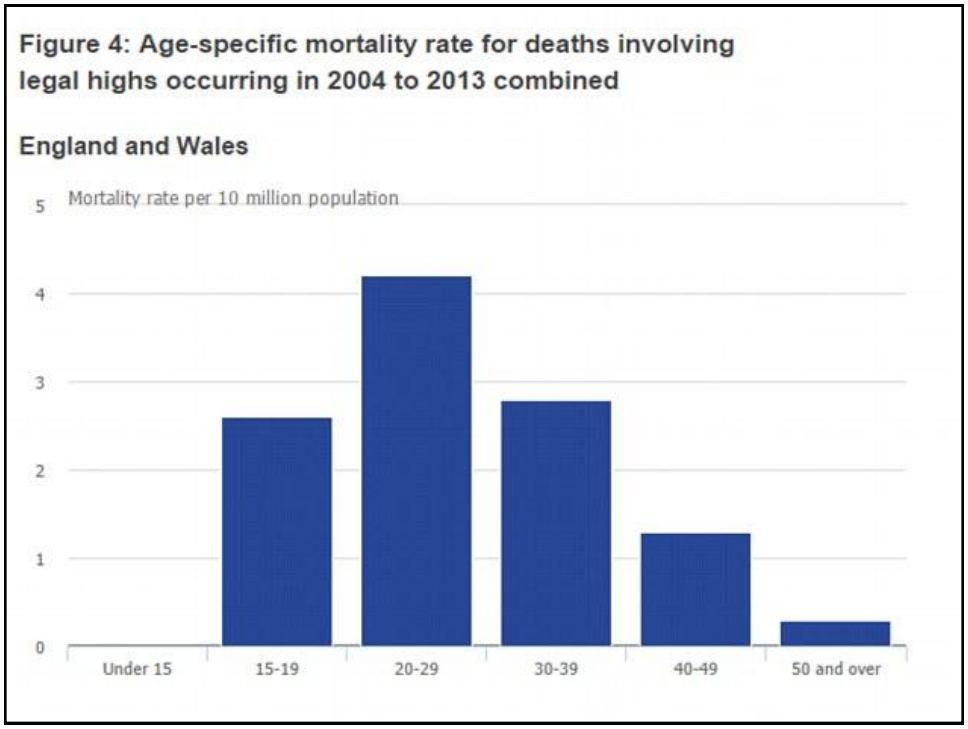
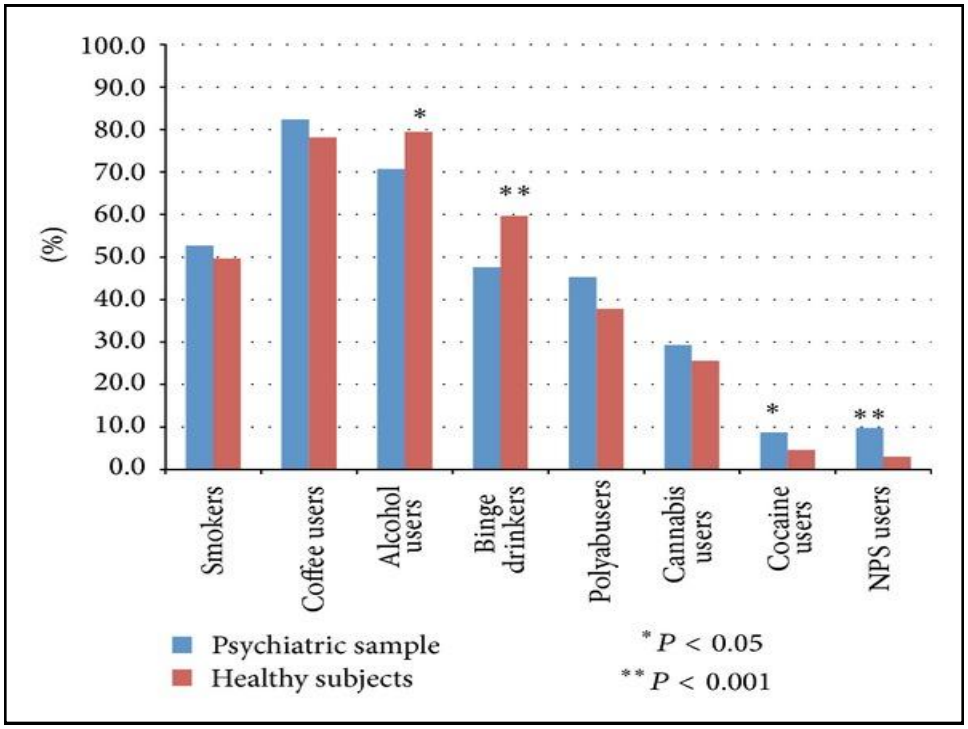
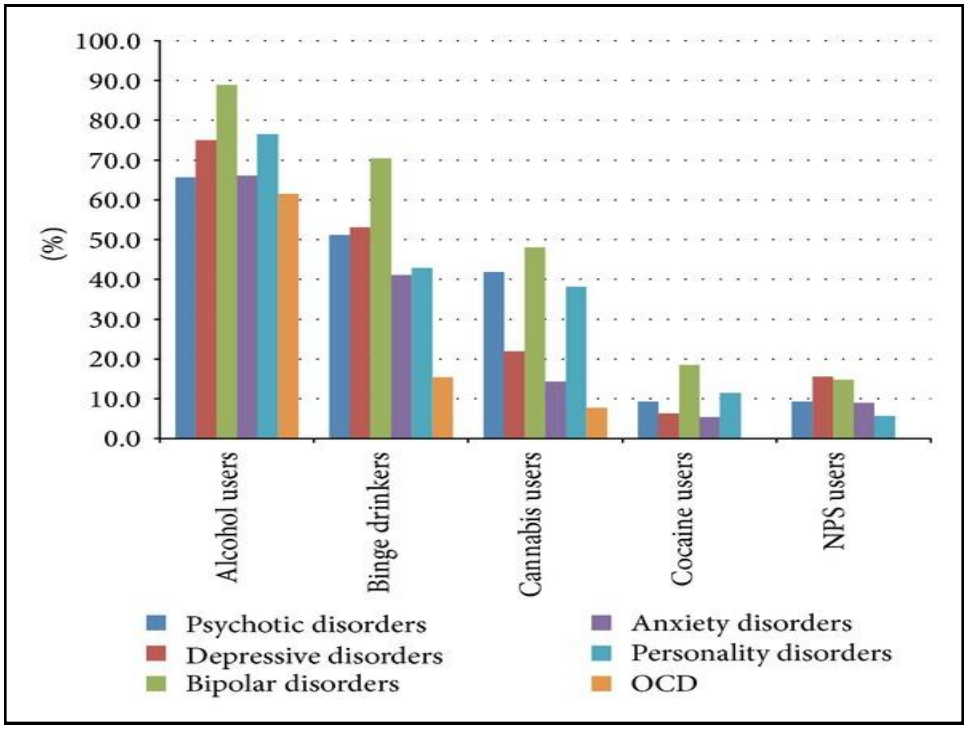


Figure 4: Age-specific mortality rate for deaths involving legal highs occurring in 2004 to 2013 combined
England and Wales
Mortality rate per 10 million population
5
4
3
2
1
0
Under 15
15-19
20-29
30-39
40-49
50 and over


100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
(%)
*
**
*
**
Smokers
Coffee users
Alcohol users
Binge drinkers
Polyabusers
Cannabis users
Cocaine users
NPS users
Psychiatric sample
Healthy subjects
* P < 0.05
** P < 0.001


100.0
90.0
80.0
70.0
60.0
50.0
40.0
30.0
20.0
10.0
0.0
(%)
Alcohol users
Binge drinkers
Cannabis users
Cocaine users
NPS users
Psychotic disorders
Depressive disorders
Bipolar disorders
Anxiety disorders
Personality disorders
OCD

Perché sono pericolose

- Il vero pericolo legato alle NSP è costituito dalla combinazione: sostanza sconosciuta, mercato alternativo, marketing innovativo.
- Complessivamente, ci troviamo ad affrontare un cambiamento storico nel consumo di sostanze ricreative con enormi interrogativi sugli effetti in acuto e a lungo termine, interrogativi sulla prevenzione e sul controllo, interrogativi sugli approcci terapeutici, e sulle complicanze psicopatologiche.

Perché sono così popolari?

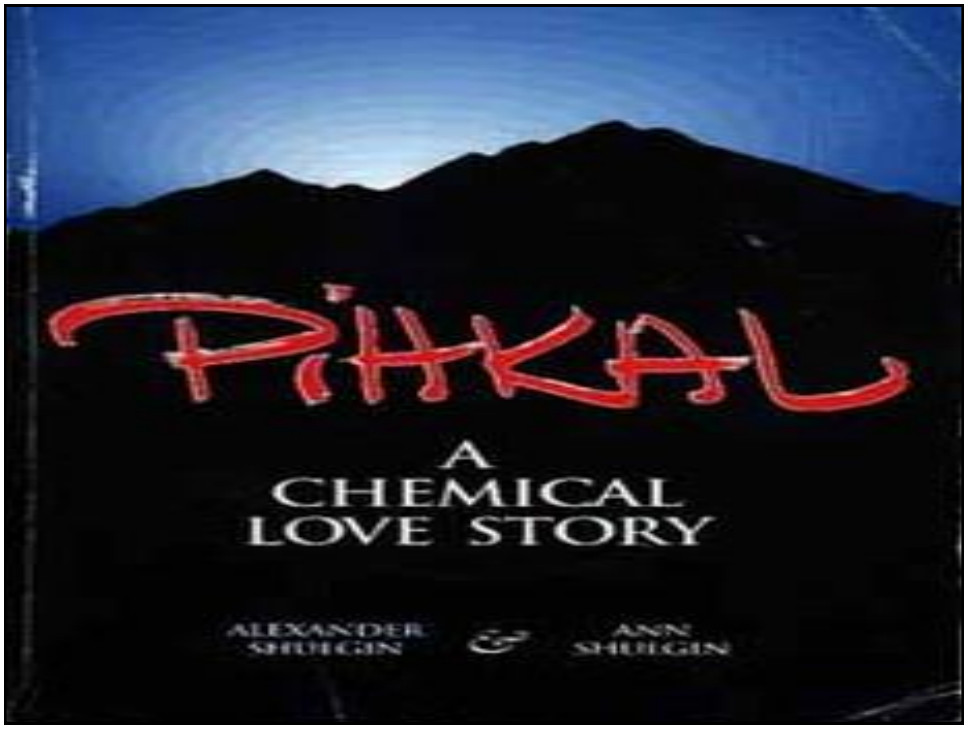
- Sono legali.
- Mimano gli effetti delle droghe tradizionali ed illecite (Xtacy per l' ecstasy).
- Danno un senso di sicurezza perché sono spesso vendute come derivati vegetali, spezie, fertilizzanti per piante, sali da bagno.

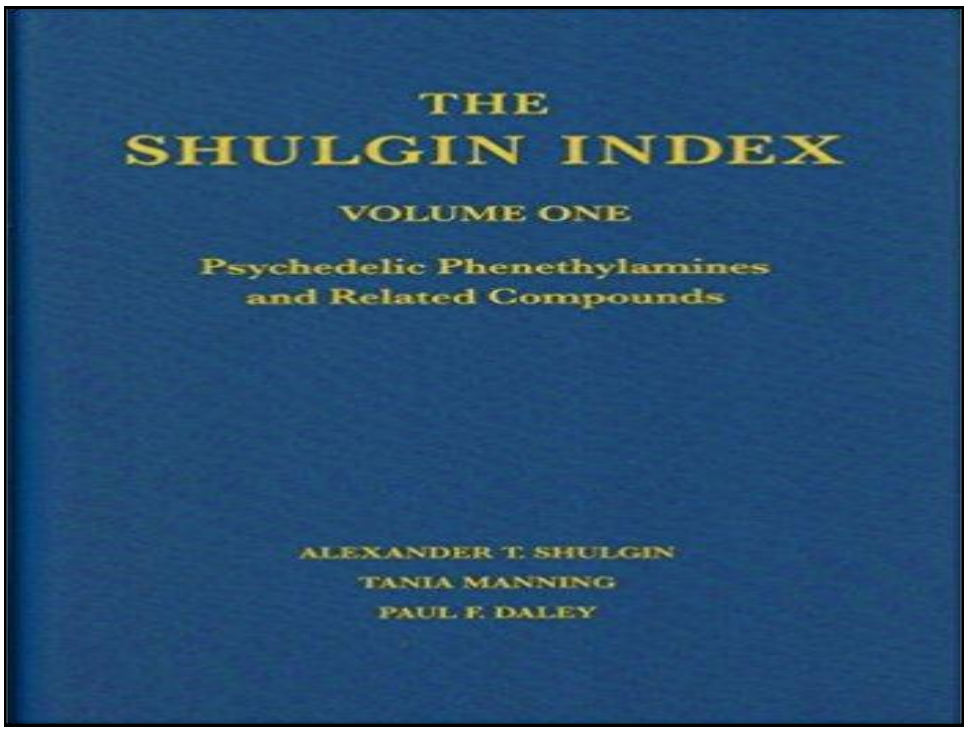
- EMCDDA, 2013; Kapka-skrzypczak et al, 2011

Come si diffondono?

- Smart or Head shops sul territorio
- Internet shops
- Research chemical stores
  - Vardakou et al., 2011;Davies et al., 2010;

- Internet shops (sono passati da 170 del gennaio 2010 a 693 del gennaio 2012. Le sostanze più vendute: kratom, salvia divinorum, hallucinogenic mushrooms, methoxetamine, 3,4-methylenedioxypyrovalerone (MPDV) 5,6-methylenedioxy-2-aminoindane (MDAI), and 5-iodo-2-aminoindan)
  - EMCDDA 2015


PiHKAL
A
CHEMICAL
LOVE STORY
ALEXANDER
SHULGIN
&
ANN
SHULGIN


THE
SHULGIN INDEX
VOLUME ONE
Psychedelic Phenethylamines
and Related Compounds
ALEXANDER T. SHULGIN
TANIA MANNING
PAUL F. DALEY

Alexander and Ann Shulgin

PIEMONTE

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AREA ARTIGIANALE CONTI 15 - 10060 - GARZIGLIANA - TO
0121341186 - info@indoorline.com - www.indoorline.com/www.indoorlinepoint.com

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VIA SAN GIUSEPPE 3 - 13900 - BIELLA - BI
3394499243 - traversodavide@fastwebnet.it - www.indoorlinepoint.com

KUSH 011 (H)
VIA S.GIULIA 7 - 10124 - TORINO - TO
0118122047 - davidejazzbiandh@gmail.com

L'ERBACCIA GROWSHOP (G H)
VIA ROMBO' 27/D - 10098 - RIVOLI TORINESE - TO
3483643383 - erbaccia2015@gmail.com

NEW BIOGROUP (G H)
VIA TORTONA 88 - 15121 - ALESSANDRIA - AL
3403181117 - newbiogroup@gmail.com - www.newbiogroup.com

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VIA SEMPIONE 5 - 13100 - VERCELLI - VC
3206405561 - newbiogroup.vercelli@gmail.com - www.newbiogroup.com

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VIA POLVERIERA 8 - 10042 - NICHELINO - TO
3407359470 - newbiogroup.torino@gmail.com - www.newbiogroup.com

NEW BIOGROUP ALBA (G H)
CORSO BRA 52/F - 12051 - ALBA - CN
3911512507 - newbiogroupalba@gmail.com - www.newbiogroup.com

OSHO'P GROWSHOP (G H C)
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011 4277094 - oshoptorino@gmail.com - www.growshoptorino.com

PANORAMIX (WIPE OUT) (G H C)
VIA XX SETTEMBRE 84/B - 14100 - ASTI - AT
0141321044 - tezzani@yahoo.it - www.growinitaly.com

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011 4367078 - tezzani@yahoo.it - www.growinitaly.com

PANORAMIX TORINO (G H C)
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011 6980782 - tezzani@yahoo.it - www.growinitaly.com

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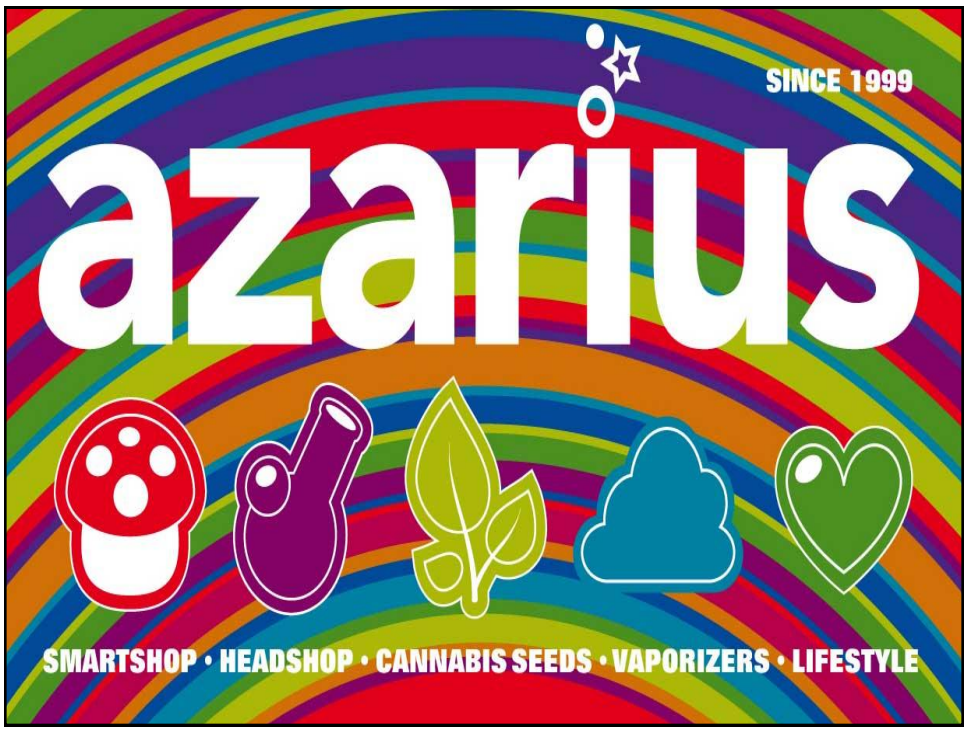
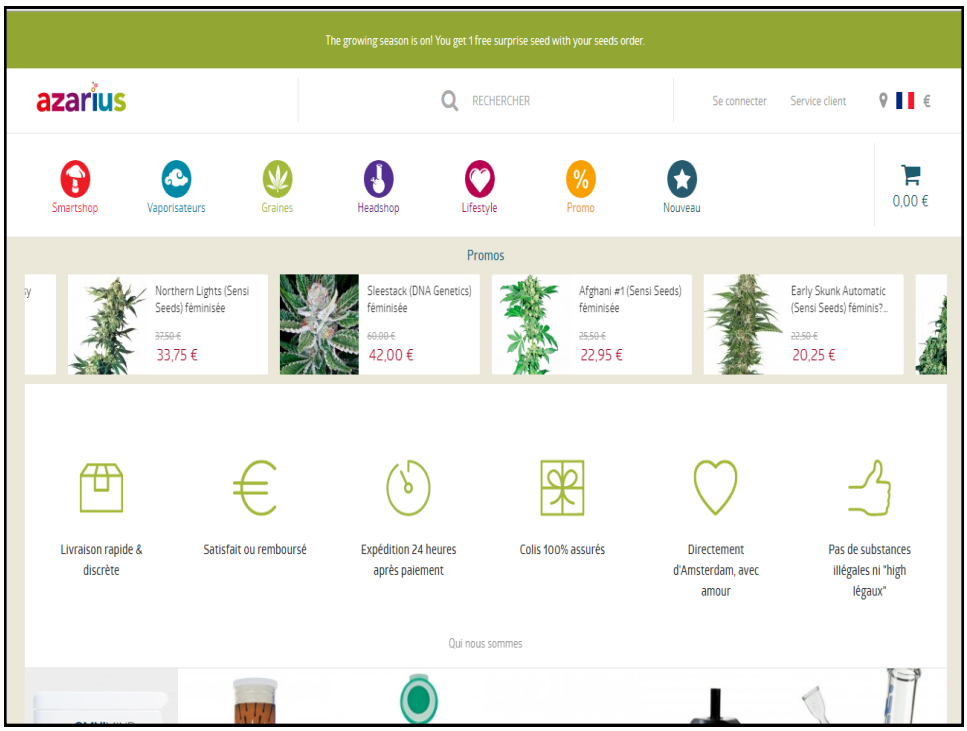
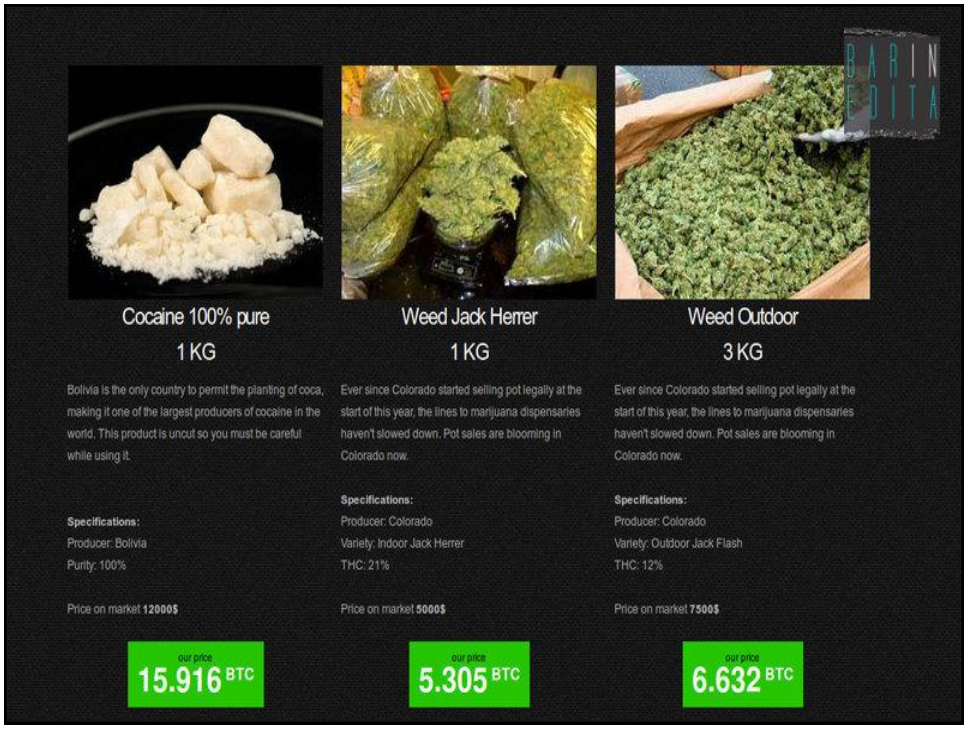
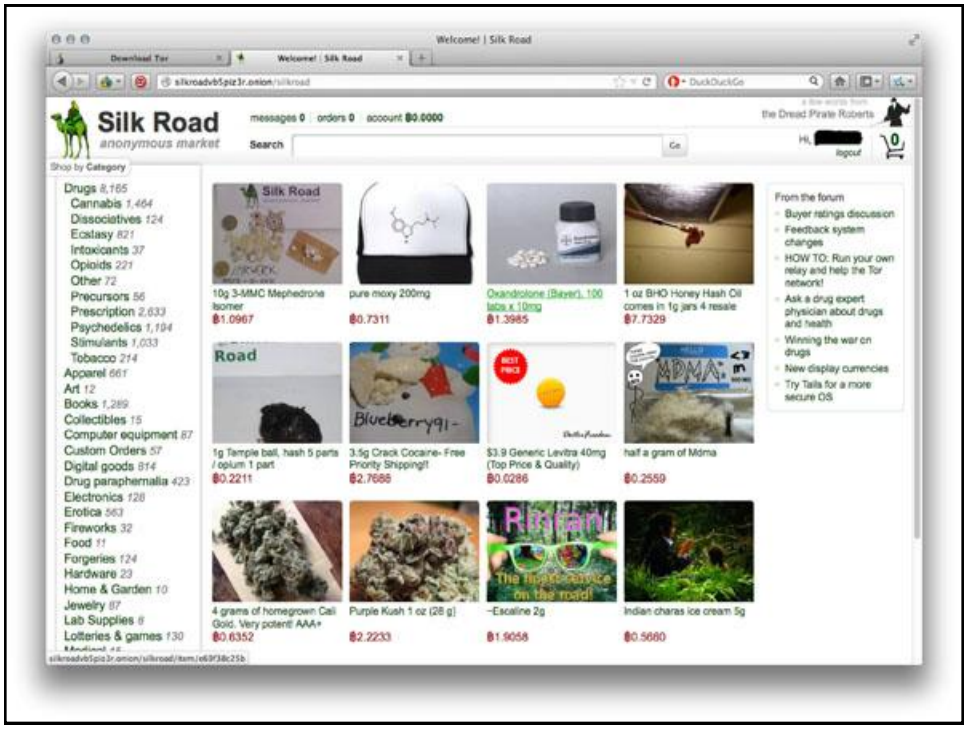
3388647208 - info@theseedside.com - www.theseedside.com




