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RADARS® SYSTEM 2022

16TH ANNUAL SCIENTIFIC VIRTUAL MEETING

FOCUS ON OVER-THE-COUNTER DRUG ABUSE: A REVIEW OF THE DIVERSION OF ANTIHISTAMINES, COUGH MEDICINES, AND DECONGESTANTS

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RADARS® SYSTEM 2022
16TH ANNUAL SCIENTIFIC VIRTUAL MEETING

AGENDA

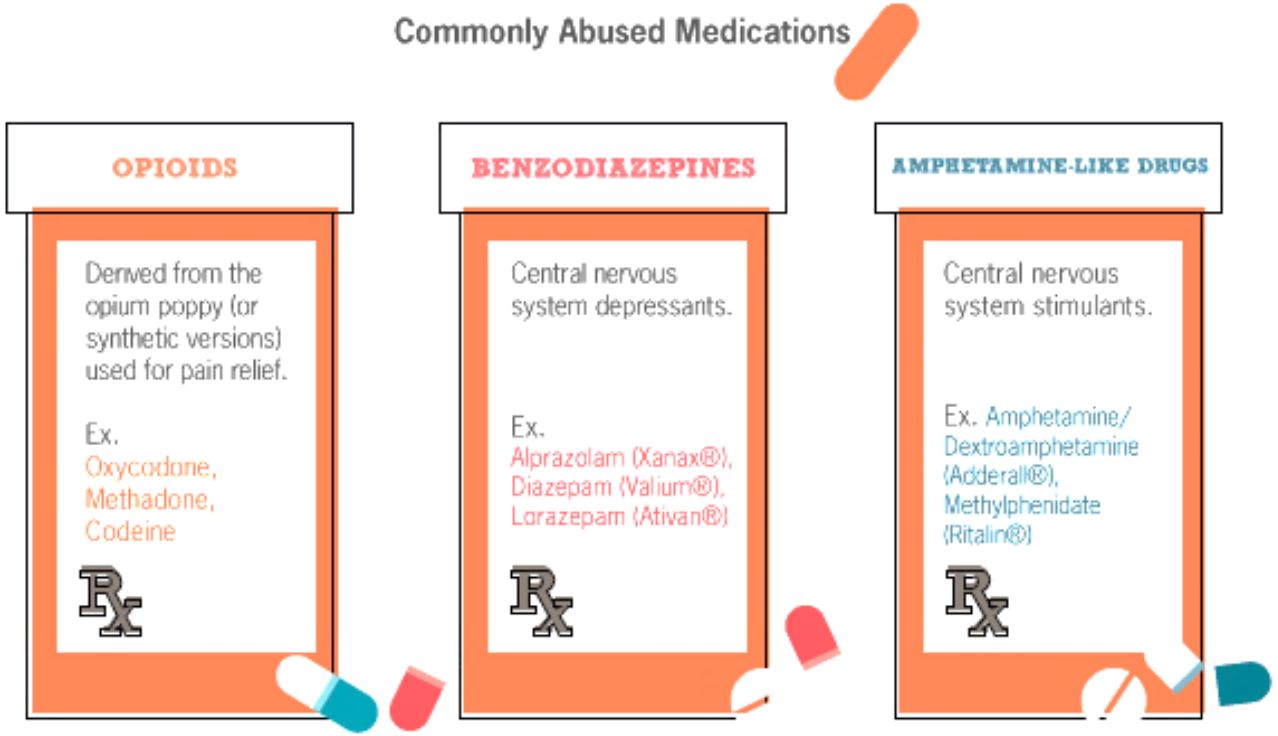
- Use of psychoactive pharmaceuticals for recreational purposes – *'pharming'*
- Misuse of over-the-counter (OTC) medications
- Conclusions: a need for drug abuse monitoring and pharmacovigilance

MISUSE OF PHARMACEUTICALS

NOT A NEW STORY:

Repeating pattern (Public Health England review, 2019)

- "What can be seen throughout many of these narratives is a story that occurs repeatedly: a new medicine arrives that offers benefits over existing medicines and is promoted as the hope for better treatment with fewer problems. *Problems with the new medicine are quickly reported by some patients and doctors but are ignored or denied, or the evidence is just lacking for some years because the research is not done. Eventually enough reports and evidence accumulate that the problems are acknowledged and then the search is on for something better and safer… and the pattern repeats.*"
- "It happened when benzodiazepines replaced barbiturates, and when z-drugs replaced benzodiazepines for insomnia. And it may be happening now as gabapentinoids are used to replace opioids for some forms of pain."



