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ADDICTION, COMORBIDITY AND NEW PSYCHOACTIVE SUBSTANCES (NPS)

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REPUBLIKA SLOVENIJA
MINISTRSTVO ZA IZOBRAŽEVANJE,
ZNANOST IN ŠPORT



Naložba v vašo prihodnost
OPERACIJO DELENO FINANCIRA EVROPSKA UNIJA
Evropski socialni sklad

1. Introduction (addiction, comorbidity/dual disorders)
2. New psychoactive substances (NPS) among patients with addiction and comorbidity
3. Case report of NPS induced psychosis

INTRODUCTION...

- the prevalence of mental disorders is higher among patients with substance use disorders compared to general population; 75% of drug service clientele had mental health problems
(Comorbidity of Substance Misuse and Mental Illness Collaborative Study (COSMIC), 2002)
- regarding prognosis in the treatment of patients with comorbid disorders, both disorders have a poorer outcome when unrecognised and undertreated

...INTRODUCTION

- poor medication compliance, high level of recidivism, rehospitalisations, high degree of symptom severity, impaired psychosocial functioning, increased risk of suicide and risky behaviour are associated with untreated disease (*Mueser et al, 2003*)
- the literature suggests that people with dual diagnosis face more barriers to receiving appropriate healthcare, both for their mental illness and for their substance abuse in addition to other physical disorders (barriers to detection and access, the quality of care is worse for people with a dual diagnosis, “diagnostic overshadowing”, systematic exclusion from the studies) – stigma (*Evans – Lacko et al., 2010*)

Lifetime prevalence (%) of substance use disorders for various DSM-III psychiatric disorders

Epidemiologic Catchment Area (ECA)

GROUP	SUBSTANCE USE (%)
General population	16,7
Schizophrenia	47,0
Any Mood Disorder	32,0
Bipolar disorder	56,1
Major depression	27,2
Dysthymia	31,4
Any Anxiety Disorder	23,7
Obsessive – compulsive disorder	32,8
Phobia	22,9
Panic disorder	35,8

DEMOGRAPHIC, CLINICAL AND HISTORICAL CORRELATES OF SUBSTANCE ABUSE

A. Demographic correlates

- gender (men)
- age (younger individuals)
- education (alcohol)
- marital status (unmarried)
- rural/urban environment

B. Clinical correlates

- antisocial personality disorder, conduct disorder in younger patients
- adherence to treatment

C. Historical correlates

- social functioning before the onset of the disease
- substance use disorder in family
- trauma and PTSD

1. Common factors models

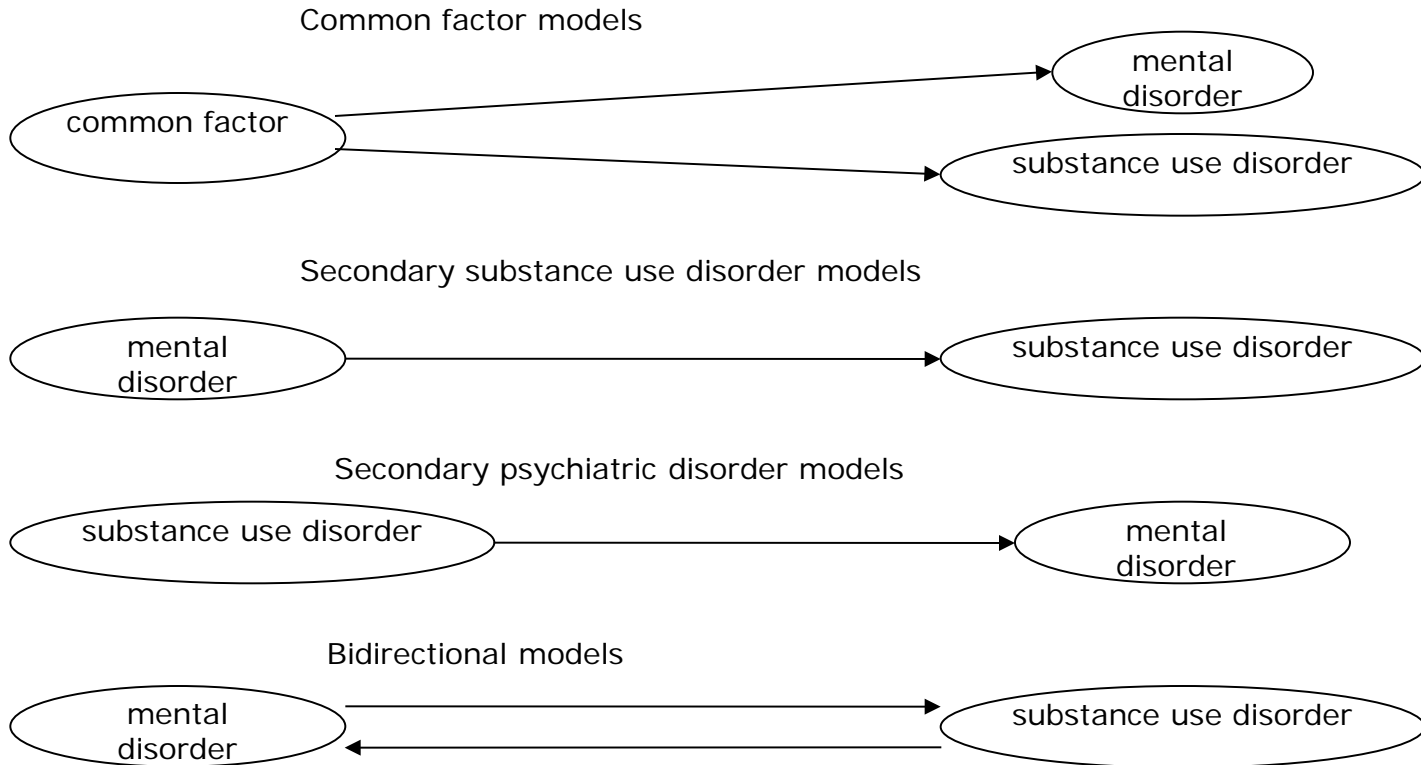
- family (genetic)
- antisocial personality disorder
- common neurobiological dysfunction
- cognitive impairment
- poverty

2. Secondary substance use disorder models

- psychosocial risk factor model
- supersensitivity model
- iatrogenic - induced sensitivity for substance abuse

3. Secondary psychiatric disorder models

4. Bidirectional models



Four theoretical models explaining increased comorbidity of mental disorders and substance use disorders

SLOVENIAN STUDY

(Segrec, Kastelic, Pregelj, 2014)

AIMS

to determine possible differences in gender, marital status, parenting, education, employment, religion, suicide in family, drug use among family members, overdoses, victimisation, history of criminal behaviour and history of previous suicide attempts among ***patients with comorbidity of substance use disorder and mental disorder*** compared to ***patients with substance use disorder without comorbid mental disorder*** in opioid addiction treatment (OST) programs in Slovenia

METHODS

- 228 consecutive patients
- willing to fulfill the questionnaire
- four different treatment centers (CPZOPD Nova Gorica, CPZOPD Pivka, CPZOPD Trbovlje, CPZOPD Piran) in Slovenia were included
- 2 groups of patients in OST programs:
 1. **patients with comorbidity of substance use disorder and mental disorder**
 2. **patients with substance use disorder without comorbid mental disorder**

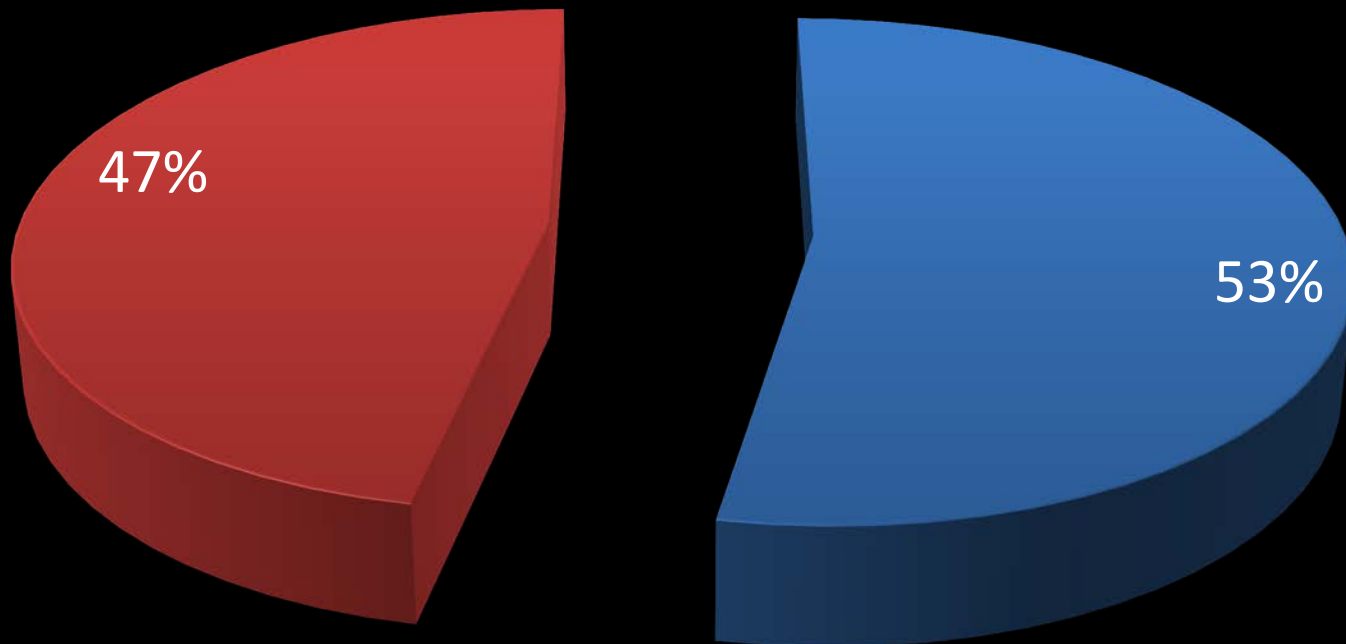
RESULTS

More than half of participants (53,1 %; 121/228) had comorbidity of substance use disorder and other mental disorder.

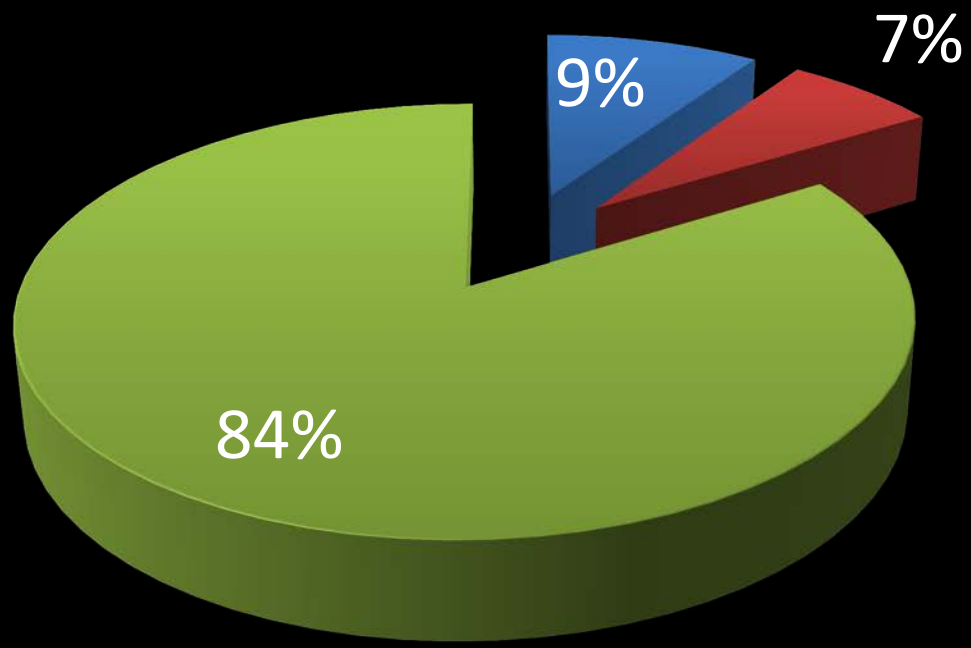
Number of patients with comorbidity (N=228)

■ comorbidity (N=121)

■ no comorbidity (N=107)



Number of patients by suicide attempt or suicide in family (N=222)

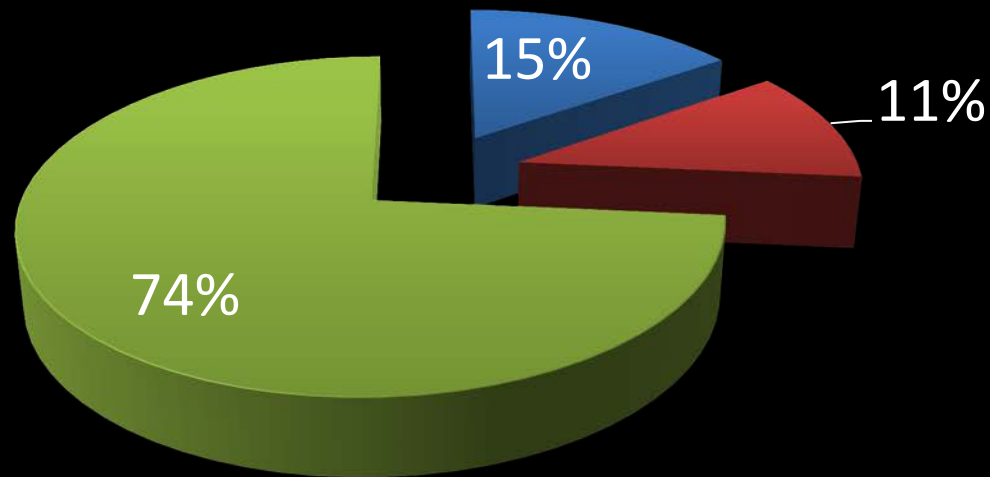


■ suicide attempt (N=21)

