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EU MADNESS PROJECT
EUROPEAN-WIDE, MONITORING, ANALYSIS AND KNOWLEDGE DISSEMINATION ON NOVEL/EMERGING PSYCHOACTIVES

EPS NPS

# High-level discussion of polysubstance abuse; focus on prescription and OTC drug misuse


## Professor Fabrizio Schifano, MD, FRCPsych



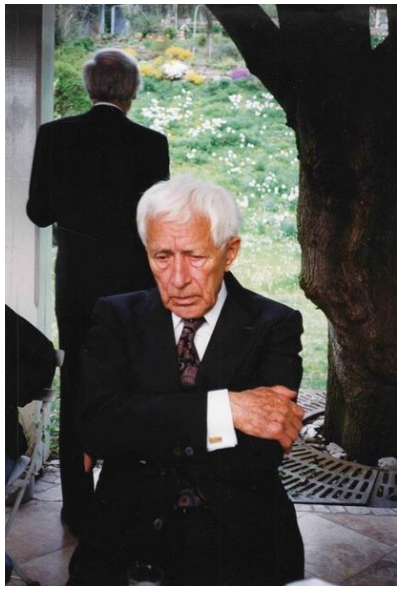
***Special thanks to Damicom srl; A Vento, MD. PhD; L Orsolini, MD***

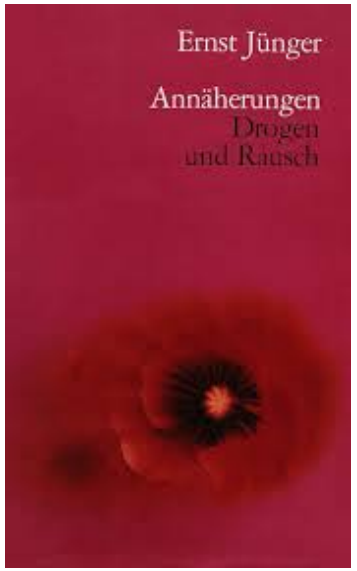


Psychopharmacology, Drug Misuse and Novel Psychoactive Substances Research Unit, University of Hertfordshire, Hatfield, Herts, UK.

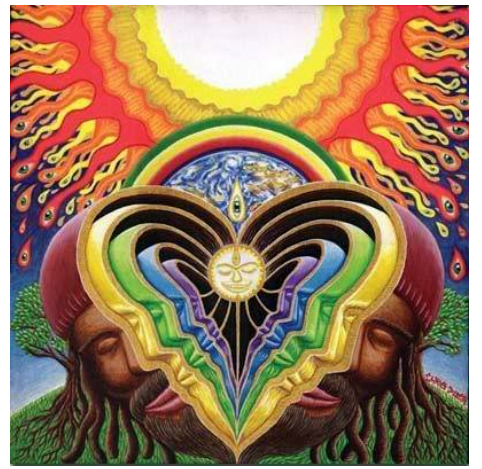
# PSYCHONAUTS and e-PSYCHONAUTS: self-appointed shamans?

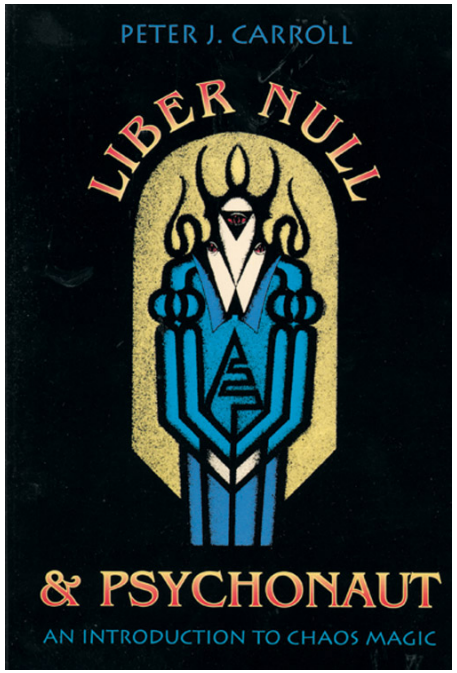
## DEFINITION AND ORIGIN OF THE TERM






**Jünger (1970).** Introduces the word 'Psychonaut' to describe individuals who took psychoactive drugs with the intention of achieving greater knowledge of what he called the 'inner universe', 'Psychocosmos'.






P.J. Carroll (1987) describes in his book 'Psychonaut', the experimental use of meditation, rituals and DRUGS as tools to reach the state of 'psychonaut' in the exploration of consciousness.

# E-PSYCHONAUTS' FEATURES

## TYPOLOGY

❖The '**Chemicals' experimenters**":

who *test the chemicals in order to document the drug's effects* and to assess whether it is safe for others to use. These subjects perceive themselves as doing it in the name of "*psychedelic research*".

❖The '**Navigators of the mind**":

who *use drugs in order to explore the frontiers of the mind* in the name of "*psychonautism*" as means to spiritual, interpersonal and psychological revelations.

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# A number of recent clinical referrals mentioning misuse of OTC and/or prescribing drugs….

1. **Opiates/opioids (tramadol; oxycodone; novel synth opioids)**
2. **Designer/exotic BDZ from the web; Z-drugs; GABA-B drugs (baclofen; phenibut)**
3. **Gabapentinoids**
4. **Anticholinergics; Antipsychotics**
5. **Antidepressants**
6. **Ketamine; esketamine**
7. **Anti asthmatics; clenbuterol**
8. **OTC (loperamide; dextromethorphan; codeine; antihistamines/promethazine)**

# NPS.finder

**Fabrizio Schifano, Flavia Napoletano, Davide Arillotta, Caroline Zangani, Valeria Catalani, John Martin Corkery, Amira Guirguis, Deja Berritta, Liam Gilgar, Alessandro Vento**

University of Hertfordshire
School of Life and Medical Sciences

# NPS FINDER

NPS.Finder® is a Damicom/Rome based crawling/navigating software, designed to automatically scan a 9-language range of psychonaut web sites/fora for new/novel/emerging molecules.

eg. *Bluelight, Erowid, isomerdesign, etc*.

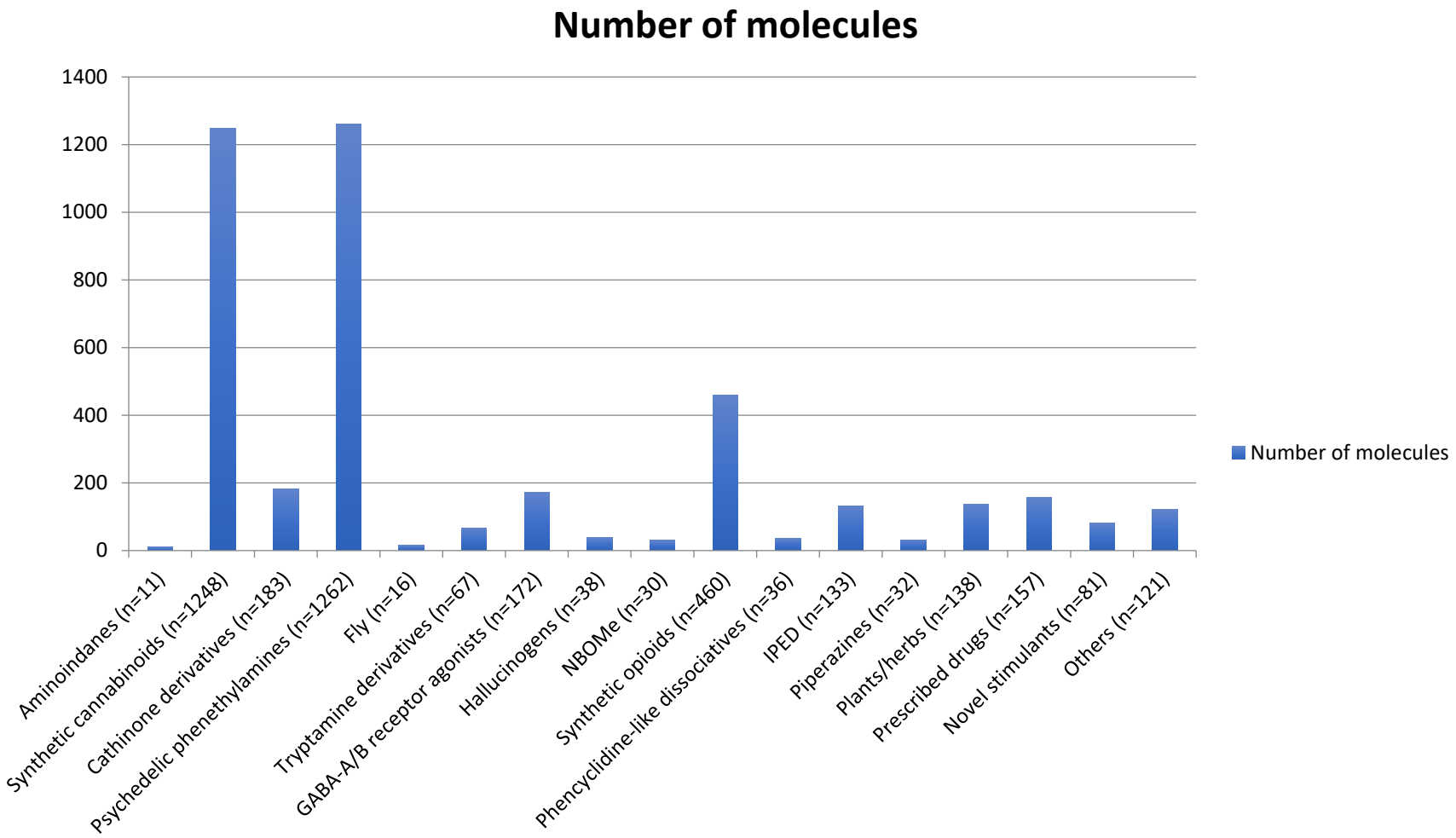
After about 27 months of web crawler activities, the number of substances identified is >6,000;