MISUSE OF PHARMACEUTICALS

NON-MEDICAL USE vs MISUSE vs DIVERSION vs ABUSE ?

MedDRA

European Monitoring Centre for Drugs and Drug Addiction

NIH National Institute on Drug Abuse

ACMD Advisory Council on the Misuse of Drugs

MISUSE OF PHARMACEUTICALS

SOURCES OF DATA:

i) Emergency Departments visits and hospital admissions related to acute intoxication states

ii) Addiction treatment admissions

iii) Internet/treatment centres/schools' surveys

iv) National poison data

v) Voluntary reports to pharmacovigilance authorities

vi) Fatalities recorded by coroners, medical examiners, and other investigators

↓

GLOBAL- OR EUROPEAN-RELATED NUMBERS ON THE ABUSE/MISUSE/NON-MEDICAL USE OF MEDICATIONS ARE ONLY PARTIALLY AVAILABLE

- Studies on the use of prescription and OTC drugs are scarce and often they do not distinguish prescription from OTC drugs and prescribed from non-prescribed use, e.g., as in the case of analgesic opioids
- The FDA and the EMCDDA are mainly focused on illicit drugs and, among prescription molecules, on already known abused molecules such as benzodiazepines and opioids

MISUSE OF PHARMACEUTICALS

- A growing use of psychoactive pharmaceuticals including over-the-counter (OTC) medications has emerged in the drug scene
- Misusing prescription drugs and OTCs involves not only risks associated with drugs, but also:

  -side-effects

  -interactions between drugs (licensed/unlicensed) and other substances and products (food/ alcohol)

  -individual variation in responses (genetic differences and comorbidities)

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

Abuse of medications that theoretically are without abuse potential

Roy R Reeves [1], Mark E Ladner [1], Candace L Perry [1], Randy S Burke [1], Janet T Laizer [1]

Editorial > Brain Sci. 2020 Oct 14;10(10):736. doi: 10.3390/brainsci10100736.

What about "Pharming"? Issues Regarding the Misuse of Prescription and Over-the-Counter Drugs

Stefania Chiappini [1], Fabrizio Schifano [1]

Review > Brain Sci. 2018 Apr 22;8(4):73. doi: 10.3390/brainsci8040073.

Abuse of Prescription Drugs in the Context of Novel Psychoactive Substances (NPS): A Systematic Review

Fabrizio Schifano [1], Stefania Chiappini [2], John M Corkery [3], Amira Guirguis [4]

MISUSE OF PHARMACEUTICALS

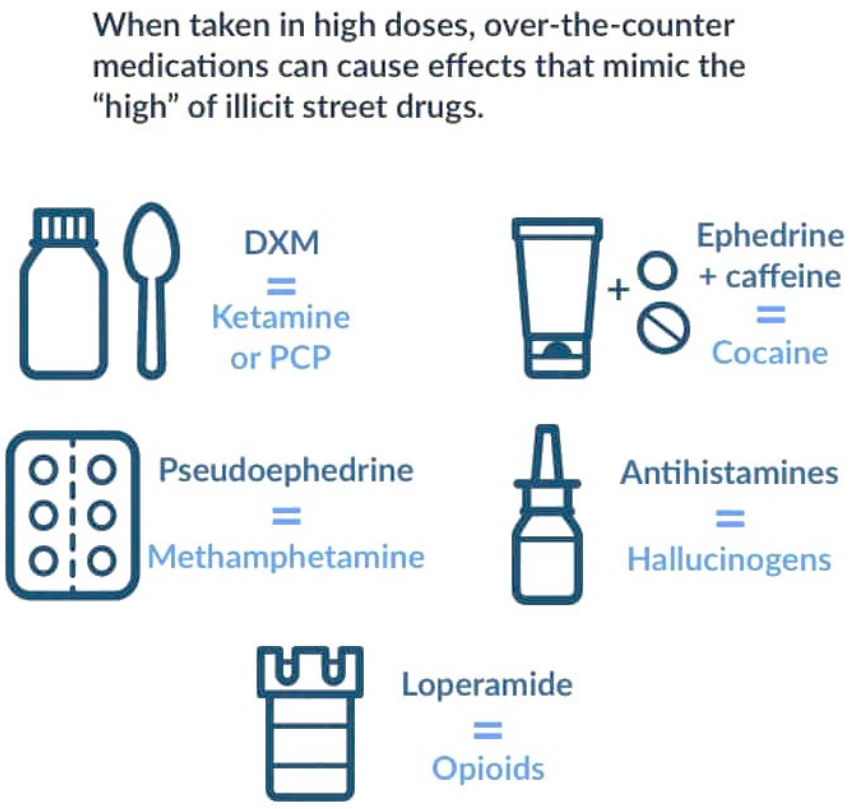
COMMON PATTERNS OF NON-MEDICAL MEDICINE USE:

- People with anxiety disorders and other mental health problems or pain may use medicines to **self-medicate** these symptoms without appropriate medical supervision or outside of accepted medical practice

- People who have no medical reasons for using medicines use them for **recreational or enhancement** purposes

- People who use opioids or central nervous system stimulants might self-medicate using benzodiazepines or Z-drugs to **increase the high, postpone opioid withdrawal or reduce the adverse symptoms** occurring after consuming stimulants

MISUSE OF OTC PHARMACEUTICALS



- Dextromethorphan (DXM)
- Loperamide
- Benzydamine (Tantum rosa ®)
- Codeine-based cough medicines
- Antihistamines (e.g., diphenhydramine, promethazine, chlorpheniramine, and dimenhydrinate)
- Pseudoephedrine-containing nasal decongestants

MISUSE OF OTC PHARMACEUTICALS

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

Their use for non-medical purposes may have developed due to their **increased availability**, **their inexpensive cost**, and the **users' perceptions of their safety**

Procured from:

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

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

Psychiatric concomitant diseases associated with OTC misuse: **depression, anxiety, somatic distress, and psychotic disorders**

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

The SMART choice (Miller, 2006):
Stigma: no negative connotation
Money: relatively inexpensive
Access: OTC drugs might be found in many home medicines cabinets
Risks: OTCs are available from medical companies
Testing: routine drug tests do not test for OTCs

Front Psychiatry. 2021 May 7;12:657397. doi: 10.3389/fpsyt.2021.657397. eCollection 2021.

Focus on Over-the-Counter Drugs' Misuse: A Systematic Review on Antihistamines, Cough Medicines, and Decongestants

Fabrizio Schifano [1], Stefania Chiappini [1 2], Andrea Miuli [2], Alessio Mosca [2], Maria Chiara Santovito [2], John M Corkery [1], Amira Guirguis [3], Mauro Pettorruso [2], Massimo Di Giannantonio [2], Giovanni Martinotti [2]

- After completion of the selection, eligibility, and screening phases, some **92 articles published up to December 2020** were here taken into consideration; case reports, surveys, and retrospective case series analyses were included
- Most articles focused here on DXM (n = 54) and diphenhydramine (n = 12). When specified, dosages, route(s) of administration, toxicity symptoms (including both physical and psychiatric ones), and outcomes were reported
- OTC drugs were obtained by various means, including family and friends, multiple doctor prescriptions, illegal online pharmacies/shops, and theft/burglary from hospitals, residences, and pharmacies

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RESULTS

- Overall, two main populations of OTC misusers were identified:

(a) patients already suffering from a health condition and/or a psychiatric disorder who became dependent on their prescription/OTC drugs due to prolonged/high-dosage use, e.g., DXM-based cough mixtures started for sinusitis, cough, nasal congestion, and then continued for years at higher dosages

(b) individuals, including substance abusers, not in treatment for a medical disorder or illness who may have started to misuse/abuse with OTC medications for recreational purposes