■ suicide attempt (N=15)

■ no (N=186)

Number of patients by substance use in family (N=223)

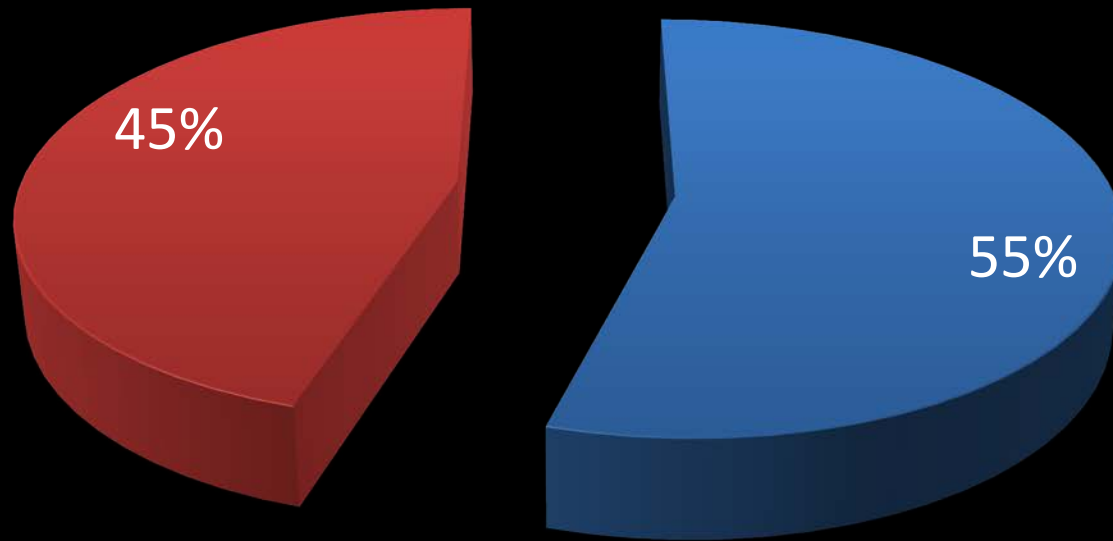


■ alcohol addiction (N=34)

■ illicit drug addiction (N=25)

■ no addiction (N=164)

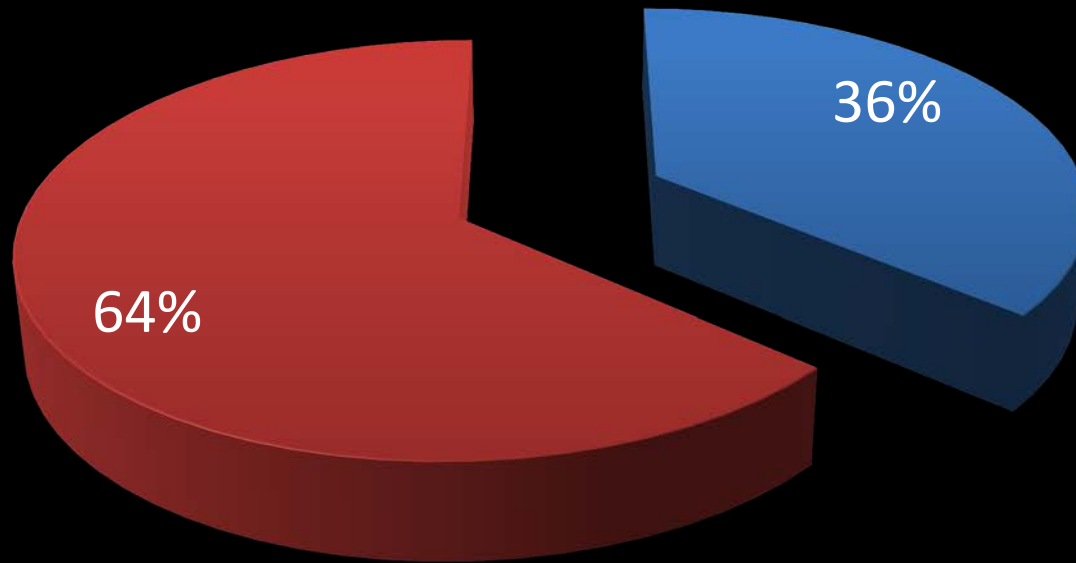
Number of patients by criminal proceedings (N=227)



■ criminal proceedings (N=124)

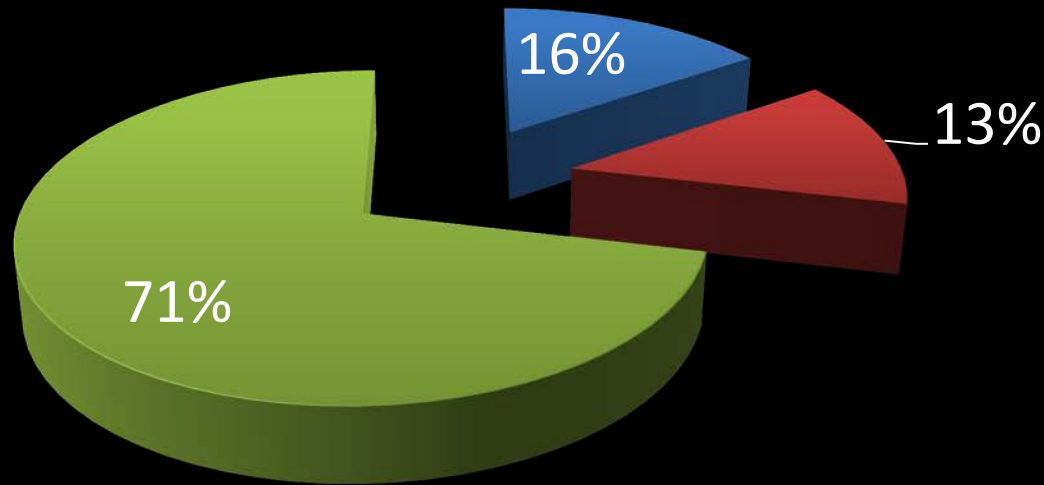
■ no criminal proceedings (N=103)

Number of patients by sentenced to prison (N=223)



■ sentenced to prison (N=81) ■ not sentenced to prison (N=142)

Number of patients by victimisation (N=227)

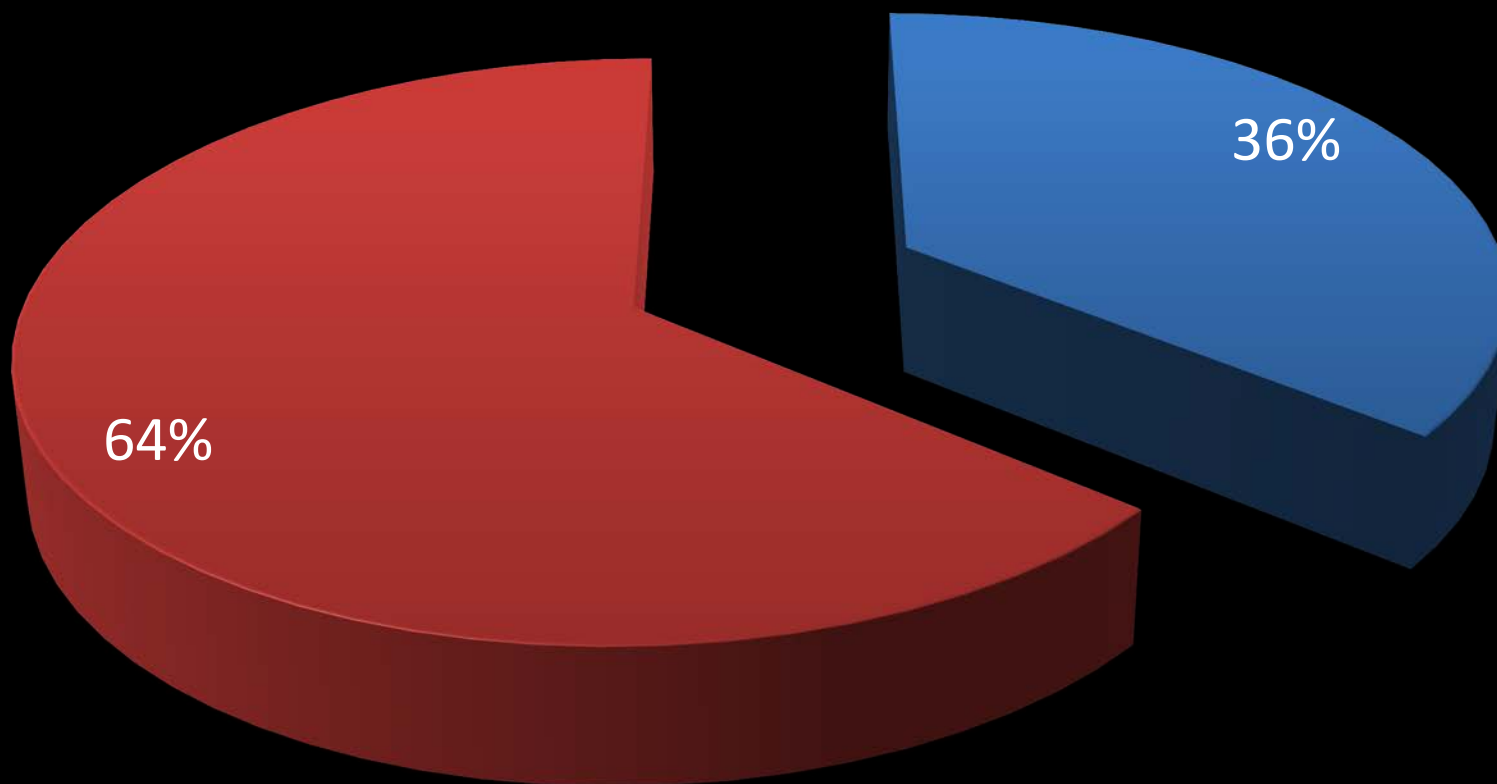


■ victimisation <16 years (N=35)

■ victimisation >16 years (N=30)

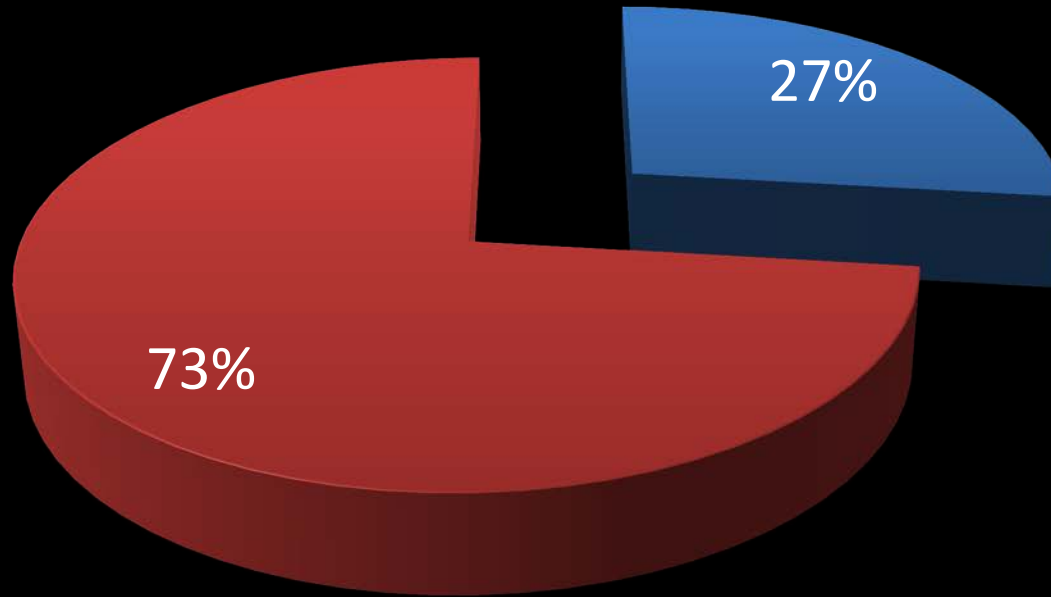
■ no victimisation (N=162)

Number of patients by history of overdose (N=228)



■ overdose ■ no overdose

Number of patients by history of suicide attempt (N=227)