www.azarius.net
azarius
Smartshop
Vaporizers
Herbs & Seeds
.com


The growing season is on! You get 1 free surprise seed with your seeds order.
azarius
RECHERCHER
Se connecter
Service client
Smartshop
Vaporisateurs
Graines
Headshop
Lifestyle
Promo
Nouveau
0,00 €
Promos
Northern Lights (Sensi Seeds) féminisée
33,75 €
Sleestack (DNA Genetics) féminisée
42,00 €
Afghani #1 (Sensi Seeds) féminisée
22,95 €
Early Skunk Automatic (Sensi Seeds) féminis?..
20,25 €
Livraison rapide & discrète
Satisfait ou remboursé
Expédition 24 heures après paiement
Colis 100% assurés
Directement d'Amsterdam, avec amour
Pas de substances illégales ni "high légaux"
Qui nous sommes


BARIN EDITA
Cocaine 100% pure
1 KG
Bolivia is the only country to permit the planting of coca, making it one of the largest producers of cocaine in the world. This product is uncut so you must be careful while using it.
Specifications:
Producer: Bolivia
Purity: 100%
Price on market 12000$
our price
15.916 BTC
Weed Jack Herrer
1 KG
Ever since Colorado started selling pot legally at the start of this year, the lines to marijuana dispensaries haven't slowed down. Pot sales are blooming in Colorado now.
Specifications:
Producer: Colorado
Variety: Indoor Jack Herrer
THC: 21%
Price on market 5000$
our price
5.305 BTC
Weed Outdoor
3 KG
Ever since Colorado started selling pot legally at the start of this year, the lines to marijuana dispensaries haven't slowed down. Pot sales are blooming in Colorado now.
Specifications:
Producer: Colorado
Variety: Outdoor Jack Flash
THC: 12%
Price on market 7500$
our price
6.632 BTC


Welcome! | Silk Road
Silk Road
anonymous market
Search
Drugs 8,165
Cannabis 1,464
Dissociatives 124
Ecstasy 821
Intoxicants 37
Opioids 221
Other 72
Precursors 56
Prescription 2,633
Psychedelics 1,194
Stimulants 1,033
Tobacco 214
Apparel 661
Art 12
Books 1,289
Collectibles 15
Computer equipment 87
Custom Orders 57
Digital goods 814
Drug paraphernalia 423
Electronics 128
Erotica 563
Fireworks 32
Food 11
Forgeries 124
Hardware 23
Home & Garden 10
Jewelry 87
Lab Supplies 8
Lotteries & games 130
10g 3-MMC Mephedrone Isomer
฿1.0967
pure moxy 200mg
฿0.7311
Oxandrolone (Biyer), 100 tabs x 10mg
฿1.3985
1 oz BHO Honey Hash Oil comes in 1g jars 4 resale
฿7.7329
1g Temple ball, hash 5 parts / opium 1 part
฿0.2211
3.5g Crack Cocaine- Free Priority Shipping!!
฿2.7686
$3.9 Generic Levitra 40mg (Top Price & Quality)
฿0.0286
half a gram of Mdma
฿0.2559
4 grams of homegrown Cali Gold. Very potent! AAA+
฿0.6352
Purple Kush 1 oz (28 g)
฿2.2233
~Escaline 2g
฿1.9058
Indian charas ice cream 5g
฿0.5660
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Try Tails for a more secure OS

Kit germinazione 12 Jiffy


Bio Vega
Bio RHIZOTONIC
Bio Flores
Bio BOOST


FREE
SPESA DI SPEDIZIONE 3.50€
GRATUITA PER ORDINI DA 49€
BARNEY'S FARM
Buddha seeds
CBD CREW
Delicious Seeds
DINAFEM
DNA GENETICS AMSTERDAM
DUTCH PASSION SEED COMPANY
Humboldt Seed Organization
Lowryder
KANNABIA Seed Company
KC Brains Holland
MINISTRY OF CANNABIS
NIRVANA
PARADISE SEEDS
DYNASTY
ROYAL QUEEN SEEDS
SEEDS OF LIFE
SAM SEEDS
Serious Seeds
SOMAS SACRED SEEDS
STRAIN HUNTERS
WORLD of SEEDS
Novità 2016
Autofiorenti
Semi CBD
IN OFFERTA

Bilancia elettronica

- **Descrizione:**
  La Bilancia elettronica più Resistente e Stabile a scapito delle dimensioni:
  - pesa fino a 500g con una precisione di 0,1g.

  Informazione:
  E' la Bilancia elettronica più resistente!
  Disponibile nei colori nero e argento.
  Display retroilluminato, piatto di pesata in acciaio inossidabile, chiusura di protezione e protezione da sovraccarico.

- **VapBong vaporizzatore portatile Descrizione:**
  VAPBONG è il non-plus-ultra tra i vaporizzatori portatili!
  I vaporizzatori consentono di estrarre il 97/98% del principio attivo della sostanza desiderata!
  Se confrontato ad un metodo per combustione, tramite il quale si estrae circa il 30% di principio attivo il resto brucia, si intuisce la validità del Vaporizzatore!!!

  Funzionamento:
  Il funzionamento è semplice ed efficace. **Il suo utilizzo permette di estrarre i principi attivi delle piante tramite un flusso di aria calda,** ma senza arrivare alla combustione. Il vapore che viene inalato contiene tutto ciò che una pianta può offrire, evitando però i residui tossici dovuti alla combustione. VapBong è realizzato interamente a mano utilizzando vetro borosilicato di alto livello (3.3), che permette una facile pulitura ed un alto livello di igiene. La qualità ottenuta dall'utilizzo del VapBong è paragonabile solo a quella di vaporizzatori fissi dal costo estremamente più elevato. Il finto pennarello permette di trasportarlo in tutta sicurezza.

  Contenuto:
  Il Kit comprende:
  n°1 vaporizzatore portatile VAPBONG
  n°1 tubo in vetro borosilicato esterno
  n°1 finto evidenziatore da usarsi come custodia / nascondiglio

ebay Motors

- Item condition:**New**Compatibility: This information is not available.Time left:4h 44m 19s (Sep 12, 201008:31:58 PDT)Bid history:0 bids[Refresh bidhistory]**Starting bid:US $13.99Your maximum bid:**US $(Enter US $13.99 or more)**Add to Watch list**Sign in for more lists**End of panel**Returns:No Returns AcceptedShipping:**FREE shipping** Standard Flat Rate Shipping Service See more services See discounts **See all details** Estimated delivery time varies.
-


LRG


AdvancedNutrients


NEWS 13
CHANNEL

J Burn Care Res. 2015 Mar-Apr;36(2):e34-7. doi: 10.1097/BCR.0000000000000067.

Honey oil burns: a growing problem.

Jensen G[1], Bertelotti R, Greenhalgh D, Palmieri T, Maguina P.

Author information

Abstract

There is an emerging mechanism of burn injury as a result of the ignition of butane, during the manufacture of a concentrate known as butane honey oil. The authors report of a series of patients who presented with this mecha description of the process that causes these burns. Patient data were gathered from the medical records of eight University of California Davis Medical Center and Shriners Hospital of Northern California. Information on the ma butane honey oil was gathered from Internet searches and published literature on the topic. The burns witnessed institutions ranged from 16 to 95% TBSA, with an average of 49.9%. The average length of stay for the patients w 114.4 intensive care unit days, with an average of 43.8 days spent on mechanical ventilation. The average age of only one patient above the age of 30 years. Accidents during honey oil production have resulted in a surge of burn during the past year. The manufacture of this product, which involves the use of volatile butane gas, is gaining in p considered to be safer than previous methods. multiple casualties with extensive burn injuries have resulted from t injuries from blast trauma or chemical burns are not likely to occur in these types of explosions and have not been reported in this article. In light of the increasing popularity of honey oil, it is important for burn care providers to gain understanding of this problem and its growing epidemiology.

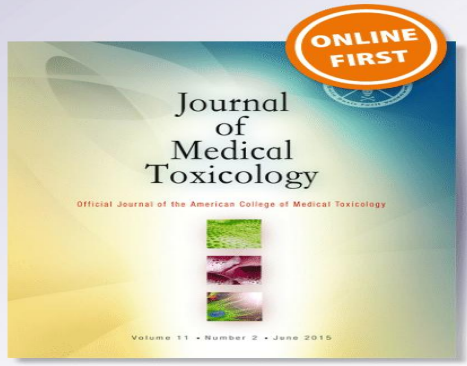
Butane Hash Oil Burns Associated with Marijuana Liberalization in Colorado

Cameron Bell, Jessica Slim, Hanna K. Flaten, Gordon Lindberg, Wiktor Arek & Andrew A. Monte

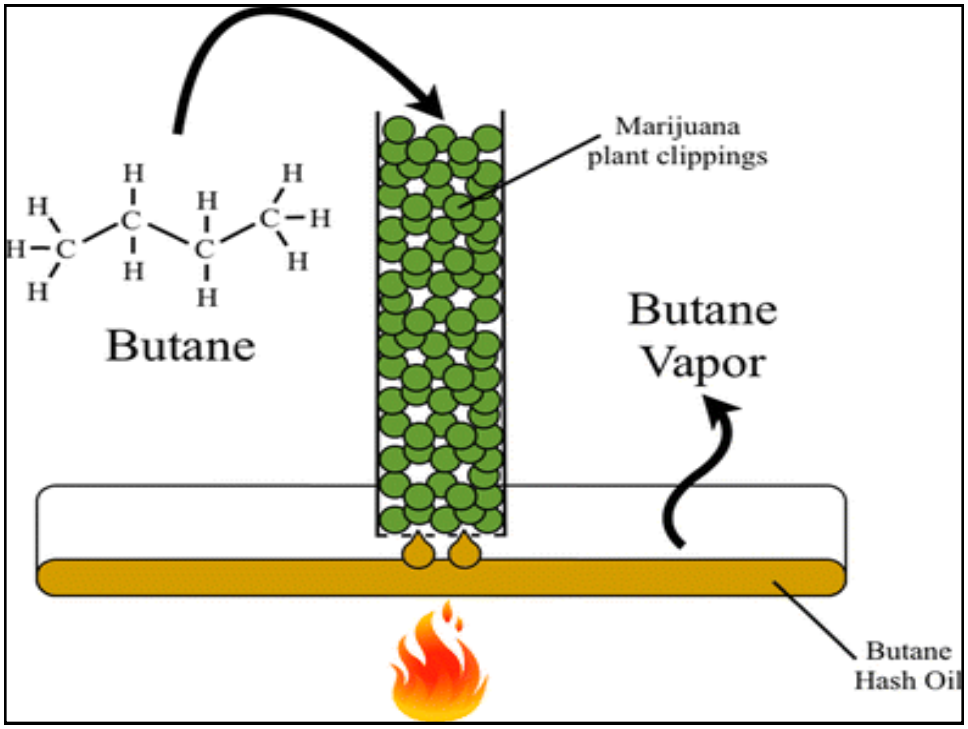
Journal of Medical Toxicology

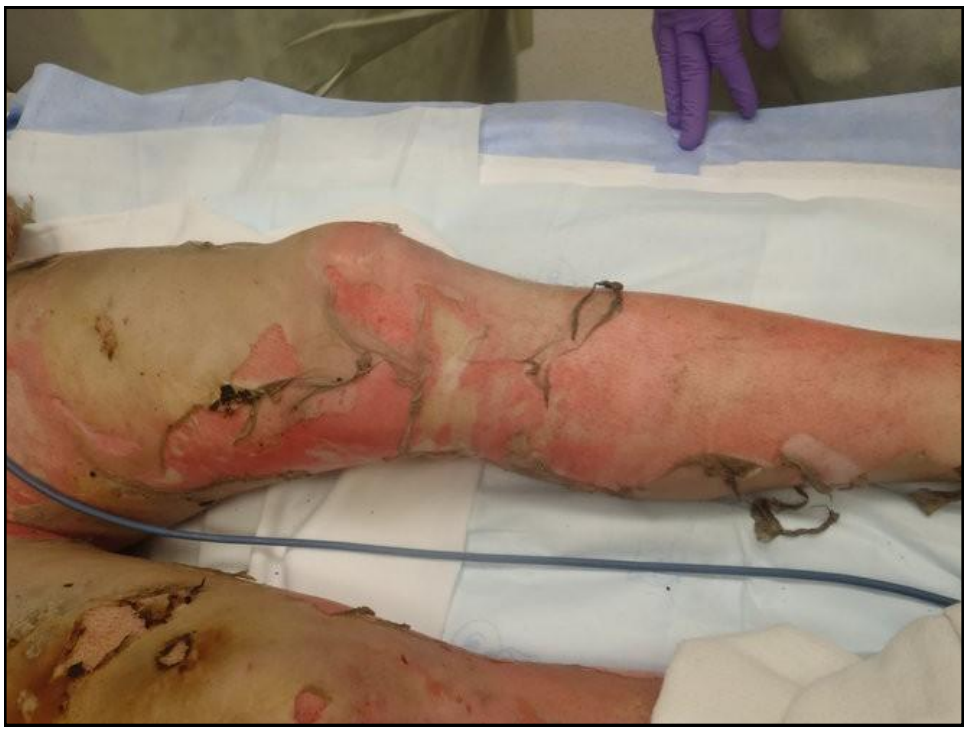
ISSN 1556-9039

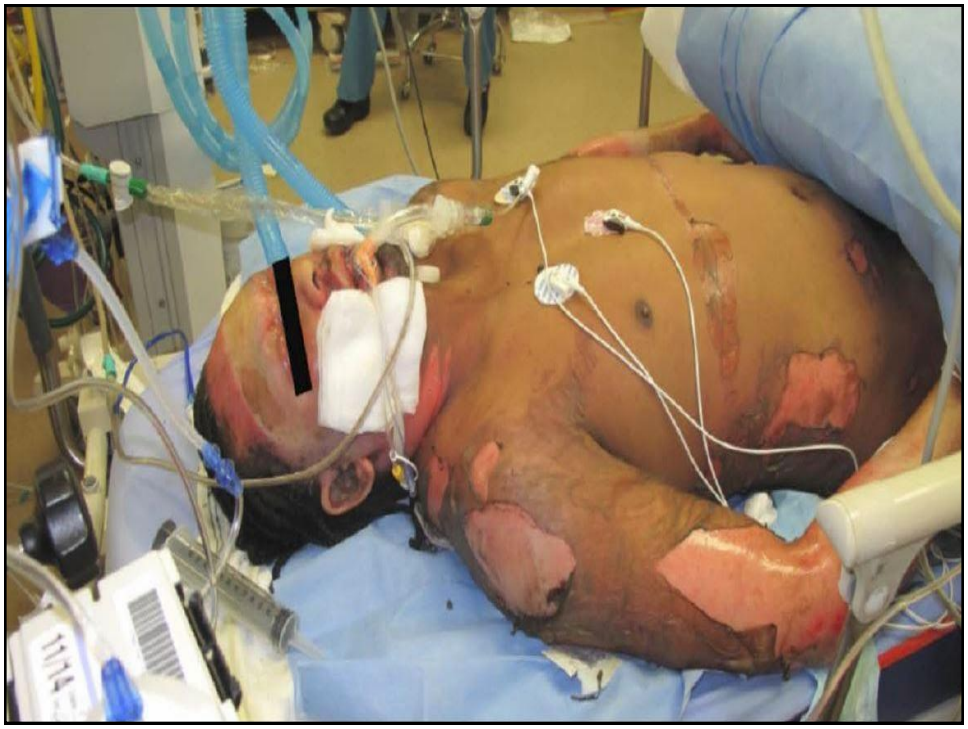
J. Med. Toxicol.
DOI 10.1007/s13181-015-0501-0



Springer

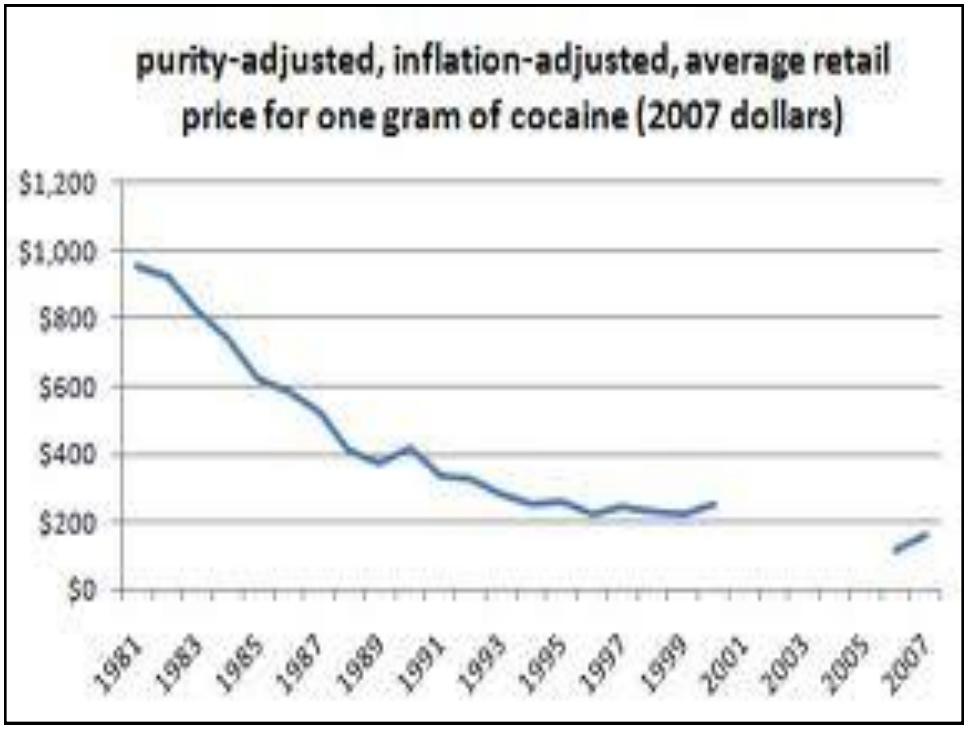

Marijuana
plant clippings
Butane
Butane
Vapor
Butane
Hash Oil






LE IENE
UNO SBALLO ESPLOSIVO
avevo ustioni di secondo e di terzo grado

Cosa si vende?



