# MEDICO-LEGAL ASPECTS OF DRUG USE INTOXICATION AND DRUGGED DRIVING, WITH A SPECIAL EMPHASIS ON THE ABUSE OF NEW PSYCHOACTIVE SUBSTANCES

PHD THESIS

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***Doctoral (Ph.D.) thesis***

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# Content

# 1 Abbreviations

## 1.1 General

**ANOVA**: Analysis of variance; **BAC**: Blood Alcohol Content; **BMP**: basic metabolic panel; **CB 1 and CB 2**: Cannabinoid receptor type 1 and 2; **CBC**: complete blood count; **CND**: Commission on Narcotic Drugs; **CSO:** Central Statistics Office; **DAT**: dopamine transporter; **DEC:** Drug Evaluation and Classification; **DECT:** Department of Emergency Medicine; **DFM:** Department of Forensic Medicine; **DRE:** Drug Recognition Expert; **DUID**: driving under the influence of drugs; **sDUID:** suspected driving under the influence of drugs; **DRUID:** Driving Under the Influence of Drugs, Alcohol and Medicines (EU project); **DRE:** drug recognition expert; **ECDD:** Expert Committee on Drug Dependence; **ED:** emergency department; **ED50:** median effective dose; **EMCDDA:** European Monitoring Centre for Drugs and Drug Addiction; **EMS:** Emergency Medical Service; **EU:** Europian Union; **ESPAD:** European School Survey Project on Alcohol and Other Drugs; **EWS:** Early Warning System; **FST:** Field Sobriety Test; **GC-FID**: Gas Chromatography - flame ionization detector; **GC-MS:** Gas Chromatography-Mass Spectrometry; **GCS:** Glasgow Coma Score; **HGN**: Horizontal Gaze Nystagmus; **HIFS:** Hungarian Institute for Forensic Sciences; **HRMS:** high-resolution mass spectrometry; **LC-MS:** Liquid Chromatography with tandem mass spectrometry; **LOD:** Limit of Detection; **LLOQ:** Lower Limit of Quantification; **MOF:** Multi-organ failure; **MDU:** Multi-drug use; **NET:** norepinephrine transporter; **NFP:** Hungarian National Focal Point; **NPS:** new psychoactive substances; **sNPS:** stimulant new psychoactive substances; **NSAPH:** National Survey on Addiction Problems in Hungary; **OF**: oral fluid; **PSS:** Poison Severity Score; **RR:** arterial blood pressure; **SDLP:** standard deviation of lateral position; **SERT:** Serotonin transporter; **Tor:** The Onion Router (network); **UK:** United Kingdom; **UN:** United Nations; **VZN:** Vertical Gaze Nystagmus; **WBE:** Wastewater-Based Epidemiology; **WHO:** World Health Organization;

## 1.2 Substances and chemical names

**4-CEC**: 4-chloro-ethcathinone**; 4Cl-α-PVP**: 4-chloro-alpha-pyrrolidinopentiophenone; **4-Cl-PPP:** 1-(4-Chlorophenyl)-2-(1-pyrrolidinyl)-1-pentanone; 1-(4-Chlorophenyl)-2-(1-pyrrolidinyl)-1-pentanone; **4-CMC**: 4-chloro-methcathinone; **4MENP**: 4-methyl-N-ethyl-norpentedrone; **4-MEC**: 4-Methylethcathinone; **4F-MDMB-BICA**: methyl 2-{[1-(4-fluorobutyl)-1H-indole-3-carbonyl]amino}-3,3-dimethylbutanoate; **4F-MDMB-BINACA**: methyl (*S*)-2-(1-(4-fluorobutyl)-1*H*-indazole-3-carboxamido)-3,3-dimethylbutanoate; **5F-AB-**

**PINACA**: *N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(5-fluoropentyl)indazole-3-carboxamide; **5F-ADB-PINACA**: *N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(5-fluoropentyl)-1*H*-indazole-3-carboxamide; **5F-AMB M**: N-[[1-(4-carboxybutyl)-1H-indazol-3-yl]carbonyl]-L-valine, 1-methyl ester; **5F-AMBICA**: N-[(1S)-1- (aminocarbonyl)-2-methylpropyl]-1-(5-fluoropentyl)-1H-indole-3-carboxamide; **5F-AMB-PINACA**: methyl (2*S*)-2-{[1-(5-fluoropentyl)-1*H*-indazol-3-yl]formamido}-3-methyl-butanoate; **5F-CUMIL-PEGACLONE:** 2,5-Dihydro-2-(1-methyl-1-phenylethyl)-5-(5-fluoropentyl)-1H-pyrido[4,3-b]indol-1-one; **5F-MDMB-PICA:** (*S*)-Methyl 2-(1-(5-fluoropentyl)-1H-indole-3-carboxamido)-3-methylbutanoate; **5F-MDMB-PINACA:** Methyl (*S*)-2-[1-(5-fluoropentyl)-1*H*-indazole-3-carboxamido]-3,3-dimethylbutanoate; **5-HT**: serotonin; **AB-CHMINACA:** *N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)indazole-3-carboxamide; **AB-FUBINACA:** *N*-[(2*S*)-1-Amino-3-methyl-1-oxobutan-2-yl]-1-[(4-fluorophenyl)methyl]indazole-3-carboxamide; **AB-PINACA:** *N*-[(1*S*)-1-(Aminocarbonyl)-2-methylpropyl]-1-pentyl-1*H*-indazole-3-carboxamide; **AB-CHMINACA**: N-[(2S)-1-amino-3-methyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)indazole-3-carboxamide; **ADB-CHMINACA:** *N*-[(2*S*)-1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)indazole-3-carboxamide; **AB-FUBINACA:** N-[(1S)-1-(aminocarbonyl)-2-methylpropyl]-1-[(4-fluorophenyl)methyl]-1H-indazole-3-carboxamide; **ADB-FUBINACA:** *N*-(1-Amino-3,3-dimethyl-1-oxobutan-2-yl)-1-(4-fluorobenzyl)-1*H*-indazole-3-carboxamide; **AMB-FUBINACA:** Methyl 2-(1-(4-fluorobenzyl)-1H-indazole-3-carboxamido)-3-methylbutanoate; **AKB-48F:** N-(adamantan-1-yl)-1-(5-fluoropentyl)-1H-indazole-3-carboxamide; **α-PVP:** (*RS*)-1-Phenyl-2-(1-pyrrolidinyl)-1-pentanone; **α-PHP:** α-Pyrrolidinohexiophenone**; AMB-CHMICA:** methyl (2*S*)-2-{[1-(cyclohexylmethyl)indazole-3-carbonyl]amino}-3-methylbutanoate; **AM/MA:** amphetamine/metamphetamine; **AMB-FUBINACA:** Methyl (2*S*)-2-{[1-[(4-fluorophenyl)methyl]indazole-3-carbonyl]amino}-3-methylbutanoate; **BZE**: benzoylecgonine; **CO:** Carbon monoxide; **COOH**: carboxyl group; **CUMYL-4CN-BINACA:** 1-(4-Cyanobutyl)-*N*-(2-phenylpropan-2-yl)-1*H*-indazole-3-carboxamide; **CUMYL-5F-P7AICA:** 1-(5-Fluoropentyl)-N-(2-phenylpropan-2-yl)pyrrolo[2,3-b]pyridine-3-carboxamide; **CUMYL-CH-MEGACLONE:** 2,5-Dihydro-2-(1-methyl-1-phenylethyl)-5-(cyclohexylmethyl)-1H-pyrido[4,3-b]indol-1-one; **CUMYL-PEGACLONE:** 2,5-Dihydro-2-(1-methyl-1-phenylethyl)-5-pentyl-1H-pyrido[4,3-b]indol-1-one; **CP47,497:** 2-[(1S,3R)-3-hydroxycyclohexyl]-5-(1,1-dimethylnonyl)phenol**; DA**: dopamine; **EDDP:** 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine; **EPh:** ethylphenidate; **EMB-FUBINACA:** ethyl(1-(4-fluorobenzyl)-1H-indazole-3-carbonyl)-L-valinate; **GHB:** Gamma-Hydroxybutyrate; **JHW-**

**122:** (4-Methyl-1-naphthyl)-(1-pentylindol-3-yl)methanone; **LSD:** lysergic acid diethyamine, **MAB-CHMICA:** N-[1-(aminocarbonyl)-2,2-dimethylpropyl]-1-(cyclohexylmethyl)-1H-indole-3-carboxamide; **MAB-CHMINACA:** *N*-[(2*S*)-1-Amino-3,3-dimethyl-1-oxobutan-2-yl]-1-(cyclohexylmethyl)indazole-3-carboxamide; **MAM-2201:** (1-(5-Fluoropentyl)-1*H*-indol-3-yl)(4-methyl-1-naphthalenyl)methanone; **MDMA:** methylendioxi-metamphetamine; **MDMB-CHMICA:** Methyl (2*S*)-2-{[1-(cyclohexylmethyl)-1*H*-indol-3-yl]formamido}-3,3-dimethylbutanoate; **MDMB-FUBICA:** methyl (2*S*)-2-({1-[(4-fluorophenyl)methyl]-1*H*-indol-3-yl}formamido)-3,3-dimethylbutanoate; **MDMB-FUBINACA:** Methyl (2*S*)-2-{[1-[(4-fluorophenyl)methyl]indazole-3-carbonyl]amino}-3,3-dimethylbutanoate; **MMB-2201:** (*S*)-Methyl 2-(1-(5-fluoropentyl)-1H-indole-3-carboxamido)-3-methylbutanoate; **MDPV**: Methylenedioxypyrovalerone; **NA:** norepinephrine; **NEH:** N-ethyl-hexedrone; **OH:** hydroxyl group; **SCs:** synthetic cannabinoids; **THC-OH:** 11-Hydroxy-Δ9-tetrahydrocannabinol; **THC-COOH:** 11-Nor-9-carboxy-delta-9-tetrahydrocannabinol; **THJ-2201:** [1-(5-Fluoropentyl)-1*H*-indazol-3-yl](1-naphthyl)methanone; U**R-144:** (1-pentylindol-3-yl)-(2,2,3,3-tetramethylcyclopropyl)methanone; **Z-drugs**: nonbenzodiazepine hypnotics

# 2 Actuality of the topic, its social embedding, possible questions, and research directions

Nearly a decade ago, in addition to classical drugs such as cocaine and amphetamines, marijuana, heroin, lysergic acid diethylamine (LSD) and other hallucinogens, hundreds of new compounds appeared and dynamic spread into the world's recreational drug market. At the end of 2020, EMCDDA monitored approximately 830 new psychoactive substances. These compounds are called designer drugs and new psychoactive substances (NPS). These designer drugs are structural or functional analogs of controlled substances and has been designed to mimic the effects of the original drugs. Typically, as a result of small structural changes, the new substances were synthetized to avoid the scope of legal regulation (they are not strictly regulated by international conventions) and to reduce their detectability during rapid toxicological tests. Due to lack of knowledge, the consumption of designer drugs seen in recent years is practically part of a human experiment. Furthermore, these modifications change the drug's pharmacokinetics, biological effects, and side effects. Some reports deal with the growing number of intoxicated people show up at emergency departments after use of NPS with adverse somatic and psychiatric effects that sometimes seem to be more severe than those induced by classical drugs with similar subjective effects.