of these, 4,335 unique molecules have been included in the database and about 1,700 (29%) of the remaining molecules resulted to be false positives duplicates.

**Most popular molecules:**

- Psychedelic phenethyllamines (around 30%)
- Synthetic cannabimimetics (around 30%)
- Novel synthetic opioids (around 11%)

# Current findings; n=4,335 NPS identified



# …the few thousands of different NPS currently available… (part 1)

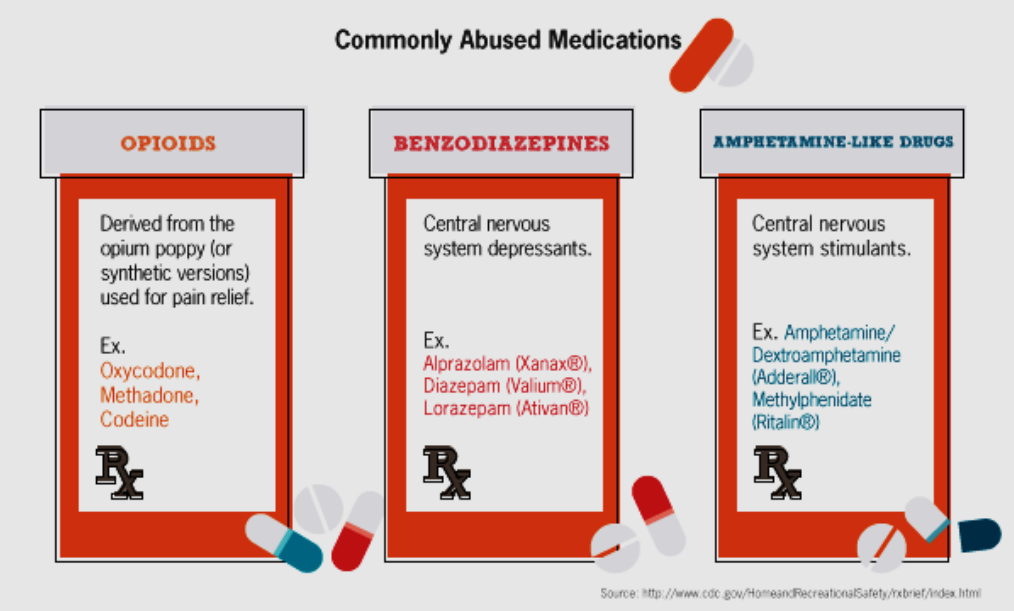
- 179 PIA/**phenethylamines**/MDMA-like drugs; amphet-type substances (fluoroamphetamine, PMA, 2C-T, 2C-B etc);
- **PIA derivatives**: 'fly'; **NBOMe**; indanes; **benzofurans** (5; 6-APB/APDB; EAPB); 'BenzoFury'
- **lysergamides** such as LSA, 1P-LSD, ALD-52, ETH-LAD, Pro-LAD, AL-LAD, LSZ and LSD-like structures
- Up to 700 synthetic **cannabimimetics;** incl: **BB-22; FPB-22;** AKB-48F; AM-2201; AM-2233;
- >100 synthetic **cathinones;** incl: mephedrone; methedrone; methylone; **alpha-PVP** etc
- **Novel stimulants**; aminorex derivatives; **4,4'-DMAR**
- **Synthetic opiates/opioids**, such as >20 fentanyls (e.g. **carfentanil);** AH-7921; IC-26; MT-45; nortilidine; W15; W18; **U-47700, U-48800, U-51,754**
- **synthetic cocaine** substitutes: RTI 111; RTI 121; RTI 126; 'fake' cocaine/**gogaine** (lidocaine+MPA+ephedrine); '**el blanco**' (ethylphenidate and benzocaine)

**Schifano, Orsolini et al. 2015; Schifano, 2015; Schifano, Orsolini et al., 2016; Schifano et al., 2016; Chiappini and Schifano, 2019; Schifano et al, 2020)**

# …the few thousands of different NPS currently available… (part 2)

- 64 **tryptamine** classical derivatives and 5 **tryptamine derivatives** such as 5-Meo-DALT; AMT; 5-Meo-AMT etc
- 126 **psychedelic phenethylamines/stimulants** from the Shulgin Index (2011); about *1,300 molecules being* covered; including DMAA
- GABA-A/GABA-B agonists: 3 **GHB-like** drugs: GHB; GBL; 1,4-BD; phenibut; baclofen; 50 **designer bdz** (phenazepam)
- **PCP-like** drugs: PCP; ketamine; methoxetamine; PCE; 3-MeO-PCP; ethylketamine; 3-HO-PCP; diphenidine, MXP etc
- **piperazines**: BZP; TFMPP
- **Herbs/plants/fungi/animals**: **Salvia divinorum**; Mytragina speciosa/**kratom**; Tabernanthe iboga/ibogaine; Kava Kava; Psychotria viridis/Ayahuasca; hydrangea; **Magnolia officinalis**; Datura stramonium; psychedelic mushrooms; bufo; sponges; flies; etc
- **medicinal products**: tramadol, oxycodone, and remaining opiates/opiods; anticonvulsants (gabapentin and **pregabalin**); antiseptics (benzydamine); DXM; **venlafaxine/'baby XTC'; bupropion; olanzapine; quetiapine/Qbomb**); stimulants (ethylphenidate; camfetamine); antiparkinsonian /anticholinergics: selegiline; tropicamide); chloroquine; anitretrovirals/'whoonga'; xylazine
- **IPEDs**: minikikke/super strength caffeine tablets; DNP; **3-FPM; clenbuterol**; herbal testosterone boosters/Tribulus terrestris; melanotan; sexual enhancers (medicines; herbal products); cognitive enhancers (aniracetam; piracetam; **modafini**l)

# Diversion of prescription and non-prescription drugs in the context of NPS




- A growing use of **psychoactive pharmaceuticals** for recreational purposes has emerged in the drug scene (Nelson et al., 2014; Schifano et al., 2018). As with them, Over-The-Counter (**OTC**) medications misuse emerged as a major public health concern (NIDA, 2011).

- Misusing prescription drugs and OTCs involves not only risks associated with drugs, but also:
  - **side-effects**
  - **interactions** between drugs (both licensed and unlicensed) and other substances and products (food/ alcohol)
  - **individual variation in responses** (genetic differences and possible comorbidities) (Benotsch et al., 2014)

South Med J. 2015 Mar;108(3):151-7. doi: 10.14423/SMJ.0000000000000256.

**Abuse of medications that theoretically are without abuse potential.**

Reeves RR[1], Ladner ME[1], Perry CL[1], Burke RS[1], Laizer JT[1].

# ‘Pharming’ phenomenon

- ‘Pharming’ (Levine, 2007): ‘pharm’ parties; ‘trail mix’; ‘chill pill’ (Haller and James, 2010)

Curr Opin Pediatr. 2007 Jun;19(3):270-4.

**"Pharming": the abuse of prescription and over-the-counter drugs in teens.**

Levine DA[1].