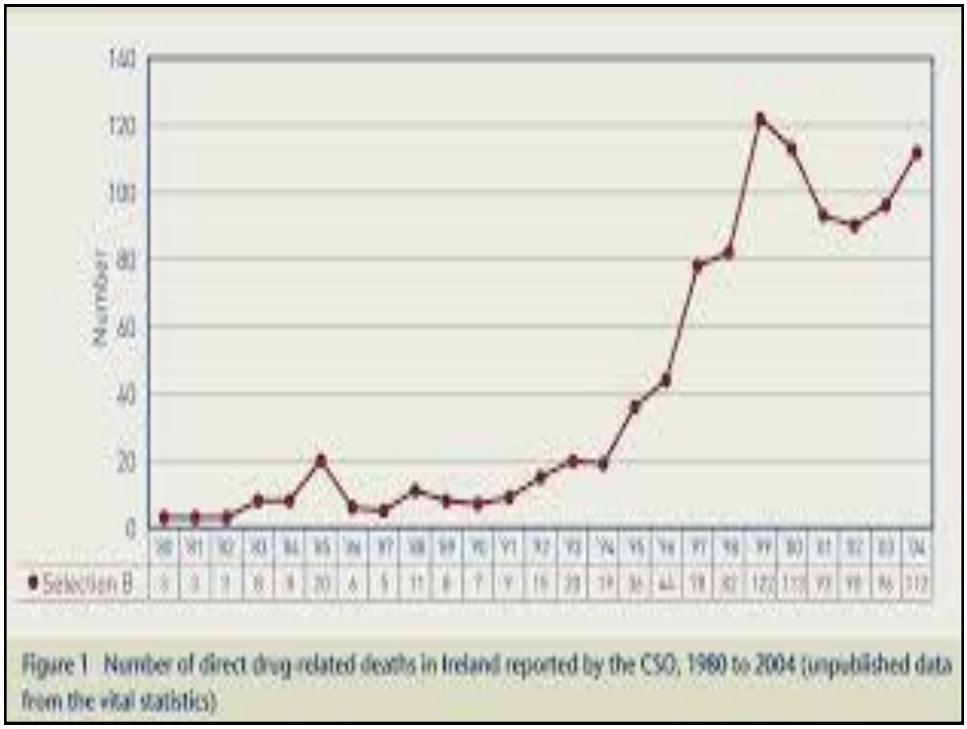


Figure 1 Number of direct drug-related deaths in Ireland reported by the CSO, 1980 to 2004 (unpublished data from the vital statistics)

- Cocaina/atropina

- Aumento del rischio di danni cardiaci.
- Il diazepam potrebbe avere attività protettiva

  - Braida D. et al. J Pharmacol Sci. 2008

- Cocaina/levamisolo (tetramisolo)
- Il 4 metil aminorex ha azione simil anfetaminica

  - Chang A. Clin Pharmacol Ther. 2010

- Il levamisolo determina neutropenia e vasculiti necrotizzanti, danno renale

  - Walsh N.M. et al:J Cutan Phatol. 2010

Hindawi Publishing Corporation
Case Reports in Rheumatology
Volume 2016, Article ID 2685267, 4 pages
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Case Report

Cutaneous Necrotizing Vasculitis and Leukopenia in a Cocaine User: Is Levamisole the Culprit?

Lara El Khoury,[1] Nabil Zeineddine,[1] Richard Felix,[2] and Mark Goldstein[3]

[1]*Internal Medicine Department, Staten Island University Hospital, 475 Seaview Avenue, Staten Island, New York, NY 10305, USA*
[2]*Pathology Department, Staten Island University Hospital, 475 Seaview Avenue, Staten Island, New York, NY 10305, USA*
[3]*Rheumatology Department, Staten Island University Hospital, 475 Seaview Avenue, Staten Island, New York, NY 10305, USA*

Correspondence should be addressed to Lara El Khoury; laraelkhoury.md@gmail.com

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Levamisole is an antihelminthic drug banned by the US Food and Drug Administration (FDA) in 2000 because of its dangerous side effects. Over the past few years, it has been identified as an adulterant in cocaine and reported to cause cutaneous vasculitis in cocaine users. The health burden of levamisole is serious since it is estimated that over 5 million Americans use cocaine and that 70% of the cocaine used in the USA contains levamisole. In this paper we report the case of a 23-year-old female cocaine user that presented with purpuric rash and skin necrosis, found to have positive c-ANCA and anti-proteinase 3 antibodies. Her skin biopsy showed fibroconnective tissue with signs of necrosis, acute and chronic inflammation, and thrombus formation. She was diagnosed with levamisole-induced vasculitis and successfully treated with withdrawal of cocaine use and local wound care.

1. Introduction

Levamisole is a veterinary antihelminthic drug that was initially approved for the treatment of several conditions including certain malignancies and rheumatoid arthritis [1, 2].

In 2000, the US Food and Drug Administration (FDA) banned the use of levamisole in the United States (US) because of dangerous side effects such as agranulocytosis and skin necrosis [3, 4].

Over the past few years, levamisole has been identified as an adulterant in cocaine, used to add weight and volume to the drug. Since 2010, numerous reports have emerged describing cutaneous vasculitis in cocaine users.

We describe a case of a 25-year-old female patient, cocaine user, presenting with painful dark discoloration of lower extremities.

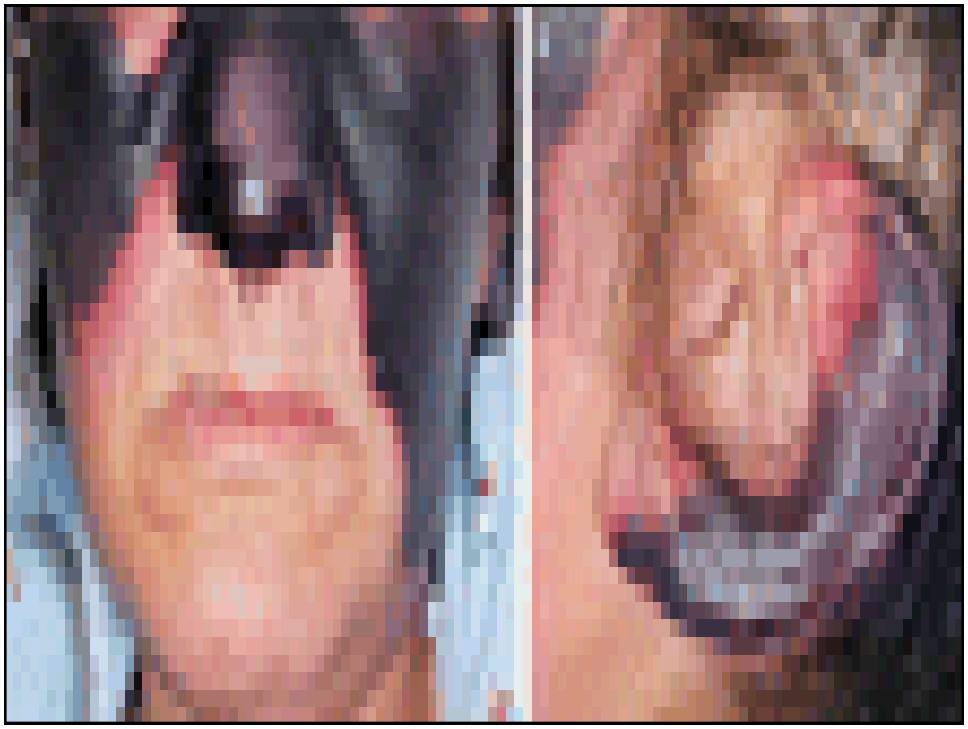
2. Case Presentation

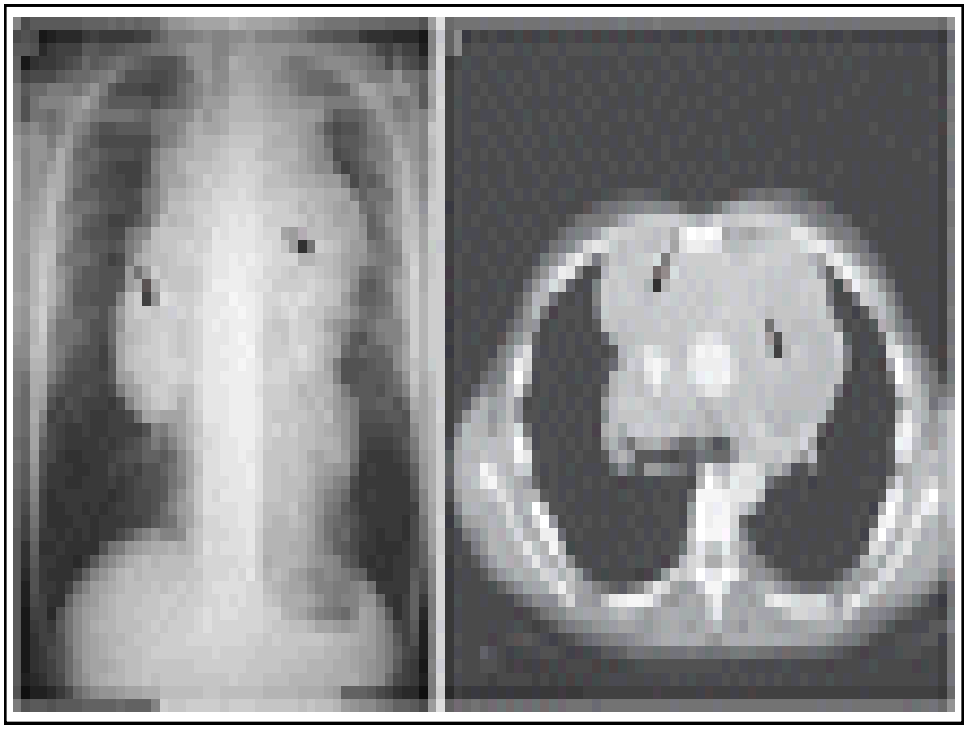
A 23-year-old African-American female patient presented to the hospital for painful skin lesions over her lower extremities and neck.

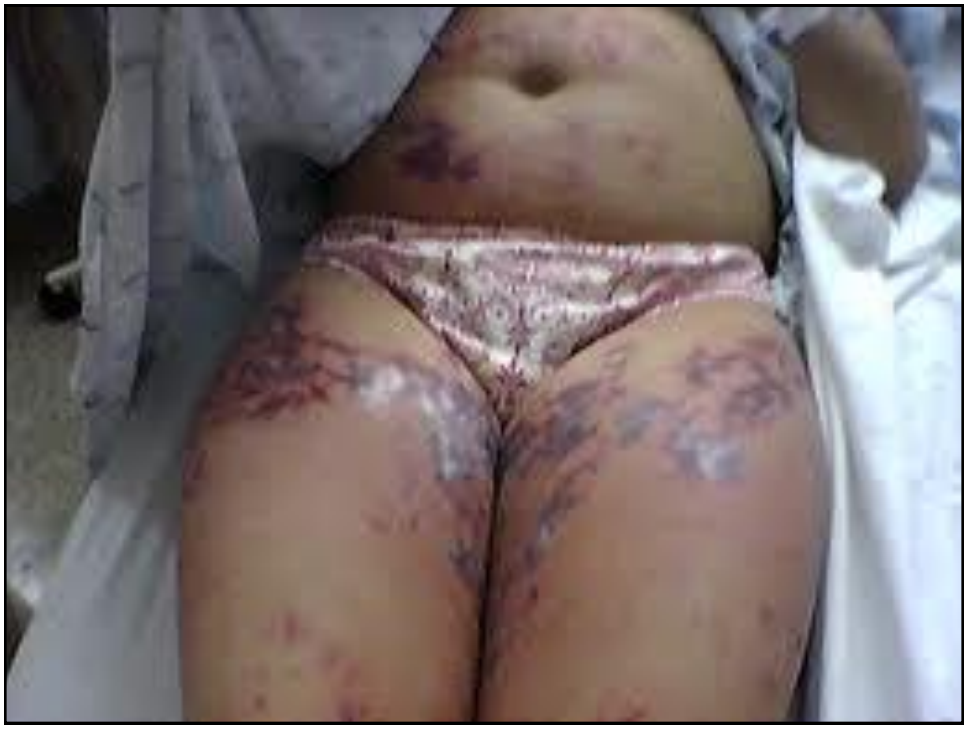
Her past medical history includes cocaine and heroin abuse and hepatitis C virus infection for which she never received any treatment. She smokes one pack of cigarettes and consumes 2–3 alcoholic drinks per day. Patient snorts cocaine on a daily basis, and her last use of cocaine occurred one day prior to her presentation.

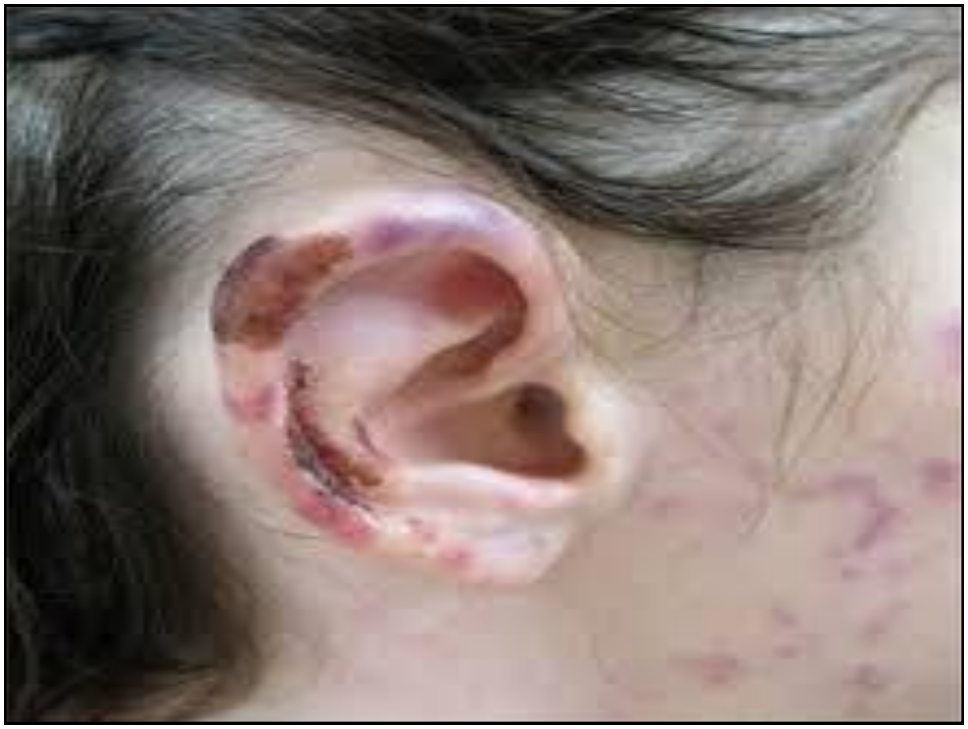
The onset of the skin lesions was acute, started seven days prior to presentation, when she started complaining of burning sensation over the anterior shins and retroauricular areas.

On presentation, patient had a temperature of 99.7 F, blood pressure of 118/67 mmHg, heart rate of 90/min, and respiration rate of 16/min. On physical exam, she had marks of prior needle injections over bilateral arms and forearms. She had hyperpigmented skin lesions over the nape of the neck, retroauricular areas, with palpable collection beneath the skin at the posterior aspect of the neck. Examination also revealed the presence of numerous, bilateral, anterior, and posterior lower extremities skin lesions, of varying sizes, purplish in color with erythematous border, nonblanching, tender, with necrotic center (Figures 1, 2, and 3). Oral mucous membranes were normal, and the rest of the physical exam was unremarkable.









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Aminorex, a metabolite of the cocaine adulterant levamisole, exerts amphetamine like actions at monoamine transporters

Tina Hofmaier [a], Anton Luf [b], Amir Seddik [c], Thomas Stockner [a], Marion Holy [a], Michael Freissmuth [a], Gerhard F. Ecker [c], Rainer Schmid [b], Harald H. Sitte [a,*], Oliver Kudlacek [a]

[a] Institute of Pharmacology, Center for Physiology and Pharmacology, Medical University of Vienna, Waehringerstrasse 13A, 1090 Vienna, Austria
[b] Clinical Department of Laboratory Medicine, Medical University of Vienna, Waehringer Guertel 10-20, 1090 Vienna, Austria
[c] University of Vienna, Department of Medicinal Chemistry, Althanstrasse 14, 1090 Vienna, Austria

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ABSTRACT

Psychostimulants such as amphetamine and cocaine are illicitly used drugs that act on neurotransmitter transporters for dopamine, serotonin or norepinephrine. These drugs can by themselves already cause severe neurotoxicity. However, an additional health threat arises from adulterant substances which are added to the illicit compound without declaration. One of the most frequently added adulterants in street drugs sold as cocaine is the anthelmintic drug levamisole. We tested the effects of levamisole on neurotransmitter transporters heterologously expressed in HEK293 cells. Levamisole was 100 and 300-fold less potent than cocaine in blocking norepinephrine and dopamine uptake, and had only very low affinity for the serotonin transporter. In addition, levamisole did not trigger any appreciable substrate efflux. Because levamisole and cocaine are frequently co-administered, we searched for possible allosteric effects; at 30 μM, a concentration at which levamisole displayed already mild effects on norepinephrine transport it did not enhance the inhibitory action of cocaine. Levamisole is metabolized to aminorex, a formerly marketed anorectic drug, which is classified as an amphetamine-like substance. We examined the uptake-inhibitory and efflux-eliciting properties of aminorex and found it to exert strong effects on all three neurotransmitter transporters in a manner similar to amphetamine. We therefore conclude that while the adulterant levamisole itself has only moderate effects on neurotransmitter transporters, its metabolite aminorex may exert distinct psychostimulant effects by itself. Given that the half-time of levamisole and aminorex exceeds that of cocaine, it may be safe to conclude that after the cocaine effect "fades out" the levamisole/aminorex effect "kicks in".

1. Introduction

Monoamine transporters for serotonin (SERT), norepinephrine (NET) and dopamine (DAT) belong to the family of Na^+/Cl^--dependent neurotransmitter transporters and remove their substrates to end synaptic transmission (Kristensen et al., 2011). Apart from this physiological role, these transporters are the targets of illicit drugs like cocaine or amphetamines (Rothman and Baumann, 2003). Amphetamines lead to a reverse action of all of these transporters and to a number of other intracellular effects which actively increase the concentration of neurotransmitters in the synaptic cleft (Sitte and Freissmuth, 2010). In contrast, cocaine raises the synaptic concentration of monoamines by inhibiting the activity of these transporters. Both classes of compounds are sold on the street market for illicit drugs at the risk of the users because both the quality and identity of the purchased drugs are without any control. This situation is alleviated by the government-supported Viennese drug prevention project 'checkit! Check your drugs', which offers cost-free and anonymous analyses of drugs. Thereby drug consumers gain information about the contents of their drug as well as possible risks of those compounds. Importantly and often to the great surprise of the user, the purchased drug does not contain the compound under the name it was sold. Recently, a survey of unknown street drugs from the 'checkit!' project revealed that a combination of amphetamine and *m*-chlorophenylpiperazine (*m*CPP) was sold under the name of methylene-dioxymethamphetamine (MDMA, 'ecstasy'; (Rosenauer et al., 2013)). Hence, the combinations of

Abbreviations: SERT, serotonin transporter; NET, norepinephrine transporter; DAT, dopamine transporter; 5-HT, serotonin; DA, dopamine; KHB, Krebs–Ringer–HEPES buffer; HPLC, high performance liquid chromatography; LC–MS, liquid chromatography–mass spectrometry.