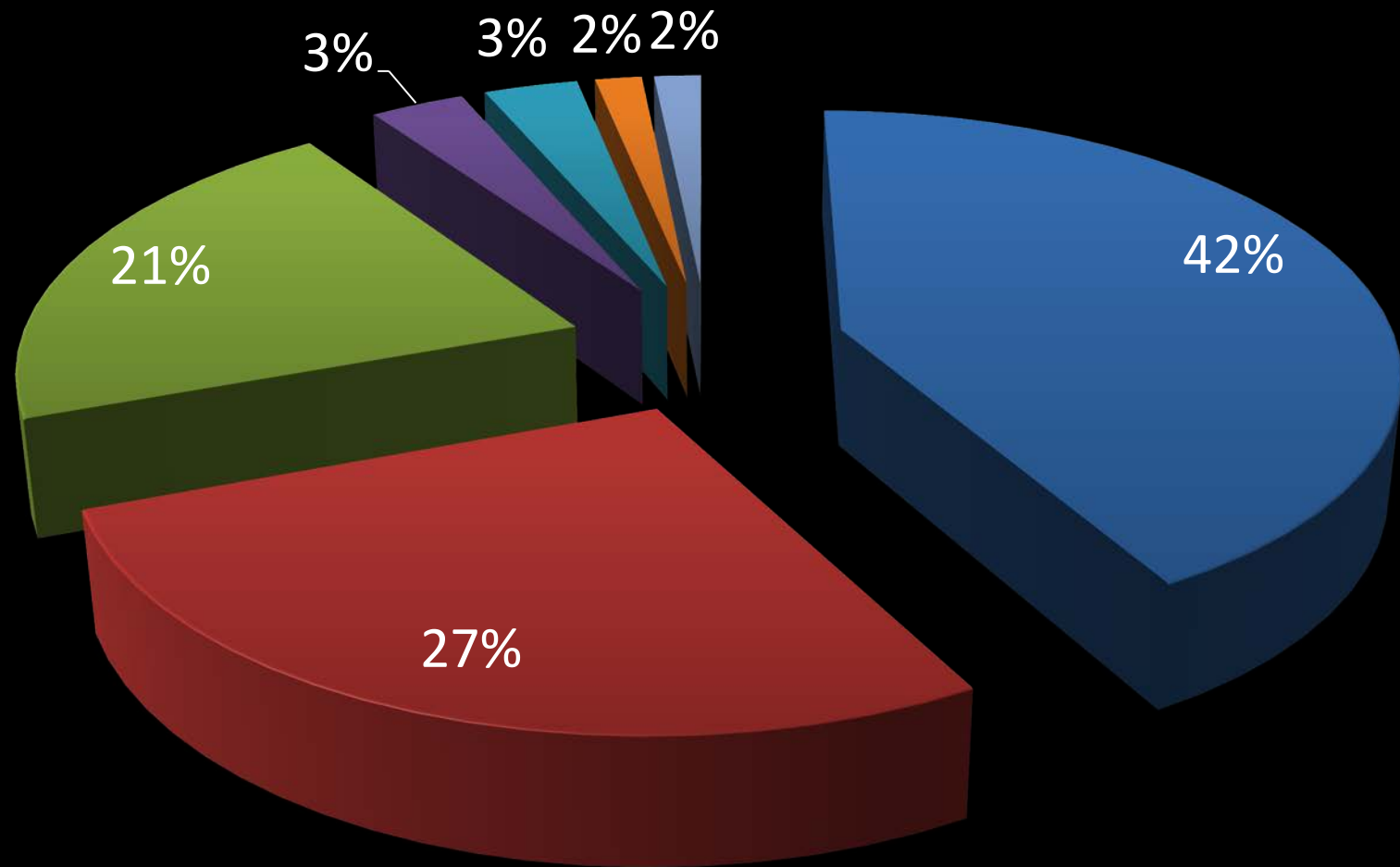


■ suicide attempt (N=61)

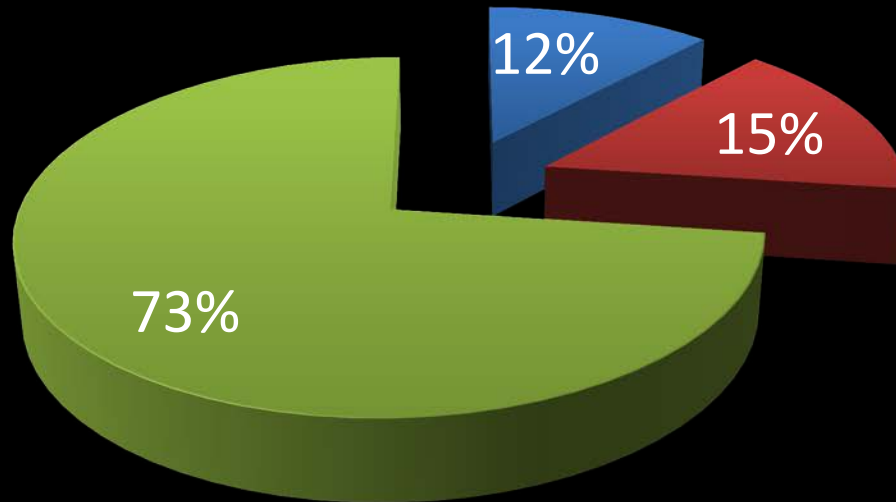
■ no suicide attempt (N=166)

Number of patients by number of suicide attempts (N=62)

■ 1 TS ■ 2 TS ■ 3 TS ■ 4 TS ■ 5 TS ■ 7 TS ■ more TS



Number of patients by time of suicide attempt (N=59)



■ last 3 months (N=7)

■ last year (N=9)

■ more than one year (N=43)

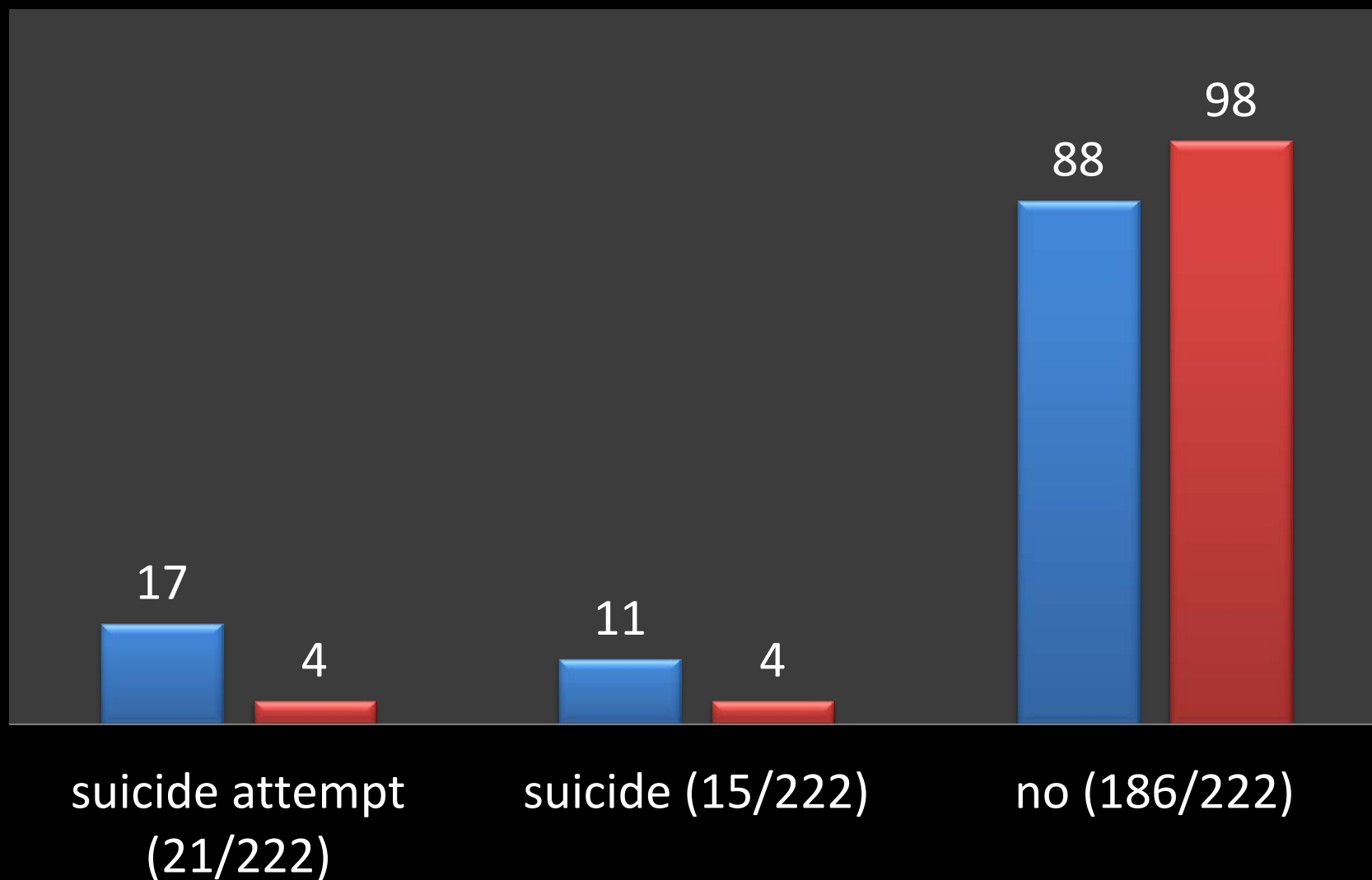
STUDY RESULTS...

There were no significant differences in gender, marital status, parenting, education, employment, religiosity, drug use among family members and probation between both groups.

In the group of patients with comorbidity of substance use disorder and other mental disorder there were significantly **more suicidal behaviour in family, previous suicide attempts, history of overdose and imprisonments** compared to the group with substance use disorder without comorbid mental disorder.

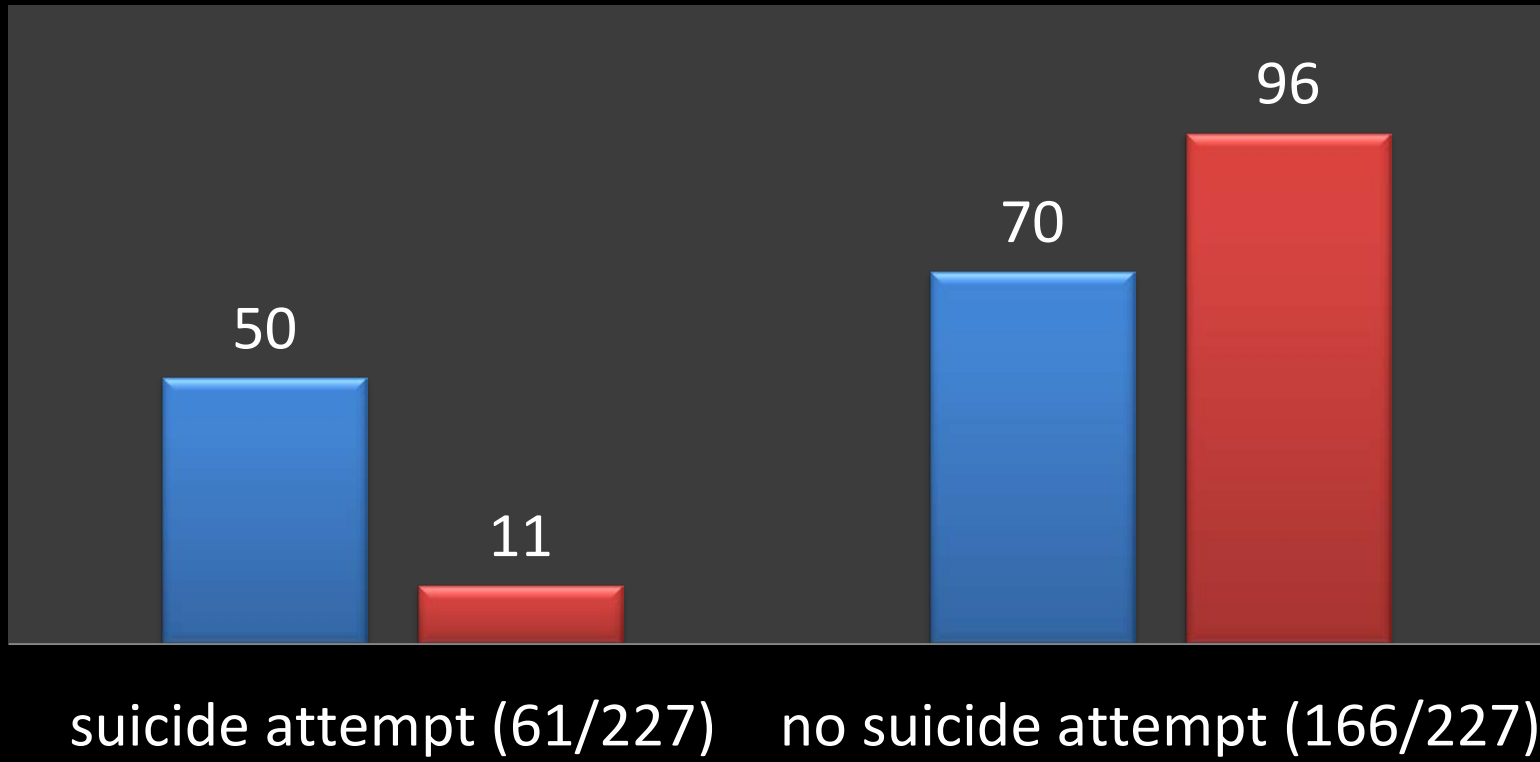
Number of patients by suicide attempt and suicide in family (p=0,001)