**Author information**

1 Department of Pediatrics, Bellevue Hospital Center, 27th Street and First Avenue, New York, NY 10016, USA. MLevine336@aol.com

**Abstract**

**PURPOSE OF REVIEW:** Prescription and over-the-counter cough and cold medication abuse is rapidly becoming a national health concern for adolescents. Increased awareness of this growing epidemic is essential toward diagnosing, treating and preventing this type of substance abuse.

**RECENT FINDINGS:** Data from surveys and poison control center records demonstrate an increased nonmedical use of prescription and over-the-counter cough and cold preparations, particularly those containing dextromethorphan. The nonmedical use of prescription medications may result in serious clinical effects with potential life-threatening complications, dependence and withdrawal syndromes. Dextromethorphan causes alterations in mental status that may contribute to judgment impairment leading to injury or fatality. Co-ingestion of other substances found in over-the-counter medications may also cause significant morbidity. Alcohol and illicit drug use is highly associated with the abuse of these medications. The incentive for abuse, such as easy accessibility, low cost and decreased perception of potential for harm, and potential interventions are described.

**SUMMARY:** The recent trend of prescription and dextromethorphan-containing over-the-counter medication abuse in adolescents is alarming. Improved awareness for these readily available, seemingly benign yet highly dangerous medications is essential. Prevention and early education on substance abuse in young teens are critical in combating this recent epidemic.

An Sist Sanit Navar. 2013 Jan-Apr;36(1):99-114.

**[Emergent drugs (II): the Pharming phenomenon].**

[Article in Spanish]

Burillo-Putze G[1], Aldea-Perona A, Rodríguez-Jiménez C, García-Sáiz MM, Climent B, Dueñas A, Munné P, Nogué S, Hoffman RS.

**Author information**

1 Universidad Europea de Canarias, Facultad de Ciencias de Salud, Servicio de Urgencias, Hospital Universitario de Canarias, Tenerife, España. gburillo@telefonica.net

**Abstract**

The use of medicines, with or without medical prescription, for recreational ends by the young population has received little attention from doctors. In the USA, one in five adolescents has used medicines for recreational purposes, and consultations in Emergency Departments for medicine abuse have exceeded those for illegal drugs. Although few data are available in Spain, such consumption is situated between 3.1 and 8.6% according to surveys. The medicines most used are dextromethorphan and methylphenidate. The former, on sale without prescription, presents a varied symptomatology, dosage and dependent metabolic action, ranging from euphoria to hallucinations. Methylphenidate, taken orally, nasally or intravenously, is used as a stimulant in substitution for cocaine and is one of the medicines most diverted onto the illicit market at the world level. In principle, other substances like modafinil and propofol present a limited incidence of non-medical use, but they have a probable abuse potential that should be borne in mind, above all in the health context. Finally, opiates like fentanyl, oxycodone and buprenorphine, with new pharmaceutical presentations, have recently become generalized in the therapeutic arsenal of many medical specialities; they are giving rise to phenomena of abuse, dependence and diversion towards the illicit market. Demands for detoxification treatment, their mixture with illegal substances, and cases of death should alert us to the abuse of these medicines.

# Diversion of prescription drugs in the context of NPS - II

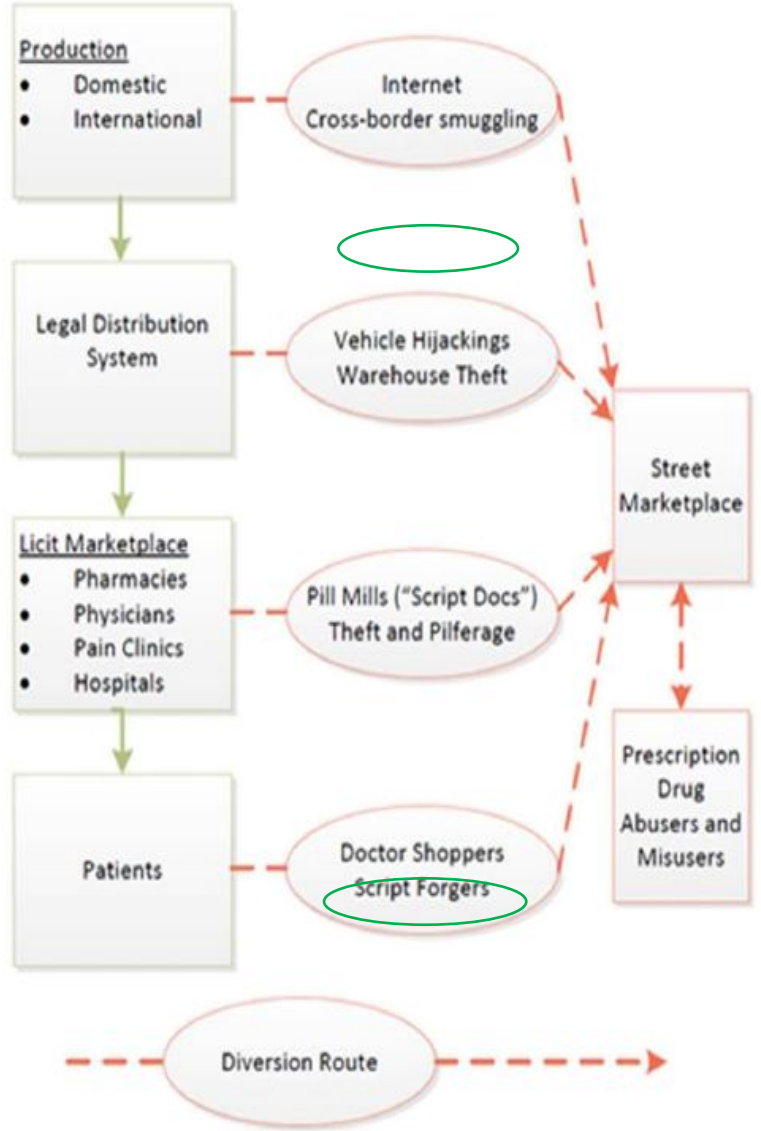
Pharmacoepidemiol Drug Saf. 2019 May;28(5):700-706. doi: 10.1002/pds.4771. Epub 2019 Mar 25.

**The diversion of nonscheduled psychoactive prescription medications in the United States, 2002 to 2017.**

Kurtz SP[1], Buttram ME[1], Margolin ZR[2], Wogenstahl K[2].

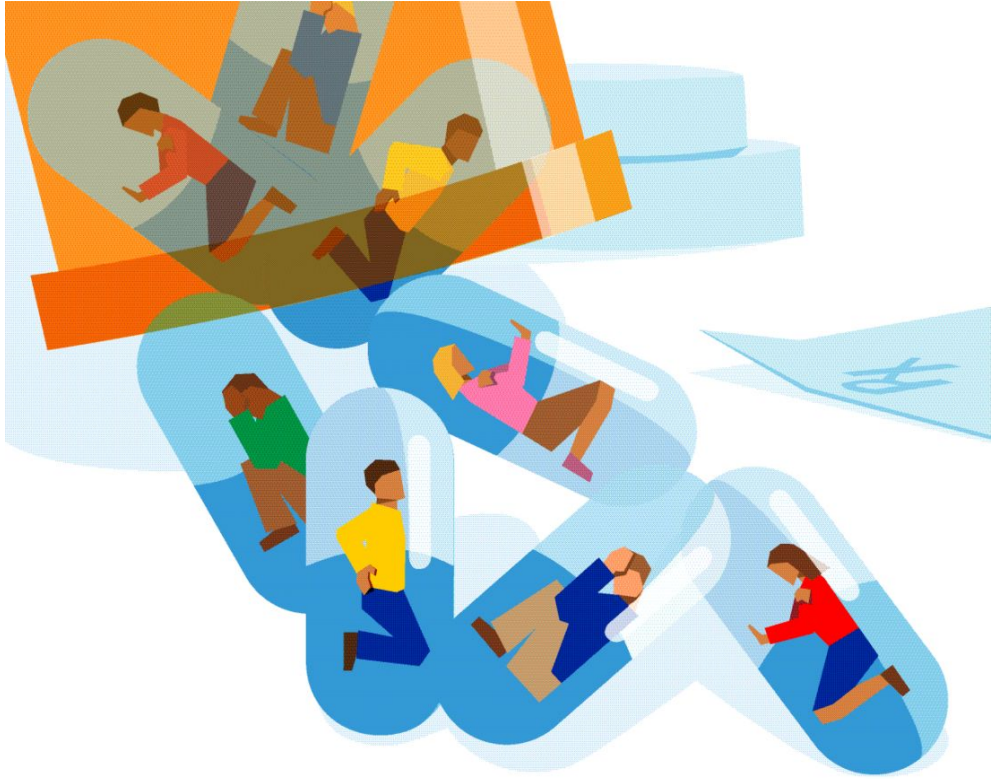
**TABLE 1** Diversion of nonscheduled psychoactive prescription drugs with more than 100 cases 2002 to 2017

| Drug Name | Drug Class | Number Cases 2002-2017 |
|---|---|---|
| Gabapentin | Antineuralgic | 983 |
| Cyclobenzaprine | Muscle relaxant | 791 |
| Olanzapine | Atypical antipsychotic | 705 |
| Quetiapine | Atypical antipsychotic | 532 |
| Trazodone | Antidepressant | 498 |
| Sertraline | Antidepressant | 194 |
| Methocarbamol | Muscle relaxant | 166 |
| Fluoxetine | Antidepressant | 157 |
| Clonidine | Anxiolytic | 150 |
| Buspirone | Anxiolytic | 145 |
| Hydroxyzine | Antihistamine/sedative | 144 |
| Amitriptyline | Antidepressant | 136 |
| Tizanidine | Muscle relaxant | 136 |
| Bupropion | Antidepressant | 125 |
| Escitalopram | Antidepressant | 103 |
| Citalopram | Antidepressant | 102 |