The diversity, unfamiliarity, and rapid change of new psychoactive substances (NPS) ***pose an increased challenge for legislation, the health care system*** and ***forensic activity.*** As the drug market is always one step ahead of legislation, risk assessment and drug control for NPS was introduced in 2012.

Despite the efforts to prevent illegal drug trade, the European drug market was characterized by the high variety and wide availability of drugs with ***increasing purity and stronger effects*** at the beginning of 2020. Several indicators show that the pattern of use becomes more and more complex as more drugs are available. This leads to multiple health hazard due to the use of increasing number of new drugs and their combinations (interactions). That’s why we need to understand the consequences of combined drug use more detailed, to reveal how ***multi-drug use*** results more serious health damage.

In this context, it is essential for health-care professionals and toxicologists to obtain valid, reliable and comparable information on the prevalence and patterns of NPS use to assess the risks associated, and also for policy-makers to target prevention and define law enforcement activities. Due to the increasingly complex drug problems, we must expand our knowledge on health, forensic activity and toxicology.

# 3 Introduction

Illegal or legally “gray zone” services on the Internet, such as dark web search and purchase sites (e.g. "Tor" search engine), as well as the use of Bitcoin and other cryptocurrencies [1] contribute greatly to the spread of new psychoactive drugs. More recently, however, it has been observed that the sale of new psychoactive drugs and designer drugs also takes place on legal platforms, for example in closed groups of social media [2], which further increases the consumers' false sense of security regarding the dangerousness and legal status of the drugs. Manufacturers often misleadingly label their products as pesticides, bath salts or simply as "legal highs" [3] so people would not try illegal drugs buy them [4].

## 3.1 Statistics

### 3.1.1 Sources of information, steps, and topics required to build a comprehensive database for monitoring NPS use

Monitoring, alerting, risk assessment and decision-making support data collection activities related to new psychoactive substances are carried out at the European Union level by the ***European Monitoring Centre for Drugs and Drug Addiction (EMCDDA)***; Hungarian data collection is coordinated by the ***Hungarian National Focal Point (NFP)*** which is the national agency of the European drug information network. The NFP collects and processes data and information of other institutions and provides them to national and international organizations to help decision making on the exploration, treatment and solution of the drug problem. One of the important data sources of this activity is the ***Early Warning System (EWS),*** which handles incoming information and alerts related to new substances.

Reliable information can be derived from seizure data (the raw substance) and toxicological data measured from biological samples, which represent the pattern of drug consumption and the appearance of new drugs.

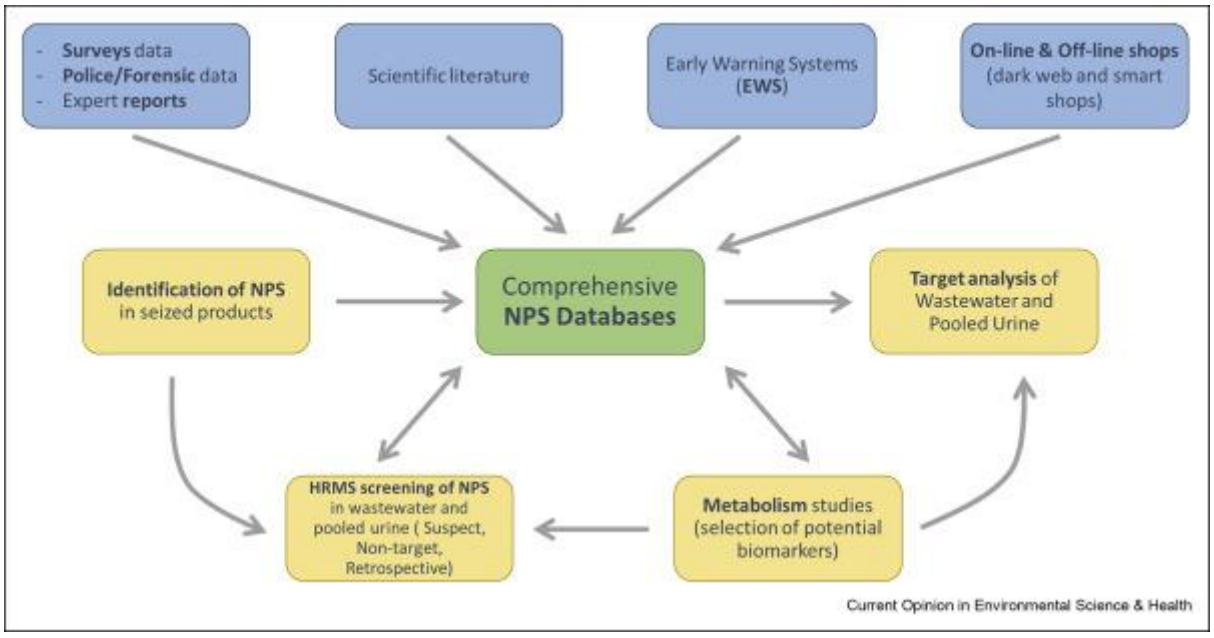
At the end of 2020, EMCDDA monitored approximately 830 new psychoactive substances, of which 46 appeared in Europe in 2020. Since 2015, around 400 previously reported new psychoactive substances have been found in Europe every year. This high number is lower than in the previous years (2014, 2015): the possible reason is that European governments are introducing increasingly effective measures against production and distribution. In addition, the authorities in China (which is the main source of new psychoactive drugs) are increasingly cracking down on illegal manufacturing laboratories [5].

The quantities of drugs seized provide important information for understanding the market of the new psychoactive drugs. In 2019, the member states of the European Union reported the

seizure of a total of 2.0 tons of new psychoactive substances, primarily in powder form. Synthetic cannabinoids and cathinones take about 60% of all seizures, another 10% of seizures are arylcyclohexylamines (mostly ketamine) analogs. Since 2008, 209 new synthetic cannabinoids, 138 synthetic cathinons, and 67 new synthetic opioids have been identified in Europe. In addition, designer benzodiazepines, synthetic opiates, tryptamines, arylcyclohexylamines, phenylamines and other substances were also present in the black market but in a much smaller proportion [5].

The ***Sewage Analysis*** CORe group in Europe has promoted and coordinated Wastewater-Based Epidemiology (WBE) campaigns for the worldwide monitoring of illicit drugs consumption since 2011, reporting the results to the EMCDDA, which considers WBE as a complementary source of information to the conventional indicators on drug use. The European project 'NPS euronet' aimed to improve the capacity to identify and assess the NPS being used in Europe. The project applied innovative analytical chemical and epidemiological methods and a robust risk-assessment procedure to improve the identification of NPS, to assess risks, and to estimate the extent and patterns of use in specific groups (e.g. at music festivals) and in the general population. [6] (Figure 1.)

Figure 1. Sources of information, steps, and topics required to build a comprehensive database for monitoring NPS use.[7]

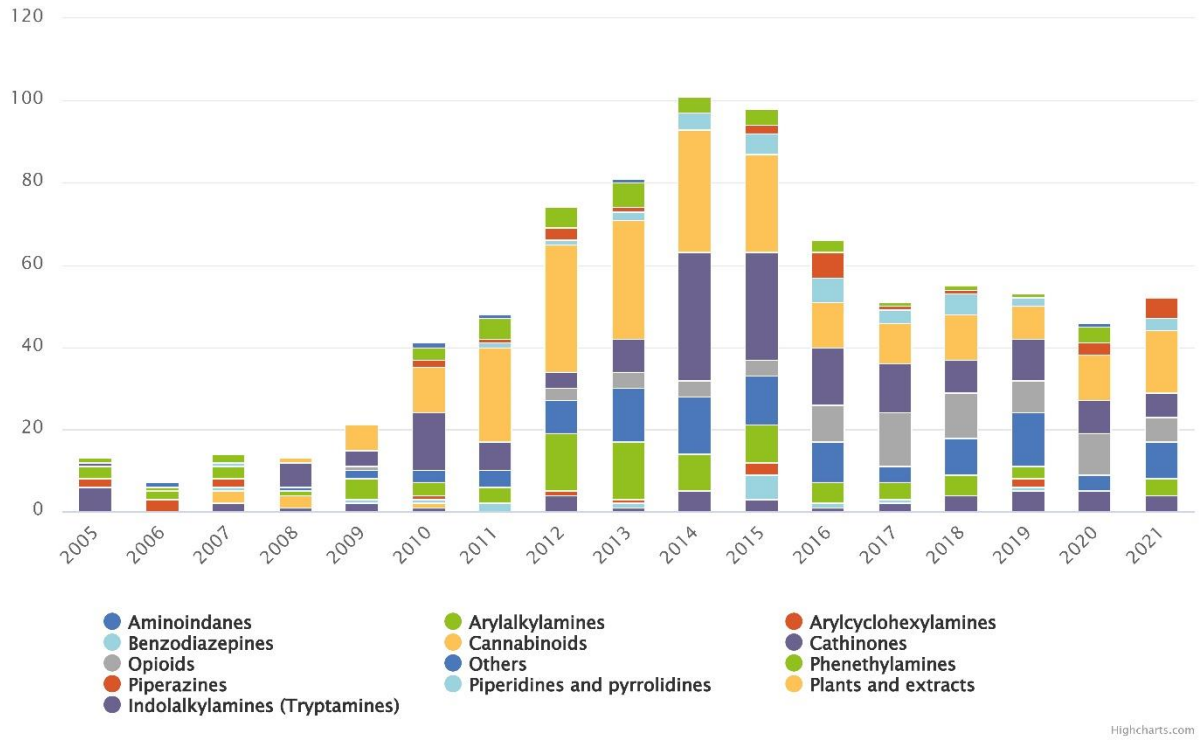



NPS: new psychoactive substances; HRMS: high-resolution mass spectrometry.