■ comorbidity ■ no comorbidity



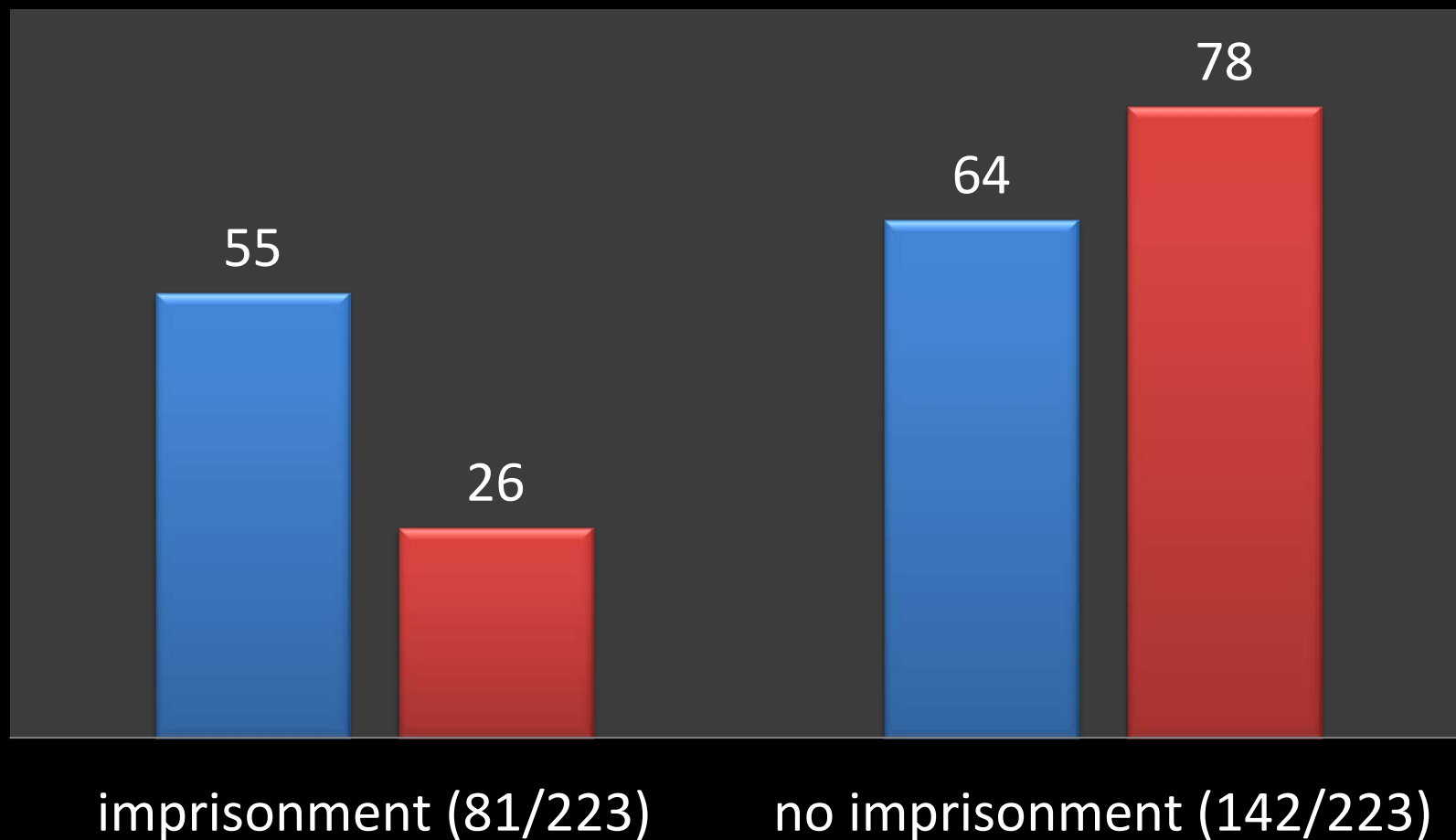
Number of patients by history of suicide attempt ($p=0,000$)

■ comorbidity ■ no comorbidity



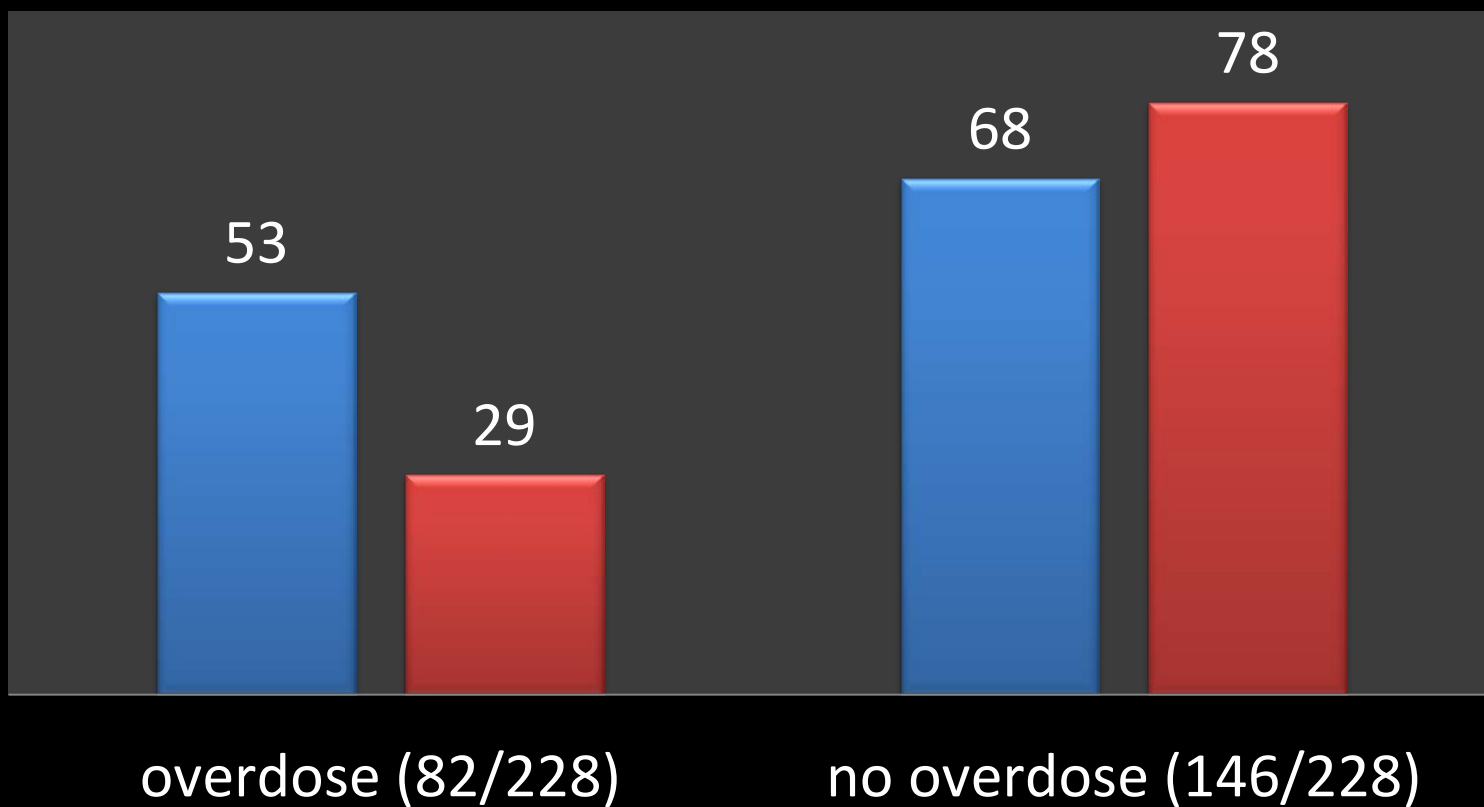
Number of patients by imprisonment (p=0,001)

■ comorbidity ■ no comorbidity



Number of patients by history of overdose ($p=0,013$)

■ comorbidity ■ no comorbidity

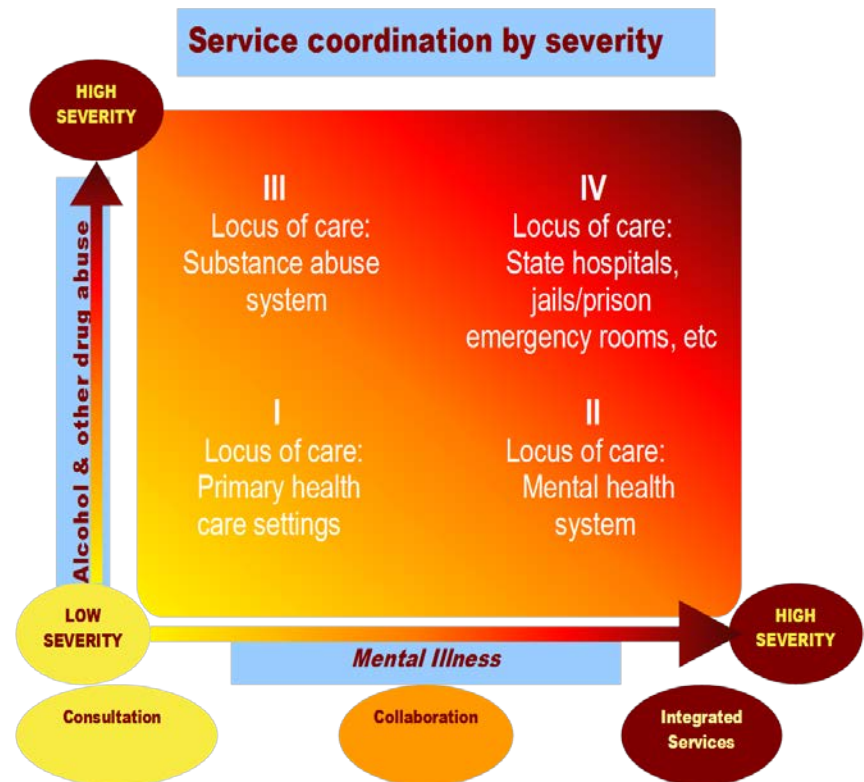
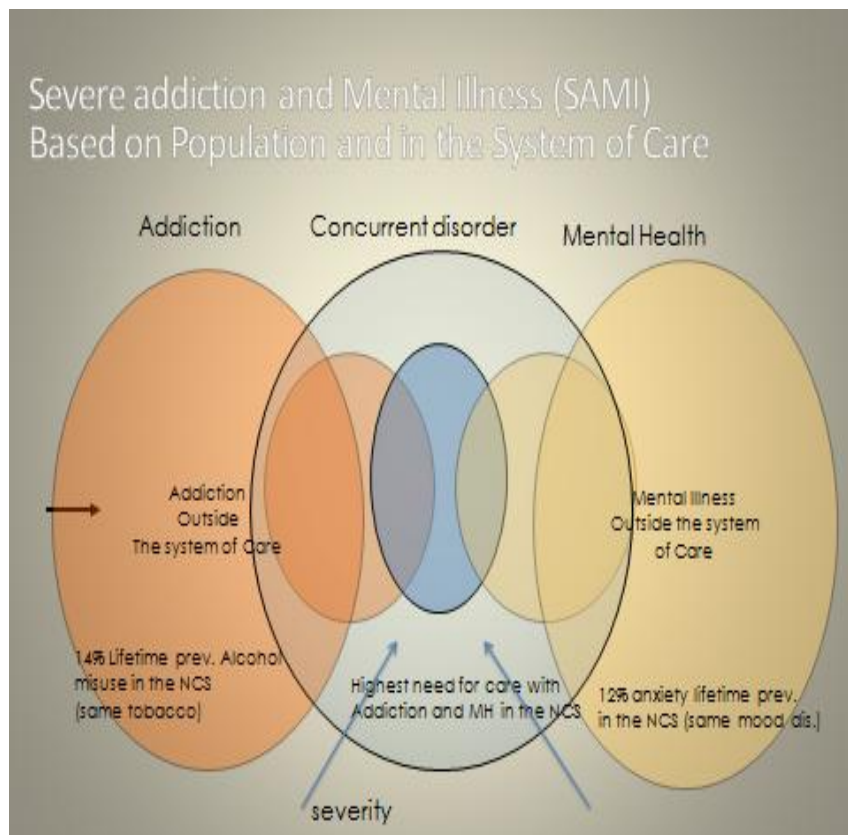


TREATMENT OF PATIENTS WITH COMORBIDITY (SUBSTANCE USE DISORDER + COMORBID MENTAL DISORDER) IN SLOVENIA

- mental health settings (outpatient, hospital)
- addiction treatment settings (18 centres across Slovenia)
- Centre for treatment of drug addiction



TREATMENT OF PATIENTS WITH COMORBIDITY (SUBSTANCE USE DISORDER + COMORBID MENTAL DISORDER) IN SLOVENIA



DAILY TREATMENT PROGRAM FOR PATIENTS WITH COMPLEX NEEDS

Program characteristics

- *Patients with comorbidity of substance use and other mental disorder*
- *Integrative treatment program (integrating psychiatric and substance abuse services/ approaches)*
- *Outpatient program – daily hospital*
- *Primarily substance-abuse treatment setting*