Prescription drug diversion routes (Kurtz et al., 2019)

# GABAPENTINOIDS



- Increasing levels of prescriptions
- Rising numbers of emergency rooms visits and related fatalities (Hakkinen et al., 2014; Parsons, 2018)
- High dosages and unusual way of consumption: intravenous; rectal ('plugging'); smoking; and 'parachuting' (emptying the content of the capsule into a pouch)
- Alone or in combination with other drugs: opiates/opioids may be concurrently prescribed to potentiate the gabapentinoids' effects
- Pregabalin is considered an 'ideal psychotropic drug' for recreational purposes to achieve specific mindsets, including: **alcohol/GHB/benzodiazepine-like effects mixed with euphoria**; to achieve **entactogenic feelings/disassociation**; and **to cope with opiate/opioid withdrawal**
- 'Liking and wanting'


CNS Neurosci Ther. 2019 May;25(5):659-660. doi: 10.1111/cns.13115. Epub 2019 Mar 4.

**Pregabalin: A range of misuse-related unanswered questions.**

Schifano F[1], Chiappini S[1].

Eur Neuropsychopharmacol. 2017 Dec;27(12):1185-1215. doi: 10.1016/j.euroneuro.2017.08.430. Epub 2017 Oct 5.

**How addictive are gabapentin and pregabalin? A systematic review.**

Bonnet U[1], Scherbaum N[2].

Psychiatr Danub. 2018 Jun;30(2):142-149. doi: 10.24869/psyd.2018.142.

**On the addictive power of gabapentinoids: a mini-review.**

Bonnet U[1], Richter EL, Isbruch K, Scherbaum N.

CNS Drugs. 2016 Jul;30(7):647-54. doi: 10.1007/s40263-016-0359-y.

**A Decade of Gabapentinoid Misuse: An Analysis of the European Medicines Agency's 'Suspected Adverse Drug Reactions' Database.**

Chiappini S[1], Schifano F[2].

J Clin Psychopharmacol. 2018 Feb;38(1):72-79. doi: 10.1097/JCP.0000000000000814.

**Is There a Potential of Misuse for Quetiapine?: Literature Review and Analysis of the European Medicines Agency/European Medicines Agency Adverse Drug Reactions' Database.**

Chiappini S, Schifano F.


Front Pharmacol. 2018 Mar 21;9:239. doi: 10.3389/fphar.2018.00239. eCollection 2018.

**Is There a Potential of Misuse for Venlafaxine and Bupropion?**

Schifano F[1], Chiappini S[1].

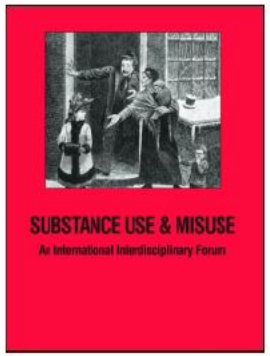
Int J Neuropsychopharmacol. 2019 Apr 1;22(4):270-277. doi: 10.1093/ijnp/pyz007.

**An Insight into Z-Drug Abuse and Dependence: An Examination of Reports to the European Medicines Agency Database of Suspected Adverse Drug Reactions.**

Schifano F[1], Chiappini S[1], Corkery JM[1], Guirguis A[1].

| Examples | Alone | Combination | Effects | ADRs | Comparison |
|---|---|---|---|---|---|
| **Pregabalin, Gabapentin** | ☑ | THC; alcohol;amphetamines; ketamine; opioids; antidepressants; and benzodiazepines | Well-being/relaxation, euphoria, and even hallucinations; withdrawal symptoms reported. | Intentional product misuse, drug abuse , and drug dependence. Fatalities reported | Pregabalin is more addictive and prone to abuse than gabapentin |
| **Bupropion, Venlafaxine** | ☑ | THC; opiates/opioids; ethanol; nicotine; caffeine; cocaine; benzodiazepines; and antidepressants | 'Amphetamine-like high' for bupropion. Venlafaxine large quantities intake ("baby ecstasy") and its withdrawal syndrome have been reported. | Misuse-/abuse-/dependence- and withdrawal-related ADRs. Fatalities reported | Bupropion may possess a higher recreational value due to its dopaminergic and stimulant-like activity, whilst the occurrence of a venlafaxine-withdrawal syndrome may be a significant issue (EMA and Yellow Card Scheme data) |
| **Quetiapine, Olanzapine** | ☑ | THC; cocaine; opioids; alcohol; antidepressants; and benzodiazepines | Quetiapine as "Susie Q," "Quell," and "baby heroin. Olanzapine as the "ideal trip terminator/modulator" after a psychedelic drug binge . | Misuse-/abuse-/dependence- and withdrawal-related ADRs. Fatalities reported | The PRR values suggested that the misuse/abuse–, dependence-, and withdrawal-related ADRs were more frequently reported for quetiapine in comparison with olanzapine. |
| **Clenbuterol, Salbutamol** | ☑ | Anabolic steroids, antipsychotics; analgesic drugs; and antidepressants | Beta2properties, with athletic performance-enhancing and muscle-building activities. Clenbuterol available from the web as 'the size zero pill', for slimming . | Misuse-/abuse-/dependence- and withdrawal-related ADRs. Fatalities reported | The PRR value for drug misuse/abuse ADRs was higher for clenbuterol than salbutamol; conversely, both overdose (including accidental and intentional) and off-label use ADRs were more frequently represented in salbutamol. |

# Quetiapine – ‘Susie Q’

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## Quetiapine Abuse Fourteen Years Later: Where Are We Now? A Systematic Review

Alessandro E. Vento, Georgios D. Kotzalidis, Marta Cacciotti, G. Duccio Papanti, Laura Orsolini, Chiara Rapinesi, Valeria Savoja, Giuseppa Calabrò, Antonio Del Casale, Daria Piacentino, Matteo Caloro, Paolo Girardi & Fabrizio Schifano

# Z-drugs - I

-Zolpidem
-Zaleplon
-Zopiclone

Addiction. 2003 Oct;98(10):1371-8.

## Abuse and dependence potential for the non-benzodiazepine hypnotics zolpidem and zopiclone: a review of case reports and epidemiological data.

Hajak G[1], Müller WE, Wittchen HU, Pittrow D, Kirch W.

Author information

1 Department of Psychiatry and Psychotherapy, University of Regensburg, Germany. goeran.hajak@bkr-regensburg.de

**Abstract**

**AIMS:** The non-benzodiazepine hypnotics zolpidem and zopiclone, which are indicated for short-term treatment of insomnia, were considered originally by physicians as almost devoid of abuse and dependence potential. Several recent publications, however, have suggested that both agents carry a significant risk of abuse. To substantiate and re-evaluate this situation, the world literature was reviewed for cases of dependence of both agents; these cases were analysed in order to identify certain underlying patterns, if evident.

**METHODS:** A systematic review based on a Medline literature search was conducted including the years 1966-2002 to assemble all available clinical case reports that were analysed for typical features of abuse and dependence according to prespecified criteria. Only case reports were of interest, and clinical studies were excluded. No limitations as to language or publication year were applied. The terms 'zolpidem', 'zopiclone' and 'abuse', 'dependence', 'addiction', 'withdrawal' and 'intoxication' were used to identify relevant publications. Potentially relevant citations were retrieved and assessed for inclusion independently by two authors.