### 3.1.2 Prevalence of NPS in Europe

The NPSs appeared in the early 2000 years but their populatity raised from 2009 and reached their peak in 2014-2015 and declining trend is more definite in the Western European countries where instead of them the classic illigal drugs and the synthetic opiates started to raise. In Hungary the declination of the NPSs is also seen but they are still popular even among the middle class population. The seizure data of NPSs show that in 2014 to new substances per week appeared in Europe while in 2021 one substance.

Figure 2 .: Number and substance classes of new psychoactive substances first reported to the EU Early Warning System between 2005 and 2021.[8]




### 3.1.3 Population and the number of designer-drug users

Although in many European countries normal population surveys have also been conducted for the NPS, relatively few data are available on their prevalence. Based on the data between 2015 and 2018 the annual prevalence of their use ***among adults*** (15–64 years) ranged from 0.1% to 1.4%, with an average of 0.6%. To determine the prevalence of different psychoactive substances in Hungary, we can rely primarily on NSAPH (National Survey on Addiction Problems in Hungary) general population surveys in the adult population. According to the 2019 NSAPH general population survey 7.9% of adults (between 18-64 years) and 14% of young adults (between 18-34 years) used some kind of illicit drugs in their lifetime. Men have used illicit drugs in higher proportion. 6.1 % of the adult population have used marijuana or

hashish in their lifetime followed by ecstasy (2.5%), synthetic cannabinoids (2.1%), amphetamines (1.5%), cocaine (1.5%) and designer stimulants (1.4%). [9]

However, the data of the self-declaration questionnaire, is significantly distorted by the fact that typically neither the dealer nor the consumer knows exactly what substance is used. Several types of synthetic compounds with different purities are used under the same "brand name" (Herbal, Cristal).

In 2015 the ESPAD (European School Survey Project on Alcohol and Other Drugs) study collected information for the first time on ***NPS use among school children*** at European level (ESPAD Group, 2016). Information was collected again in 2019 for NPS use in general and, concentrating on synthetic cannabinoid and synthetic cathinone use. Twenty-two EU Member States participated in both surveys, representing 61.6% of the European Union's 15-16-year-old population. The ESPAD average for lifetime NPS use was 3.4 %, with the highest rates reported in Estonia (6.6 %) and Latvia (6.4 %) and the lowest rates reported in Finland, Portugal and North Macedonia (about 1 %), the Hungarian ratio was 3.7 %. The average prevalence of lifetime use was the same for boys and girls. When the students were asked specifically about the NPS consumption, 3.1 % of them reported that they have used synthetic cannabinoids at least once in their lifetime (ranging from 1.1 % in Slovakia to 5.2 % in France), Hungary: 4.9 %. 1.1 % of them reported lifetime use of synthetic cathinones with the highest rates found in Ireland (2.5 %) and Cyprus (2.4 %), Hungary was 1.9 %. On average, boys reported a slightly higher prevalence of use. [10]

Athough the number of people who consume these drugs in Europe is relatively low, in most European countries their consumption is the highest among the most ***vulnerable, high-risk groups***. The use of synthetic cannabinoids, cathinones and opiates is especially high among ***marginalized groups, such as homeless people or inmates in prisons***, and is often associated with other health and social problems. [11] [12]

## 3.2 Legal background and judgment

### 3.2.1 Risk assessment and legal control of new psychoactive substances at EU level

The international regulation of narcotic drugs and psychotropic substances ***is based on three UN conventions:*** (1) 1961 'Narcotics Convention' ("Uniform Convention on Narcotic Drugs of 1961 as amended by the 1972 Protocol of the United Nations") [UN61]; promulgated by: Legislative Decree 4 of 1965. (2) 'Psychotropic Convention' ('1971 Convention on Psychotropic Substances') [UN71]; promulgated by the Legislative Decree 25 of 1979. (3) 'Precursor

Convention' ("UN Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, dated 20 December 1988, Vienna") [UNSZ88], promulgated by Act Law of 1998. The amendments to the lists of the three conventions are decided by one of the UN bodies, the Commission on Narcotic Drugs (CND). The evaluation review is carried out by the Expert Committee on Drug Dependence (ECDD) of the World Health Organization (WHO), if: a) one of the signatories to the 1961 or 1971 Convention announces the need for an amendment, b) the CND requests this, c) the preliminary review recommends the evaluation review, or d) the WHO becomes aware of the production of a new substance that may pose a particularly serious risk to public health and has no recognized medicinal utility.

During the review of psychoactive substances, the Expert Committee takes into account the following criteria: 1) Similarity to known substances and effects on the central nervous system 2) Addiction potential, 3) Actual abuse and/or evidence of likelihood of abuse and 4) Therapeutic usefulness.

In Hungary, the legal status of the new psychoactive substances is defined by the 2005 XCV. Act on Medicines for Human Use and Amendments to Other Laws Regulating the Pharmaceutical Market. The minister responsible for health classifies certain substances or groups of compounds as new psychoactive substances, after a preliminary professional evaluation of the substance or group of compounds has been carried out by the expert body designated in the government decree (§ 15/B of Act XCV of 2005).

### 3.2.2 Abuse of new psychoactive substances

The ***abuse of new psychoactive substances is regulated by Act C of 2012 of the Criminal Code***. Hungary's regulations are among the strictest in the European Union. Similarly to Latvia, our country is the other member state which punishes the possession of new psychoactive substances with imprisonment (EMCDDA and EUROJUST 2016). The ***export, import, production, transport, and possession*** of such materials can be punished by imprisonment for up to 3 years (under certain circumstances up to 5 years). Trade of new psychoactive substances, offer them, their transfer and introduce into the black market is punishable by imprisonment from 1 to 5 years (or under certain circumstances up to 8 years) (§ 184 of Act C of 2012). Penalties are weaker if the active substance content of the seized material does not exceed the “small amount” fixed by law (§ 461 of the Criminal Code). For classical illicit drugs these implementations of crimes entail higher penalties. Unlike classical drugs, the ***consumption*** of new psychoactive substances is not considered a crime. Hungarian legistlation sets two different

kinds of crimes: one is the drug consumption itself, the other is the driving under the influence of drug. Medicolegal proving is easier in the first, the influence is a challening clinical and forensic problem.

### 3.2.3 Driving Under the Influence of Drugs (Section 237 Act C of 2012)

According to the EMCDDA European regulations, the law must be enforceable and dissuasive. In Hungary, driving under the influence of drugs is punishable by law with the same severity as driving under the influence of alcohol. ‘Any person who operates a railway or aircraft, a motorized vessel, or a motor vehicle on a public road or a publicly accessible private road ***under the influence of any substance - other than alcohol*** from the consumption of alcoholic beverages - that has the capacity to impair one's ability to drive is guilty of a misdemeanor punishable by imprisonment not exceeding two years.’

From a practical point of view, one of the biggest problems is the scientific proof (forensic medical evidence) of whether the driver was under the influence of drugs during driving. As an alternative approach, the zero-tolerance model is used in some European countries: regardless of whether influence can be proven - the crime is also committed by consumption. In some countries, driving under the influence of drugs is punishable, in other countries, proceedings can be initiated due to the condition of the driver being unfit to drive or endangering road safety. Hungary belongs to the latter group.

The Criminal Code originally penalized only drunk driving. Whith the spread of drug consumption the number of people driving under the influence of drugs and causing serious accidents increased significantly. Thus from March 1999 the sanctions of drugged driving were added to the previous Criminal Code.

## 3.3 Backgroud for the new psychoactive substances

In this thesis, we focus on synthetic cannabinoids and cathinones, so in this chapter we concentrate only on these two groups of substances.

The official information (EMCDDA, WHO) about NPSs follows the pharmaceutical logic (pharmacokinetics, dynamics) and describes the information mainly from case reports/series, retrospective toxicological data reviews, driving under the influence of drugs (DUID) reports, criminal/forensic cases, self- and controlled drug administration studies, and consumer experiences from the darknet. The majority of case reports originate from emergency

department (ED) visits; toxicological data of poison control center calls, hospitalized psychiatric cases, and law enforcement drug recognition examiner (DRE) evaluations.

The various types of NPS have a rapid turnover on the market; those with unpleasant physical or psychological symptoms for the consumer vanish in a short period of time. Only drugs that are constantly searched for by drug users may be included in the legislation's drug lists. In these conditions, research and detection are difficult.

### 3.3.1 Synthetic cannabinoids (SC's)

In 2006 new products called "Spice", "K2", "Herbal" appeared in Europe and were sold as "legal" cannabis [13] [14]. In Hungary the highest number and quantity of SC seizures was in 2014. Since then a gradual decrease has been observed followed by stagnation.

The first synthetic cannabinoids were synthesized by Roger Adams in the 1940s as antiemetics, later they were entered into the clinical medicine as appetite stimulant.

SCs are smuggled from the producing country (mainly from China) in a powder or liquid form. The active ingredient is dissolved in an organic solvent (e.g. acetone) sprayed on dried plant debris, for example on damiana (Turnera diffusa), medicinal sedum or white mallow (Althaea officinalis) and the solvent dried. [1] Overdosing may occur during manufacture because it is challenging to manually distribute the active component on plant debris. In addition, the impurities (heavy metals, residues of the organic solvents) can also perform their own toxic effects. The prepared dried plant mixture is filled into cigarettes and sold.[15]

Little information is available about the recommended single, daily, occasional or regular doses of SCs, especially when a new substance is entered into the black market. The consumer can get information about "how to use" from the dealer or from blogs. Due to the rapid turn over, the dealer often does not know the active ingredient of the product, he may know only the main group of compounds (SC, cathinone). It can be dangerous if a new active substance with higher efficiency is introduced into the market (ADB-FUBINACA [16], 5F-MDMB-BICA) because its toxic dose is lower than the previously distributed compounds.

Like THC synthetic cannabinoids bind to ***CB1 and CB2 receptors*** and therefore their effects are similar to cannabis. This receptor is part of the endocannabinoid signaling system, which can modify behavior, mood, pain, appetite, sleep, and the immune response.[17] However, in many cases, the appearance of clinical symptoms and side effects are more severe than expected.

THC is only partial agonist of cannabinoid receptors and has a lower CB1 and CB2 receptor affinity, while ***SCs are full agonists***. [18]

CB1 receptors are mainly located in the central nervous system (CNS), especially in the amygdala, cingulate cortex, prefrontal cortex, hypothalamus, hippocampus, nucleus accumbens, ventral tegmental area and the cerebellum but in smaller extent they can be found in the periphery. CB2 receptors are primarily ***located*** in the periphery, especially on the cells of the immune system, and can be found high number in the spleen and lymph nodes. Their activation increases the cytokine release and immune cell migration, possibly modulating inflammatory pain. [19]

The effect of synthetic cannabinoids appears 1-5 minutes after consumption and lasts for 1-2 hours, but in some cases it can last for 10-15 hours, however, it is highly characteristic for the way of consumption.