DEXTROMETORPHAN

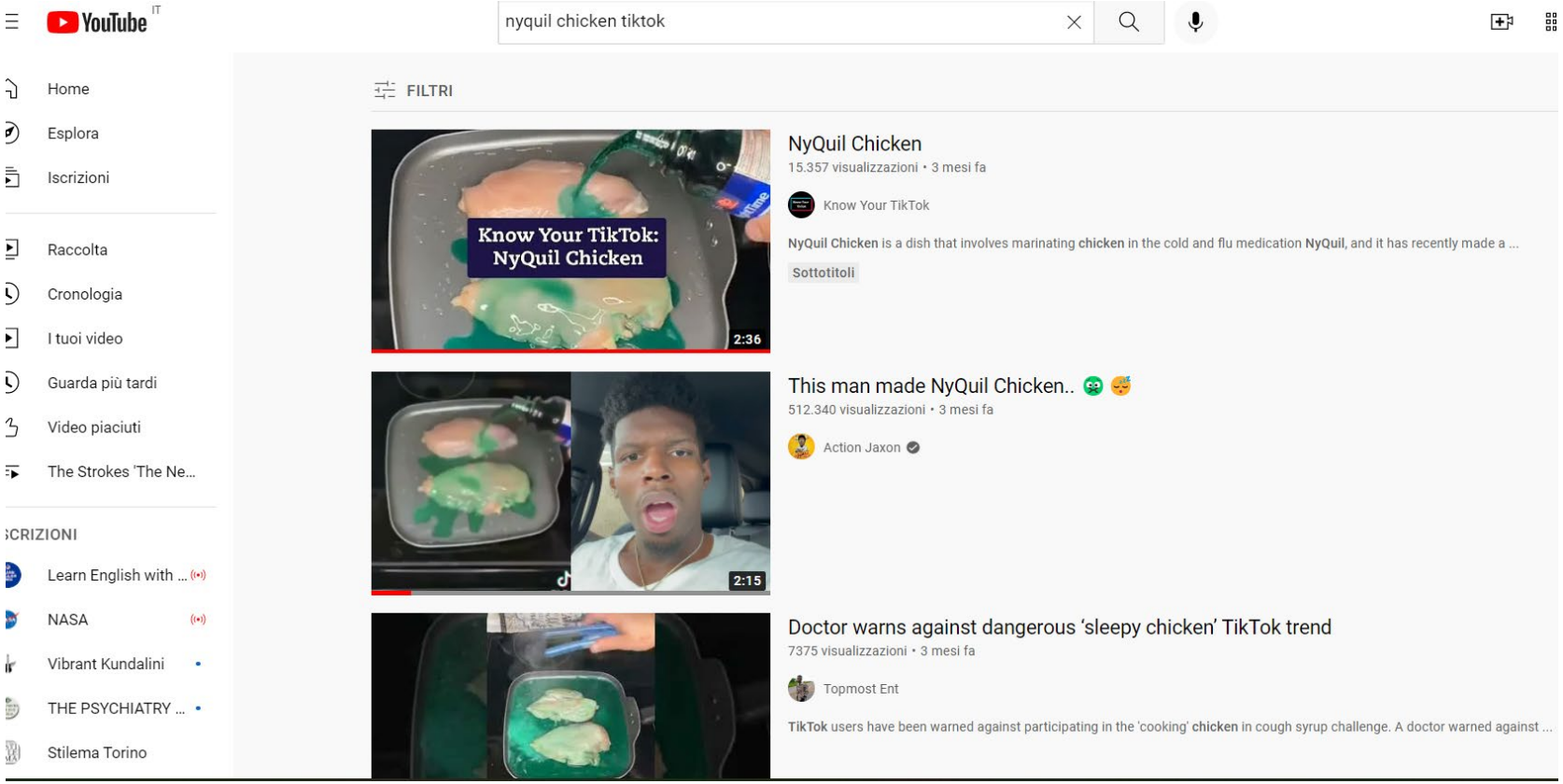
- DXM is a cough suppressant and opioid derivative with dose-dependent sedative, dissociative, and stimulant properties
- Psychotropic effects are mostly related to its metabolism to its active metabolite dextrorphan, an **NMDA antagonist**. Dextrorphan is also thought to exert **adrenergic effects** by inhibiting peripheral and central catecholamine reuptake. Further, DXM has specific **serotonergic and sigma-1 opioidergic properties**
- **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 results in **withdrawal symptoms**