Patients characteristics

- *Comorbidity of substance use disorder and other mental disorder*
- *Drug free or on substitution therapy (methadone, buprenorphine, slow-release morphine)*
- *Lapse or relapse is not reason for exclusion*

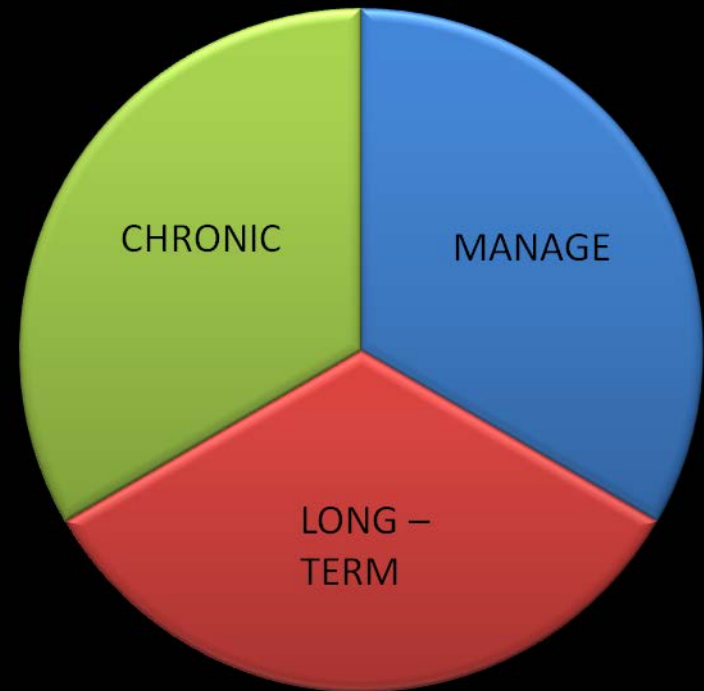
COMORBIDITY - TREATMENT APPROACHES

(Sacks et al, 2008)

Traditional view

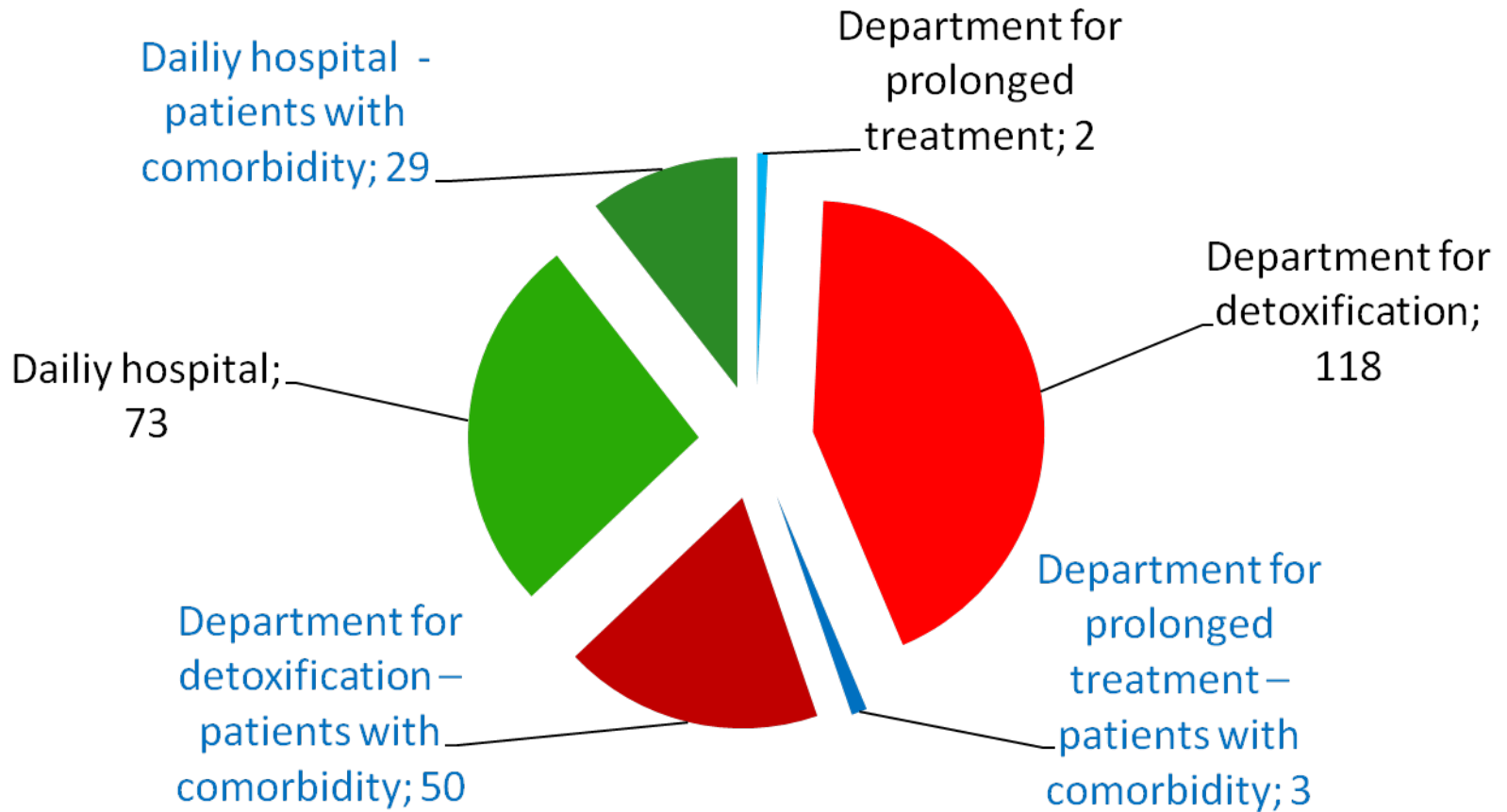


“Modern” view

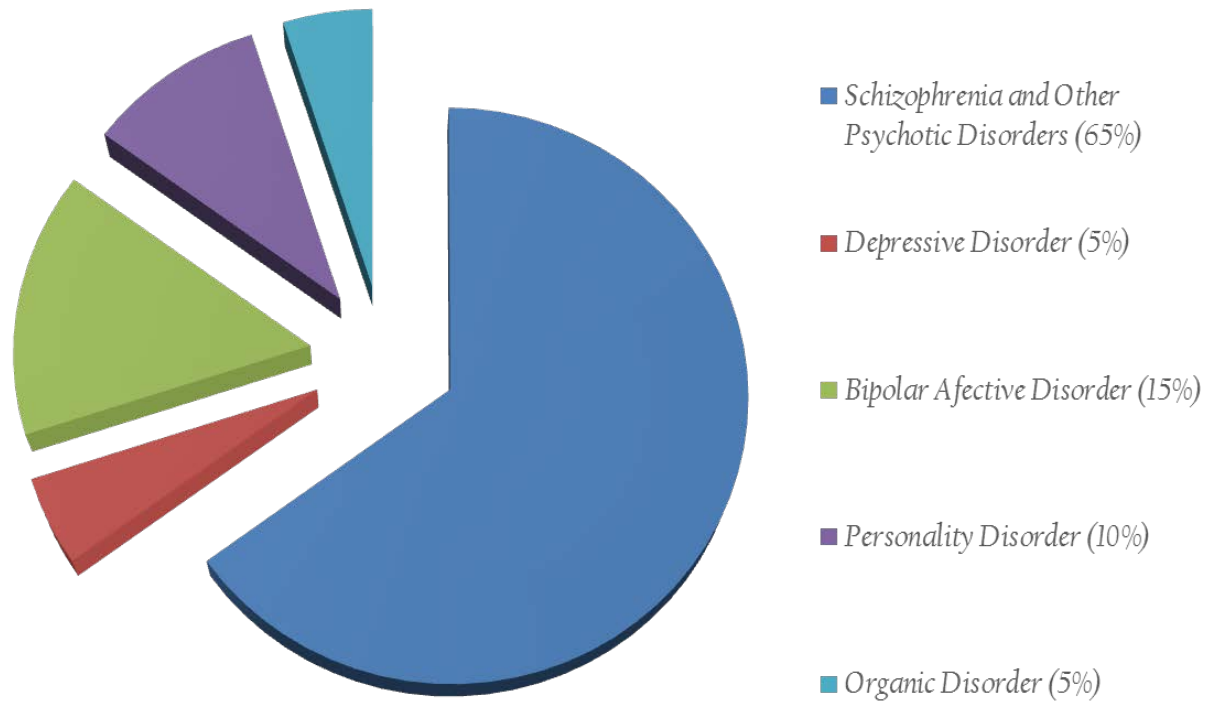


NUMBER OF PATIENTS ADDMITTED TO CZOPD in 2013

Addmitions - departments



COMORBID PSYCHIATRIC DISORDERS



NEW PSYCHOACTIVE SUBSTANCES (NPS) - TERMINOLOGY

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

- “designer drugs”
- “legal highs”
- “herbal highs”
- “research chemicals”, “bath salts”, “plant food”

- internet „smart shops“ or „head shops“

NPS DEFINITION

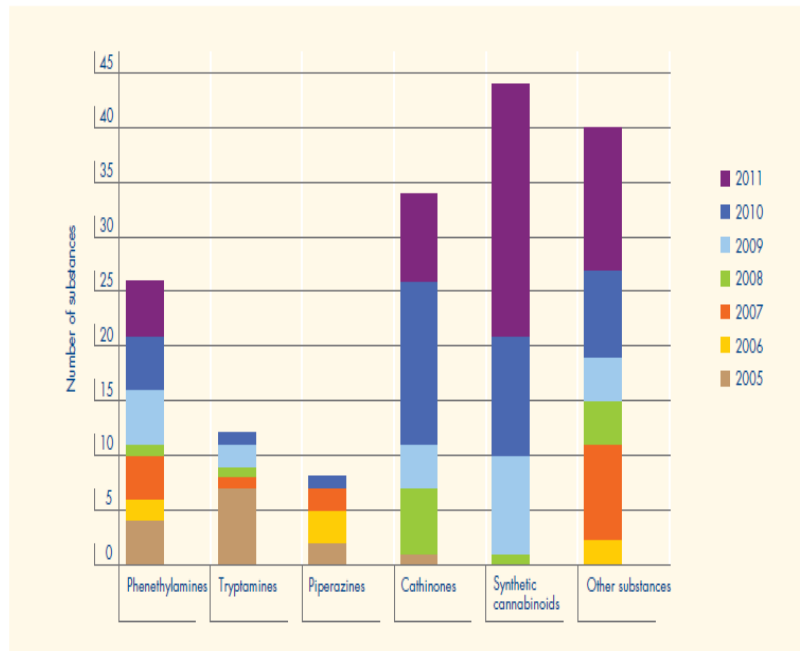
- the term 'designer drugs' had been traditionally used to **identify synthetic substances**
- but has recently been broadened to include **other psychoactive substances that mimic the effects of illicit drugs**
- and are produced by **introducing slight modifications to the chemical structure of controlled substances to circumvent drug controls.**



NPS

- between 2005 and 2011, **164 new psychoactive substances** were formally notified through the early warning system
- in 2011, for the third consecutive year, a record number of substances (49) were detected for the first time in Europe, up from 41 substances in 2010 and 24 in 2009
- about two thirds of the newly notified substances reported in 2011 were **synthetic cannabinoids** or **synthetic cathinones**

Figure 20: Main groups of new psychoactive substances identified through the early warning system since 2005



NB: Number of new psychoactive substances notified to the European early warning system under Council Decision 2005/387/JHS. See EMCDDA online drug profiles for information about phenethylamines, tryptamines, piperazines, cathinones and synthetic cannabinoids. The category 'other substances' includes various plant-derived and synthetic psychoactive substances, which do not strictly belong to any of the other chemical families, and a small number of medicinal products and derivatives.

Source: Early warning system.