The psychological and behavioral effects are similar to THC, but the effect lasts for a shorter period of time, is stronger, and several other side effects have been observed. SCs cause similar symptoms, which can be modified by the method of consumption and the different chemical structure. The most characteristic psychological ***effect is the so-called "stoned" feeling***, which means relaxation, slowing down, euphoria, and lethargy. Confusion, anxiety, fear, time distortion, depersonalization, psychotic episodes, hallucinations, paranoia, suicidal ideation can also be observed but to a lesser extent. The most common physical symptoms are dry mouth, hyperaemic conjuctiva, hypertension, tachycardia, nausea, and vomiting. In addition, myocardial infarction [20], acute renal failure [21], seizures, aggressive and violent behavior can also occure. [22] [23] At low to moderate doses, THC/SCs increases sympathetic and inhibits parasympathetic activity, often leading to tachycardia and increased cardiac output. At higher doses THC/SCs increases parasympathetic activity, leading to hypotension and bradycardia. [20]

10 minutes after smoking a “Spice Diamond” mixture containing 0.3 g of CP47,497 altered mood and perception, tachycardia, dry mouth, and red conjunctiva were observed on the participants as acute effects. No adverse effects were registered in psychomotor tests, although the subjects felt moderately impaired. The objective effects disappeared within 6 hours, but the participants reported "minor post-drugged effects" (fatigue and exhaustion, hangover-like effect) that were still present the next day. [13]

***Repeated/chronic use of SCs*** is associated with impairment in executive functions and emotional processing. These alterations are associated with depression and schizotypal traits and symptoms. [24] [25]

Participants of an interpretive phenomenological analysis report that SCs ***cause addiction very quickly*** (even after a few uses), what they did not experienced before. [26]

A ***withdrawal syndrome*** has been described among daily users, characterized by increased craving of drug, tachycardia, hypertension, nausea, diaphoresis, nightmares and muscle twitches. No severe morbidity or mortality has been reported from withdrawal. [27]

The psychoactive symptoms of ***acute SC-intoxication*** were agitation or irritability, restlessness, anxiety, confusion, short-term memory, cognitive impairment, and psychosis. The physical signs are dilated pupils, hyperaemic conjunctiva, nausea, vomiting, slurred speech, shortness of breath, hypertension, tachycardia, chest pain, muscle twitches, and sweating or skin pallor. [27] Unfortunately, most published data on acute intoxication do not include toxicological results and are based on SC consumers' self-report.

There is no clear toxidrome, only a collection of symptoms related to previous SC consumption. Toxicological analysis to identify the active substance is time-consuming and expensive, so the patient's drug use is not verified. There is no antidote; treatment in toxicology departments is supportive (benzodiazepines, intravenous hydration); if the patient exhibits psychotic symptoms, anti-psychotic medication is required. The intoxication generally lasts for 2-5 hours, and the majority of patients recovered within 24 hours. [16] [28]

### 3.3.2 Synthetic cathinones

The main source countries, where NPS are sold openly by chemical and pharmaceutical companies, are China and India. However, a small number of illicit laboratories have also been detected in EU countries, such as in the Netherlands and Poland, where mainly synthetic cathinones were produced.

Synthetic cathinones appeared first in the black market in 2004 as legal substitutes of illegal stimulants such as amphetamine, cocaine, and MDMA. In Hungary synthetic cathinones were introduced into the black market in 2010. The first substance was mephedrone followed by MDPV, pentedrone, 4-MEC and α-PHP [29]. Since 2017, the most frequently seized synthetic cathinone was N-ethylhexedrone.

Cathinons are typically available in the black market as powder, white or brown crystalline form, capsules, and rarely tablets, and are often mixed with other synthetic cathinones or caffeine, lidocaine, and benzocaine. They are often advertised as bath salts, plant food, jewelry cleaner, or phone screen cleaner, and signed as "not for human consumption."

The majority of users snort them, but oral, intravenous, sublingual, rectal application, or inhalation are also common.[30] Intravenous drug users often replace heroin by synthetic cathinones. [31]

Synthetic cathinones have similar chemical structure to cathinone and methcathinone, the former is an extract of the ***catha edulis*** leaves. The plant, which belongs to the Celastraceae family and is widely ***consumed as a stimulant*** in Yemen, Somalia, Djibouti and Ethiopia. It's active substances (cathinone) is not stabile, it decomposes within two days. Cathinone differs from amphetamine with a beta-keto group on the β-carbonium atom. [32]

The desired effects of cathinons are euphoria, increased concentration and performance, talkativeness, increased empathy, and libido. [33] Hunger and sleepiness are disappear, that's why they are popular drugs in dance clubs (disco-drugs). [34] [35]

The main side effects are agitation, panic attacks, paranoia, hallucinations, aggressive behavior, psychosis, paresthesia, muscle spasm. [30] Cardiovascular effects include tachycardia, systolic and diastolic blood pressure may be elevated [4] [36], but cardiomyopathy and sudden cardiac arrest can also occur. [37] [38] Synthetic cathinones typically have a vasoconstrictor effect on the periphery, resulting in pale, cold, cyanotic limbs. Laboratory abnormalities such as metabolic acidosis, hypokalemia, hyperglycemia can also occur. [39] Rhabdomyolysis, delirium, liver and kidney failure, and multi-organ failure (MOF) occur in the most severe cases. [30]. Hyperthermia is common in severe intoxications, sometimes with fatal outcome. [30] There have been numerous cases of poisoning and overdose with fatal outcomes have been described in the literature. [40]

As the consumers often combine substances, little is known about the ***consequences of long-term use*** of cathinones. [41] They occasionally seek medical attention for psychotic symptoms, delusions, and hallucinations. [42]

The psychoactive effects (MDPV) can occur even after taking very small amounts of the substance, typical doses are between 5 and 30 mg, although users sometimes report taking doses of 50 mg or more (up to 200 mg if tolerance develops). Additionally, repeated intake of doses within a short period of time is common. The effect is strongest 60-90 minutes after ingestion, then becomes moderate for another 3-4 hours, and finally disappears after 6-8 hours. According to some surveys, at a party, mephedrone is typically used in a larger amount (between 0.5 and 1.9 g) divided into several smaller "single doses" that can last on average 9-10 hours, or even longer (24-48 hours).[35]

Cathinons are interact with dopamine (DA), norepinephrine (NA) and serotonin (5-HT) transporters (DAT, NET and SERT) in a similar way as cocaine or MDMA. Acting as transporter blockers and/or monoamine releasers the monoamine content of the synaptic gap

increases and it leads to hyperstimulation of the postsynaptic receptors. Cathinones differ in their efficacy, selectivity, and affinity for monoamine membrane transporters and receptors. Depending on their chemical structure they stimulate the different monoamine systems in a different degree. As a result, their effects can be predominantly dopaminergic (psychostimulant and reinforcing properties, high abuse and addiction potential), noradrenergic (sympathomimetic stimulation, cardio- and psychostimulant effects), serotonergic (hyperthermia, seizures, paranoia, and hallucinations), or a combination of the three. [33]

## 3.4 NPS issues and challenges in forensic practice

### 3.4.1 Drug consumption and detectability

Basically, the consumption of new psychoactive drugs is not considered a crime but the confirmation of NPS use from body fluids is a critical issue in emergency, toxicology and forensic practice. To prove drug consumption, analysis of urine sample is sufficient. Urine is the most common matrix for drug testing because of its non-invasive collection, higher drug and/or metabolite concentrations than in blood, and longer detection window than either from blood or oral fluid. Unfortunataly, the routine ***rapid urine tests*** are not suitable for detection of designer drugs, their analysis by gas chromatography-mass spectrometry or by liquid chromatography-tandem mass spectrometry is necessary. These determinations are not routinely available, and generally do not provide help in the acute management of intoxicated patients. They applied only for medico-legal purposes.

The ***analitical determination of metabolites*** extend the detection window. From the standpoint of the drug's pharmacokinetics, mode of action, and duration, research and knowledge of NPS metabolism and the creation of apparently active and inactive metabolites are crucial. The detection of OH metabolites of SCs can be important from the point of view of drug impairment, while COOH metabolites are useful for verifying drug consumption. Beside detection of the parent compounds of SCs, the screening for their metabolites provides a reliable confirmation of consumption, in particular, when the parent compound is under the limit of detection.[43] [44]

### 3.4.2 Drug impairment and traffic

Drug use affects fitness to drive, but it is difficult to determine to what extent, with what probability, and in what quality. Several drugs can impair traffic-related tests (i.e. measuring sedation, drowsiness, divided attention, continuous perceptual-motor coordination, speed and accuracy of decision making, vigilance and short-term memory). [45] The drug's dose, the effects

on the drug user's body, the length of time since the drug was used, and other factors all contribute to being under the influence.

The Hungarian Criminal Code does ***not define neither the concept of the impairment state***, nor difference between legal and illegal drugs, i.e. it does not categorize between prescribed, regularly taken medicines, classic drugs on the drug list, and new psychoactive substances. Furthermore, unlike alcohol, it does not establish a "legal impairment limit" for drug use, i.e. a blood concentration level below which drug use is not considered an offense or a crime. Only a toxicological analysis of the blood sample and clinical medical legal evaluation of the results could prove that the person was actually under the influence of drugs or alcohol.