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	hyperexicatability	
	memory impairment	poor motor control	

Dose-related DXM psychic effects (**therapeutic range: from 60 to 120 mg/day in divided doses**)

DEXTROMETORPHAN

THE 'SLEEPY CHICKEN' CHALLENGE



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*’)
- Even though safe within normal dosages (2-16mg), at higher dosages (>50mg) **CNS depression, electrocardiogram abnormalities** and **fatal cardiotoxicity** have been described

- 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**

LOPERAMIDE

Overview of loperamide misuse-abuse-/dependence-/withdrawal-related Adverse Drug Reactions (ADRs) as reported to the EudraVigilance (EV) database

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

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

	LOPERAMIDE ADRs
Time-frame considered	08/2005–08/2017
Total number of 'suspect' ADRs	7,895
Misuse-abuse-/dependence-/withdrawal-related ADRs	**1,983 (1,983/7,895= 25.11%)**
Number of unique patients reported to the database	434
Age-range most typically represented	18-64 yy (4,577/ 7,895= 57.9%)
ADRs most typically represented	drug use disorder 742 (742/1,983=37.4%), intentional overdose 502 (502/1,983=25.3%), intentional product misuse 296 (296/1,983=14.9%)
Gender most typically represented	Female (F/M ratio:4,401/3,397=1.29)
Loperamide identified as the sole drug	182 cases (182/434=41.9%)
Concomitant drugs most typically represented in the remaining (434-182) 252 cases	Antidepressants in 44 cases (44/252= 17.5%); SSRIs most typically reported; Benzodiazepines in 40 cases (40/252=15.9%); Opioids in 23 cases (23/252=9.13%); Other psychotropic drugs in 21 cases (21/252=8.3%); Antipsychotics in 11 cases (11/252=4.36%); Mood stabilizers in 9 cases (9/252=3.57%)
Resulted in death	305/1,983 (15.34%, corresponding to 94/434 cases: 21.6%)
Suicides	373 ADRs, corresponding to 42/434 cases; 9.67%

BENZYDAMINE

Curr Neuropharmacol. 2021 Oct 18;19(10):1728-1737. doi: 10.2174/1570159X19666210113151136.

The Benzydamine Experience: A Systematic Review of Benzydamine Abuse

Chiappini Stefania [1], Miuli Andrea [2], Mosca Alessio [2], Pettorruso Mauro [2], Guirguis Amira [3], Corkery John Martin [1], Martinotti Giovanni [2], Di Giannantonio Massimo [2], Schifano Fabrizio [1]

- Benzydamine hydrochloride (BZY) is **a non-steroidal anti-inflammatory drug** (NSAID) with analgesic, antipyretic, and antimicrobial properties, available since 1966 for the symptomatic treatment of acute inflammatory states of the oral and vaginal mucosae. It is dispensed distributed without prescription and marketed for external use in various formulations including mouthwash, vaginal douche preparations, and capsule forms
- The **maximum oral daily dose** of BZY **is 150–200mg** and psychiatric adverse effects have not been reported at this dosage
- Relatively little is known about the effects of BZY on the central nervous system. **Neurological symptoms such as dizziness, vertigo, hyperactivity, excitation, and convulsions have been reported because of high-dosage (500 – 3,000 mg) systemic ingestion**. Dose-dependent psychotropic effects including anxiety, agitation, paranoia, and hallucinations; (specifically visual hallucinations, with insects and monsters being reported, have been described. So-called **BZY "trips"** are anecdotally reportedly characterized by feelings of happiness, euphoria, and ego-dystonic hallucinatory experiences, which appear generally to resolve spontaneously in 2-3 days
- Over the last 20 years or so, evidence has emerged regarding the widespread recreational use of BZY in various countries, including **Brazil, Italy, Romania, Poland and Turkey**