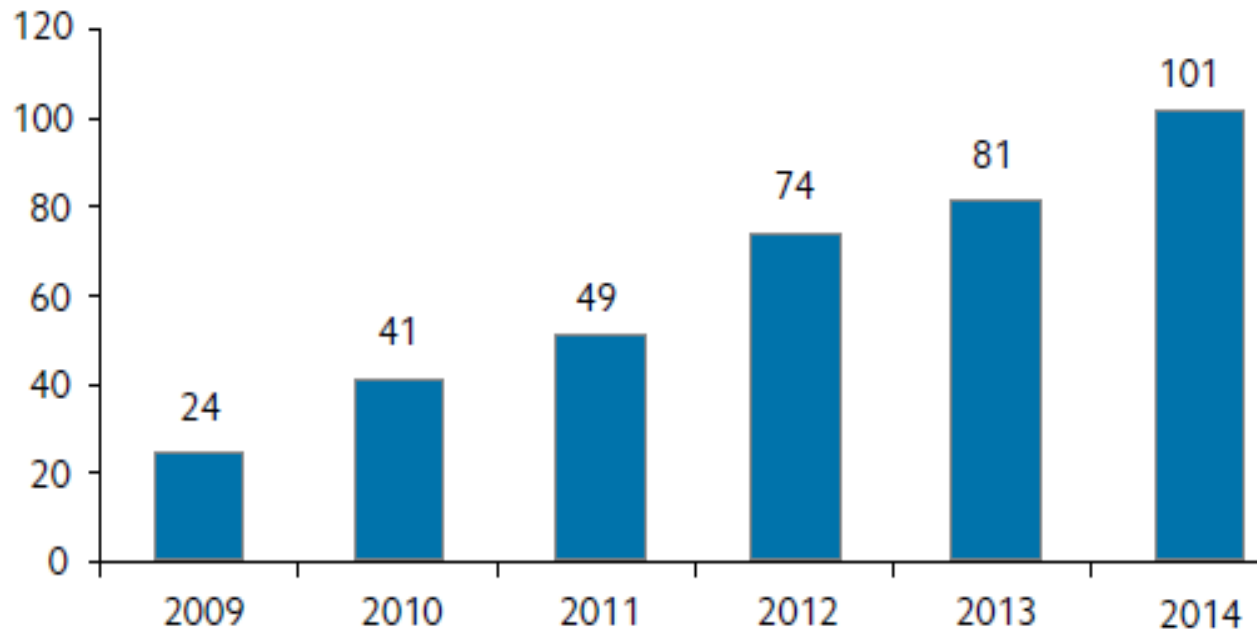


Figure 1.1. Number of psychoactive substances with use reported for the first time within the European Union

INTERNET AVAILABILITY (“smart shops” , “head shops”)

Table 10: Ten new psychoactive substances or ‘legal highs’ most commonly offered for sale in online shops surveyed in 2011 and 2012

	Number of online shops offering the product		
	January 2012	July 2011	January 2011
Kratom (natural)	179	128	92
Salvia (natural)	134	110	72
Hallucinogenic mushrooms (natural)	95	72	44
Methoxetamine (arylcyclohexylamine)	68	58	14
MDAI (aminoindane)	65	61	45
6-APB (benzofuran)	54	49	35
MDPV (cathinone)	44	32	25
4-MEC (cathinone)	43	32	11
Methiopropamine (thiophene)	39	28	5
5-IAI (aminoindane)	38	27	25

Source: EMCDDA

- the number of online shops offering to supply customers in at least one EU Member State with psychoactive substances or products likely to contain them has continued to increase.
- in the January 2012 snapshot, **693 online shops** were identified, up from 314 in January 2011 and 170 in January 2010

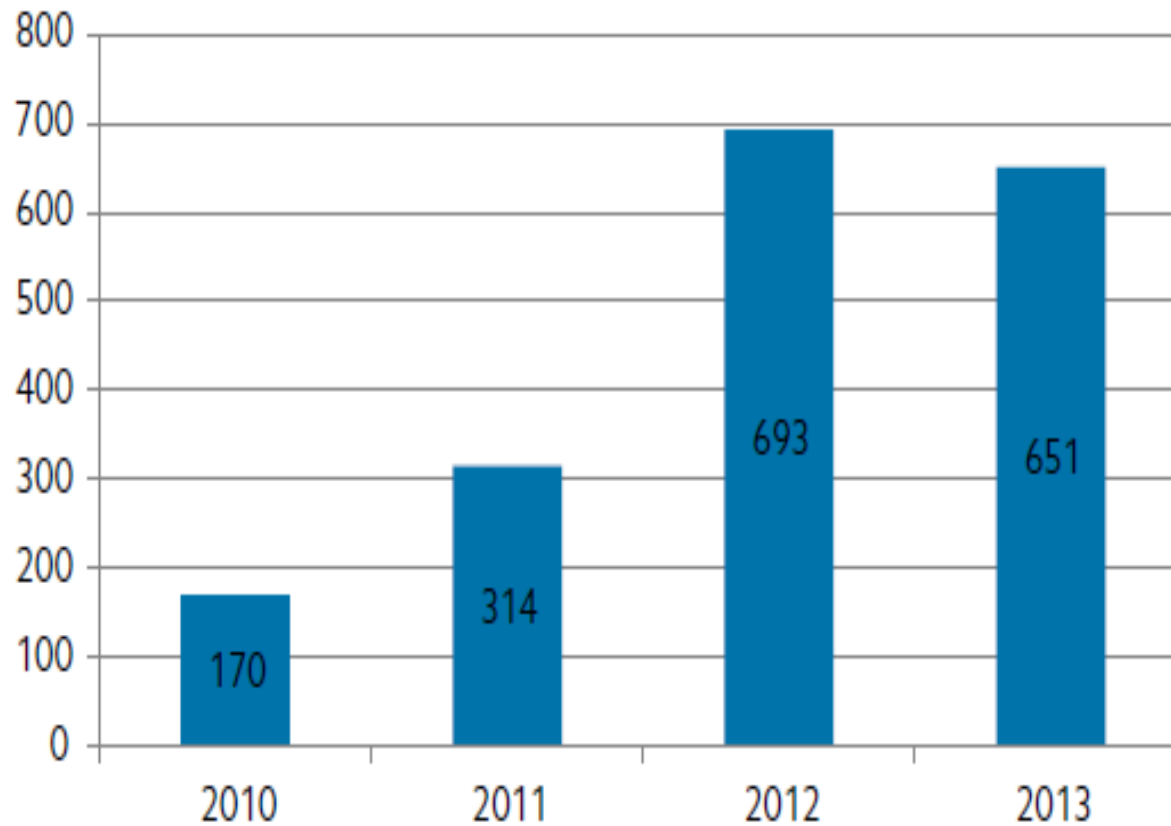


Figure 1.2. *Number of internet NPS shopping sites in Europe per year identified by the EMCDDA's targeted internet study (snapshot)⁸*

“ADVANTAGES OF NPS”

- high availability,
- relatively good price,
- legality,
- lack of possibility to detect them with routine urine tests
- “safety”
- “natural products”



NPS - CATEGORIES

Six main groups of substances present in this market, i.e.:

1. synthetic cannabinoids,
2. synthetic cathinones,
3. ketamine,
4. phenethylamines,
5. piperazines,
6. plant-based substances,
7. miscellaneous substances (that contain recently identified NPS which do not fit into the forementioned groups).

CATEGORIES (Madras, 2012)

- 1. Stimulants:** synthetic cathinones and amphetamines[eg. mephedrone, MDPV, pyrovalerone, pentylone, pentedrone, APVP (alpha-pyrrolidinovalerophenone), methylone, naphyrone, 4-MEC (4-methylethcathinone), 5-IT (5-2-aminopropyl indole), fluoroamphetamine, and many, many others];
- 2. Cannabinoids (CB):** synthetic CB1 agonists (e.g. JWH-018,073; CP-47,497; Am-694; HU-210, and hundreds of other molecules);
- 3. Hallucinogens:** phenethylamines, benzylphenethylamines (e.g. 2C-Bfly, Br-fly, Br-dragonfly);
- 4. Synthetic opioids:** MPPP (1-Methyl-4-phenyl-4-propionoxypiperidine), dextrorphan, dezomorfin (crocodile).

“SPECIFIC GROUPS” OF USERS

- **“clubbers”**
- **LGBT, MSM – “cham sex”**
 - increasing concern about the emergence of a new trend among some sub-groups of gay men involving the injection of illicit drugs, including cathinones and methamphetamine, in a practice known as ‘slamming’
 - usually takes place at ‘chem sex’ parties (Bourne et al., 2014) where mephedrone is typically used in parallel or in combination with other drugs such as methamphetamine (London), GHB/GBL, cocaine (France) and sildenafil (‘Viagra’) to enhance sexual experiences
 - parties 8h – 3D (Spire et al., 2013) with the participants frequently engaging in risky sexual practices such as not using condoms and sharing multiple partners (Stuart, 2013).
 - highly elevated risk of the spread of blood-borne and STD
- **adolescents**
- **iv.drug users**
- **“psychonauts”**

Injection of synthetic cathinones, EMCDDA, 2014; Neptune, 2015

NPS AND COMORBIDITY

- **somatic complication** (mild to severe - cardiovascular, neural, gastrointestinal and respiratory, fatal outcomes)
- **psychiatric complications** (acute intoxications, wide spectrum of possible psychiatric effects is described after use of NPS and also psychiatric complications in group of patients with comorbid mental health disorders; most often we can find descriptions of agitation, insomnia, anxiety, temporary mood disturbances, delirium, psychosis and suicidality)
- “NPS induced” or relapse of pre-existed psychiatric disorder

Table 1.3. Number of deaths related to drug poisoning with a mention of a novel psychoactive substance, by specific substance, England and Wales, 2013

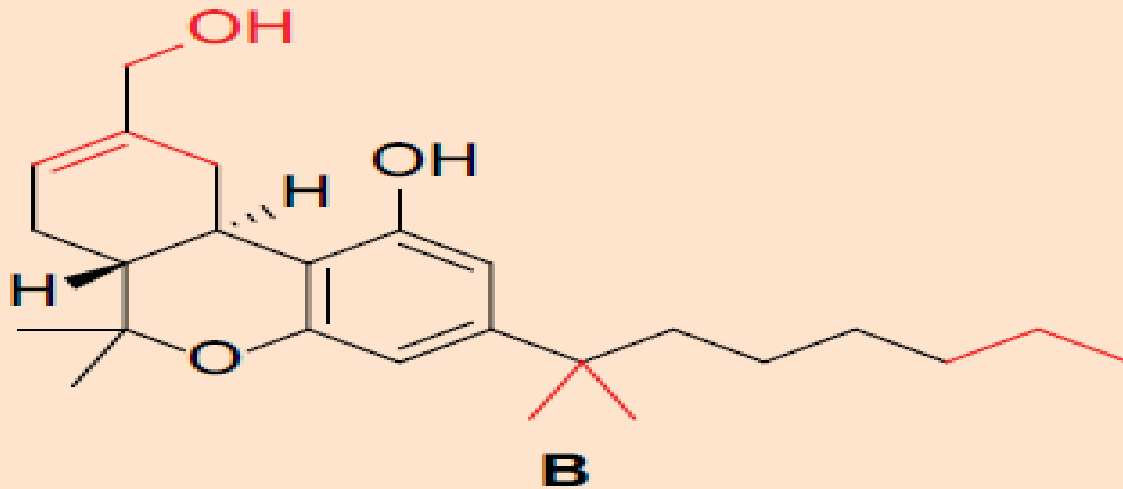
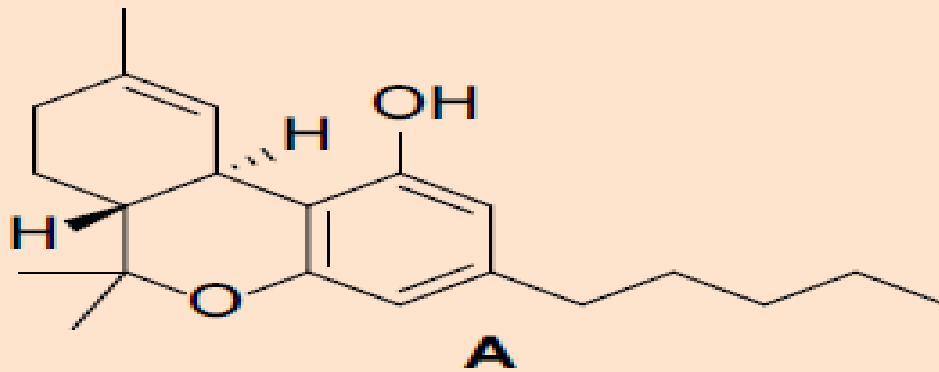
Substance	Sole drug mentioned in coroner's report	Any drug mentioned in coroner's report
1-(benzofuran-6-yl)-propan-2-amine	0	2
2-(1H-indol-5-yl)-1-methylethylamine	0	1
4-fluoroephedrine	0	0
4-fluoromethcathinone	1	1
4-methylamphetamine	0	1
4-methylethcathinone	1	3
Alpha-methyltryptamine	4	7
BZP	0	1
Cathinone*	0	1
Desoxypipradrol	0	0
Fluoromethcathinone	0	0
Gamma-hydroxybutyrate (GHB)/ gamma-butyrolactone (GBL)	10	18
Khat	0	0
Legal high	0	0
Mephedrone	1	18
Methiopropamine	1	4
Methoxetamine	1	2
Methylenedioxypropylone	1	2
Methylone	1	4
Synthetic cannabinoid	0	0
TFMPP	0	0
1-(benzofuran-5-yl)-propan-2-amine	0	3
1-(benzofuran-5-yl)-N-methylpropan-2-amine	0	1
APB	2	3
2-diphenylmethylpyrrolidine	0	1
4-Methoxymethcathinone	0	1
N-Methyl-3-phenyl-norbornan-2-amine	1	1
Fluoromethamphetamine	0	1
MDDA	0	1

*Where cathinone was found in the text of the coroner's report and no further derivative breakdown was available. This does not represent the total number of deaths relating to the group 'cathinones'.

Source: Deaths related to drug poisoning with a mention of NPS in the coroner's report, by specific substance, England and Wales, deaths registered in 2013.⁶³

SYNTHETIC CANNABINOIDES...