### 3.4.3 Drug intoxication/ postmortem toxicology (direct/related death)

On the black market for new, often highly potent, synthetic substances is rapidly expanding. The direct impact of these changes can be seen in the number of fatal drug overdoses in the EU in 2017, which totaled 8 238 people, as well as individuals seeking help from treatment providers or emergency services. In 2016, 7% of drug-related acute toxicity caused by NPS was observed in hospitals. Because of their low cost, easy availability, and high potency, NPSs appear to be causing more problems, with increased use among marginalized groups such as the homeless and prison populations. [2]

It is also critical, from a medical, statistical, and legal standpoint, to recognize fatal intoxication caused by NPS, as well as other deaths that may be related to NPS. Deciding this requires extensive knowledge of historical data, witness statements, previous medical treatment, and a list of regular medications. The possibility of an overdose is usually not obvious at the scene of death, in a public environment (street), or in the absence of special drug consumption equipment (needle, syringe, pipe, the drug itself) and during the autopsy, no specific findings can be found in the case of an overdose. That is why, in the absence of toxicological testing, general macroscopic and microscopic examination results can be easily misinterpreted as natural death or sudden cardiac death. Therefore, in the absence of a definite cause of death, toxicological analysis is recommended in all cases, especially in the case of a young person, given specific historical data. Because the lethal dose or blood concentration of NPS has not been determined, a direct or indirect causal relationship between drug use and mortality should be considered following the toxicological analysis. Lethal blood concentrations can only be assumed on the basis of case studies in the literature.[40 46 47 48]

# 4 Study I. – Clinical symptoms and blood concentration of new psychoactive substances (NPS) in intoxicated and hospitalized patients in the Budapest region of Hungary (2018-19)

## 4.1 Introduction

The acute health consequences of drug use could be provided by hospital emergency data, allowing the detection and monitoring of new patterns in substance use. The sentinel center monitoring program of the EMCDDA reported data of 31 European emergency sites from 21 countries (not including Hungary) in the period 2013-2017, offering a non-representative, but comparable dataset on drug-related hospital emergencies in Europe, including cases of NPS which were found in 9% of the cohort over the 4 years' period. The geographical distribution of NPS was highly variable, and the predominant NPS class changed from cathinones to SCs by 2016-2017. [49]

By 2014, designer drug seizures accounted for an increasing proportion (up to 60%) of all illicit drug seizures in Hungary. This trend was reflected in the increasing number of hospitalization related to designer drugs. However, this trend reversed in 2017 and 2018, with designer drugs accounting for only 38% of all seizures. The most common group was synthetic cannabinoids (SC) at 67%, followed by cathinone-type stimulants at around 30% of cases (App. Table A1).

There were no large-scale reports of NPS poisonings in Hungary in recent years, so it is not known whether the decline in designer drug seizures reflects the true prevalence of their use or not.

## 4.2 The main factors causing intoxication

NPS are popular mainly among high school students, young adults, segregated people, and prisoners because of their ***easy availability***, they can be ordered online, and they are ***cheap*** compared to other classical drugs or alcohol. Besides, they ***cannot be detected*** with the commonly used urine drug test, but have similar effects to illegal marijuana and stimulants, and therefore they are consumed as their "legal" alternatives. This property may be attractive to those who are regularly tested for drugs (e.g. drug diversion participants (an alternative to imprisonment), withdrawal treatment, candidates for workplace drug testing, driving licence renewal, law enforcement, firefighters, armed forces, prisoners or probationers, mine workers and athletes).

In most cases, the dealer (street, online) has information about the particular class of substance (SC, synthetic cathinon), but ***not the exact type of substance*** he is currently selling. The material sold is also categorized in this way on the internet shop site. Thus, the consumer can only know the group of materials he has ordered. The dealer suggests the dosage or the consumers can share their experiences and suggestions via the website chat. This uncertainty is relevant when, due to criminal law considerations, a new substance is introduced into the market (5F-MDMB-PICA → BICA) and probably the recommended dose for the previous one is no longer valid. Inappropriate dosing and individual sensitivity can lead to unpredictable effects and side effects.

The active substance of SCs is smuggled in powder form and the final product is prepared in the target country. The active substance is dissolved in acetone and then sprayed onto herbal mixture. If the active substance is poorly soluble in acetone a solution-suspension mixture is sprayed on the matrix which is not evenly ***distributed on the plant*** and can result "hot spot" formation. The appearance of the final product resembles to marijuana. The active substance may contain other impurities (such as residual acetone), preservatives (benzyl benzoate) and additives (e.g. high level of vitamin E, probably to mask toxicological analysis or Beta2-adrenergic agonist e.g. clenbuterol to reduce sympathomimetic effects as tremor, tachycardia, anxiety). The dried herbal mixture is toxicologically neutral, but may ***contain toxic substances*** such as pesticides.

Unlike THC, SCs are ***full agonists of CB1 and CB2*** receptors and can produce strong effect at low concentrations, so it is easy to accidentally overdose them. In the cannabis products other active cannabinoids are also present (e.g. cannabidiol) which have anti-anxiety, anti-psychotic and appetite stimulant properties. These substances balance the psychoactive effects of THC in a given degree but there are no such compounds in the SCs. Cathinones have a high abuse potential and are often applied more times a day which increase the risk of overdose.

Drug-intoxicated patients are usually ***treated symptomatically***. In hospital care, there is no possibility to perform quantitative toxicological tests, which are costly and time-consuming. Typically, when the treating physicians receive the toxicology results the patient has cleared up and has left the hospital. As a result, the type and blood concentration of the NPS that caused the poisoning is not known during the hospital care. General knowledge about toxic blood concentrations or about their pharmacokinetics (e.g. half-life) are not available.

## 4.1 The aims of the study I.

To explore these unknown factors, we conducted a prospective study in collaboration with the Emergency Department and Clinical Toxicology of the Péterfy S. Hospital, Budapest (DECT), to answer the following questions:

- ***which NPS*** caused the most frequent intoxications between 1 April 2018 and 30 March 2019 in Budapest and its region;
- what are the ***most common symptoms*** of NPS intoxication;
- whether there is a relationship between their blood concentration and the severity of the ***clinical symptoms; and***
- to determine the ***half-life*** of NPS following toxicological analysis of time-series blood samples taken at hospital admission.

## 4.2 Materials and methods

The study was approved by the Human Investigation Review Board of the University of Szeged (permission number: 155/2018-SZTE).

All intoxicated patients from Budapest and its region (about 3 million inhabitants) were admitted to DECT (8.500 patient/year). Approximately 700 persons who received in-patient care with a history of chronic drug use served the basis for patient selection. Blood sampling and detailed recording of clinical symptoms were conducted on selected patients.

Patient selection fulfilled the following criteria:

- patients were transported by the Emergency Medical Services (EMS) within an hour of the EMS call to the inpatient ward of the DECT,
- the medical history was indicative of NPS, and
- the patients cooperated in repeated blood-sampling and a few hours observation.

The exclusion criteria were:

- medical history or clinical symptoms of intoxication other than NPS or other classical of illicit drugs (e.g., alcohol, medicines, pesticides, CO, etc.),
- transportation to DECT was not by EMS or delayed arrival to the ward (>1 h) by EMS,
- oral or written objection of cooperation.

At the arrival and first examination at the DECT the selected patients were under the influence of drugs, thus, legally incompetent to consent or refuse participation in the study. Therefore, the ethical committee approved the study with implementing post-recovery rejection of inclusion. The patients initial will was noted, and as soon as they sobered up enough to make

legally valid declarations they were offered to opt out of the study. A small number of patients officially refused participation (n=15), but a large number of patients were non-compliant upon recovery and left the hospital without informing or consulting the medical staff (n=19). Between the 1 st of April 2018 and the 30 th of March 2019, 116 patients suspected of NPS intoxication were selected by the above detailed criteria of those who were transported to the DECT. EMS recorded the history of drug use from patients and witnesses at the scene, as well as, clinical symptoms. Intoxication was diagnosed by the EMS physician and by experienced emergency toxicology specialists of the DECT. Gender, age, and main symptoms were registered at the scene by the EMS staff. More detailed symptoms were registered upon admittance by the staff of DECT, and included Poison Severity Score (PSS) [4], Glasgow Coma Score (GCS), blood pressure, heart rate, body temperature, blood glucose, and other routine investigations. Medical history and prescribed medications were reported by the patients. Clinical laboratory testing involved complete blood count (CBC), basic metabolic panel (BMP), electrolyte, lipid, hepatic and kidney function panels. Blood samples for psychoactive substance measurements were taken through a needle thumbtack – introduced for supportive therapy and medication – into 5-ml sodium citrate-containing tubes at admittance (0 h) and 1, 3, and 5 h later. To prevent cross contamination during repeated sampling, the cannula was flushed with 1.0 ml Vitamin C injection (100 mg/ml), according to the local protocol. Analysis of blood samples and data processing were performed at the Department of Forensic Medicine (DFM) at the University of Szeged. Blood samples were transferred for analysis once or twice every two weeks. Both clinical data and blood samples were blindly assessed. Eleven patients left the hospital within 3 h after admittance without informing the staff, so sampling remained incomplete.

Blood samples were stored and transferred at 4°C. Analysis was directed to alcohol, 20 classical illicit drugs and medicines (psychoactive prescription drugs: benzodiazepines, tramadol, zolpidem), 50 stimulant NPS, and 28 SCs. The list of substances and their cut off values have already been published. [46] [50] Illicit, licit drugs and stimulant NPS were analysed by GC-MS following liquid/liquid extraction and derivatization by MSTFA or HFBA [5–7]. Blood samples were analysed for SCs by LC-MS/MS followed by precipitation with acetonitrile and ammonium sulphate, vortex mixing, and centrifuging. The supernatant was evaporated and resolved in the mixture of formic acid, water and acetonitrile for LC-MS/MS analysis. [44] Alcohol concentration was determined by head space method (GC-FID). From May 2018, the SC drug CUMYL-CH-MEGACLONE was only qualitatively analysed due to the absence of a

certified standard. Clinical data were evaluated by a forensic and a toxicology expert. Association between blood concentration and clinical symptoms was studied only for NPS.

Drug frequencies were statistically analysed by chi-square test. Terminal half-life (t1/2) was estimated by ‘ $t(1/2) = \ln(2) \cdot \lambda Z$ ‘where $\lambda Z$ is the first order terminal elimination rate constant. The value of $\lambda Z$ is determined by unweighted least-squares regression of the terminal part of each individual log-linear concentration-time profile, using at least 3 measurement points. Linear regression was fitted by GLM procedure in SASVR (9.4 (2016) using VR Studio in SASVR University Edition environment. The onset of terminal elimination phase was determined as the time when the slope of the regression line turned negative. Half-life was not determined when less than 3 measurements were available. The outlier analysis was performed by ROUT method (PRISM software, GraphPad Inc., La Jolla, CA), by setting the Q value to 1%. [51]

## 4.3 Results

### 4.3.1 Distribution of positive cases

The present study included 116 patients who were suspected of intoxication by a NPS-type drug at hospital admission.

Figure A1 shows the frequency of the detected substance groups and their combinations. Table A1 presents the frequency of each substance, their concentrations or concentration ranges at admission. Only 96 patients (82%) were tested positive for at least one substance, including 51 patients with the presence of NPS (44% of the total population). SCs could be detected in 48 cases, classical illicit drugs in 29 cases, alcohol in 27 cases, benzodiazepines in 17 cases, and cathinones in 4 patients. The most frequently detected drugs, both alone and in combination, were 5F-MDMB-PINACA and 5F-MDMB-PICA; n = 23 and n = 23, respectively, followed by THC (n = 15), amphetamine (n = 12) and clonazepam (n = 11). Out of the 48 SC users, 18 used 5F-MDMB-PINACA alone, 15 used 5F-MDMB-PICA alone and 1 patient used only CUMYL-CH-MEGACLONE.