* Corresponding author. Tel.: +43 1 40160 31323.
E-mail address: harald.sitte@meduniwien.ac.at (H.H. Sitte).

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Cocaina nera

- Cocaina contenente tiocianato di ferro e di potassio, rame e grafite usati per superare i controlli dei cani e i narcotests tradizionali
  - Laussmann et al 2014

- Cocaina + sildenafil e analoghi
- Usata per potenziare la prestazioni sessuali, aumenta notevolmente il rischio di IMA
  - Dronet 2011

- Speedball: cocaina associata ad eroina.
- Rischio di depressione respiratoria dopo la fine dell'effetto stimolante della cocaina
  - Dronet 2011

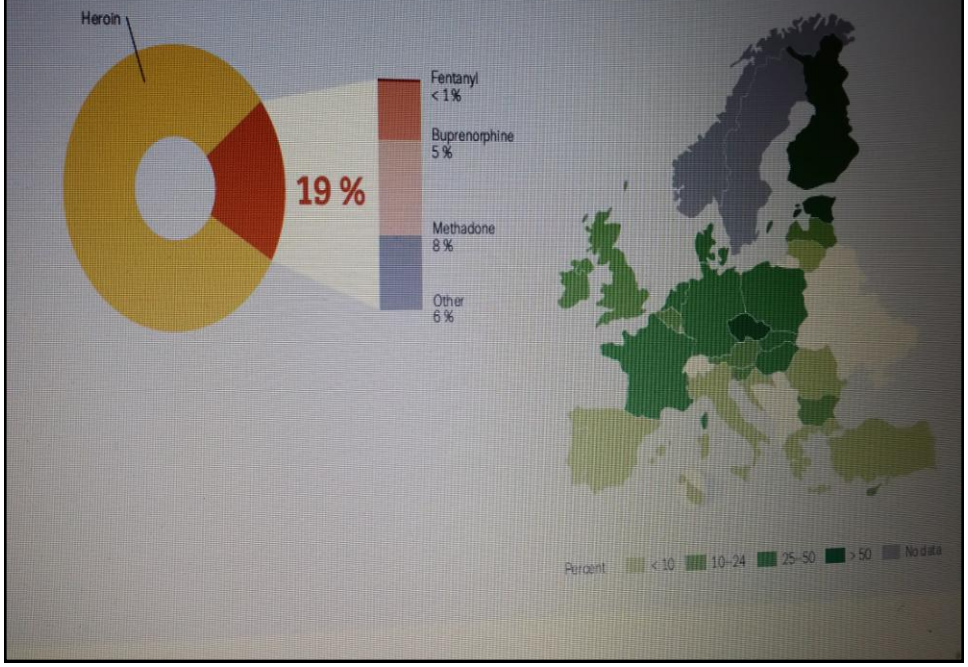
- Cocaina/alcol=cocaetilene
-
- Aumentato rischio di danno cardiaco, epatico, immunitario. Aumento di 18/25 rischio di morte.
  - Andrews et al. J Addict Dis. 1997

- Segnalate intossicazioni da sintacaina, analogo sintetico della cocaina.
  - Lonati et al 2014
- Presenti in commercio altri derivati sintetici quali dimetocaina e 3-fluorobenzoiloxy-tropano
  - EMCDDA 2013

Synthetic opioids: an increasing concern

While heroin remains the most commonly used opioid, synthetic opioids are being increasingly misused. In 2014, 18 European countries reported that more than 10 % of all opioid clients entering specialised services presented for problems primarily related to opioids other than heroin (Figure 2.9); an increase from 11 countries in 2013. Opioids reported by treatment entrants include methadone, buprenorphine, fentanyl, codeine, morphine, tramadol and oxycodone. In some countries, non-heroin opioids now represent the most common form of opioid use among treatment entrants. In Estonia, for example, the majority of treatment entrants reporting an opioid as their primary drug were using fentanyl, while in Finland and the Czech Republic, buprenorphine is the most frequently misused non-heroin opioid.

Treatment entrants citing opioids as primary drug: by type of opioid (left) and percentage reporting opioids other than heroin (right)



LETTER TO THE EDITOR

DOI:10.5055/jom.2014.0XXX

MT–45: A NEW, DANGEROUS LEGAL HIGH

To the Editor:

Epidemiological data confirm that the use of new psychoactive substances is on the rise around the world.[1] Numerous reports have described medical emergencies associated with the consumption of unconventional drugs of misuse bought in "head" or "smart" shops or online.[2] New psychoactive substances, also referred as "legal highs," "smart drugs," or "research chemicals," are a large group of both plant derivatives and synthetic compounds, also in combination, purposefully designed as legal alternatives to illicit substances of abuse. The most popular and widely-spread new psychoactive substances are synthetic cannabinoids and synthetic cathinones, however, various different compounds such as amphetamine-like molecules, arylcyclohexylamines, synthetic hallucinogens, prescription drugs and hormones have been found in recreational products marketed as legal highs.[1]

In 2013, a study of Kikura-Hanajiri and colleagues performed on recreational products marketed in Japan after the introduction of generic scheduling of synthetic cannabinoids, revealed the presence of new types of psychoactive substances as MT-45 and AH-7921, never found before.[3] In 2014, the Swedish National Focal Point has signaled the presence of MT-45 in biological samples of 11 men deceased after consumption of recreational substances. Furthermore, still in Sweden, MT-45 was analytically confirmed in biological samples of two cases of acute intoxication and in a person suspected of a crime. In particular, MT-45 femoral blood concentration in the 11 deceased ranged between 0.33 and 1.9 µg/kg, and the substance was associated with other drugs of abuse. The Swedish National Board of Forensic Medicine concluded that in one case, MT-45 was the cause of death (femoral blood concentration of 1.9 µg/kg).[3] MT-45, IUPAC name 1-cyclohexyl-4-(1,2-diphenylethyl)piperazine, is a piperazine derivative with a molecular weight of 348.52428 g/mol. Currently, it is available as a research chemical only.

Analgesic activity evaluated in mice by the tail-pinch method via subcutaneous and intraventricular dose of MT-45 isomers showed that S(+) enantiomer and racemate were more potent than morphine, while R(–) isomer displayed weak activity. Naloxone stereospecific binding assay showed that S(+) enantiomer was more active than racemate, while in morphine stereospecific binding assay the results were opposed. Hill's coefficient was 1.21, 0.56, 0.78 and 1.22 for R(–) isomer, S(+) isomer, racemate and morphine, respectively. These results suggested that R(–) enantiomer and morphine interacted with opiate receptors in a similar mode, while S(+) isomer acted in a different manner.[4]

A study performed on both mice and rats showed that the activity of S(+) isomer was slightly more potent than that of racemate. Differently , it was highly more potent than that of R(–) isomer. In rabbits, racemate and S(+) isomer produced a negligible hyperglycemic and miotic effect.[5] Additionally, preclinical studies also highlighted the potential abuse liability of S(+) isomer.[4] In this regard, structure-activity studies suggested that the nitrogen at 4 position played a key role in determining the morphine-like effect of MT-45.[7]

In conclusion, MT-45 is a little-known substance and no study has evaluated its pharmacological and toxicological properties in humans. Preclinical studies have demonstrated that this piperazine derivative exerts an analgesic activity more potent than that of morphine. Unlike morphine, it produces a low miotic effect and this particular could cause misdiagnosis compromising the pharmacological treatment that is based on opioid antagonists such as naloxone. In addition, recent evidence suggest that recreational products currently available contain a combination of MT-45 and A-834735, 5-fluoro-PB-22, 4-methylbuphdrine and 4-methoxy-alpha-PVP increasing the risk of severe side effects.[8] MT-45 could become a new public health concern, thus, the vigilance is highly recommended in order to monitor and prevent the spread among drug users.

Maurizio Coppola, MD, Department of Addiction, ASL CN2, Alba, Italy.

Raffaella Mondola, MD, Department of Mental Health, ASL CN1, Saluzzo, Italy

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LETTER TO THE EDITOR

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W–15: A NEW, POTENTIAL OPIOID OF ABUSE

To the Editor:

In recent years, epidemiological and clinical information have highlighted a significant increase in the use of new psychoactive substances around the world.[1] These compounds, sold in smart shops, research chemical stores and online, include both synthetic molecules and plant derivatives mimicking the psychotropic effects of traditional and illicit drugs of abuse.[1]

In 2013, in addition to many new synthetic cannabinoids, cathinones, phenethylamines and arylalkylamines, five synthetic opioids have been officially notified for the first time to the European Monitoring Centre For Drugs And Drug Addiction (EMCDDA) via the Early Warning System (EWS).[2] Among them, W-15, IUPAC name 4-chloro-N-[1-(2-phenylethyl)piperidin-2-ylidene]-benzenesulfonamide, appears to be the less known and the most potentially dangerous. W-15 is an analgesic opioid chemically unrelated to other opioid medicines.

It was synthesized in 1981 by Knaus, Warren and Ondrus and patented in the 1984.[3] Knaus and colleagues synthesized numerous piperidylidene-2-sulfon(cyan)amide derivatives with analgesic agonist or analgesic agonist-antagonist activity.[4] Starting to the general chemical structure (Figure 1), they prepared various compounds wherein R1, R2, R3 and R4 groups were replaced with various different chemical substituents.

In particular, W-15 was obtained adding the C6H5(CH2)2 and SO2-C6H4-4-Cl group in R1 and R2 position, respectively (2). Analgesic activity was investigated using the phenylquinone writhing assay in male Swiss albino mice. This test showed that W-15 exerted an analgesic effect 5.4 times more potent than that of morphine.[4] Specifically, five male Swiss albino mice weighing 18–22 g were used to test the analgesic activity of W-15 and its analogues. The test compound, suspended in a solution of physiological saline and Tween 80™ surfactant, was administered subcutaneously, and 30 minutes later all mice received intraperitoneally a 0.03 percent phenyl-p-benzoquinone solution in a volume of 0.1 mL/10 g of body weight. This test showed that 0.007 mg/kg of W-15 caused a reduction in the total number of writhes exhibited by mice greater than 50 percent As a comparison, the same result was produced by

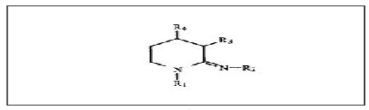


Figure 1. R1 substituent:C6H5(CH2)2.

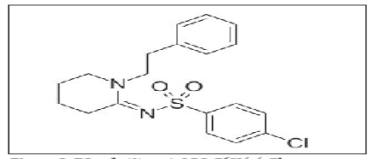
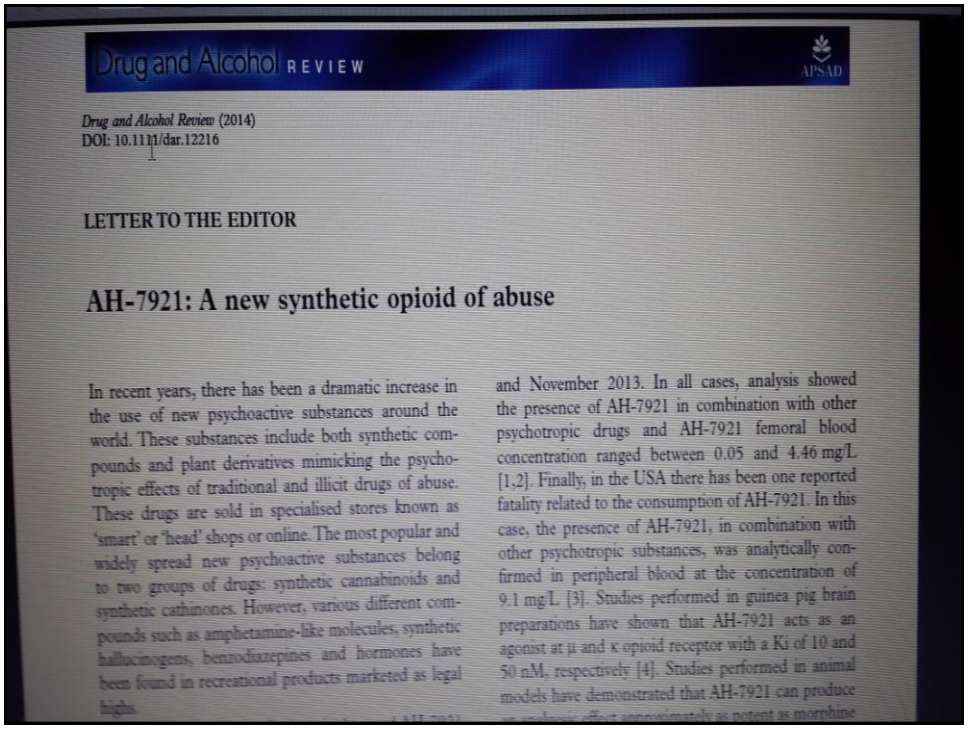


Figure 2. R2 substituent: SO2-C6H4-4-Cl.

0.038 mg/kg of morphine, 50.0 mg/kg of aspirin and 56.0 mg/kg of dextropropoxyphene.[2]

To date, W-15 is sold in online research chemical stores and it is labelled as a "potent analgesic opioid not for human consumption." However, self experiences reported within the drug forums suggest a certain popularity among drug users.[5,6] Furthermore, other potent analgesic opioids belonging to the "W" family such as W-18 are available in online research chemical stores increasing the risk of a global spread among opioid derivatives users.[5]

In conclusion, W-15 is a little-known substance and no study has evaluated its pharmacological and toxicological properties in humans. Preclinical investigations performed using the phenylquinone writhing test have demonstrated that this opioid exerts an analgesic activity more potent than that of morphine. It is available in online research chemical stores and consequently it is easily accessible to a large public. Moreover, W-15 is considered a legal substance in many countries and this fact could



Drug and Alcohol REVIEW

APSAD

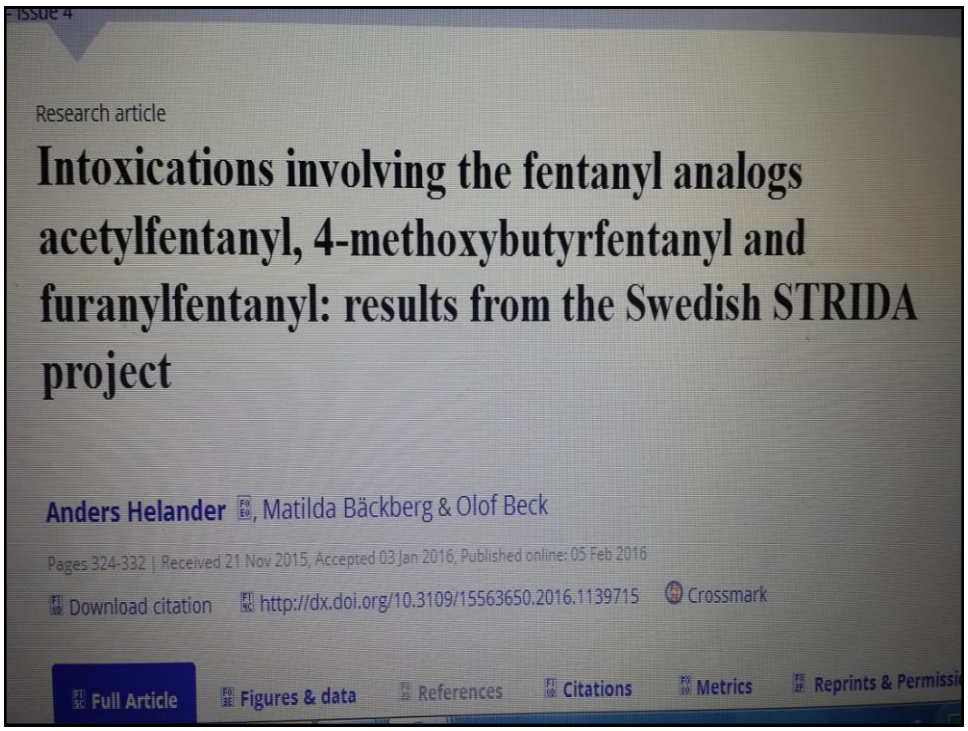
Drug and Alcohol Review (2014)
DOI: 10.1111/dar.12216

LETTER TO THE EDITOR

AH-7921: A new synthetic opioid of abuse

In recent years, there has been a dramatic increase in the use of new psychoactive substances around the world. These substances include both synthetic compounds and plant derivatives mimicking the psychotropic effects of traditional and illicit drugs of abuse. These drugs are sold in specialised stores known as 'smart' or 'head' shops or online. The most popular and widely spread new psychoactive substances belong to two groups of drugs: synthetic cannabinoids and synthetic cathinones. However, various different compounds such as amphetamine-like molecules, synthetic hallucinogens, benzodiazepines and hormones have been found in recreational products marketed as legal highs.

and November 2013. In all cases, analysis showed the presence of AH-7921 in combination with other psychotropic drugs and AH-7921 femoral blood concentration ranged between 0.05 and 4.46 mg/L [1,2]. Finally, in the USA there has been one reported fatality related to the consumption of AH-7921. In this case, the presence of AH-7921, in combination with other psychotropic substances, was analytically confirmed in peripheral blood at the concentration of 9.1 mg/L [3]. Studies performed in guinea pig brain preparations have shown that AH-7921 acts as an agonist at μ and κ opioid receptor with a Ki of 10 and 50 nM, respectively [4]. Studies performed in animal models have demonstrated that AH-7921 can produce



Issue 4

Research article

Intoxications involving the fentanyl analogs acetylfentanyl, 4-methoxybutyrfentanyl and furanylfentanyl: results from the Swedish STRIDA project

Anders Helander, Matilda Bäckberg & Olof Beck

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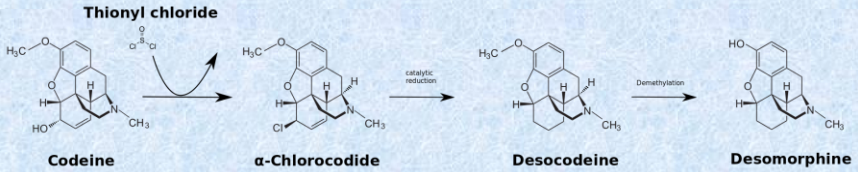
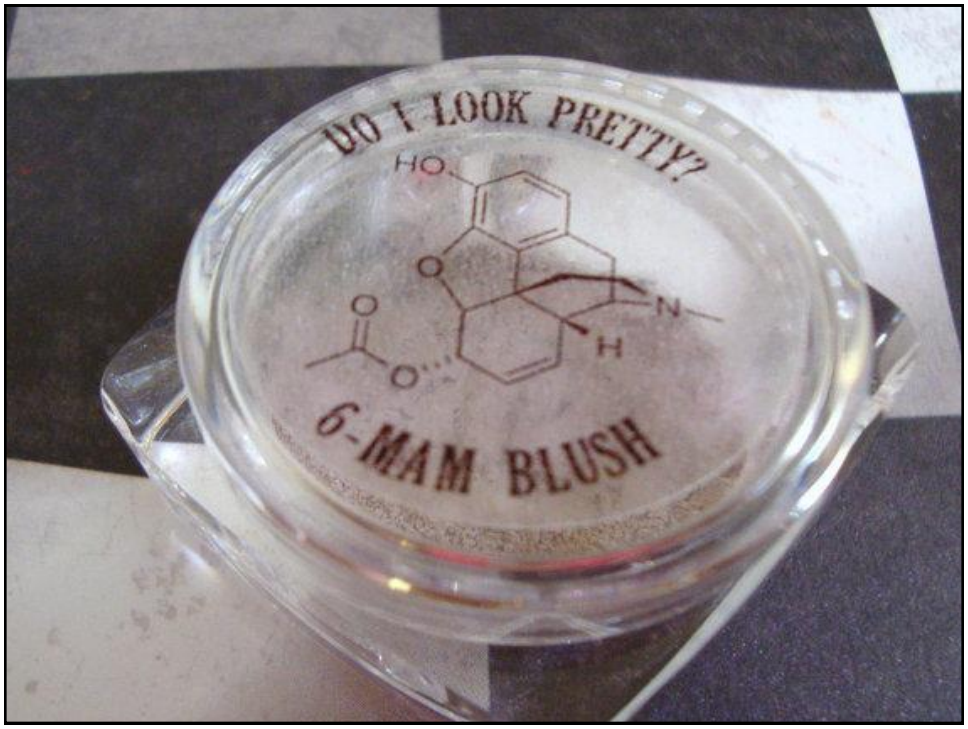
Desomorfina