BENZYDAMINE

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- BZY was included in April 2010 in the list of **Novel Psychoactive Substances (NPS)** by the EMCDDA and by Europol. Consistent with this, in Turkey BZY was moved in 2012 into **prescription status**
- A range of neurobiological mechanisms may be involved in the BZY-related onset of these psychiatric symptoms, including:

i) **cross-sensitivity with other substances of abuse**. Indeed, preclinical studies suggested that BZY may show a powerful reinforcing effect in animals previously administered with heroin and cocaine

ii) **BZY affinity with CB1 cannabinoid receptors**

iii) **at high dosages (e.g. 2,000-2,500mg), BZY might influence the dopaminergic regulation of limbic-striatal interplay**

iv) **BZY-related serotonergic 5HT-2A activation**, which may be associated with an **indole group within the BZY chemical structure.** and may explain the BZY-related visual hallucinations alteration

- BZY acute toxicity in oral dosages of 500–3,000 mg include signs and symptoms of CNS stimulation, including seizures, hyperreflexia, tachycardia, paraesthesia, excitation, hyperarousal/hyperactivity, and convulsions; moreover, frequent psychiatric symptoms after ingestion of BZY preparations include visual hallucinations, particularly in the form of zoomorphic visions, referential concerns, and paranoia. No BZY-related deaths have been here reported in the literature

CODEINE

- **Calming effects:** being an opioid, it determines rewarding and pleasant effects; relief from tension and anxiety; and decreased aggression
- 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** have been reported, 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**

> J Psychoactive Drugs. Nov-Dec 2020;52(5):453-462. doi: 10.1080/02791072.2020.1797250. Epub 2020 Aug 4.

"Purple Drank" (Codeine and Promethazine Cough Syrup): A Systematic Review of a Social Phenomenon with Medical Implications

A Miuli [1], G Stigliano [1], A Lalli [1], M Coladonato [1], L D'Angelo [2], F Esposito [3], C Cappello [1], M Pettorruso [1], G Martinotti [1 4], F Schifano [4], M Di Giannantonio [1]

> J Psychopharmacol. 2021 Jan 10;269881120959615. doi: 10.1177/0269881120959615. Online ahead of print.

Beyond the 'purple drank': Study of promethazine abuse according to the European Medicines Agency adverse drug reaction reports

Stefania Chiappini [1], Fabrizio Schifano [1], John Martin Corkery [1], Amira Guirguis [2]

PROMETHAZINE

J Psychopharmacol. 2021 Jun;35(6):681-692. doi: 10.1177/0269881120959615. Epub 2021 Jan 10.

Beyond the 'purple drank': Study of promethazine abuse according to the European Medicines Agency adverse drug reaction reports

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- Promethazine is a histamine (H1) receptor antagonist that is commonly used for symptomatic relief of nausea and vomiting, for allergic conditions, motion sickness and common cold, and for short-term use treatment of insomnia in adults or as a paediatric sedative
- It is classified as **a first-generation antihistamine molecule** which, compared with second-generation antihistamines, easily penetrates the blood-brain barrier and is associated with adverse effects such as moderate/intense sedation
- During the past 15 years the abuse of promethazine, especially from OTC and prescription cough and cold medicines and at higher-than-recommended dosages, has been reported
- **Toxicity might result in severe impairment of cognitive and psychomotor functions** due to central nervous system (CNS) depression/reduced levels of consciousness, and may cause **fatalities**

PROMETHAZINE

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Analysis of promethazine abuse/misuse/dependence/withdrawal cases recorded by the EudraVigilance (EV), 2003-2019