**RESULTS:** A total of 36 cases for zolpidem were identified, most of them reported in recent years, and 22 cases for zopiclone. Both sexes were involved to a similar extent; and cases were reported in all age groups. In extreme cases, dose increases reached a factor of 30-120 above the recommended doses. The majority of patients had a history of former drug or alcohol abuse and/or other psychiatric conditions.

**CONCLUSION:** On the basis of world-wide prescription numbers, which are approximately twofold higher for zolpidem (1,338,774,000 tablets from June 2001 to June 2002 in Europe, Japan and United States) than for zopiclone (664,897,000 tablets during the same period in Europe and Japan), the relative incidence of reported dependence similar for both drugs and remarkably lower than that of benzodiazepines used for the treatment of disturbed sleep. The findings offer the conclusion that zolpidem and zopiclone are relatively safe drugs. However, as both drugs are psychotropic drugs, patients with a history of abuse or dependence and those with psychiatric diseases seem to be at increased risk of abuse of these agents.

# Z-drugs - II

**Table 1. Characteristics of 2 Types of Problematic Self-Administration of Hypnotic Drugs[a]**

| Characteristic | Recreational Abuse | Chronic Quasi-Therapeutic Abuse |
|---|---|---|
| Description | Intermittent or chronic use of high doses, often in a pattern of polydrug abuse | Long-term use by patients that is inconsistent with accepted medical practice |
| Example | Large doses of diazepam or flunitrazepam used in combination with opioids or alcohol | Nightly use of triazolam as hypnotic for years despite physician's recommendation to the patient that the medication be stopped |
| Population | Polydrug abusers; often young and male | Patients with and without histories of alcohol or drug abuse, with the former being over-represented; elderly and chronic pain patients are also over-represented |
| Motive for use | To get "high" (alcohol-like intoxication) | Patients often report that a motive for use is to treat insomnia; patients may report unsuccessful efforts to cut down use and use to relieve or avoid withdrawal |
| Route of administration | Usually oral, but sometimes intranasal or intravenous | Oral |
| Dose level | Higher than usual therapeutic doses | Therapeutic doses |
| Pattern of use | Intermittent or chronic, but most often intermittent | Chronic |
| Source of drug | Often illicit | Often licit, however may involve deception of prescriber to obtain drug (eg, multiple physicians) |
| Incidence | Relatively rare compared to the rate of prescription, but similar to abuse of other illicit substances such as opioids or cocaine | Relatively prevalent compared to the rate of prescription |
| Problems | Involvement in illicit drug culture with associated legal and health risks; overdose; memory impairment; risk of accidents; withdrawal syndrome | Memory impairment; risk of accidents; falls and hip fractures in elderly; withdrawal syndrome |

## Misuse of benzodiazepines and Z-drugs in the UK

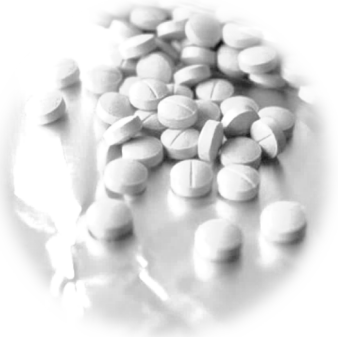
V. Kapil [a1], J. L. Green [a2], C. Le Lait [a2], D. M. Wood [a3] ...

DOI: https://doi.org/10.1192/bjp.bp.114.149252 Published online by Cambridge University Press: 02 January 2018

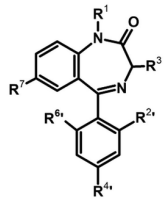
Summary

Benzodiazepines and Z-drugs are commonly prescribed for insomnia and anxiety syndromes and there is increasing concern regarding their misuse. Using an internet-based questionnaire we found that of 1500 respondents 7.7% (*n* = 116) had misused one or more of these medications. Almost 15% of those misusing at least one of these drugs did so once weekly or more often. The main reasons reported for their use were to help sleep (66.4%), to cope with stress (37.1%) and/or to get high (31.0%). A total of 31% obtained the medications from multiple sources; healthcare professionals (55.2%) and friends/family (39.7%) most commonly. Our study can be used to inform prevention measures for their misuse.

# DESIGNER BENZODIAZEPINES (DBDZ)

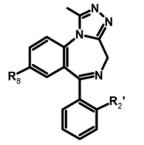


**1,4-Benzodiazepines**

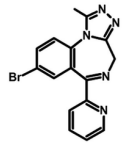


| | R1 | R3 | R7 | R2' | R4' | R6' |
|---|---|---|---|---|---|---|
| Diclazepam | $CH_3$ | H | Cl | Cl | H | H |
| Flubromazepam | H | H | Br | F | H | H |
| Nifoxipam | H | OH | $NO_2$ | F | H | H |
| Meclonazepam | H | $CH_3$ | $NO_2$ | Cl | H | H |
| 3-Hydroxyphenazepam | H | OH | Br | Cl | H | H |
| Cloniprazepam | Methylcyclopropane | H | $NO_2$ | Cl | H | H |
| Fonazepam | H | H | $NO_2$ | F | H | H |
| Norflurazepam | H | H | Cl | F | H | H |
| Ro5-4864 | $CH_3$ | H | Cl | H | Cl | H |
| Nitemazepam | $CH_3$ | OH | $NO_2$ | H | H | H |
| Methylclonazepam | $CH_3$ | H | $NO_2$ | Cl | H | H |
| Ro7-4065 | $CH_3$ | H | Cl | F | H | F |
| Phenazepam | H | H | Br | Cl | H | H |

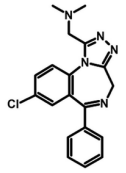
**Triazolobenzodiazepines**



| | R8 | R2' |
|---|---|---|
| Bromazolam | Br | H |
| Clonazolam | $NO_2$ | Cl |
| Flualprazolam | Cl | F |
| Flubromazolam | Br | F |
| Flunitrazolam | $NO_2$ | F |
| Nitrazolam | $NO_2$ | H |

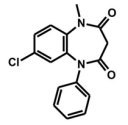


Pyrazolam



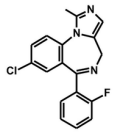
Adinazolam

**1,5-Benzodiazepines**



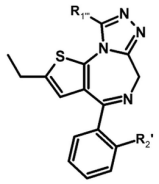
Clobazam

**Imidazobenzodiazepines**

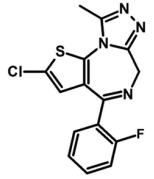


Midazolam

**Thienotriazolodiazepines**



| | R1''' | R2' |
|---|---|---|
| Deschloroetizolam | $CH_3$ | H |
| Etizolam | $CH_3$ | Cl |
| Metizolam | H | Cl |



Fluclotizolam

- Pharmaceutical drug candidates that have **never been approved** for medical use (e.g., clonazolam, deschloroetizolam, diclazepam, flubromazepam, and pyrazolam); compounds that were synthesized by a simple **structural modification of a registered drug** (e.g., flubromazolam); and **some active metabolites of registered benzodiazepines** (e.g., desmethylflunitrazepam marketed under the name of fonazepam) (Zawilska et al., 2019)
- Several DBZD have been placed under national control (ACMD, 2017; UNODC, 2017; WHO, 2017)
- Sold on the illicit drug market as counterfeit forms of diazepam and alprazolam, together with fentanyl or synthetic cannabimimetics (Zawilska et al., 2019)
- Toxic effects may last for several days (e.g. phenazepam and flubromazolam), and may include respiratory depression and death when concomitantly used with other CNS depressant drugs (Moosmann and Auwärter, 2018)
- Chronic use of DBZD results in the development of tolerance, as well as psychological and physical dependence

# Diversion of OTC drugs in the context of NPS

1

OTC remedies may be used to achieve psychoactive effects, such as **positive effects and stimulating experiences** and for **self-medication purposes**, such as enhancing studying, pain management, improving health, weight loss, relaxation, sleep assistance (Friedman RA, 2006; Quintero et al., 2006; McCabe and Boyd, 2012; Schroeder and Ford, 2012; LeClair et al., 2015)

2

Their use for non-medical purposes may have developed due to their **increased availability**, **their inexpensive cost**, and the **users' perceptions of their safety** (LeClair et al., 2015; Schroeder and Ford, 2012)

3

**Procured from:**

- family members
- -international pharmacies
- from the Internet (rather than 'sketchy' drug dealers)

4

The **initial genuine** use of the medication is mostly reported, however **intentional experimenting** suggested by other users may happen

5

Usual practice of **mixing different OTCs and prescription drugs/other illicit drugs in order to enhance their effects**