- Derivato della morfina con potere analgesico 8/10 volte quello della morfina
- Sintetizzata negli anni trenta, è ritornato alla ribalta dal 2003 perché usata come sostituto dell'eroina soprattutto nei paesi dell'est.
- Dal 2010 la produzione clandestina a partire dalla codeina (krokodil) è fortemente aumentata con la messa in commercio di prodotti contenenti numerose impurità responsabili di gravi vasculiti.
  - Gahr et al 2012

Cos’è la U-47700, la nuova droga che ha fatto la prima vittima in Italia



Una molecola killer ha ucciso 27 eroinomani
Dall'Afghanistan a Torino: la strage l'estate scorsa

Eroina gialla: letale il mix di metorfano, paracetamolo e caffeina

- Eroina “gialla” al centro delle indagini per la morte per overdose di quasi 20 giovani fra Udine e Mestre


SOLVAY
BICARBONATO
DI SODIO PURISSIMO
MILLE USI
PER MILLE OCCASIONI
TACHIPIRINA
paracetamolo
TACHIDOL
ZUCCHERO
AMIDO
DI MAIS
CAFFEINA
Solidal
CAFFÈ ARABICA 100%

Kratom

AMERICAN

KRATOM

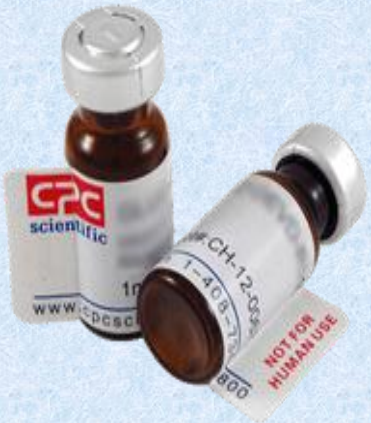
ASSOCIATION

- Può dare tolleranza e dipendenza
- Registrati vari decessi per overdose
- Può determinare ipotiroidismo

  - Singh et al 2014; Neerman et al 2013; Sheleg et al 2011; Nelsen et al 2010;

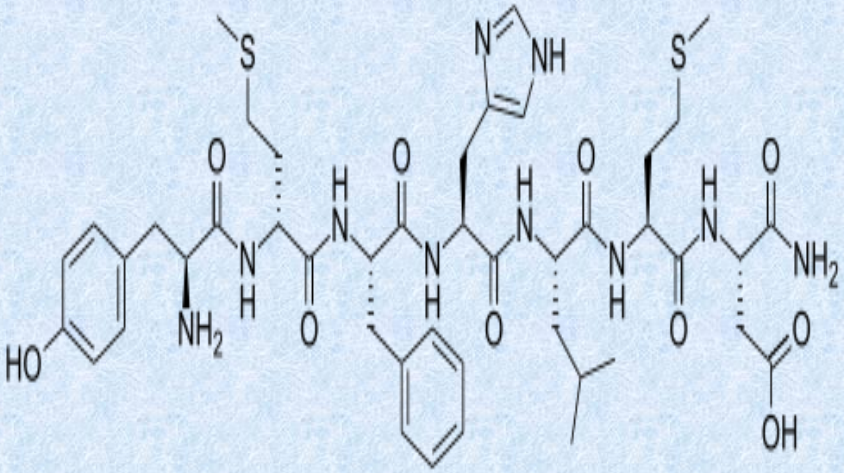
…ma con cosa abbiamo a che fare?

kambo



Bufo

Deltorfina A (oppioide)



Bufotenina (triptamina)

Format: Abstract ▾ Send to ▾

J Forensic Sci. 2017 Sep 8. doi: 10.1111/1556-4029.13641. [Epub ahead of print]

The Biological Effects of Kambo: Is There a Relationship Between its Administration and Sudden Death?

Aquila I[1,2], Gratteri S[1], Sacco MA[1], Fineschi V[2], Magi S[3], Castaldo P[3], Viscomi G[4], Amoroso S[3], Ricci P[1]

Author information

Abstract

Kambo is a substance obtained from the skin secretions of a frog, Phyllomedusa bicolor, popular in the Amazon region, which is administered via the transdermal route. We report a case of 42-year-old man found dead in his house. Near the corpse, a plastic box labeled as "Kambo sticks" was found. The man was a chronic consumer of Kambo and no previous pathology or genetic disease emerged in clinical history from the declaration of his general practitioner. Autopsy investigations and toxicological analysis were performed. The histopathological examination showed left ventricular hypertrophy. Toxicological screening was negative for ethanol and other drugs. Phyllocaerulein, phyllokinin, and deltorphin A were isolated from the Kambo sticks but only deltorphin A was detected in blood sample. We describe the first forensic case of death associated with Kambo administration. We attempt to explain how its use could be related to the cause of sudden death in this case.

KEYWORDS: Phyllomedusa bicolor; autopsy; drugs; forensic sciences; kambo; sudden death

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Cureus

Open Access Case Report

DOI: 10.7759/cureus.2770

Can Overuse of Kambô Cause Psychosis?

Renitha Roy [1] , Aparna Baranwal [2] , Eduardo Espiridion [3]

1. Frederick Memorial Hospital, West Virginia School of Osteopathic Medicine 2. Medical Student, West Virginia School of Osteopathic Medicine, Lewisburg, USA 3. Psychiatry, Frederick Memorial Hospital, Frederick , USA

Corresponding author: Eduardo Espiridion, edjen19meg@gmail.com
Disclosures can be found in Additional Information at the end of the article

Abstract

Kambô is an emerging ritual, which involves the application of the toxin produced by Phyllomedusa bicolor to a freshly burnt area to heal chronic diseases of the mind and body. Due to the widespread use of kambô, more cases of symptomatic health conditions are being discovered. In this case study, we report a patient with psychosis potentially due to the kambô ritual.

Categories: Psychiatry, Public Health
Keywords: phyllomedusa bicolor, kambô, toxin-induced psychosis, giant leaf frog toxin, shaman ritual, neurochemical effects of toxin

Introduction

Kambô is an emerging ritual, which involves the application of a toxin produced by a giant leaf frog, Phyllomedusa bicolor, to a freshly burnt skin area. This is being used to heal the chronic diseases of the mind and body. Due to the widespread use of kambô, more cases of symptomatic health conditions are being observed. In this case report, we report a patient who presented with new-onset psychotic symptoms, potentially due to the kambô ritual.

Case Presentation

The patient is a 33-year-old Caucasian female, who was brought to the local emergency room by the police. The police were repeatedly called by the patient about rapes and shootings in her community. On the day she was brought to the hospital, the patient called the police under a fake name and complained that her husband was raping another individual. She was making nonsensical comments, including being ritualistically haunted by her father and sister. The patient was found to be unmarried and lived alone but was adamant about being married to a celebrity. She had no significant psychiatric history prior to this incident. After acknowledging that she was a certified shaman and practices healing through the utilization of the kambô ritual, she claimed that she uses the kambô toxin to alleviate her chronic pain. Her frequency of performing the ritual changed from once per month to up to nine times per month. She presented with characteristics of paranoia, anxiety, bizarre delusions, labile mood, and panic attacks. On physical examination, scars were noted on the patient's legs from the burns and administration of the toxin. She subsequently had an unremarkable extensive medical workup. As part of her treatment plan, the patient was started on risperidone and she gradually improved after nine days in the hospital psychiatry unit.

Discussion

Phyllomedusa bicolor is a giant leaf frog that secretes toxins that potentially contain peptides,

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Berauschte Heilpraktiker schweigen

Polizei und Staatsanwaltschaft ermitteln. Die meisten Seminarteilnehmer kommen aus Hamburg. Einige wurden bereits aus dem Krankenhaus entlassen

CHRISTOPH HEINEMANN
AXEL TIEDEMANN

HAMBURG/HANDELOH :: Der Massenrausch von 30 Heilpraktikern in einem Tagungszentrum in Handeloh (Niedersachsen) bleibt rätselhaft – der Zustand der Betroffenen ist nach Auskunft von Behörden aber inzwischen weitgehend stabil. Am Sonntag konnten einige der zwischen 25 und 55 Jahre alten Teilnehmer eines Fortbildungsseminars aus dem Krankenhaus entlassen werden. Die Polizei konnte die Heilpraktiker, von denen die meisten in Hamburg leben, bislang aber noch nicht vernehmen.

Nach dem Vorfall waren die Betroffenen auf mehrere Kliniken im Umkreis verteilt worden. Fünf Patienten nahm auch die Asklepios Klinik in Harburg auf. „Die waren völlig außer Rand und Band", sagte ein Sprecher der Klinik dem Abendblatt. Man habe sie angesichts heftiger Halluzinationen am Bett fixieren müssen, damit sie sich und andere nicht gefährden. Immer mal wieder gebe es bei einzelnen Drogenpatienten solche Erscheinungen. „Aber in dieser Häufigkeit haben wir das auch noch nicht erlebt", hieß es aus der Klinik.

Die Heilpraktiker waren völlig außer Rand und Rand. Einige mussten im Bett fixiert werden, weil sie nach Stunden noch so stark halluzinierten.
M. Eberenz, Asklepios Kliniken

Die Rettungskräfte hatten die Heilpraktiker am Freitag mit Wahnvorstellungen, Krämpfen, Schmerzen, Luftnot und Herzrasen am Tagungszentrum „Tannheimat Inzmühlen" angetroffen. In einem Krankenhaus in Buchholz und in der Harburger Klinik mussten die Betroffenen kurzzeitig auf der Intensivstation behandelt werden und waren für Stunden nicht ansprechbar.

Welche Substanz die Heilpraktiker sich genau zugeführt haben, ist noch nicht abschließend geklärt. Die Polizei geht davon aus, dass die Gruppe mit dem Psychedelikum 2C-E experimentiert hat, das in Szenekreisen als „Aquarost" bekannt und seit Ende 2014 wegen unerforschter Nebenwirkungen für Psyche und Körper verboten ist. Dies konnten die Ärzte in Harburg nicht bestätigen. Es habe sich aber eher um eine stark halluzinogene Droge wie LSD als etwa um Kokain gehandelt.

In den bisherigen Gesprächen mit ihren behandelnden Medizinern schweigen die eigentlich fachkundigen Heilpraktiker aber zum Unfallhergang und zur Frage, was sie in den Rausch gebracht hat. Die Gesprächsbereitschaft stieg auch nicht, als die Betroffenen im Laufe des Sonntagabends wieder „etwas klarer" wurden, wie es aus dem Umfeld der Klinik in Harburg heißt.

Weil die Heilpraktiker rechtliche oder auch berufliche Konsequenzen befürchten? So ermitteln inzwischen die Polizei und auch die Staatsanwaltschaft wegen des Verstoßes gegen das Betäubungsmittelgesetz. Die Ermittler haben am Wochenende in der Harburger Asklepios Klinik auch Blut- und Urinproben gefragt, um Beweismittel zur Hand zu haben. In Polizeikreisen wird für denkbar gehalten, dass die Heilpraktiker bei dem Fortbildungsseminar die medizinische Wirkung des verbotenen Stoffs an eigenen Beispiel erproben wollten. Auch eine Verwechslung von unterschiedlichen Präparaten und eine versehentliche Einnahme der Psychodroge konnte offenbar nicht ausgeschlossen werden.

Zur Unfallzeit waren keine Mitarbeiter des Tagungszentrums mehr vor Ort. „Wir sind absolut schockiert, zuvor hatten wir mit der Seminargruppe nur gute Erfahrungen", sagte eine leitende Mitarbeiterin der Tannheimat Inzmühlen dem Abendblatt. Die Seminarleiterin sei bereits mehr als dreimal mit wechselnden Gruppen in dem Zentrum zu Gast gewesen. Bei den Heilpraktikern handele es sich um „solide, anständige, seriöse und ehrliche Leute". Viele Teilnehmer hätten in der mittlerweile Umgebung von Handeloh ihre Behandlungspraxen.

Auch beim Hamburger Landesverband Deutscher Heilpraktiker rätselt man noch über die Hintergründe. „Die Lage können wir überhaupt noch nicht einschätzen", sagte der stellvertretende Landesvorsitzende Torsten Seidl. Rund 750 Heilpraktiker seien in der Hansestadt registriert. „Weitere Informationen haben wir auch noch nicht."

Die Einnahme von Drogen zur Bewusstseinserweiterung oder eine Art Selbsterfahrung mit Medikamenten gehöre allerdings in keiner Weise zur Aus- oder Fortbildung des Berufs. Das würde dem „völlig widersprechen", so Seidl, der seine Praxis in Geesthacht betreibt. Viele Mitglieder des Heilpraktikerverbands hatten deshalb am Wochenende aus Sorge um ihr Berufsbild in der Öffentlichkeit bereits nach den Hintergründen des Vorfalls in Niedersachsen gefragt.

Der Massenrausch führte am Freitag auch zu einem seltenen Großeinsatz von Rettungskräften in der Nordheide. Den Einsatzkräften habe sich ein „ungewöhnliches, aber nicht schönes Bild" an der Tagesstätte geweigt, sagte der Feuerwehrsprecher im Landkreis Harburg, Matthias Köhlbrandt.

Menschen hätten mit Krämpfen auf dem Rasen gelegen, andere seien orientierungslos durch den Garten getorkelt. Mit rund 160 Einsatzkräften waren Feuerwehr und Ärzte schließlich bis zum Abend vor Ort. Auch einen weiteren Einsatz hätte die Feuerwehr am Freitag jedoch noch stemmen können. „Wir hatten noch genügend Rettungswagen im Landkreis – das war noch im grünen Bereich", sagt Köhlbrandt.

Rettungskräfte brachten die berauschten Heilpraktiker in mehrere Kliniken
dpa/Blatt

RINTELN

Beste Jugendfeuerwehr kommt aus Niedersachsen

:: Die Jugendfeuerwehr Möllenbeck aus dem niedersächsischen Rinteln hat beim Bundeswettbewerb der Jugendfeuerwehren die Deutsche Meisterschaft errungen. Das Team scharte sich in Montabaur Platz eins vor den Jugendfeuerwehren aus Schwarzenbek (Schleswig-Holstein) und Stralsund (Mecklenburg-Vorpommern). Dabei gingen die 30 besten Teams aus Deutschland mit den Geburtsjahrgängen 1997 bis 2005 an den Start. Sie messen sich in Löschübungen und beim Staffellauf.

BAD SEGEBERG

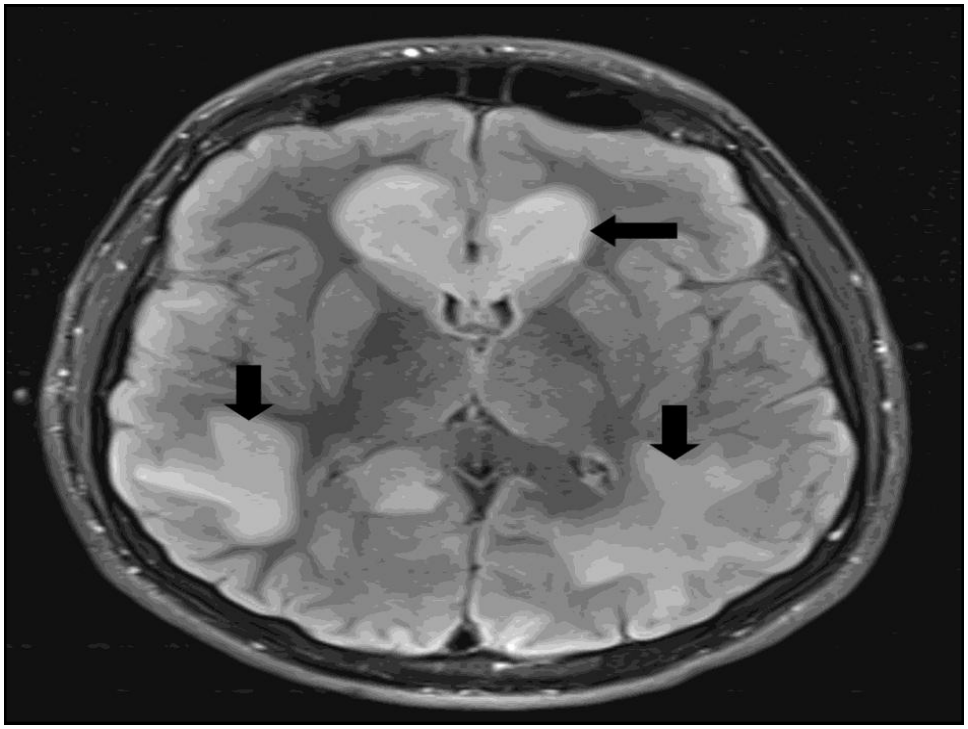
Karl-May-Spiele enden mit Rekordbesuch

:: Mit einem Besucherrekord sind am Sonntag die Karl-May-Spiele in Bad Segeberg zu Ende gegangen. Zur 64. Saison mit 72 Vorstellungen von „Im Tal des Todes" kamen seit Juni 346.677 Zuschauer. Das Karl-May-Abenteuer für die nächste Saison steht bereits fest: Der Klassiker „Der Schatz im Silbersee" soll vom 25. Juni bis zum 4. September 2016 aufgeführt werden. Dann begehen die Freilichtspiele am Kalkberg ein Jubiläum – 50ste Spielzeit. Winnetou Jan Sosnick soll auch 2016 wieder mitspielen.

Sie suchen ein neues

Mystery surrounds hallucinatory chaos at German homeopathy conference

29 intoxicatins induced by 25i-nbome



New cannabis

KEEP
CALM
AND
LOVE
BUDDER

Budder o Miele di cannabis

- Arriva dalla california un estratto di olio di hashish al 99.7% di THC
- Usato a scopo terapeutico, è entrato a far parte dell'uso ricreativo

Cannabinoidi sintatici

- Agonisti sintetici dei recettori cannabinoidi spesso più potenti del delta-9-THC sintetizzati oltre 40 anni fa.
- Trovati in sostituti della cannabis dal 2008 (JWH-018), popolari dal 2004.

- A parte il gruppo definito "cannabinoidi classici" (HU-210), costituito da molecole con struttura dibenzopiranica simile al delta-9-THC, le altre molecole non sono chimicamente correlate al THC.
- Generalmente si tratta di molecole lipofile, con 22-26 atomi di carbonio e molto volatili
- Numerosi episodi di psicosi associata al loro consumo
- Segnalati tra gli effetti collaterali: tachicardia, ipertensione, crisi epilettiche,agitazione psicomotoria, rabdomiolisi, insufficienza renale, infarto del miocardio.
- Segnalati casi di abuso, tolleranza e astinenza.
- Aumento di 30 volte del rischio di accesso DEA rispetto agli utilizzatori di cannabis naturale

Hurst et al, 2013; Tuv et al., 2012; Every-Palmer, 2011; EMCDDA, 2011; Every-Palmer, 2010; Auwarter et al, 2009 Muller H 2010, Zimmermann US 2009;

Anche oltre 100 volte più potenti del THC

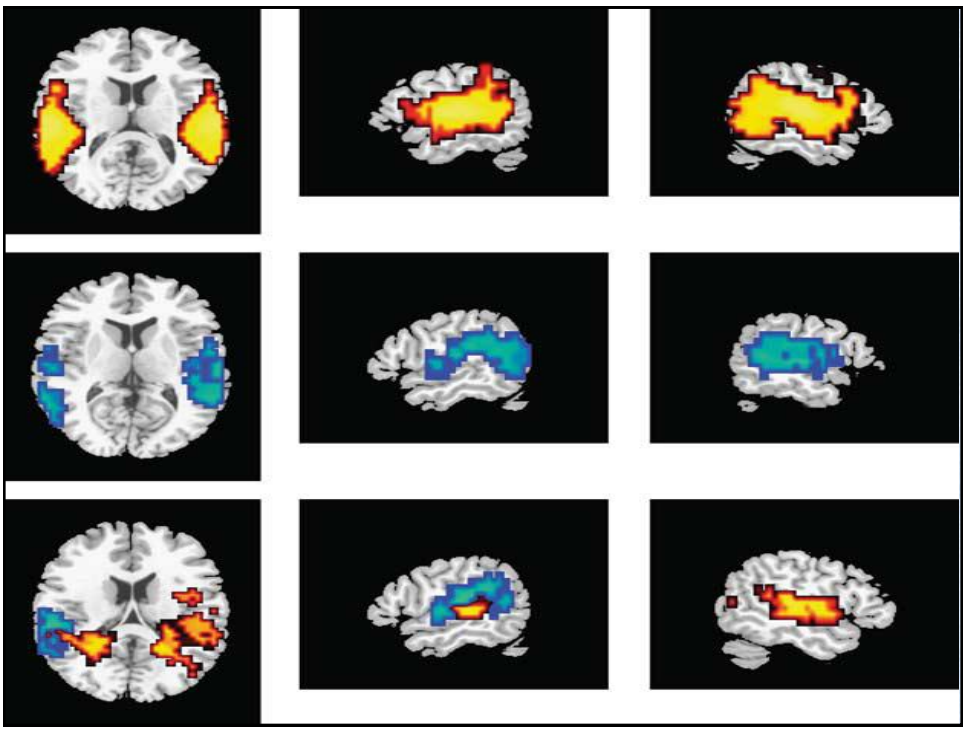
Gli agonisti dei recettori cannabinoidi possono aumentare i livelli di dopamina nello striato e nella corteccia prefrontale. Possono aumentare i livelli di glutammato e ridurre quelli del GABA nella corteccia prefrontale.