	Individual cases (% of total within parentheses)
Total abuse/misuse/dependence cases	1,543 single cases; Number of ADRs:11,796
Age range	
Adult (19-64yrs, mean age: 31.8yrs, SD 26.55-37.05)	648 (42.0%)
Adolescent (10-18yrs, mean age, 15.9yrs, SD 14.3-17.77)	23 (1.5%)
Elderly (> 65yrs, mean age, 72.3yrs, SD 70.85-73.7)	25 (1.6%)
Neonatal (hours-days, mean age, 24hh, SD 16.6-27.4)	14 (0.9%)
Infant (months-1yr, mean age, 10months, SD 7-13)	7 (0.45%)
Child (< 10yrs, mean age 5yrs, SD 3.6-6.3)	4 (0.35%)
Male/Female	235/461: 0.51
Most represented ABUSE/MISUSE/DEPENDENCE-related ADRs according to the PTs:	557 (557/1,543: 36.1%)
ABUSE-RELATED ADRs	458(458/557: 82.2%)
Drug abuse	300
Drug abuser	15
Drug diversion	1
Intentional product misuse	117
Intentional product use issue	9
Substance abuse	11
Substance abuser	3
Substance use	2
DEPENDENCE-RELATED ADRs	44 (44/557: 7.9%)
Dependence	4
Drug dependence	39
Substance dependence	1
WITHDRAWAL-RELATED ADRs	55 (55/557: 9.8%)
Withdrawal syndrome	19
Drug withdrawal convulsions	1
Drug withdrawal neonatal syndrome	18
Drug withdrawal syndrome	17
Outcome	Fatal 310 (310/557: 55.6%) Unknown 161 (161/557: 28.9%) Recovered/Resolved 55 (55/557: 9.9%) Recovering/Resolving 18 (18/557: 3.3%) Not recovered/Not resolved 13 (13/557: 2.3%)
Promethazine-cases alone	74 (with maximum dosage 2,500mg)
Promethazine-cases with other drugs	Most cases (122) were over 100mg (max 8,000mg)
Most common *psychoactive substances* used	Alcohol: 114 Cocaine: 68 Cannabis: 16 Ketamine: 4 Amphetamine: 1
Most common *prescription drugs* used	Opioids: 1,187 Benzodiazepines: 914 Antidepressants: 871 Antipsychotics: 437 Z-drugs: 222 Mood Stabilisers: 197

OTHER ANTIHISTAMINES

Diphenhydramine/DPH antihistamine moiety of dimenhydrinate/DH

Diphenhydramine recommended dose is

50mg, no more than 3x daily

300mg = mild euphoria and hallucinations

Over 1,000mg daily = extreme instance of

abuse

PSEUDOEPHEDRINE

Sympathomimetic properties, exerting a stimulating action on **alpha, beta1-, and beta2-** adrenergic receptors	**ACUTE EFFECTS** • stimulant effects, e.g. euphoria, insomnia, diminished sense of fatigue, anorexia, and accelerated thinking; • psychotic symptoms with auditory and visual hallucinations, persecutory delusions, fear, disorganized behaviour might develop after high-dose consumption	**CHRONIC EFFECTS** • dependence might be developed after long-term use • withdrawal symptoms: dysphoria, restlessness, abnormal perceptions	**Due to the possibility to be used to manufacture the class A controlled drug methylamphetamine**, restrictions have been in place in the UK to manage the risk of products containing pseudoephedrine and ephedrine; in the US, a prescription is not needed in most States, and in remaining States there are limits on how much an adult subject can buy each month	Brand names and street names: "Chalk", "Crank", "Meth", "Speed"; 'Russian Cocktail' includes pseudoephedrine consumed together with potassium permanganate and acetylsalicylic acid diluted in water; common brand names: Sudafed®, Nexafed®, Zephrex-D®; Claritin® includes pseudoephedrine and loratadine

CONCLUSIONS

- OTC misusing issues are both widespread worldwide and popular
- **Vulnerable categories** included adolescents and young adults, although real prevalence figures remained unknown, due to a lack of appropriate monitoring systems
- OTC recreational intake appeared to be associated with **high/very high dosages; idiosyncratic routes of administration** (e.g., snorting, IM, IV); and associated with **ingestion of both licit** (e.g., alcohol, prescription opioids, benzodiazepines, other OTCs)**; and illicit** (e.g., cannabis, cocaine, ketamine, etc.) **drugs**

CONCLUSIONS

- Non-existence of information on abuse/misuse potential of a new medicines 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 services should be aware of new drug abuse trends, and consider the **eventual diversion** of medicines and **the risk of polysubstance abuse**
- **Education** of both clinicians and users
- **Pharmacovigilance**

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH
EudraVigilance Human
NEW

FDA
FAERS
FDA Adverse Event Reporting System

ACKNOWLEDGEMENTS

The conference organization

My Supervisors: Fabrizio Schifano; John M. Corkery; and Amira Guirguis

University of Hertfordshire UH

Thank you for the attention!