**Figure A1.:** Distribution of individual substances among intoxicated patients

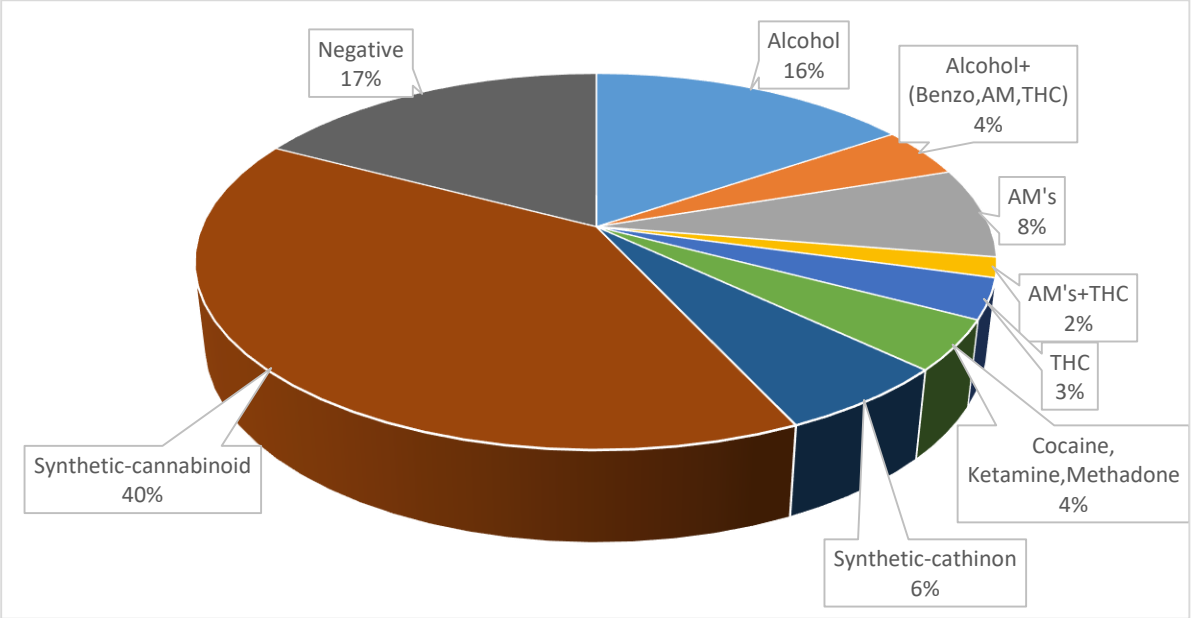



**Table A1**.: The prevalence of individual substances with their cut off values and concentration ranges in the blood samples taken at admittance. [51]

| **Substances** | **Cut off (ng/ml)** | **Alone (N)** | **Comb. (N)** | **Together (N)** | **Blood cc. at admittance (ng/ml)** |
|---|---|---|---|---|---|
| THC | 1 | 6 | 4 | 10 | 1.40 – 5.82 |
| THC-COOH | 5 | 7 | 8 | 15 | 9.46 - 109 |
| Amphetamine | 10 | 3 | 9 | 12 | 12.1 - 828 |
| MDMA | 10 | 1 | 5 | 6 | 59.3 - 867 |
| Benzoyl-ecgonine* | 10 | 1 | 1 | 2 | 122 - 1931 |
| Methadone | 10 | | 2 | 2 | 25.6 - 136 |
| Ketamine | 10 | | 2 | 2 | 440 - 585 |
| GHB | 5 (µg/ml) | 1 | | 1 | 477 µg/ml |
| Clonazepam | 10 | 2 | 9 | 11 | 17.5 - 520 |
| Alprazolam | 10 | 2 | 3 | 5 | 17.4 - 114 |
| Temazepam | 10 | | 1 | 1 | 98.1 |
| N-ethyl-hexedrone | 20 | 2 | 1 | 3 | 10.1 - 138 |
| 4-CMC | 20 | 1 | | 1 | 117 |
| 5F-MDMB- PINACA | 0.005 | 18 | 5 | 23 | 0.046 – 2.54 |
| 5F-MDMB- PICA | 0.001 | 14 | 9 | 23 | 0.024 – 8.21 |
| CUMYL-CH-MEGACLONE | ** | 1 | 1 | 2 | quantitative |
| Alcohol (>0.5 g/l) | 0.05 | 17 | 11 | 28 | 0.69 – 3.35 g/l |

20 intoxicated cases were negative for the substances analyzed.

### 4.3.2 Gender and age distribution of NPS users

The ratio of males both among the patients tested positive and among NPS users was 82%, the dominant age group was 18-24 years in both subpopulations (Table A2).

**Table A2**. Gender and age distribution of all investigated patients, positive cases, and NPS users [51]

| Gender | Investigated Patients (n=116) | | Positive cases (n=96) | | NPS users (n=51) | |
|---|---|---|---|---|---|---|
| | (abs) | % | (abs) | % | (abs) | % |
| Man | 96 | 82.8 | 79 | 82.3 | 42 | 82.4 |
| Woman | 20 | 17.2 | 17 | 17.7 | 9 | 17.6 |
| **Total** | **116** | **100** | **96** | **100** | **51** | **100** |
| | | | | | | |
| Age groups | Investigated Patients | | Positive cases | | NPS users | |
| | (abs) | % | (abs) | % | (abs) | % |
| <18 | 10 | 8.6 | 8 | 8.3 | 3 | 5.9 |
| 18-24 | 49 | 42.3 | 41 | 42.7 | 23 | 45.1 |
| 25-34 | 40 | 34.5 | 35 | 36.5 | 19 | 37.3 |
| 35-49 | 15 | 12.9 | 11 | 11.5 | 6 | 11.7 |
| ≥50 | 2 | 1.7 | 1 | 1 | 0 | 0 |
| **Total** | **116** | **100** | **96** | **100** | **51** | **100** |

### 4.3.3 Prevalence of multi-drug use

30% (35 patients) of the total population used more than one drug. The most common combinations of designer drugs were: 5F-MDMB-PINACA with alcohol (n = 3), clonazepam (n = 2) AM/MDMA (2), and 5F-MDMB-PICA with THC (n = 4), clonazepam (n = 3), alcohol (n = 1), and in one case the two SCs with each other.

### 4.3.4 Clinical symptoms of SC users

The status and symptoms were evaluated separately at the scene, on-site by the EMS and bystander, during transportation and at admission to the hospital.

In majority of SC positive cases the witnesses used the following phrases to describe the condition of the patient: unconscious, "asleep", lying on the ground or on a bank. In a few cases, the family or friends called for help and in one case the patient voluntarily asked for help because of suicidal ideation. The ***symptoms were similar*** at the scene among 5F-MDMB-PINACA and 5F-MDMB-PICA users: unconsciousness (n=15), confusion (n=6), aggressive behavior (n=3), hallucination (n=2), agitation (n=2), vegetative symptoms (n=3) involving nausea, weakness, tachycardia, and sweating), epileptic seizure (n=2). Depressive state of consciousness was predominant, with a smaller proportion of positive psychiatric symptoms (confusion, paranoia*, hallucination*, agitation, aggressiveness). In psychotic cases, the history referred to pre-existing psychiatric* disorders. The presence of vegetative symptoms (nausea, vomiting) was uncommon (Table A3).

**Table A3:** Symptoms of 5F-MDMB-PINACAand 5F-MDMB-PICA consumers at the scene

| | Symptoms | 5F-MDMB-PINACA (N: 18) | 5F-MDMB-PICA (N: 15) |
|---|---|---|---|
| *AT THE SCENE* | passer-by / family | 15/4 | 8/6 |
| | unconscious / lying on the ground / sleeping | 9 | 6 |
| | confusion | 4 | 2 |
| | agitation | 2 | - |
| | aggressive behaviour | 2 | 1 |
| | hallucination / paranoia * | - | 2 |
| | nausea, vomiting | 2 | 1 |
| | difficulty walking | 1 | - |
| | epileptic seizure | 1 | 1 |
| *AMBULANCE* | Improve during transport | 8 | 5 |
| | Therapy | midazolam, haloperidol* | supportive |
| | Already treated at DECT | 12 | 11 |

The transport time in Budapest was less than 1 hour, exact data of duration were not available. During transportation the condition of almost one third of the patients improved, and only those with positive psychiatric symptoms required medication (midazolam, haloperidol), the others received supportive therapy. Two thirds of them were already treated several times in the hospital with intoxication.

The frequency of symptoms of those who were intoxicated by 5F-MDMB-PINACA and 5F-MDMB-PICA detected at hospital admission is presented in Table A4. We found no significant difference ($p>0.05$) in the prevalence of symptoms when the two most frequent SCs were compared. The most common psychiatric symptoms of the 33 SC users were bradypsychia (n=21), slurred speech (n = 21), and confusion (n = 10). Among somatic symptoms slow pupillary light reflex was found in almost all patients, hyperaemic conjunctiva in 27% and tachycardia in 24% of cases.