# DEXTROMETHORPHAN (DXM)


The **"SMART"** choice (Miller et al., 2006):
**Stigma**: there is no negative connotation
**Money**: it is a relatively inexpensive OTC drug
**Access**: it is OTC and found in many home medicine cabinets
**Risks**: DXM is available from medical companies
**Testing**: routine drug tests do not test for DXM

- DXM is a cough suppressant and opioid derivative
- Since its introduction on the market its abuse emerged, especially among **adolescents** (Sheridan et al., 2016)
- Dissociative effects through its metabolism by cytochrome CYP2D6 to dextrorphan, an **NMDA antagonist**. Dextrorphan is also thought to exert **adrenergic effects** by inhibiting peripheral and central catecholamine reuptake. Further, DXM has specific **serotonergic and sigma-1 opioidergic properties** (Miller et al., 2005)
- **Toxicity from coformulatory compounds**, i.e. hepatotoxic effects from acetaminophen; anticholinergic effects from diphenhydramine; depressant effects from ethanol; and sympathomimetic effects from pseudoephedrine
- The abrupt cessation of the drug resulting in physical withdrawal symptoms (Caffrey and Lank, 2018)

| STAGE 1 (100 -200mg) | STAGE 2 (200-400mg) | STAGE 3 (300-600mg) | STAGE 4 (>600mg) |
|---|---|---|---|
| trance-like euphoria | impairment of motor, cognitive, and perceptual functioning | mild dissociation | complete psychophysical dissociation and 'out of body' experiences ('robo-ing', 'robo-copping', or 'robo-tripping') |
| sense of well-being | mild hallucinations | feelings of physical distortion | violent behaviours |
| profound empathy | slurred speech | anxiety | psychotic symptoms, including paranoia, delusional beliefs, perceptual distortion, and vivid auditory and visual hallucinations |
| social relaxation | lethargy | hallucinations | possible death |
| | ataxia | hyperexcitability | |
| | memory impairment | poor motor control | |

Dose-related DXM psychic effects (**therapeutic range: from 60 to 120 mg/day in divided doses**) (Levine, 2007; Martinek et al., 2017; Miller, 2005; Romanelli and Smith, 2009; Storck et al., 2016).

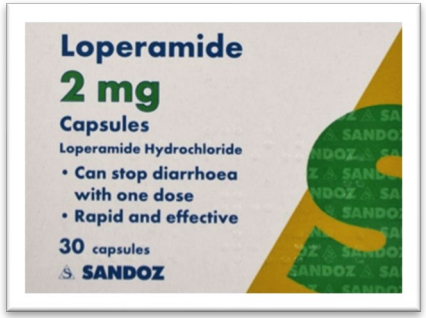
# CODEINE cough and cold medications

- **Calming effects:** being an opioid, it determines rewarding and pleasant effects; relief from tension and anxiety
- Combined with promethazine is popular as '**purple drank**' or 'purple lean', 'sizzurp', 'dirty sprite', as mixed with soft drinks and candy syrups
- Side effects: dizziness, blurred vision, nausea, memory problems
- **Coma and death**, especially when codeine is combined with other sedative drugs or depressant substances, such as alcohol
- Chronic use of codeine and 'purple drank' can lead to the development of **drug tolerance or dependence**

(Chiappini S, **Schifano F**, Corkery JM, Guirguis A Beyond the 'purple drank': Study of promethazine abuse according to the European Medicines Agency adverse drug reaction reports. J Psychopharmacol. 2021)

/rhodonite for stress / promethazine for sleep / a rabbit toy for children / my deep condolences [original art]


# LOPERAMIDE




PLoS One. 2018 Oct 4;13(10):e0204443. doi: 10.1371/journal.pone.0204443. eCollection 2018.

**Is there such a thing as a 'lope' dope? Analysis of loperamide-related European Medicines Agency (EMA) pharmacovigilance database reports.**

Schifano F[1], Chiappini S[1,2].

- It is a **peripherally acting opioid derivative** used as an OTC antidiarrheal, long considered a drug with low abuse potential
- It has been reported for its euphoric effects ('**lope highs**') and its use to alleviate opiate/opioid withdrawal ('**poors' methadone**')
- Although safe within normal dosages (2-16mg), at higher dosages (>50mg, up to 800mg) **CNS depression, electrocardiogram abnormalities** (QTc > 650ms) and **fatal cardiotoxicity** have been described (Chiappini and Schifano, 2018)
- Some also take advantage of cytochrome inhibitors, such as cimetidine and grapefruit juice, as well as P-GlycoProtein inhibitors, such as quinidine and pepper, to raise serum levels of the drug
- Loperamide **will not show up on a standard urine drug screen**
- Management of loperamide toxicity includes extended consideration of decontamination, treatment of respiratory depression, and monitoring and treatment of potential cardiotoxicity: **naloxone** has been used for loperamide-provoked respiratory depression (Caffrey and Lank, 2018).

# Other prescription drugs

Through the blockade of the muscarinic receptors, anticholinergic drugs **inhibit dopamine reuptake and storage, accounting for the euphoric and hallucinogenic effects** (Naja and Halaby, 2017)

- **Abuse of anticholinergic antiparkinsonian drugs,** normally used to ameliorate EPS caused by either Parkinson's disease or antipsychotic drugs: **Biperidine; Benztropine; Orphenadrine; and Procyclidine** (Dose and Tempel, 2000; Gjerden et al., 2009; Marken et al., 1996; Reeves et al., 2015)

- **Tropicamide** is an antimuscarinic drug usually prescribed as an ophthalmic solution reported to be self-administered IV for recreational purposes (Bersani et al., 2013)

**Desired and toxic effects of anticholinergic misuse/abuse**

| Desired and reported subjective effects | Toxic effects |
|---|---|
| Euphoria | Insomnia |
| Stimulation | "Atropinism" (dry mouth, blurred vision, tachycardia, anhidrosis, urinary retention) |
| Increased sociability | Aggression |
| Anxiolysis | Psychosis (hallucinations, paranoia, ideas of reference) |
| Increased energy | Temporal distortion |
| Disinhibition | Cognitive impairment |
| Enhanced sexual pleasure | Delirium |
| "Self-medication" of depressive, negative, and extrapyramidal symptoms | Hyperpyrexia |
| | Coma |
| | Death |

**True abusers** could be recognised because they feign EPS, repeatedly 'lose' their medications or request unnecessary dose increases.

3 distinct groups of abusers (Marken et al., 1996) :

I. those individuals without valid medical need for the medication consuming it only for **its mind-altering effects**;

II. those with a valid indication for the use of anticholinergics who also abuse them for their mind-altering effects;

III. those who have **an appropriate medical indication** for the agents and appear to be using anticholinergics to relieve EPS, depression or negative schizophrenic symptoms

**ANTICHOLINERGIC TOXICITY**

| PLANTS | DRUGS | POLYPHARMACY |
|---|---|---|
| Jimson Weed<br>Datura<br>Belladonna | Antihistamines:<br>Diphenhydramine<br>Doxylamine<br><br>Oxybutynin (incontinence) | Many drugs have anticholinergic properties (Ex: tricyclic antidepressants (TCAs), atypical antipsychotics |
| Effects are primarily caused by antagonism at muscarinic receptors. | | |
| ALTERED MENTAL STATUS | Delirium<br>Seizures<br>*"Mad as a hatter"* | if patient develops agitated delirium may develop rhabdomyolysis |
| BIG | Mydriasis<br>*"Blind as a bat"* | |
| HOT | Hyperthermia<br>*"Hot as hell"* | Decreased ability to sweat and excitatory motor activity may lead to increased temperature |
| DRY | Dry mucous membranes<br>Lack of sweating<br>Urinary retention<br>*"Dry as a bone"* | |
| FAST | Tachycardia | |

# Is medicinal ketamine associated with urinary dysfunction issues? Assessment of both the European Medicines Agency (EMA) and the UK Yellow Card Scheme pharmacovigilance database-related reports (Schifano N, Chiappini S, Schifano F, LUTS 2020)