Determinano una ipersensibilizzazione post-sinaptica alla dopamina

Non contengono cannabidiolo, una sostanza ad azione neuroprotettiva ed antipsicotica presente nella cannabis

- Studi di neuroimaging evidenziano gli effetti opposti di delta-9-THC e cannabidiolo in numerose aree cerebrali coinvolte nell'apprendimento, attività motoria, emozioni, processi visivi ed uditivi.

Every-Palmer S 2011; Winton-Brown et al., 2011 Zuardi et al., 2009;



spiceophrenia

I sintomi psicotici indotti dai cannabinoidi sono mediati dai recettori CB1. l'antagonista CB1 sr141716 blocca l'effetto pro-psicotico (Huestis 2001)

I neuroni GABA prefrontali sono ricchi di CB1 che se attivati riducono la trasmissione gabaergica inibendo l'inibizione dopaminergica e producendo un aumento della trasmissione dopaminergica

Gardner 2005

- Compared with the use of natural cannabis, the use of SCRAs may cause more frequent and more severe unwanted negative effects, especially in younger, inexperienced users. Psychosis and psychosis-like conditions seem to occur relatively often following the use of SCRAs, presumably due to their high potency and the absence of CBD in the preparations. Studies on the relative risk of SCRAs compared with natural cannabis to induce or evoke psychosis are urgently needed.
  - Van Amsterdam et al 2015

- Il rischio di psicosi aumenta con l'uso di cannabis ad alta potenza e con quello di cannabinoidi sintetici. Il precoce inizio del consumo incrementa ulteriormente il rischio.
  - Murrey et al 2016

Affinità per il recettore CB1

- THC is a weak, partial agonist of the cannabinoid subtype 1 receptor (CB1R), whereas SCs act as potent, full agonists at the same receptor. Moreover, THC displays a modest affinity (KI = 35–80 nmol) at the CB1R, whereas SCs typically display a higher affinity (KI = 27–29 nmol), with the highest affinity (KI = .1 nmol) achieved by the AM-694 compound.
  - Fattore, 2016

Psicosi da cannabinoidi sintetici

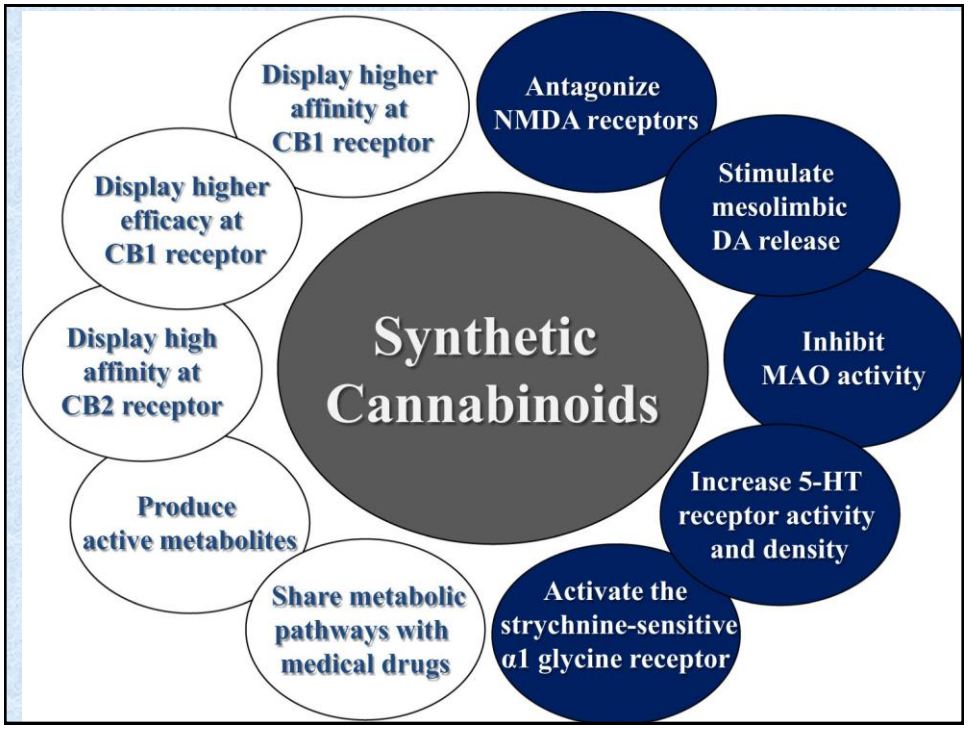
- Maggiore incidenza di sintomi positivi all'esordio in pz psicotici con abuso di cannabis
- Dopo 6 mesi maggiore incidenza di sintomi negativi
- Riduzione del volume della corteccia prefrontale, cingolata e del cervelletto (elevato contenuto CB1)

- Ratt et al. 2013

Non solo recettore cb1

- 1) stereoselectively inhibit currents through recombinant homo-oligomeric 5-hydroxytryptamine 3 serotonin receptors
- 2) increase 5-hydroxytryptamine 1A receptor density and messenger RNA expression in the rat hippocampus
- 3) act as antagonists at the *N*-methyl-D-aspartate receptor
- 4) inhibit monoamine oxidase activity,
- 5) modulate the function of strychnine-sensitive α1 glycine receptors
- 6) affect the functioning of the cytokine network.
- Moreover, the CB2R agonist JWH-133 increases glutamate uptake, whereas MAM-2201 inhibits glutamate release at Purkinje cell synapses via activation of presynaptic CB1Rs and induces a concentration-dependent suppression of gamma-aminobutyric acid release.

- Fattore, 2016



Attività epigenetica

Cannabinoid	Epigenetic Alteration	Biological Target	Associated Effect or Consequence	References
Cannabis	Increased CpG DNA methylation at promoter	Human peripheral blood cells	Negative correlation between CB_1R methylation and mRNA levels in schizophrenic cannabis users	(59)
Cannabis	$^{Met/Met}$ *COMT* gene genotype and promoter CpG DNA methylation	Human adolescent peripheral blood cells	Less likely cannabis dependence and decreased risk of psychosis	(63)
THC[a]	H3K4me3, H3K9me2; Promoter, gene body	Adult rat brain (NAc)	Decreased *Drd2* gene mRNA levels in response to in utero THC exposure	(32)
THC[a]	H3K9me2, H3K9me3; Promoter, gene body	Adult rat brain (NAc shell)	Increased *Penk* gene mRNA levels in response to adolescent THC exposure	(33)
THC[a]	CpG DNA methylation at promoters, intergenic regions, especially in gene bodies	Adult rat NAc with parental THC exposure	Altered methylation enriched in genes implicated in synaptic plasticity	(15)
THC	H3K4me3, H3K9me3, H3K27me3, H3K36me3; Promoters, intergenic regions, gene bodies	Differentiating mouse lymph node cells	Genome-wide alterations in histone modifications associated with dysregulated genes and noncoding RNAs	(34)
THC	Increased *HDAC3* expression	Human trophoblast cell line BeWo	Gene dysregulation during placental development	(72)
THC[a]	DNA methylation at CpG islands; miRNAs	Cerebellum and peripheral T cells of simian immunodeficiency virus-infected macaques	Altered DNA methylation, mRNA and miRNA expression profiles	(39)
THC	miRNAs	Mouse myeloid-derived suppressor cells	Altered mRNA, miRNA, and differentiation profile	(37)
THC	miRNAs	Intestine of simian immunodeficiency virus-infected macaques	Altered miRNA profile and intestinal epithelial cell composition	(36)
Exogenous Anandamide	Increased global DNA methylation	Spontaneously immortalized human keratinocytes (HaCaT cell line)	Decreased expression of differentiation-related genes and altered cell differentiation	(53)
Exogenous Anandamide	miRNAs	Mouse lymph node cells	Altered interleukin production and inflammatory response	(38)
HU-210, JWH-133 Cannabinoid Agonists	H3K9me3; Global levels	CB_1R- and CB_2R-expressing human glioma stem-like cells (U87MG and U373MG lines)	Induction of differentiation, inhibition of gliomagenesis	(31)
HU-210 Cannabinoid Agonist[a]	miRNAs	Adolescent rat brain (entorhinal cortex)	Altered miRNA profile	(80)

Effetti dell'uso cronico

- Studi di neuroimaging hanno evidenziato una riduzione della sostanza grigia del talamo e del cervelletto in abusatori di cannabinoidi sintetici rispetto ai controlli
- L'uso cronico di cannabinoidi sintetici ha ridotto del 20% la disponibilità di recettori D2 e D3 nello striato. La concentrazione di recettori è ritornata alla norma dopo la disintossicazione.
  - Weinstein et al 2017

Research Report

European Addiction Research

Eur Addict Res 2015;21:315–320
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Published online: May 28, 2015

Thalamic and Cerebellar Gray Matter Volume Reduction in Synthetic Cannabinoids Users

Serdar Nurmedov[a] Baris Metin[b] Sehadet Ekmen[b] Onur Noyan[a]
Onat Yilmaz[c] Asli Darcin[d] Nesrin Dilbaz[b]

[a]NPISTANBUL Neuropsychiatry Hospital, [b]Uskudar University, [c]Kasimpasha Military Hospital, and [d]Kanuni Sultan Suleyman State Hospital, Istanbul, Turkey

Key Words
Addiction · Neuroimaging · Synthetic drugs · Synthetic cannabinoids · Thalamus · Cerebellum · Gray matter · Volumetric magnetic resonance imaging

Abstract
Background: Synthetic cannabinoids are compounds that bind cannabinoid receptors with a high potency and have been used widely in Europe by young people. However, little is known about the pharmacology and morphological effects of this group of substances in the brain. This study is aimed at investigating the morphological differences among synthetic cannabinoids users and healthy controls. ***Methods:*** Voxel-based morphometry was used to investigate the differences in brain tissue composition in 20 patients with synthetic cannabinoids use and 20 healthy controls. All participants were male. ***Results:*** Compared to healthy controls, voxel of interest analyses showed that regional grey matter volume in both left and right thalamus and left cerebellum was significantly reduced in synthetic cannabinoids users ($p < 0.05$). No correlation has been found between the age of first cannabis use, duration of use, frequency of use and grey matter volume. ***Discussion:*** These preliminary results suggest an evidence of some structural differences in the brain of synthetic cannabinoids users, and point the need for further investigation of morphological effects of synthetic cannabinoids in the brain.

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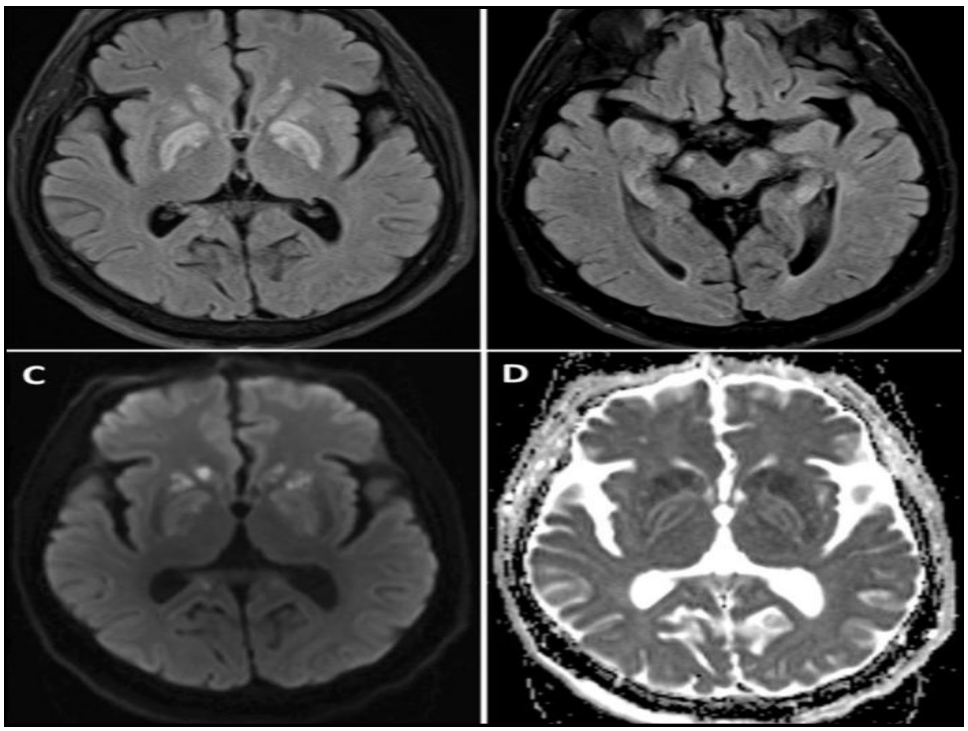
Introduction

Cannabinoids have been used widely, for recreational or medical reasons, for a very long time. The primary active compound of the hemp plant *Cannabis sativa* is delta9-tetrahydrocannabinol (delta9-THC). Psychoactive cannabinoids cause euphoria, enhancement of sensory perception, tachycardia, anti-nociception, difficulties in concentration, and acute impairment of memory in humans; cognitive disturbances may remain after withdrawal.

G protein-coupled cannabinoid receptors are responsible for the acute effects of, and development of tolerance to, cannabinoids. The hippocampus, cerebellum, and striatum are the main areas in the brain where cannabinoid 1 (CB1) receptors and its variant, CB1A, have been found [1].

In last five years, substances named 'Spice' in Europe, 'K2' in the United States, 'Bonzai', 'Jamaika', 'Jamaika

Serdar Nurmedov
NPISTANBUL Neuropsychiatry Hospital
Istanbul (Turkey)
E-Mail serdarnurmedov@gmail.com



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The effects of synthetic cannabinoids (SCs) on brain structure and function

A. Livny[a,b], K. Cohen[c], N. Tik[a], G. Tsarfaty[a,d], P. Rosca[e], A. Weinstein[c,*]

[a] Department of Diagnostic Imaging, Sheba Medical Center, Tel-Hashomer, Israel
[b] The Joseph Sagol Neuroscience Center, Sheba Medical Center, Tel Hashomer, Israel
[c] Department of Behavioral Science, Ariel University, Science Park, Ariel, Israel
[d] Sackler Faculty of Medicine, Tel-Aviv University, Tel-Aviv 40700, Israel
[e] Department for the Treatment of Substance Abuse, Ministry of Health, Jerusalem, Israel

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KEYWORDS
Synthetic cannabinoids;
Cannabis;
N-back;
Go-No-Go task;
Executive function;
fMRI;
Grey-matter;
VBM

Abstract
There is an increasing use of "Novel Psychoactive Substances" containing synthetic cannabinoids worldwide. Synthetic cannabinoids (SC) are highly addictive and cause severe adverse effects. The purpose of our study was to assess whether chronic use of SC alters brain volume and function. Fifteen SC chronic users and 15 healthy control participants undertook an MRI scan to assess brain volume and function while performing a working memory N-back task and a response-inhibition Go-No-Go task. SC users showed impaired performance on the N-back task but not on the Go-No-Go task. They also showed reduced total gray matter volume compared with control participants, as well as reduced gray matter volume in several cortical regions including the middle frontal gyrus, frontal orbital gyrus, inferior frontal gyrus, insula, anterior cingulate cortex and the precuneus. Moreover, SC users showed diminished brain activations in the precuneus, cuneus, lingual gyrus, hippocampus and cerebellum while performing the N-back task. No differences were found in brain activation while performing the response-inhibition task. This is the first study showing overall reduced grey matter volume and specific reduced grey matter volumes in chronic SC users. Furthermore, this study showed for the first time impairment in the neural brain mechanisms responsible for working memory in SC users. Our results of reduced grey matter density and diminished activation during a working memory task in SC users, may suggest vulnerability of the frontal-parietal network in chronic SC users.

* Corresponding author.
E-mail address: avivwe@ariel.ac.il (A. Weinstein).
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0924-977X/

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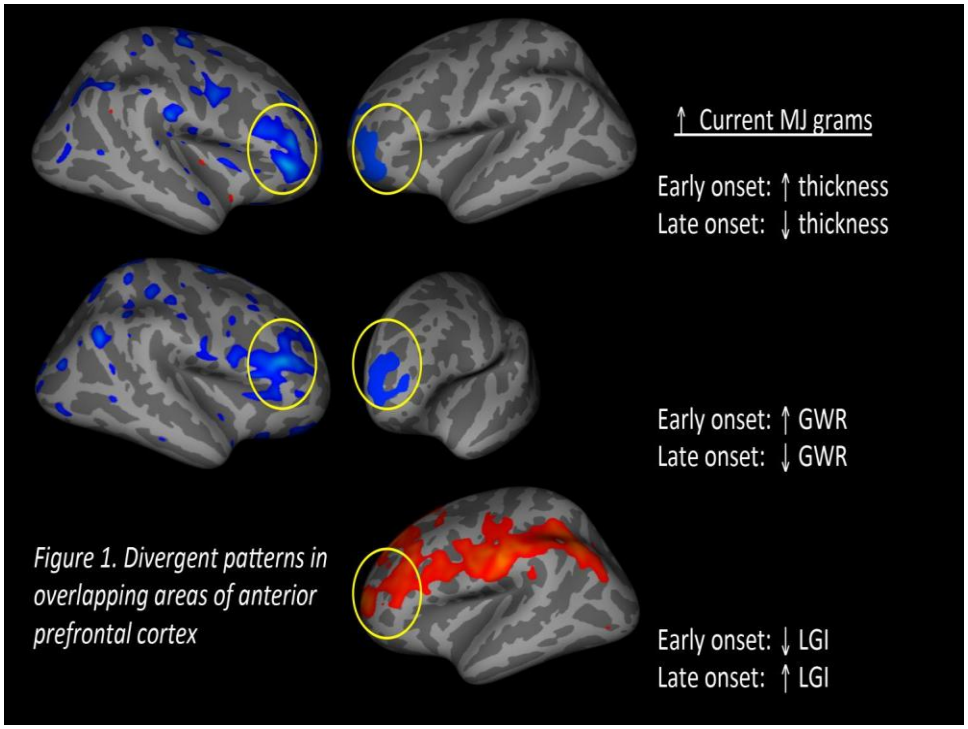


Figure 1. Divergent patterns in overlapping areas of anterior prefrontal cortex

Allerta!

- L'intossicazione acuta da cannabinoidi sintetici si associa ad un rischio di suicidio enormemente più alto di quello associato all'intossicazione da cannabis naturale
  - Fattore, 2016

Allerta!

- La cannabis induce il CYP1A2 e riduce i livelli di clozapina e olanzapina

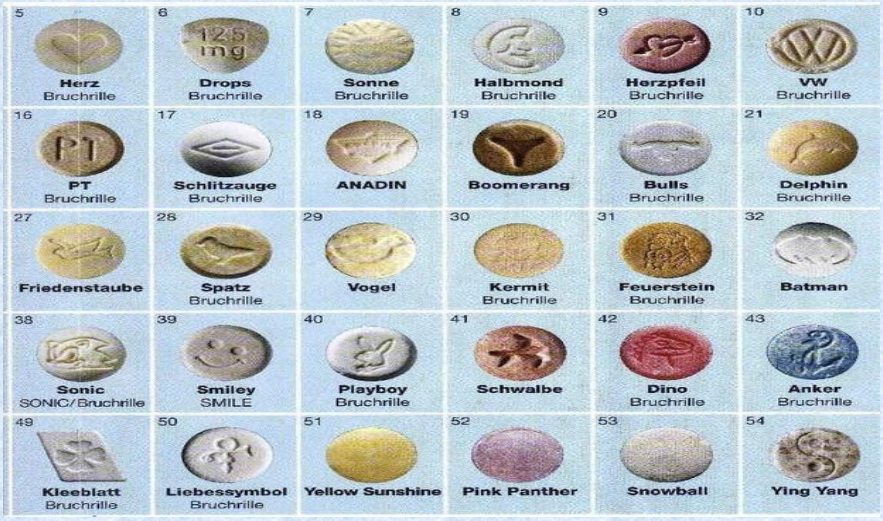
Leweke 2007; D'souza 2008, Gaetani s et al 2009 Parolaro D. et al. Exp Neurol 2010
- Roser P.et al. World j Biol Psy. 2010

- MAM-2201 inibisce in maniera potente i seguenti citocromi: CYP1A2, CYP2A6, CYP2B6, CYP2C19, CYP2D6, UGT1A1, UGT1A4, UGT1A6, UGT1A9, and UGT2B7.
  - Kong et al 2017

Allerta!