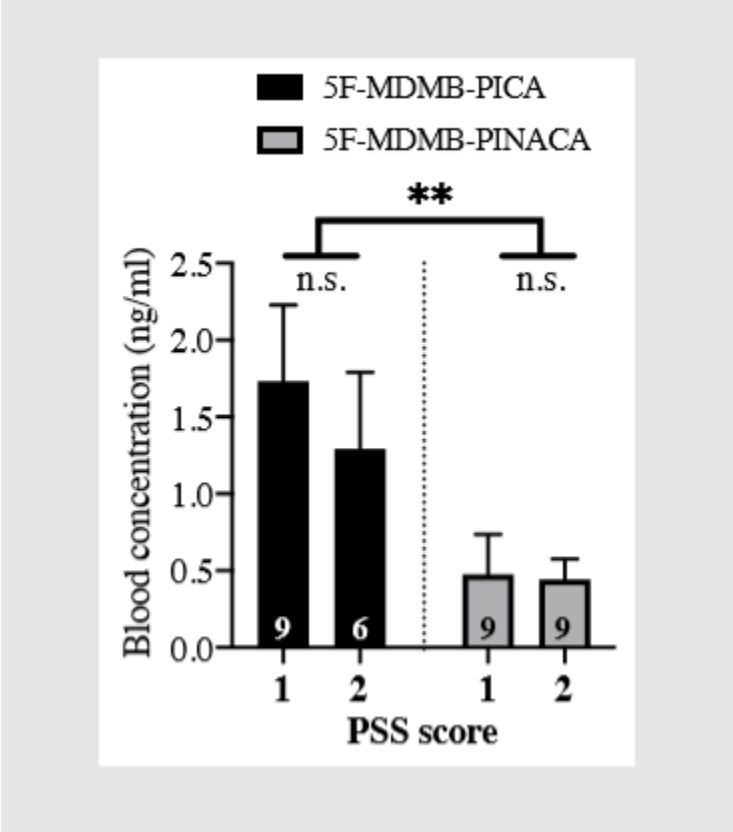
**Table A4:**Symptoms of 5F-MDMB-PINACA and 5F-MDMB-PICA consumers at the hospital [51]

| Organ system | Symptoms | 5F-MDMB-PINACA (n=18) | 5F-MDMB-PICA (n=15) | Sum (n=33) | Prev. (%) |
|---|---|---|---|---|---|
| *Central nervous system* | unconsciousness | 8 | 4 | 12 | 36.3 |
| | bradypsychia | 10 | 11 | 21 | 63.6 |
| | somnolence | 3 | 3 | 6 | 18.2 |
| | confusion | 6 | 4 | 10 | 30.3 |
| | aggression | 2 | 2 | 4 | 12.1 |
| | agitation | 4 | 2 | 6 | 18.2 |
| | slurred speech | 2 | 2 | 4 | 12.1 |
| | hallucination | 0 | 1 | 1 | 3.03 |
| | paranoid psychosis | 0 | 1 | 1 | 3.03 |
| | repulsiveness | 0 | 1 | 1 | 3.03 |
| | disorientation | 0 | 1 | 1 | 3.03 |
| *Gastrointestinal system* | dysarthria | 0 | 1 | 1 | 3.03 |
| | vomiting | 1 | 2 | 3 | 9.09 |
| | malaise | 2 | 2 | 4 | 12.1 |
| *Neuromuscular system* | hyperactive DTR | 2 | 0 | 2 | 6.06 |
| | hypoactive DTR | 0 | 1 | 1 | 3.03 |
| | convulsion | 1 | 1 | 2 | 6.06 |
| | ataxia | 0 | 1 | 1 | 3.03 |
| *Cardiovascular system* | tachycardia (HR>100/min) | 3 | 5 | 8 | 24.2 |
| | hypertension (Sys. BP > 130) | 6 | 3 | 9 | 27.3 |
| | hypotension (Sys BP < 100) | 2 | 3 | 5 | 15.2 |
| *Eyes* | mydriasis | 1 | 3 | 4 | 12.1 |
| | miosis | 3 | 0 | 3 | 9.09 |
| | slow pupillary light reaction | 17 | 15 | 32 | 97.0 |
| | conjunctival hyperemia | 4 | 5 | 9 | 27.3 |
| | nystagmus | 0 | 2 | 2 | 6.06 |
| *Other* | erythema | 2 | 0 | 2 | 6.06 |
| | hyperventilation | 0 | 1 | 1 | 3.03 |
| | metabolic acidosis | 0 | 1 | 1 | 3.03 |

$p>0.05$ by chi-square test when the frequency of symptoms was compared

We compared the PSS score for the two main SCs, 5F-MDMB-PINACA (PSS median ± SD: 1.5 ± 0.5, n = 18) and 5F-MDMB-PICA (PSS median ± SD: 1 ±0.5, n=15) and found no difference in overall symptom severity ($p>0.05$). The frequencies of PSS 1 and 2 were not different between the two SCs ($Chi^2$ test: $p = 0.56$, Fisher's exact test: $p = 0.72$). No patient in the study had a PSS = 3 (Figure A2.).

Figure A2.: Change in PSS score in light of SC blood concentration




### 4.3.5 Blood concentration of SCs

The initial (0h) blood concentrations of both compounds were from <0.1 ng/mL to 2.54 (5F-MDMB-PINACA) and 8.211 (5-MDMB-PICA) ng/mL.

When stratified by PSS score at hospital admission, a two-way ANOVA (Figure A2) of blood levels of 5F-MDMB-PINACA and 5F-MDMB-PICA revealed an overall significant difference between the toxic concentrations of the 2 SCs (2-way ANOVA: $p = 0.0075$).

In addition, blood concentrations were significantly lower for patients with PSS = 1 for 5F-MDMB-PINACA (median: 0.19 ng/mL, mean ± SE: 0.47 ± 0.26 ng/mL, n = 9) than for 5F-MDMB-PICA (median: 2.16 ng/mL, mean ± SE: 1.73 ± 0.5 ng/mL, n = 9; Fisher LSD test: $p = 0.0155$), but not different in patients with PSS = 2 (median 5F-MDMB-PINACA: 0.25 ng/ml, mean ± SE: 0.44 ± 0.26, n = 9; 5F-MDMB-PICA median: 0.88 ng/ml: mean ± SE: 1.73 ± 0.49, n = 6; Fisher LSD test: $p = 0.1302$). ***These results suggest that the toxicity of 5F-MDMB-PINACA is higher than that of 5F-MDMB-PICA.*** However, no statistical correlation between symptom severity (PSS score) and blood concentrations was found, presumably due to the low number of cases.

Appendices 4, 5 show detailed clinical signs and blood concentrations of patients intoxicated by 5F-MDMB-PINACA, 5F-MDMB-PICA, CUMYL-CH-MEGACLON, and two cathinones, respectively. Only abnormal laboratory results were reported.

### 3.4. Therapy of SC intoxicated patients

More than half of the patients left the hospital arbitrarily after feeling better. The duration of treatment of these patients was a few hours shorter than of those who were emitted. Most symptoms resolved within 12-13 hours an average (ranged from 1 to 27 hours). (Table A5)

**Table A5:** Therapy of the SC intoxicated patients

| **Therapy** | **5F-MDMB-PINACA (N=18)** | | **5F-MDMB-PICA (N: 15)** | |
|---|---|---|---|---|
| Midazolam/ Clonazepam/ Dormicum | 4 | | 1 | |
| Haloperidol | - | | 2 | |
| Cerucal | 1 | | - | |
| Supportiv | 14 | | 12 | |
| **Emission** | N | t (h) | N | t (h) |
| Discharge | 4 | 7 | 6 | 13,5 |
| Arbitrary | 14 | 9,4 | 6 | 12 |

N: number of patients, t: interval of treatment

#### 4.3.6 Half-life of 5F-MDMP-PINACA and 5F-MDMP-PICA

A sufficient number of cases of 5F-MDMB-PINACA and 5F-MDMB-PICA users was available to calculate half-life of these substances. According to our calculation the median half-life of 5 F-MDMB-PINACA was 2.50 h, and of 5F-MDMB-PICA it was 2.68 h for. Based on outlier analysis, we excluded the values of 7 patients; outliers are indicated by *italics* in Table A6. Other combinations involving midazolam, clonazepam and alcohol did not seem to affect the half-life of SCs, but the low case number did not allow for quantitative analysis of those combinations.

In one SC combination (5F-MDMB-PINACA and 5F-MDMB-PICA), the metabolism of the former SC was prolonged (t1 / 2 = 224 h), while the half-life of the other was decreased (t1 / 2 = 0.77 h) which may indicate competitive inhibition of metabolism.

**Table A6**: Individual half-life of 5F-MDMP-PINACA and 5F-MDMP-PICA alone and in combination [51]

| (Table 5) | **5F-MDMP-PINACA** | | | (Table 6) | **5F-MDMP-PICA** | | |
|---|---|---|---|---|---|---|---|
| P. No | Conc. | Other subst. (conc.) | $t_{1/2}$ | P. No | Conc. | Other subst. (conc.) | $t_{1/2}$ |
| 3 | 1.063 | | 2.65 | 2 | 3.39 | | 2.03 |
| 4 | 0.471 | | 2.07 | 5 | 2.58 | | 3.23 |
| 5 | 0.408 | | 6.10 | 7 | 2.16 | | 4.49 |
| 8 | 0.270 | | 2.35 | *9* | *0.821* | | *11.9* |
| *9* | *0.250* | | *78.4* | 11 | 0.391 | | 2.64 |
| 13 | 0.182 | | 3.65 | 12 | 0.369 | | 2.70 |
| 16 | 0.098 | | 0.98 | 13 | 0.148 | | 1.29 |
| **Median** | | | **2.50** | **Median** | | | **2.68** |
| **± SD** | | | **1.76** | | | | **0.99** |
| | **in combination with** | | | | **in combination with** | | |
| 1 | 2.54 | Midaz. (44.2) | 2.03 | 3 | 3.01 | Midaz. (628) | 1.78 |
| 2 | 1.17 | Midaz. (97.8) | 1.59 | 6 | 2.38 | 7-am-cl. (53.8) | 2.67 |
| 10 | 0.216 | Clonaz. (129) | 5.31 | 10 | 0.449 | Midaz. (16.8) | 1.18 |
| 12 | 0.188 | Clonaz. (643) | 2.73 | 16 | 8.21 | Alc. (1.57) | 1.85 |
| *14* | *0.178* | *Clonaz. (520)* | *38.4* | 17 | 2.40 | Alc. (1.08) | 2.38 |
| 15 | 0.121 | Midaz. (30.0) | 3.52 | 18 | 1.73 | Alc. (0.41) | 1.82 |
| 20 | 0.125 | Alc. (0.69) | 3.94 | 19 | 0.361 | Alc. (1.22). 7-am-cl. (29.1) | 4.77 |
| 21 | 0.075 | Alc. (2.43) | 4.50 | 20 | 6.05 | THC (3.04) | 3.31 |
| 22 | 0.299 | NEH (138) | 6.85 | 21 | *1.27* | *THC (2.75)* | *11.6* |
| | | | | 22 | 0.693 | THC (1.82). 7-am-cl (40.5) | 2.68 |
| *23* | *0.215* | *PICA (0.088)* | *224* | *23* | *0.088* | *PINACA (0.215)* | *0.77** |
| **Median** | | | **3.73** | **Median** | | | **2.38** |
| **± SD** | | | **1.75** | **± SD** | | | **1.06** |

**P. No**.: list number of patients in Table 5 and 6.; **Conc**.: concentration at admittance (ng/ml), for alcohol (g/l); **Midaz.**: midazolam**. Alc.**: alcohol. **Clonaz**.: Clonazepam; **7-am-cl**: 7-amino-clonazepam; **NEH**: N-ethyl-hexedrone. **PICA**: 5F-MDMP-PICA; **PINACA**: 5F-MDMP-PINACA; * this combination was excluded from the $t_{1/2}$ calculation

### 4.3.7 Synthetic cathinone intoxications

A 23-year-old male regular drug user consumed ***4-chloromethcathinon (4-CMC)***. His blood concentration at admittance was 117 ng/ml with clinical symptoms of hyperactivity, confusion, constrained movements and sputter speech.