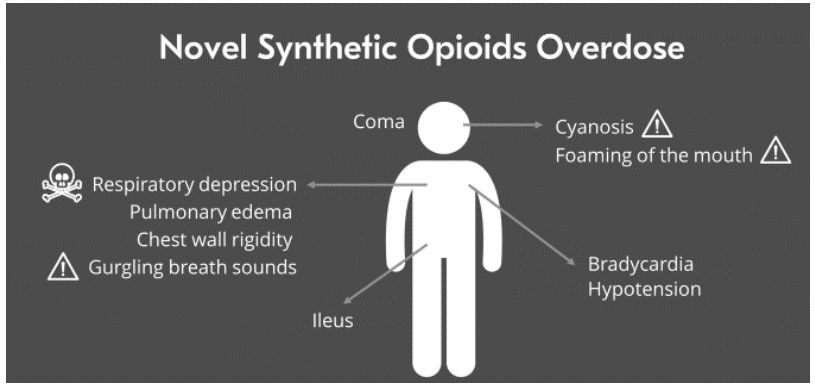
- Ketamine prescribing is being increasingly considered for psychopathological conditions. A range of ketamine-associated urinary dysfunction (KAUD) issues are typically described in ketamine misusers
- Analysis of both the 2005-2017 European Medicines Agency (EMA) and the 2006-2018 UK Yellow Card Scheme (YCS) pharmacovigilance databases.
- Out of a total of 9,971 ADRs (210 'suspect' single cases), 1,758 ADRs (**17.7%; 194 cases) referred to renal/urinary disorders,** typically kidney/ureter (922 ADRs) or bladder/urethra (837 ADRs). Ketamine was the sole drug administered in 156/194 (80.4%) cases.
- ADRs occurred in the 1 month-1 year time interval after the start of ketamine administration; in 30 cases the ADR occurred within 48 hours.
- YCS data were consistent with EMA findings, with some 50/217 (23%) ADRs referring to renal/urinary disorders.
- Current datamay only represent a gross underestimate of the KAUD real prevalence issues. Until safety concerns are resolved, it is here suggested that **chronic treatment involving higher doses/repeated exposure to ketamine be restricted to the context of controlled trials or clinical audits**.

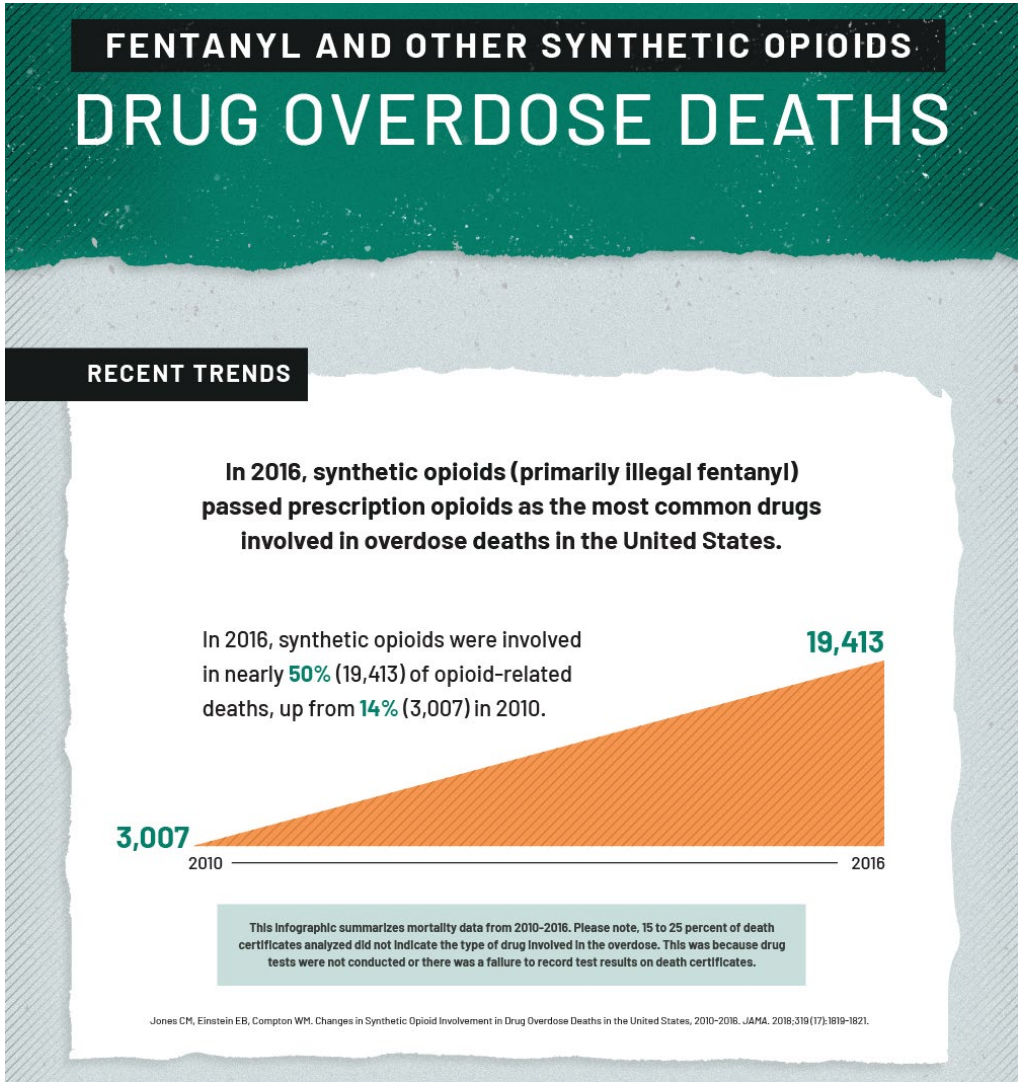
Milano G, Chiappini S, Mattioli F, Martelli A, **Schifano F.** beta-2 Agonists as Misusing Drugs? Assessment of both **Clenbuterol**- and Salbutamol-related European Medicines Agency Pharmacovigilance Database Reports. Basic Clin Pharmacol Toxicol. 2018 Aug;123(2):182-187.

- A recent years' increase in misusing levels of image- and performance- enhancing drugs (IPEDs) has been observed.
- Out of these drugs, beta-2 agonists have recently emerged for their potential of misuse, especially for slimming and bodybuilding purposes.
- To this perspective, **clenbuterol ('the size zero pill')** has been reported as being both popular and widely available from the illegal market

# New/Novel Synthetic Opioids - I

- Opioid crisis
- Diverted prescription opioid analgesics (e.g., oxycodone, hydrocodone, hydromorphone), failed opioid drug candidates (e.g., benzamide derivatives), and various legal and illegal fentanyl analogues (e.g., acetylfentanyl, furanylfentanyl, carfentanil)
- Low cost of materials and equipment required for clandestine laboratory production and enormous profit potential
- There is little information available regarding the pharmacology and the toxicology of NSOs in abuse settings
- More than one naloxone dose in case of overdose (up to 12 mg)