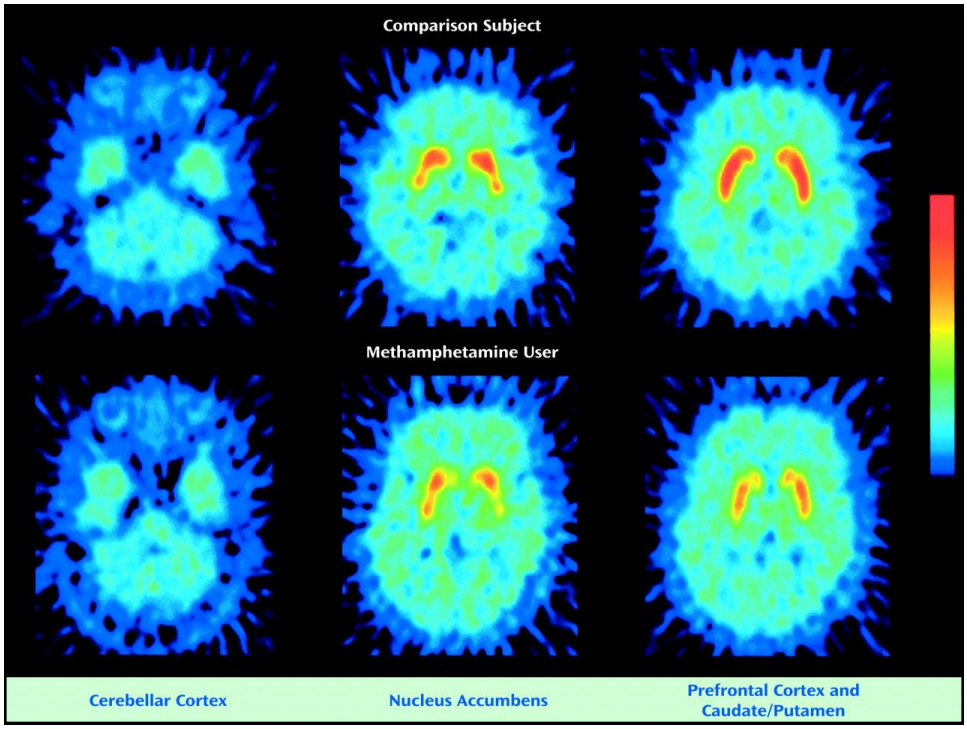
- Attenzione all'associazione tra uso di cannabinoidi sintetici e HPPD.
  - Coppola et al 2017

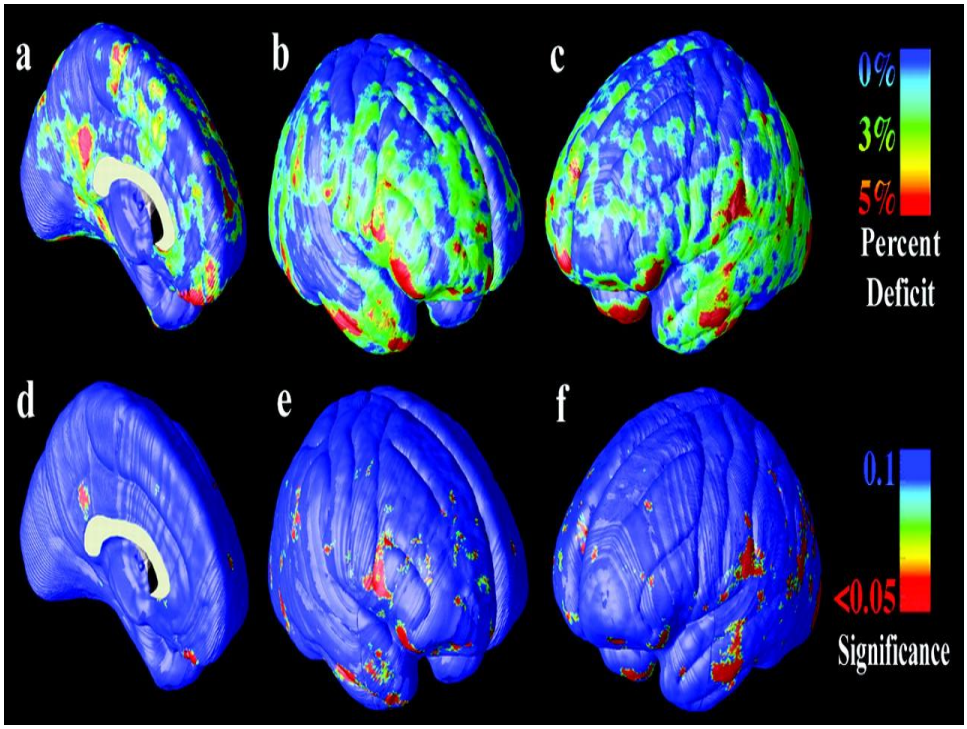
Anfetamine e met-anfetamine

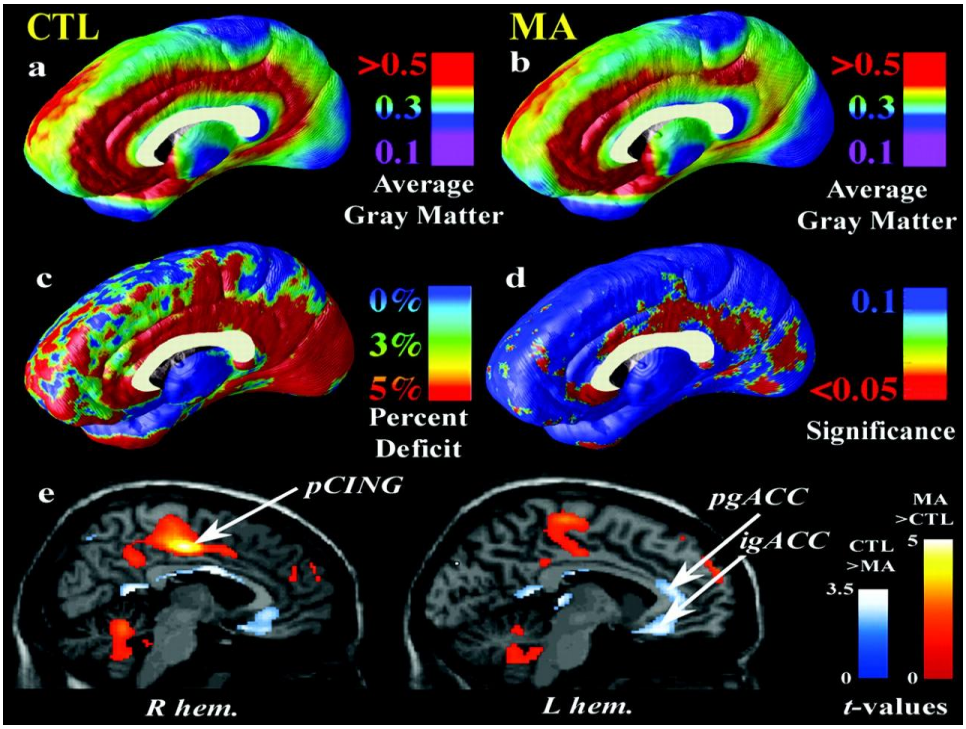


- L'abuso di derivati anfetaminici è molto diffuso soprattutto tra i giovani e gli sportivi.
- Nuovi derivati vengono continuamente messi in commercio per eludere la legge sulle droghe d'abuso
- L'uso di queste droghe può determinare psicosi paranoidi persistenti in soggetti vulnerabili e in persone non predisposte.
- Le anfetamine determinano riduzione del volume dell'ippocampo, alterazione della struttura dei lobi frontali, temporali, occipitali, ipertrofia della sostanza bianca ed ipotrofia ed ipoplasia della sostanza grigia. Un uso precoce determina un minor sviluppo del volume cerebrale per accelerata perdita di neuroni. Tali evidenze giustificano lo sviluppo di sintomi psicotici, alterazioni dell'umore, della cognitività, del comportamento e dell'impulsività.

- Vollenweider et al 1998;Nakama et al 2011; Schwarta et al 2010; Tomphson et al 2004;


Comparison Subject
Methamphetamine User
Cerebellar Cortex
Nucleus Accumbens
Prefrontal Cortex and Caudate/Putamen

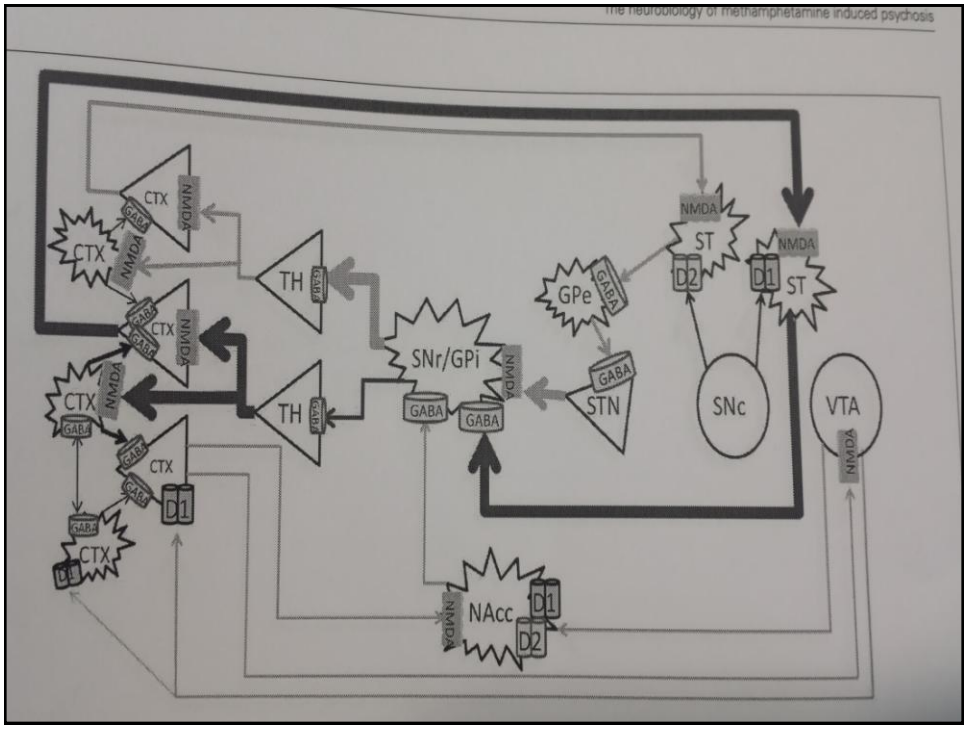

a
b
c
d
e
f
0%
3%
5%
Percent Deficit
0.1
<0.05
Significance



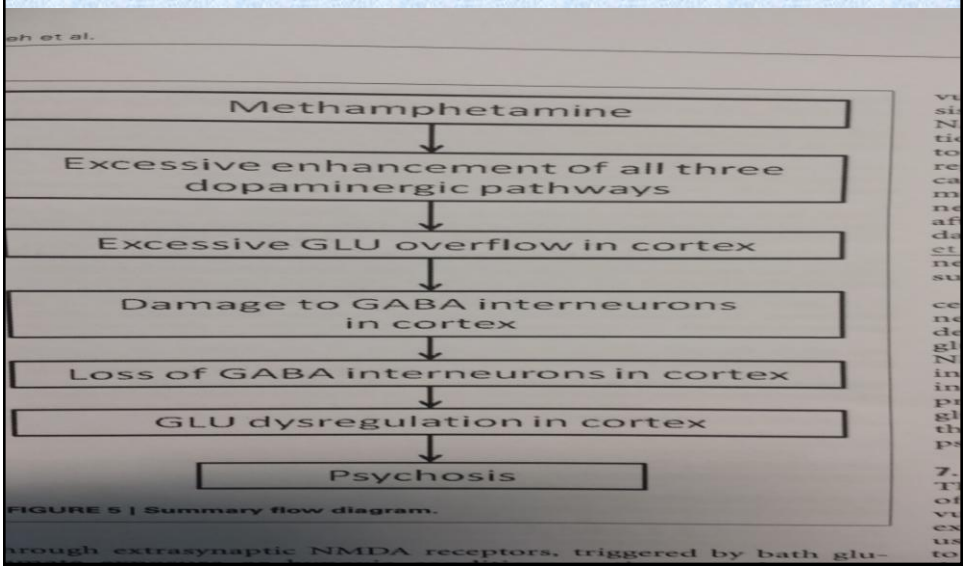
Tossicità da anfetamine

- Aumento attività diretta e indiretta dei recettori NMDA
- Aumento ca intracellulare
- Aumento H2O2, O2
- Riduzione GSH
- Riduzione SOD
- Alterazione permeabilità cellulare
- Alterazione funzione mitocondriale
- Infiammazione
- citolisi

- Cunha-Oliveira et al 2013



Met-Anfetamine e psicosi



Tossicità da metaboliti delle amfetamine

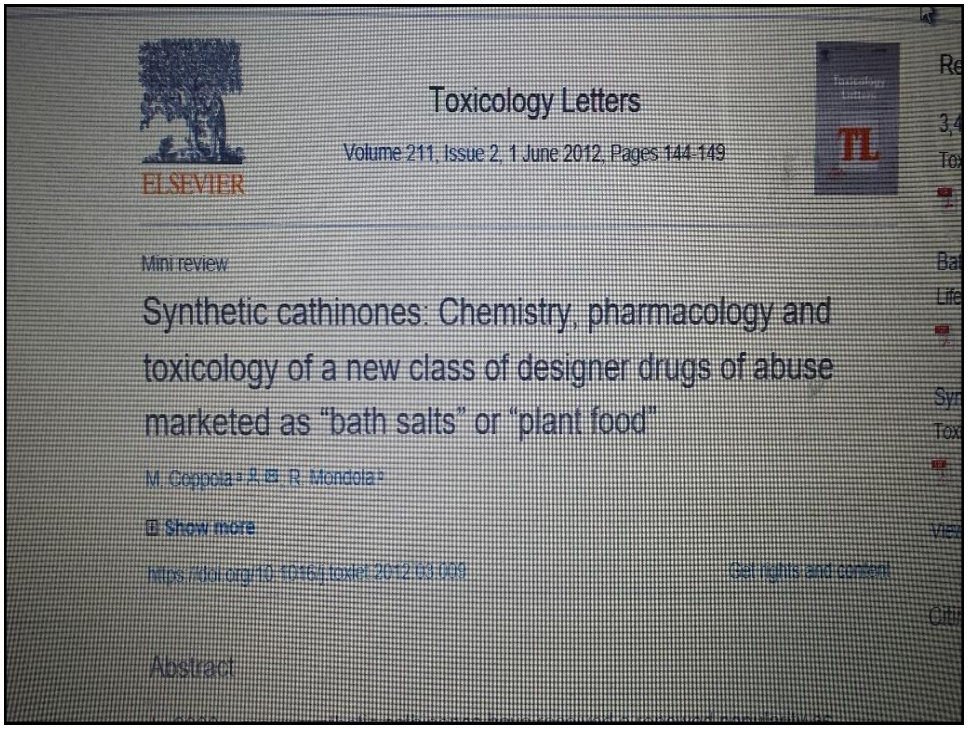
- Derivati del metabolismo delle amfetamine e metanfetamine quali ortochinone, chinone-tioetere sembrano responsabili di parte considerevole della neurotossicità. Questi composti utilizzerebbero il trasportatore del glutadione per attraversare la barriera ematoencefalica e determinerebbero la neurodegenerazione soprattutto delle cellule serotoninergiche. Il pretrattamento con fluoxetina riduce il danno serotoninergico mentre il glutadione ridotto potrebbe ridurre complessivamente la neurotossicità.

- Ferrarelli et al 2009

Catinoni sintetici


Diablo
Kurt Buzzz


Mephedrone
MEPHEDRONE
HARMFUL
1.032 g
HARMFUL
1.032 g



Toxicology Letters
Volume 211, Issue 2, 1 June 2012, Pages 144-149

Mini review

Synthetic cathinones: Chemistry, pharmacology and toxicology of a new class of designer drugs of abuse marketed as "bath salts" or "plant food"

M. Coppola a, R. Mondola a

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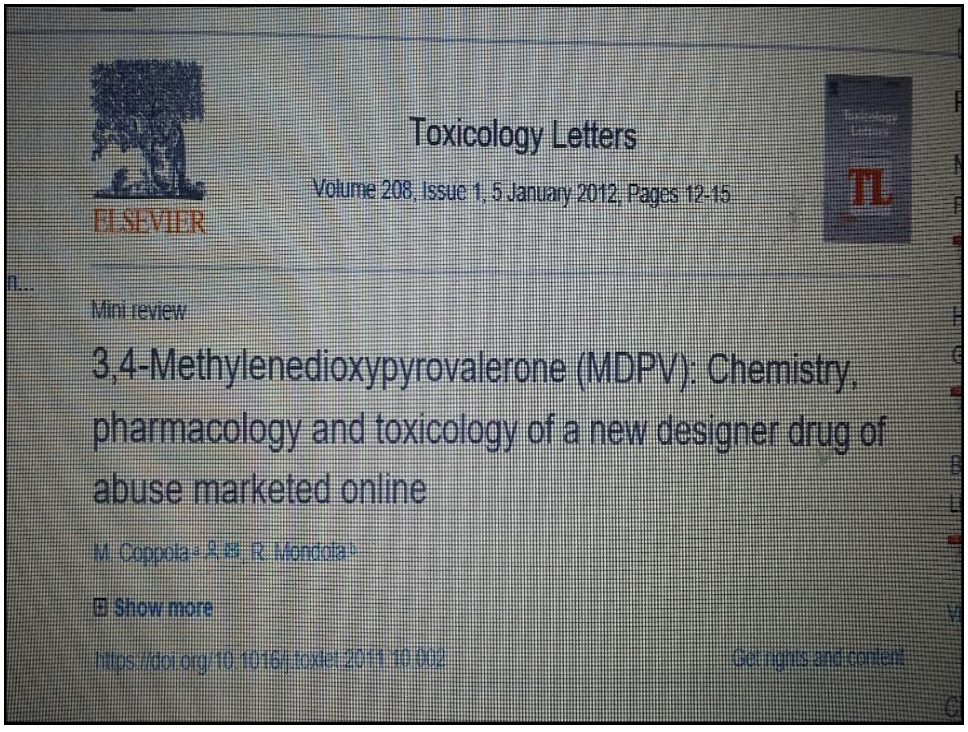
https://doi.org/10.1016/j.toxlet.2012.03.009 Get rights and content

Abstract



Toxicology Letters
Volume 208, Issue 1, 5 January 2012, Pages 12-15

Mini review

3,4-Methylenedioxypyrovalerone (MDPV): Chemistry, pharmacology and toxicology of a new designer drug of abuse marketed online

M. Coppola a, R. Mondola a

Show more

https://doi.org/10.1016/j.toxlet.2011.10.002 Get rights and content

- Derivati feniletilaminici sintetizzati a partire dagli anni 20
- Casi di abuso nell'ex URSS negli anni 70 e USA negli anni 90
- Recentemente apparsi sul mercato delle droghe ricreative e venduti come Sali da bagno o fertilizzanti per piante
- Hanno un'azione simile a quella di MDMA e cocaina
- Alcune molecole come MDPV sono molto liposolubili e presentano un'azione dopaminergica più potente di quella della cocaina
- Alto rapporto Da/5-HT
- Grande potere di rinforzo positivo e alta capacità di indurre abuso, tolleranza e dipendenza
- Segnalati numerosi casi di psicosi, crisi epilettiche, ipertermia, sindrome serotoninergica e morte cardiaca associati al loro consumo.
  - Baumann MH
  - Coppola and Mondola, 2011, Coppola and Mondola, 2012; Mugele et al 2012; Borek et al, 2012
  - ;


Mephedrone
PLANT FOOD
2g
WARNING


Butylone
www.ForeverInject.com

Psicosi: diagnosi e terapia

- Producono episodi psicotici simil schizofrenici in persone sane e possono esacerbare i sintomi psicotici in pz schizofrenici
- La familiarità per psicosi e la personalità pre-morbosa aumentano il rischio di psicosi
- Determinano episodi psicotici con marcata componente produttiva
- Grave l'agitazione psicomotoria
- L'uso di stimolanti produce alterazioni neuronali permanenti come riduzione della densità del trasportatore della dopamina, danno assonale, alterazioni del sistema neurotubulare, alterazione della proteina gsk3 beta.
- Grave la compromissione a carico del sistema serotoninergico con alta frequenza di disturbi dell'umore
- Relativamente efficace l'uso degli antipsicotici sui sintomi positivi.
- Elevato il rischio di discontrollo e suicidio
- Elevata la compromissione cognitiva
    - **Coppola and Mondola, 2012;** Lieberman 1987; Chen 2003; Iyo 2004; Peleg-Raibstein 2009

In caso di abuso/dipendenza il bupropione potrebbe avere un ruolo terapeutico

- **Coppola and Mondola, 2012; Lev-Ran, 2012;Li IH et al. Neu. Image 2010; Przekop P et al. Am J Psy. 1997;** Shoptaw SJ Cochrane Database Syst. Rev 2009**; Lerner AG et al. 2002/2003; Blessing 2003**

Allerta!