- CRA (synthetic cannabinoid receptor agonists)
- **legal alternatives to marijuana**
- *'Spice Gold', 'Spice Silver', 'Spice Diamond', 'K2', 'Bliss', 'Black Mamba', 'Bombay Blue', 'Blaze', 'Genie', 'Zohai', 'JWH -018, -073, -250', 'Kronic', 'Yucatan Fire', 'Skunk', 'Moon Rocks', 'Mr. Smiley'*
- most of them were developed in the 1980s and the 1990s in the context of pharmaceutical research projects
- 4 main groups: Their most common group, the **JWH series** (e.g., JWH-018, JWH-073, JWH-210) was created by John W. Huffman at Clemson University. The **AM series** (e.g. AM-694) was designed by Alexandros Makriyannis. **HU group** (e.g. HU-210) was designed at Hebrew University, and **CP group** (e.g. CP 47,497) was created by Pfizer laboratories (e.g. Madras, 2012).
- not detectable by routine urine tests



Chemical structure of classical cannabinoids: Δ^9 -tetrahydrocannabinol (A), and of the synthetic cannabinoid HU-210 (B). The differences between the synthetic cannabinoid and the controlled substance tetrahydrocannabinol are highlighted in red.

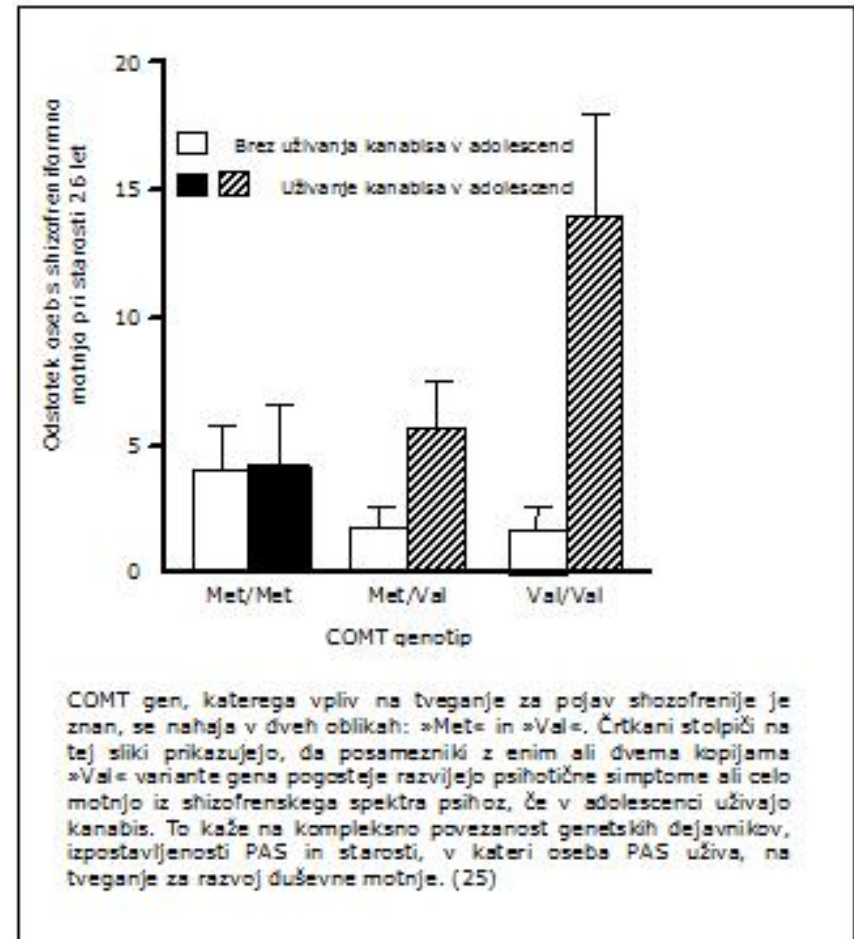
...SYNTHETIC CANNABINOIDES – pharmacology

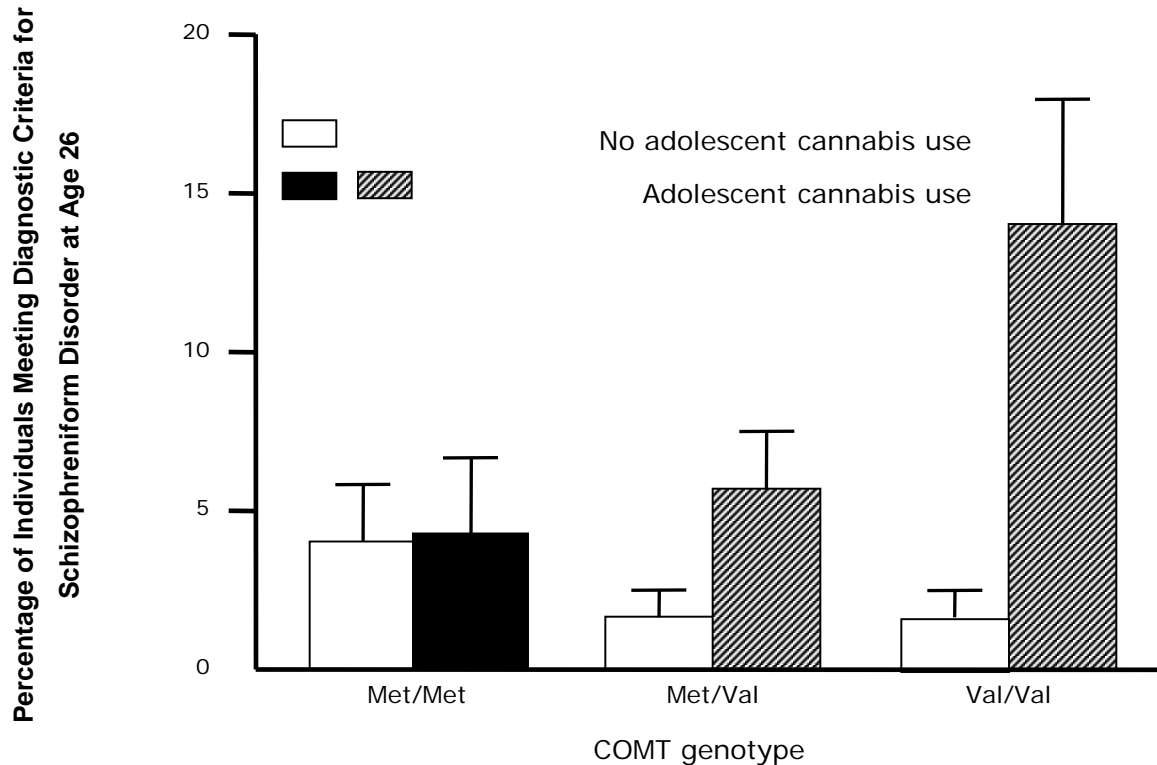
(Sziliy and Bitter, 2013; Fattore and Fratta, 2011))

- unlike delta-9-tetrahydrocannabinol (THC), most synthetic cannabinoids are **potent full agonists of cannabinoid receptors**, and they bind not only **CB1, but CB2** receptors as well
- compared with THC, JWH-018 possesses approximately a fourfold **higher affinity to the cannabinoid CB1 receptor** and **10-fold higher affinity to CB2 receptor** (Aung et al., 2000; Huffman and Padgett, 2005)
- being full agonists, the psychoactive effects (and side-effects) of these compounds can be **more explicit** than that of THC
- a **greater potential for overdose** and severe, sometimes life-threatening adverse effects (Jerry et al., 2012; Seely et al., 2012).
- **absence of canabidiol (CBD)** – a naturally occurring product in cannabis which has antipsychotic properties (Deiana, 2012)
- “desired” effects of these compounds are marijuana-like symptoms, (relaxation, sedation, euphoria and perceptual alterations)

CANNABIS AND PSYCHOSIS

- research in relation to the association between use of cannabis amongst young people and the subsequent risk of developing a psychotic illness
- first significant research (1987, Sweden, 50000 subjects)
- heavy cannabis use at age 18 years was found to increase the risk of later schizophrenia 6-fold
- early cannabis use carries a greater risk for schizophrenia than later cannabis use (by age 18 years)





The above figure shows that variations in a gene can affect the likelihood of developing psychosis in adulthood following exposure to cannabis. The Catechol-O-Methyltransferase (**COMT**) gene regulates an enzyme that breaks down dopamine, a brain chemical involved in schizophrenia. It comes in two forms: Met and Val. **Individuals with one or two copies of the Val variant have a higher risk of developing schizophrenic-type disorders if they used cannabis during adolescence (dark bars).** Those with only the Met variant were unaffected by cannabis use. These findings hint at the complexity of factors that contribute to comorbid conditions; however, more research is needed.

Source: Caspi A, Moffitt TE, Cannon M, McClay J, Murray R, Harrington H et al. [Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction.](#) Biol Psychiatry 2005; 57 (10): 1117-27.

...SYNTHETIC CANNABINOIDES – psychiatric side effects

- acute psychopathological symptoms related to consumption range from **anxiety, agitation and irritability to alteration of time perception, memory and concentration disturbances, confusion or psychosis like episodes characterized by paranoid delusions and hallucinations** (Sziliy and Bitter , Jerry et al., 2012; Seely et al., 2012).
- case reports of **induced psychotic symptoms** due to spice use and **relapse of psychosis in patients previousy history of psychosis** (Jerry et al., 2012; Seely et al ; Hurst et al, 2011; Muller et al., 2010; Every-Palmer ,2011; Gunderson et 2012; Glue eta l., 2013; Celofiga et al., 2014; *Every-Palmer, 2011*)
- risk of developing psychosis and to facilitate the manifestation of the disorder in vulnerable individuals (Frattore and Fratta, 2011; Sziliy and Bitter, 2013)

Fattore L, Fratta W. Beyond THC: the new generation of cannabinoid designer drugs. *Frontiers in Behavioral Neuroscience* 2011; 5: 1-12.

Jerry J, Collins G, Stroom D. Synthetic legal intoxicating drugs: The emerging “incense” and “bath salt” phenomenon. *Cleveland Clinic Journal of Medicine* 2012; 79(4):258-64.



The American Journal of Psychiatry, VOL. 168, No. 10

LETTERS TO THE EDITOR | October 01, 2011

Psychosis Associated With Synthetic Cannabinoid Agonists: A Case Series

Donald Hurst, M.D.; George Loeffler, M.D.; Robert McLay, M.D., Ph.D.

Am J Psychiatry 2011;168:1119-1119. doi:10.1176/appi.ajp.2011.11010176

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- Hurst et al (2011)
- 10 healthy men
- acute psychosis after spice use
- auditory and visual hallucinations to paranoid delusions, from thought blocking to disorganized speech, from anxiety and insomnia to stupor and suicidal ideation
- hospital treatment 6-8 days
- antipsychotic 7
- 5-8 remission of psychosis after 5 – 8 days, after 5 months still presented in others

PERIPHERAL EFFECTS

(Frattore and Fratta, 2011)

- **gastrointestinal effects**, such as nausea, vomiting, and retching, are the most common after consumption of Spice
- **cardiovascular effects**, such as extremely elevated heart rate and blood pressure, chest pain, and cardiac ischemia are among the most dangerous consequences (Canning et al., 2010; Schneir et al., 2011; Seely et al., 2011).
- occasional inappropriate laughter, injected conjunctiva, xerostomia, and nystagmus have been described as well (Auwärter et al., 2009; Schneir et al., 2011).
- **metabolic effects**, such as hypokalemia, hyperglycemia, and acidosis
- and **autonomic effects**, such as fever and mydriasis (Seely et al., 2011; Simmons et al., 2011a)

Box 13.1. *Summary of features of acute SC toxicity*

Central nervous system

Agitation, tremor, anxiety, confusion, somnolence, syncope, hallucinations, changes in perception, acute psychosis, nystagmus, convulsions, coma