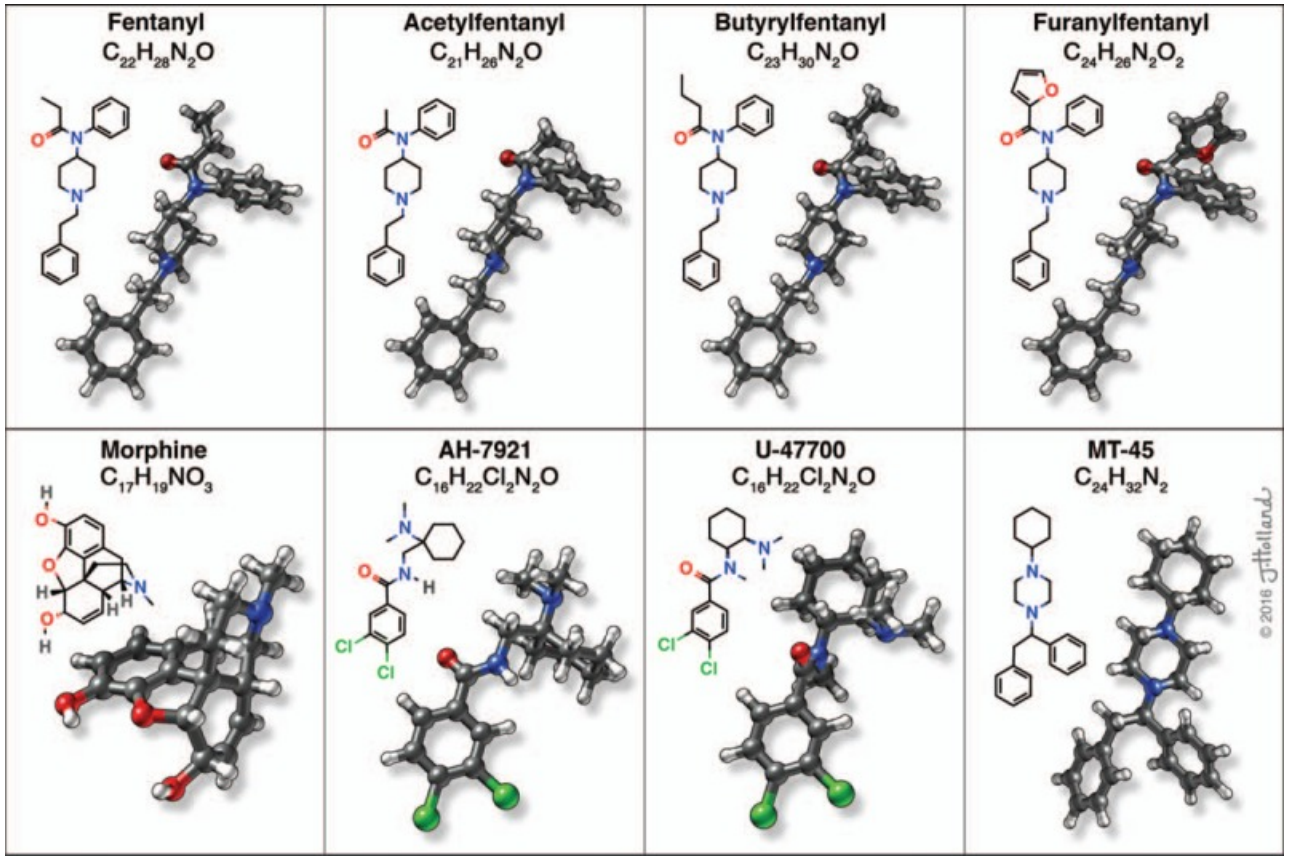


# New Synthetic Opioids - II


- Available from the dark web ('China White', 'Synthetic Heroin', 'Street Oxy')
- Identified from heroin batches as well (Zawilska et al., 2017)

| Route of administration | Dose | | | Action | | |
|---|---|---|---|---|---|---|
| | Light | Common | Strong | Onset | Duration | After-effects |
| **Morphine** | **5–10 mg** | **15–20 mg** | **>30 mg** | | | |
| Insufflation | | | | 10–30 min | 4–5 h | 1–12 h |
| Intravenous/intramuscular | | | | 0–1 min | 2–4 h | 1–12 h |
| **Heroin** | | | | | | |
| Insufflation | 7.5–20 mg | 20–35 mg | 35–50 mg | 10–15 min | 3–6 h | 1–24 h |
| Smoked | 5–15 mg | 15–25 mg | | 5–10 min | 3–5 h | 1–24 h |
| Intravenous | | 5–10 mg | 8–15 mg | 0–5 min | 4–5 h | 1–24 h |
| **Fentanyl** | | | | | | |
| Intranasal | 10–25 µg | 25–50 µg | 50–75 µg | | | |
| Transdermal | 12.5 µg/h | 25–50 µg/h | 50–100 µg/h | 2–4 h | 48–72 h | |
| Buccal | | | | 15–30 min | 1–4 h | |
| Insufflated | | | | 15–30 min | 1–4 h | |
| **Acetylfentanyl** | | | | | | |
| Oral | 1–3 mg | 3–5 mg | 5–7 mg | Minutes | Hours | 1–8 h |
| **Acryloylfentanyl** | | | | | | |
| Insufflation | 5–12.5 µg | 12.5–25 µg | 25–47.5 µg | 1–5 min | 10–30 min | 1–2 h |
| **Butyrylfentanyl** | | | | | | |
| Oral | 0.4–0.8 mg | 0.8–1.5 mg | 1.5–3 mg | 15–30 min | 3–4 h | 1–4 h |



# New Synthetic Opioids-III


| Opioid | FDA | Relative Potency | Lethal Dose |
|---|---|---|---|
| Morphine | ✓ | 1x | 1 Pea |
| Heroin | ✓ | 2x | 1 Sunflower Seed |
| Fentanyl | ✓ | 100x | 1 Sesame Seed |
| Sufentanil | ✓ | 500x | 1 Grain of Sand |
| Carfentanil | ✗ | 10,000x | 0.5 Grains of Salt |

# *Opioids in the NPS Finder:*

quantitative and qualitative analysis

Arillotta D, **Schifano F**, Napoletano F, Zangani C, Gilgar L, Guirguis A, Corkery JM, Aguglia E, Vento A. Novel Opioids: Systematic Web Crawling Within the e-Psychonauts' Scenario. Front Neurosci. 2020 Mar 18;14:149. doi: 10.3389/fnins.2020.00149.

After a thorough screening, opioids were **subdivided** into:

## •ATC/prescribing opioids (according to WHO): ~47

This list includes 4 fentanyls (**alfentanil, fentanyl, remifentanil, sufentanil**)

## •Herbals: ~18

This list includes opium and poppy straw derivatives, **Mitragyna speciosa/kratom, Salvia divinorum/Sally D** and derivatives (salvinorin A and Salvinorin B ethoxymethyl ether)

## •Fentanyl analogues: ~237 (including **ohmefentanyl and carfentanyl derivatives**, respectively 6300 and 10000 times more powerful than morphine)

## •Miscellaneous: ~134

This list includes some **morphine derivatives**, some precursors and molecules not yet classified elsewhere or not included above

# Further suggestions from the psychonauts' world (1)

- **6-Methylenedihydrodesoxymorphine:** a potent μ-opioid agonist, *80x stronger than morphine*.
- **BDPC alias Bis(2,4-dinitrophenyl)carbonate or bromadol**: studies assigned a value of *504 times the potency of morphine* for the more active trans-isomer. BDPC/bromadol (Ki = 1.49 nM for MOR)
- **Cyclazocine:** it is a KOR agonist and MOR partial agonist also having high affinity for the DOR; *psychotomimetic, dysphoric, and hallucinatory* effects.
- **Cyprenorphine:** mixed agonist–antagonist effects at opioid receptors, like those of buprenorphine. However the effects are somewhat different, as it produces *pronounced dysphoric and hallucinogenic effects* which limit its potential use as an analgesic.
- **O-desmethyltramadol/Krypton:** considerably *more potent as μ-opioid agonist compared to tramadol*. It also shows comparatively far lower affinity for the δ- and κ-opioid receptors. It is also an antagonist of the serotonin 5-HT2C receptor, at pharmacologically relevant concentrations, via competitive inhibition.
- **Embutramide:** potent opioid analgesic and sedative drug that is **structurally related to methadone**. Presents with a very narrow therapeutic window; used for euthanasia of a range of different animals; been reported as being *used for suicide by people with access to the drug*.

# Further suggestions from the psychonauts' world (2)

- **Levallorphan:** as an *agonist of the κ-opioid receptor* (KOR), can produce severe mental reactions.
- **Levomethorphan (note dextromethorphan as well):** potent agonist of all three of the opioid receptors, μ, κ (κ1 and κ3 but notably not κ2), and δ, as an *NMDA receptor antagonist, and as a serotonin-norepinephrine reuptake inhibitor*. Can produce dysphoria and psychotomimetic effects such as dissociation and hallucinations.
- **Levorphanol**: Relative to morphine, lacks complete cross-tolerance and possesses greater intrinsic activity at the MOR and shows a *high rate of psychotomimetic side effects* such as hallucinations and delusions.
- **Nalorphine:** an antidote according to ATC classification. Side effects such as dysphoria, anxiety, confusion, and hallucinations, and for this reason, is no longer used medically. It act at the μ-opioid receptor (MOR) where it has antagonistic effects, and at the *κ-opioid receptor* (KOR) (Ki = 1.6 nM; EC50 = 483 nM; Emax = 95%) where it exerts *high-efficacy partial agonist/near-full agonist* characteristics.

# Remember.... (Schifano, 2020; Psychother Psychosomatics):

- '……for most prescription molecules here discussed, including gabapentinoids, one should here emphasize that pre-marketing processes were not able to appropriately identify their misuse and abuse potential

- Pre-authorization trials, however, typically involve the administration of carefully controlled, daily limited, therapeutic dosages, and subjects with a current/previous history of drug misuse are excluded

- Hence, the possible potential of molecules for abuse will be fully appreciated only when the real-world client population, **involving vulnerable individuals**, is exposed to it……'

# CONCLUSIONS - I



- Non-existence of information on abuse/misuse potential of a medicine interacting with the CNS does not mean that a specific medicine does not actually produce these effects
- Healthcare professionals who work in emergency departments, general practice, and mental health/addiction services should be aware of new drug abuse trends, and consider the **possible diversion** of medicines and **the risk of polysubstance abuse**
- Education of both clinicians and users is critical in order to **identify clinical related-issue**s, exert special caution with **vulnerable categories**, and to treat and prevent **the adverse effects and the potential toxicity of OTC and prescription drugs**