Gli stimolanti possono determinare ipertermia

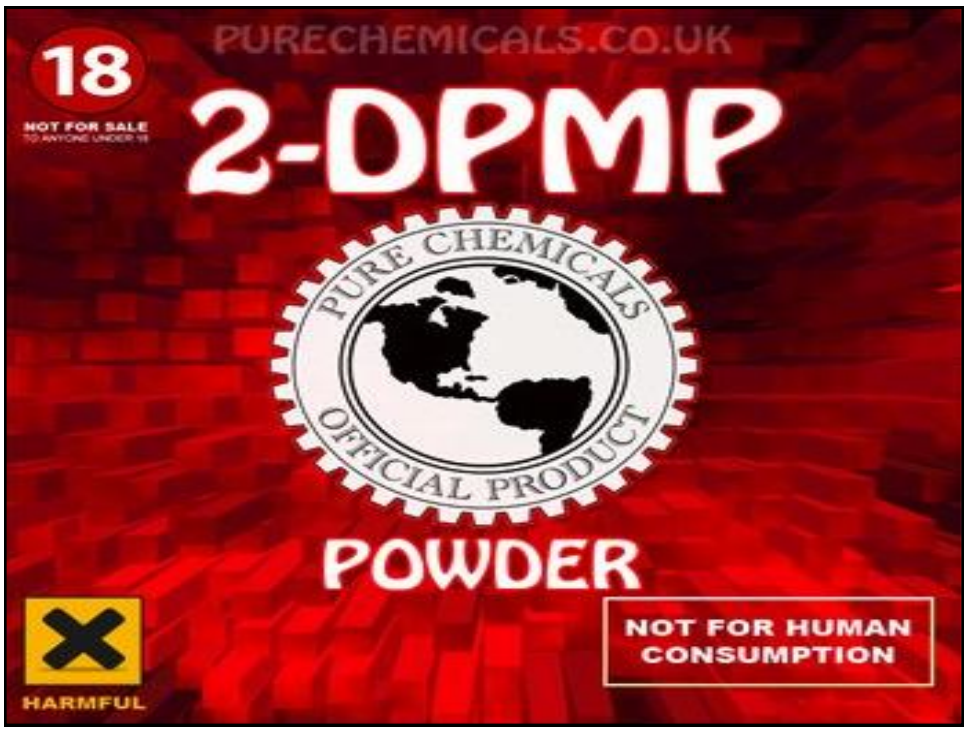
L'uso di antipsicotici tipici aumenta il rischio di ipertermia maligna e disturbi cardiaci.

Olanzapina e clozapina potrebbero essere utili nel ridurre la temperatura di pazienti agitati con ipertermia

- **Li IH et al. Neu. Image 2010**
- **Przekop P et al. Am J Psy. 1997**
- Shoptaw SJ Cochrane Database Syst. Rev 2009
- **Lerner AG et al. 2002/2003**
- **Blessing 2003**

Oltre le anfetamine


2-dpmp
Tigerfood.co.uk


PURECHEMICALS.CO.UK
18
NOT FOR SALE
2-DPMP
PURE CHEMICALS
OFFICIAL PRODUCT
POWDER
NOT FOR HUMAN CONSUMPTION
HARMFUL

- Pipradrolo, desoxipipradrolo, difenilpirrolidine sono molecole chimicamente correlate alle feniletilamine e classificate come research chemicals recentemente apparse nel mercato delle droghe ricreative.
- Agiscono come inibitori della ricaptazione e rilasciatori di catecolamine.
- Sono molecole molto lipofile.
- Nell'accumbens il pipradrolo ha mostrato di essere più potente della cocaina nell'incrementare i livelli di dopamina.

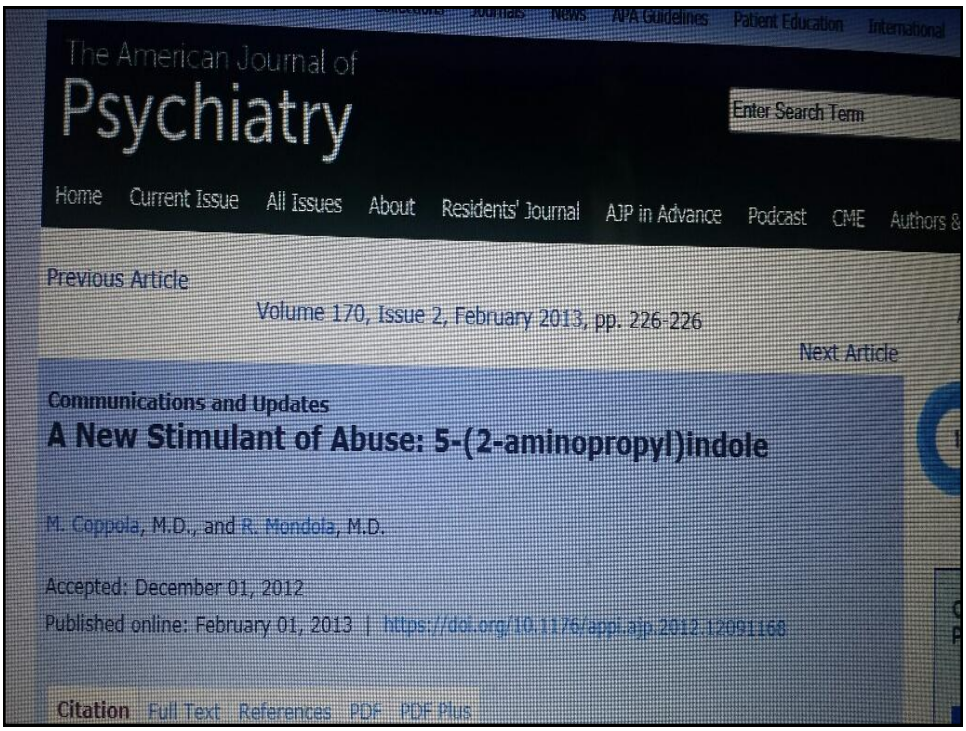
• Coppola et al, 2012

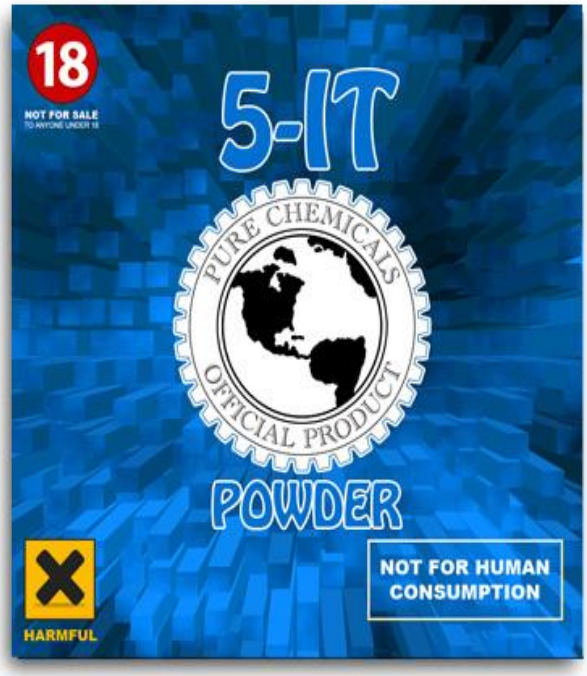
- Segnalati vari casi di intossicazione con presenza di gravi e duraturi sintomi psicotici (deliri, allucinazioni) associati ad agitazione psicomotoria, ipertensione, tachicardia, ipertermia.
- Segnalati casi di infarto del miocardio ed aritmie.

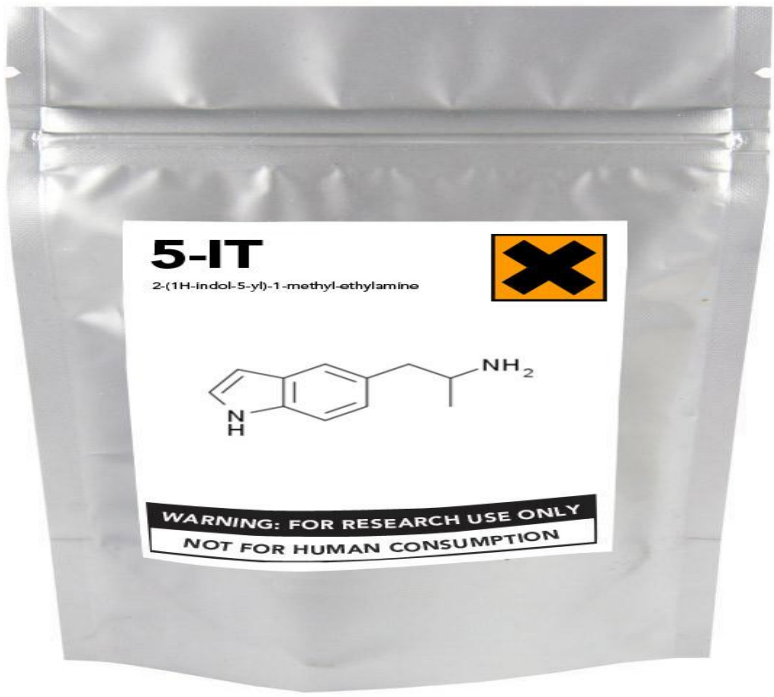
• Coppola et al, 2012

Allerta!

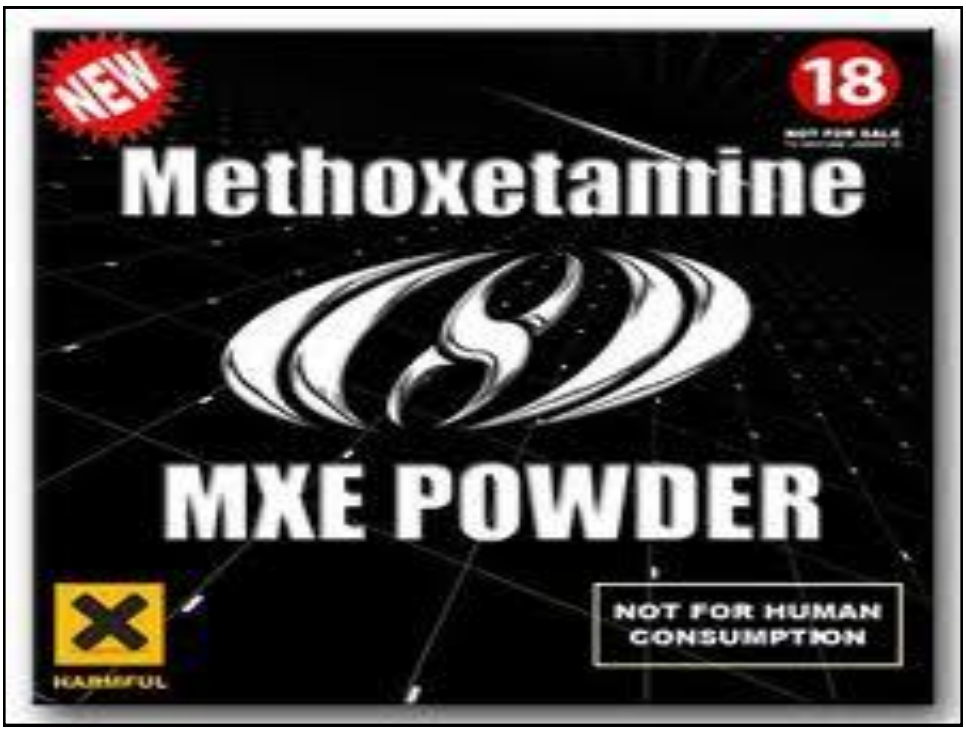
- Trovati in associazione con fluorotropocaina e glaucina con aumento del rischio di cardiotossicità.
- Nel trattamento dei sintomi sono da preferire le BDZ e da evitare, per quanto possibile i D2 bloccanti molto potenti.
  - Coppola et al, 2012

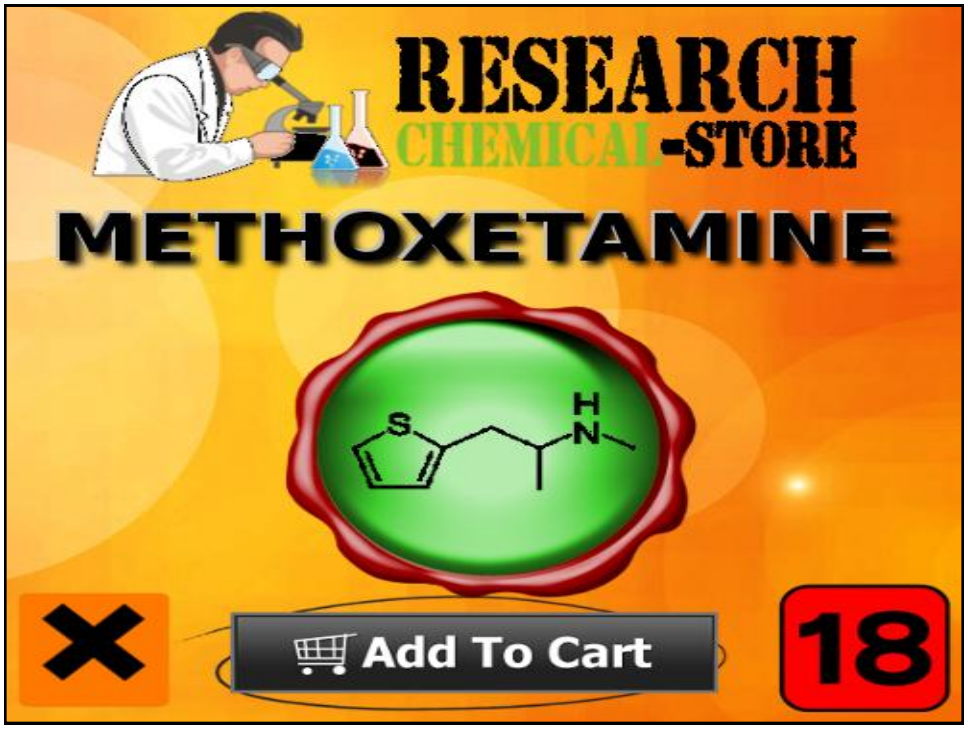



18
NOT FOR SALE
5-IT
PURE CHEMICALS
OFFICIAL PRODUCT
POWDER
NOT FOR HUMAN CONSUMPTION
HARMFUL


5-IT
2-(1H-indol-5-yl)-1-methyl-ethylamine
NH2
N
H
WARNING: FOR RESEARCH USE ONLY
NOT FOR HUMAN CONSUMPTION

- Isomero dell'alfa-metiltriptamina
- Limitatissime le informazioni farmaco-tossicologiche
- Potrebbe agire come inibitore della ricaptazione e releaser delle monoamine. Inoltre, agirebbe come agonista non selettivo dei recettori serotoninergici e inibitore delle MAO
- Molti casi di intossicazione e 16 decessi associati al consumo di questa sostanza
- In due casi, il 5-it è stata l'unica sostanza ritrovata e potenziale causa della morte.
- L'effetto clinico sembra essere quello di un potente stimolante con lunga durata di azione
  - BEWSD, 2012; Seetohul et al, 2012





- Recentemente, analoghi della ketamina e del PCP quali methoxetamine e motoxidine sono apparsi sul mercato delle droghe ricreative.
- Questi farmaci, antagonisti del recettore NMDA, si sono resi responsabili di intossicazioni e decessi in vari paesi compresa l'Italia.

- Wikstrom et al, 2012 Corazza et al, 2012

- L’ intossicazione acuta è sovrapponibile a quella da ketamina.
- Possibili importanti sintomi cerebellari
- Possibili episodi psicotici con marcata componente allucinatoria
- La lamotrigina può migliorare i sintomi psicopatologici indotti dalla ketamina e potrebbe prevenire i deficit indotti dalla sostanza

  - Shields et al, 2012; anand et al, 2000; Brody et al, 2003

Allucinogeni benzodifuranici

- Allucinogeni sintetizzati negli anni 90 a scopo di ricerca sul sistema serotoninergico
- Il più popolare è il bromodragonfly, potente agonista 5HT2A e 5HT2C.
- La sua potenza è comparabile a quella dell'LSD ma la durata d'azione è molto più lunga
- L'azione sui recettori alfa-1-adrenergico e 5HT vasali sono il probabile meccanismo d'azione della vasocostrizione indotta da queste molecole.
- Il bromodragonfly si è reso protagonista di vari decessi, episodi psicotici e necrosi tessutali in vari paesi.

- Coppola et al, 2012

Allerta!

- L'uso di questi allucinogeni espone al rischio di grave vasospasmo e necrosi.
- Necessaria la somministrazione di vasodilatatori quali ACE inibitori, nitrati, calcio-antagonisti o nitroprussiato.

- Coppola et al, 2012

miscellanea

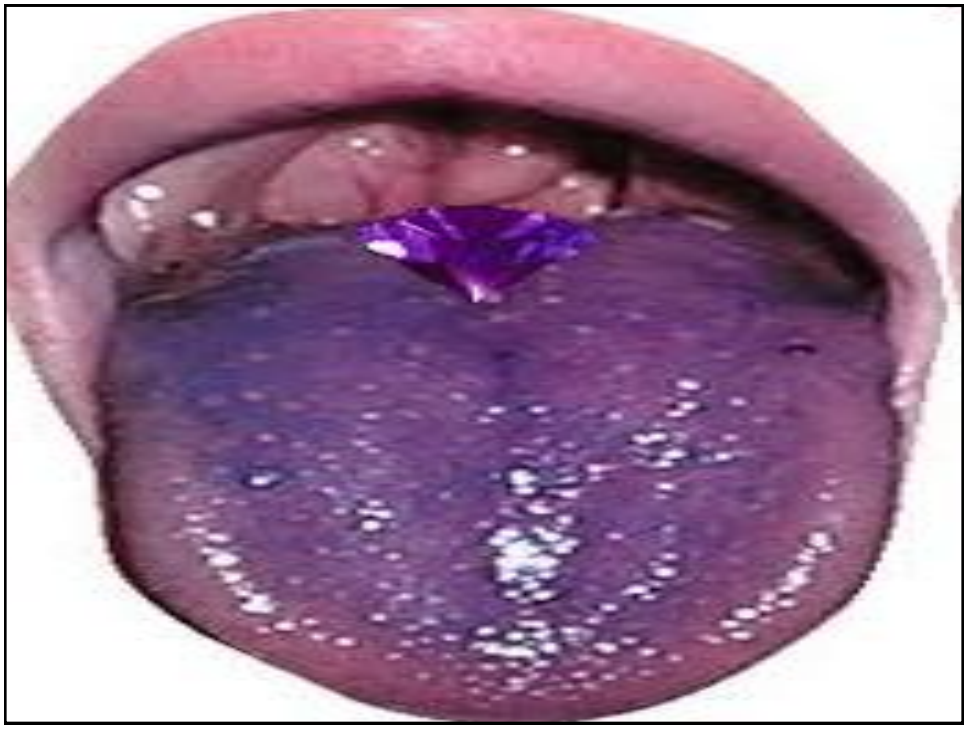
- Segnalati casi di intossicazione acuta con psicosi e crisi epilettiche dovute alle beta carboline presenti nel Peganum Harmala
  - Frison G et all. Forensic Sci Int 2008

- Psicosi acute e croniche con considerevole aggressività associata all'uso di steroidi.
  - Talih et al 2007

- Episodi psicotici e maniacali in pazienti con o senza vulnerabilità associalti all'uso di energy drinks ad elevato contenuto di caffeina
  - Wang et al 2015

Yaba tablets


Purple
Drank
Grape-Flavored
Beverage



Nuove tendenze

- Vaping
- Inhaling household products (computer cleaning products, rubber cement etc)
- Smoking alcohol
  - NIDA 2016, Allen et al 2016

Cannabis light

- Influorescenze di cannabis sativa
- Decine di varianti
- Delta-9-THC <0.2%
- Oltre 300 rivenditori in Italia

In teoria, non c’è nessuna differenza tra teoria e pratica, ma in pratica c’è

Lawrence Peter "Yogi" Berra