Cardiac

Tachycardia, hypertension, chest pain, palpitations, ECG changes

Renal

Acute kidney damage

Muscular

Hypertonia, myoclonus, muscle jerking, myalgia

Other

Cold extremities, dry mouth, dyspnoea, mydriasis, vomiting, hypokalaemia

Loss of eyesight and speech also reported

STIMULANTS NEUROBIOLOGY

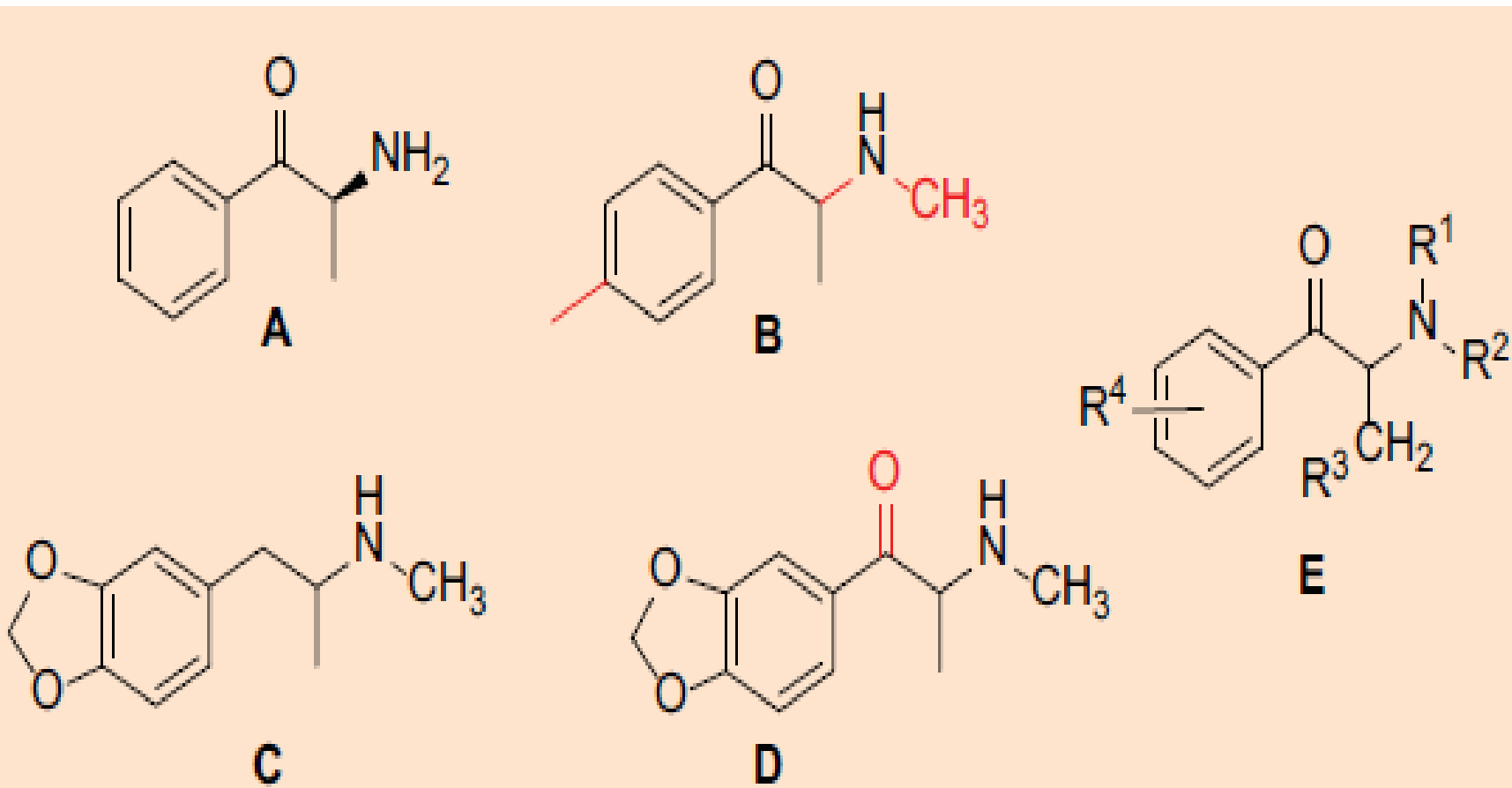
- ***euphoria, heightened alertness, increased energy, the sense of well-being, intensified emotions***
- increased synaptic concentrations of monoamines-DA, 5-HT, NE through several different mechanisms
- rewarding and powerfully addictive effects
- increase of DA levels in the nucl.accumbens in mesocorticolimbic pathway
- mesocorticolimbic pathway plays a critical role in stimulant reward

SYNTHETIC STIMULANTS

- **synthetic cathinones** (stimulants, hallucinogenes in higher doses),
- methylenedioxypropylone (MDPV), butylone, ethcathinone, ethylone, 3- and 4-fluoromethcathinone, mephedrone, methylone, pyrovalerone, 3-MeOMC; 3-MMC; 4-BMC; 4-MEC; 4-MeO-a-PVP; 4-MeO-PBP; 4-MeO-PV9; 4-MPD; 4F-PV8; 4FPV9; 4F-PVP; a-PBT; a-PHP; a-PVT; dibutylone; DL-4662; ethylone; MDPPP; MOPPPP; NEB;
- mephedrone (*'m-cat', 'meph', 'drone', 'miaow'*) and methylone (*'explosion', 'top cat'*)
- **piperazines mCPP, BZP**

SYNTHETIC CATHINONES

- the natural analogue to synthetic cathinones is the active compound in the leaves of the **khat plant** (*Catha edulis*), which have been chewed for centuries in parts of Africa and the Arabian Peninsula for their stimulant properties
- like amphetamines, cathinones act as **CNS stimulants**, although they are generally *less potent than amphetamine*
- synthetic cathinones are amphetamine-like behavioural stimulants which have similar effects to amphetamine ***on monoamine reuptake, including serotonin, dopamine and noradrenaline***; they also have a similarly **strong sympathomimetic effect**
- **bupropion** is the only cathinone derivative that carries a medical indication in the US and Europe; (depression and as a smoking cessation)



Chemical structures of cathinone (A), mephedrone (B), MDMA (C) and methyldone (D). Differences between controlled substances (i.e. cathinone and MDMA) and synthetic derivatives of cathinones (i.e. mephedrone and methyldone) are highlighted in red. The molecular structure of generic cathinone derivatives is represented in structure (E). The 'R' groups indicate locations of the molecule where modifications can occur to produce a wide range of cathinone derivatives.

SYNTHETIC CATHINONES - EFFECTS

- **euphoria, increased concentration, the urge to move, talkativeness, reduced appetite and wakefulness; desired effects also include stimulation, enhanced appreciation of music, mood elevation, reduced hostility, improved mental function and increased energy**
- **at higher doses, perceptual distortions or hallucinations and the empathogenic properties of mephedrone have been reported**
- **increase sexual thoughts, intensify sexual desire, enhance sensuality, improve sexual functioning and prolong sexual performance**

SYNTHETIC CATHINONES ADVERSE EFFECTS

1. **Cardiovascular side effects:** hypertension, tachycardia, arrhythmias, Q-T prolongation, chest pain, heart attacks, collapse of cardiovascular system, peripheral vasoconstriction;
2. **Neurological side effects:** seizures, cerebral edema, stroke, mydriasis, dizziness, memory loss, tremors, motor automatisms, parkinsonism, headache, hyperreflexia, paraesthesia, hyperkinesia;
3. **Respiratory side effects:** nasal irritation, nose bleed, breathing ;
4. **Gastrointestinal side effects:** nausea, vomiting, anorexia, abdominal pain, sore throat;
5. **Other side effects:** serotonin syndrome, muscle rigidity, rhabdomyolysis, kidney failure, thermoregulatory changes, hyponatraemia, sweating, chills, bloodshot eyes, skin rash; long-term i.v. use is associated with weight loss, cachexia, immune system alterations and infections e.g. thrombophlebitis, abscesses or septicemia
6. **Fatal outcomes**

*Box 9.1. Some common unwanted effects of mephedrone,
as reported by users^{17,37,43,48,52,57,65}*

Jaw clenching

Reduced appetite

Nasal irritation and nose bleeds

Nausea and vomiting

Discolouration of extremities and joints

Insomnia and/or nightmares

'Head rush'

Inability to concentrate and/or to focus visually

Memory problems

Altered conscious levels

Anxiety

Agitation

Hallucinations and delusions

Headaches

Tremors and convulsions

Raised body temperature

Chest pains

Elevated heart rate

Box 9.2. Features of acute mephedrone toxicity

Cardiovascular

Hypertension, tachycardia, chest pain, palpitation, diaphoresis, hot flushes, shortness of breath, palpitations, cardiac arrest, peripheral vasoconstriction

Cognitive

Confusion, improved concentration, alertness, amnesia, cravings, empathy/feelings of closeness, dysphoria

Dermatological

Unusual sweat odour, rash

ENT

Sore nasal passages, mouth/throat pain, epistaxis

Gastrointestinal

Nausea/vomiting, anorexia, dry mouth, abdominal pain, sore mouth/throat

Metabolic

Elevated creatinine, metabolic acidosis

Neurological psychiatric/ psychological

Anxiety, panic, depression, irritability, lack of motivation, anhedonia, sexual arousal, sociability, euphoria, insomnia, bruxism, headache, dizziness/light-headedness, tinnitus, seizures, nystagmus, mydriasis, blurred vision, numbness, blue/cold extremities, fever, paraesthesias, visual and auditory hallucinations, paranoid delusions, intensification of sensory experiences, reduced consciousness, agitation, aggression, short-term psychosis, short-term mania

Musculoskeletal

Increase in muscle tone, trismus

Respiratory

Dyspnoea

Serotonin syndrome

SYNTHETIC CATHINONES' PSYCHIATRIC ADVERSE EFFECTS

(Sziliy and Bitter, 2013)

- **agitation, anger, irritability,** restlessness, insomnia, **concentration and memory disturbances,** transient paranoid thoughts, hallucinations and anxiety, transient **depressive** mood alterations, **suicidal ideas, delirium-like syndromes,** transient **psychotic symptoms** during acute intoxication or delirium psychotic episodes in mentally otherwise healthy consumers, and probably can exacerbate symptoms of patients living with psychotic disorders
- drug-induced psychotic states are not uncommon among synthetic cathinone

Electroconvulsive therapy improves persistent psychosis after repeated use of methylenedioxypropylvalerone ("bath salts").

Penders TM, Lang MC, Pagano JJ, Gooding ZS.

Author information

Abstract

The use of synthetic cathinone drugs, known popularly as "bath salts," may lead to persistent visual hallucinations and paranoia with repeated use. This is the first case report known to the authors suggesting that such symptoms may persist despite discontinuing the use of psychoactive bath salts. As is the case with other such symptoms associated with use of stimulant drugs of abuse, these symptoms are resistant to pharmacologic treatment, and electroconvulsive therapy can be a useful treatment modality in such situations. This report adds to evidence for efficacy of electroconvulsive therapy in the management of stimulant-induced persistent psychotic symptoms.

PMID: 23609518 [PubMed - in process]

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TOXICOLOGY OBSERVATION

Psychosis from a Bath Salt Product Containing Flephedrone and MDPV with Serum, Urine, and Product Quantification

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Christian A. Tomaszewski

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Case Report

"Bath Salts" Intoxication: A Case Report

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We present a case of a potentially lethal ingestion of "Bath Salts." After presentation, we briefly review the epidemiology and pathology of "bath salts" ingestion.

...SYNTHETIC CATHINONES' PSYCHIATRIC ADVERSE EFFECTS

- 2 cases of MDPV induced psychosis, remission after 4 days (Antoniwicz, 2011)
- 5 cases of MDPV induced psychosis (first episode), remission after a few days after treatment with low doses of risperidon, olanzapin, haloperidol (Farkas, 2013)
- 34 cases of intoxications with bath salts – 4 psychotic symptoms (Benzie et al, 2011)
- 26 year old man , 1 week th with diazepam, lorazepam (Kim et al, 2011)
- 19-year old girl, after mephedrone ingestion agitation vs catatonia, resolved after 72 hours – th haloperidol, lorazepam (Kolli et al., 2013)

WITHDRAWAL SYMPTOMS - STIMULANTS

- **“crash”**(dysphoria, anxiety, agitation→craving →fatigue, increasing depression, anhedonia, decreased mental and physical energy, intense desire for sleep, insomnia-replaces drug craving →hypersomnolence, intense hunger (a few days))
- **“protracted withdrawal”**- symptoms opposite stimulans intoxication: 90-120 days after discontinuation of substance use (*mild dysphoria, difficulty concentrating, anhedonia, lack of energy, short-term memory disturbance, irritability; suicidality!*)
- prolonged in MA users
- significant changes in brain functioning lasting more than 6 months

NPS IN SLOVENIA

(Mina Pas, DrogArt)

- 3-MMC (3-metoxymetchatinon) –"SLADOLED",
- 4-MEC (4-metoxyetchatinon),
- GHB/GBL (gama – hidroksibutyrat acid , gama-butyrolacton),
- metylon (street name "bka"),
- 4-FA (4-fluoroamfetamin),
- 25x-NBOMe (street name "nebome"),
- AMT (alpa-metiltriptamin),
- 2-CB (2,5-dimetoksi-4-bromofenetilamin)

A CASE REPORT: BATH SALT INDUCED PSYCHOSIS

- 24 year old man
- previously treated at psychiatrist - addiction, anxiety
- OST – buprenorphin 8 mg/d
- Psychiatric Emergency Outpatient Clinic
- logorrhoic, desorganised behaviour, delusions of persecutions and reference, haptic hallucination, anxious, impaired insight
- reported use of pentedrone for the first time the day before (0,5 g – snorted)
- admission to psychiatric hospital

A CASE REPORT: BATH SALT INDUCED PSYCHOSIS

- treated with antipsychotic risperidon 6 mg , lorazepam 2 mg, ziprasidone 120 mg and buprenorphin 2 mg (2. and 3. day 0,4 mg)
- after 3 days psychotic symptoms resolved, ziprasidone and risperidon discontinued after 10 days, 4 th day introduction of quetiapin up to 300 mg
- discharged after 23 days; therapy with buprenorphin, quetiapine and BZ's – and admitted to Center for treatment of drug addiction

PENTEDRONE

- 2- (methylamino)-1-phenylpentan-1-one (pentedrone)
- synthetic cathinon
- A fatal Case of Pentedrone and alpha-Pyrrolidinovalerophenone Poisoning described in literature
(Sycutera et al, 2015)



Thank you for attention.