3 patients were tested positive for ***NEH***. 26 years old male patient combined NEH (138 ng/ml) with 5F-MDMB-PINACA (0.229 ng/ml) and produced sympathomimetic symptoms as shivering and fever. Other patient (41.8 ng/ml NEH) produced serotoninergic (hallucination, paranoia) and sympathomimetic symptoms as agitation, irritability, increased blood pressure and tachycardia. Finally, the third patient with a blood concentration 129 ng/ml NEH displayed symptoms of confusion, disorientation and hypoactive deep tendon reflexes. Due to the low number of cases, connection between symptom severity and NEH concentration in the blood could not be established.

The patients intoxicated by synthetic cathinones received benzodiazepines (n=5) and antipsychotic treatment (n=2, and were transferred to Psychiatric Department), the others received only supportive therapy.

## 4.4 Discussion

In this work, we focused on mainly the clinical signs of intoxication caused by synthetic cannabinoids and cathinones in connection with their blood concentrations, the laboratory results were presented earlier. [51] The most common symptoms of SC intoxication are already summerized in the literature. [52] [18] [53] [22] Although it would be important to make a correct diagnosis and subsequent statistical analysis, in most cases this is not possible in the clinical practice. Among patients who were suspected by NPS intoxication the presence of NPS was detected in 44% what indicates that NPS intoxication cannot be distinguish from other drug intoxications based on clinical symptoms.

Both in the sample and among NPS users the ratio of man was 82%, the age group maximum was 18-25 years in both cases. This distribution is similar to that received in a general population survey in Hungary. [9]

The ***lower designer drug rate than expected*** could be due to several reasons. The ***patients self-reported*** (or may have misreported) that they have consumed "herbal", "bio-herbal", "zsálya", "crystal" prior to intoxication. In absence of specific symptoms or analytical results, and as the symptoms caused by different other substances are often overlapped. In many cases NPS intoxication produces non-specific symptoms which may overlap with the symptoms of certain

***psychiatric disorders***. The presence of psychiatric illness is a high-risk factor for development of substance use disorder. Substance use may "trigger" psychiatric illness, but the progression of a psychiatric illness is independent of substance use. Substance use, mainly in early adulthood, is closely linked in time to the onset of symptoms of psychiatric illness (= substance-induced state). Self-treatment by drugs is also common among drug users as a remedy to alleviate the symptoms of a psychiatric illness. Thus, intoxicated patients are admitted with a dual diagnosis of substance use disorders and psychiatric conditions (mood disorders, personality disorders, schizophrenia, other psychosis-related conditions). [54 55]

In lack of these information the doctor does not suspect intoxication by other drugs and qualifies the case as NPS intoxication. During hospital care there is no possibility to perform costly and time-consuming quantitative toxicological analysis, and the ***rapid urine tests do not detect*** the presence of NPS. In the practice, the patients typically ***receive symptomatic therapy without antidote***, so the exact substance and its blood concentration is not essential to know. Furthermore, due to the short treatment time the analytical results, if they are, are available when the patient has already left. The 44% rate of NPS users within the investigated population raises the probability that ***data in the literature*** about NPS consumption (case reports, statistical data) may have low reliability as they are based on self-reported data without toxicological analysis. Thus, there is ***no real feedback for clinicians*** to confirm or disprove the presumed diagnosis.

In case of sporadic mass poisonings (e.g. ADB-FUBINACA in 2017 or 5F-MDMB-BICA in 2020) the toxicological screening for “ultrapotent” new drugs is essential from legislative point of view and for mass communication.

Beside NPS, the patients enrolled in the study also consumed alcohol, THC, benzodiazepines (depressant), amphetamine-type stimulants, classical illicit drugs, and their combinations. Drug users take more substances together to enhance the desired effect and to reduce undesired side effects. [28]

The clinical symptoms of the SC consumers we examined were typically unconsciousness followed by psychomotor resuscitation. To a lesser extent, positive psychiatric symptoms (confusion, agitation) also occurred. Ophthalmic examinations seem to be useful as almost all patients had slow pupillary response and hyperemic conjunctiva, mydriatic or myotic pupils. There was no correlation between the SCs blood level and the severity of symptoms. Previously, severe toxicity was observed by the DECT clinicians of patients used AB-FUBINACA and ADB-FUBINACA. In the contrary, SCs in the current study did not lead to fatal or life-threatening outcomes, their PSS score never exceeded 2.

***Cathinones act on*** the monoamine systems: dopamine agonism has a variety of psychoactive effects, serotonin agonism has hallucinations and paranoia, and noradrenaline agonism has sympathomimetic effects. Mild poisoning is most commonly accompanied by nausea, palpitations, headache, chest pain, vertigo, and short-term amnesia, while the main symptoms of severe poisoning are agitation, psychosis, tachycardia, hyperthermia, hypertension, and seizures. In the present study, only two cathinones, 4-CMC and N-ethyl-hexedrone, were detected. In in vitro studies 4-CMC was characterized as an inhibitor of noradrenaline and dopamine reuptake, what is consistent with the clinical symptoms we observed. NEH is a potent dopamine and serotonin reuptake inhibitor; its effect on noradrenaline reuptake is less pronounced [56 57]. In our study, the intoxicated patients showed predominantly sympathomimetic and serotonergic symptoms, whereas noradrenaline-mediated effects were moderate or weak.

Both the present study and data in the literature [28] show that the average onset of toxic symptoms typically resolves with supportive ***therapy*** within half a day, in some cases requiring only depressant and antipsychotic medication.

In the present study, ***SCs were much more frequently detected than cathinones*** what is in concordance with the seizure data (App. Table A1). This difference can also be attributed to several factors. While SCs are stable for 1-2 weeks in stored blood samples, the concentration of some cathinone (e.g. 4-CMC) may have decreased below the detection limit during storage leading to false negative results [58 59]. The effective and toxic doses of SCs are near to each other and are much lower than those of cathinones what means a higher risk of overdose. Although the toxicological analysis aimed to detect new substances selected according to the seizure data from the previous years the symptoms observed may have been caused by substances not analyzed. Similar negative cases were reported in the Swedish STRIDA project, in which the prevalence of classical illegal and designer drug use was examined among patients suspected by drug use [60]. AB-CHMINACA and MDMB-CHMICA poisoning was examined in another study [11] and, similarly to our results, they did not find connection between blood concentration and severity of symptoms. In both studies the dose of the SCs and the time period between drug use and symptom registration were absent.

Based on the existing clinical experiences and laboratory results these data do not offer information about the toxic or the lethal concentration of the analyzed compounds. Aside from consumer tolerance, the effects of active hydroxyl-metabolites should also be taken into consideration. As similar blood SC levels were detected in asymptomatic, hospitalized and deceased subjects [61 62], future studies are needed to explain the exact relationship between blood levels and symptom severity.

Before calculation of half-lives of 5F-MDMB-PINACA and 5F-MDMB-PICA individual data were filtered for outliers; data of four patients were removed. These outliers may indicate the presence of other substances not analyzed and which may delay drug clearance or metabolic polymorphism. The extreme half-life of the combination of the two SCs suggests competition for metabolism, so these results were also excluded from the calculation. Due to the relatively ***short half-life*** of 5F-MDMB-PINACA and 5F-MDMB-PICA (2.65 and 2.7 hours, respectively, Table A8), symptoms of 15 patients out of 37 SC users were alleviated (usually within one hour). The uncertain time period between SC use and sampling may explain the large differences in the initial blood concentrations. The difference can also be attributed to the increased tolerance of the regular drug users, who were about twice as much as first time users. As compared the two SCs, ***5F-MDMB-PINACA seems to be be more toxic*** than 5F-MDMB-PICA. In in vitro CB1 receptor binding assay 5F-MDMB-PINACA had a lower ED50 (15.7 nM = 5.94 ng / ml) than 5F-MDMB-PICA (27.6 nM = 10.37 ng / ml) and this higher affinity accompanies by higher toxicity [63]

## 4.5 Limitations

The limitations of the study are mostly the consequences of incomplete clinical data collection. The study lacked information about the exact chemical name, timing, dose, and form of administration of the drug, as those are not routinely recorded by EMS on site, and patients were admitted based on signs of intoxication. The EMS staff did not use the same standardized medical questionnaire at the scene, as at DECT which would have allowed assessment of symptom progression over time. The time of consumption were not known their timeline of medical observation started by the arrival of the ambulance on to the spot.

## 4.6 Conclusions

- In the Budapest region, nearly half of the suspected illicit drug/NPS intoxicated patients used SCs, especially 5 F-MDMB-PINACA and 5 F-MDMB-PICA.
- When intoxication existed, the symptoms caused by different substances or substance groups such as SCs and cathinones were not specific for the substance, making differentiation impossible even for experienced clinicians.
- Prospective studies with larger sample size are needed to establish a correlation between blood concentrations of these two substances and severity of clinical symptoms, as the high number of combined drug intoxications reduced the number of single NPS users

to a small sample. Symptoms of SCs tested were nonspecific, especially beyond the peak of intoxication, when stimulants and SCs do not show definite differences in the overall clinical condition. Our study supports anecdotal clinical experience that SCs (except the FUBINACAs) do not tend to cause severe adverse reactions which are life-threatening or require ICU care.

- The time-series blood sampling protocol gave an opportunity to determine the half-life of 5 F-MDMB-PINACA (2.65 h) and 5 F-MDMB-PICA (2.70 h). The short half-life explains why the symptoms of 15 out of 37 single SC users partially resolved during transportation to the hospital (approximately one hour).
- As the pattern of NPS, especially of synthetic cannabinoids, changes regularly in the black-market, follow-up studies are necessary to investigate the hazard of any new NPS. Our findings will serve as important references for further studies aiming to evaluate major shifts on the drug market and of drug use habits related to the global pandemic of 2020.

# Study II. – Comparative analysis of suspected DUID and drivers involved in accidents under the influence of drugs

## 5 Introduction

The examination of the effects of new psychoactive substances (synthetic cannabinoids, cathinones) is still an important area of research because many new drugs are discovered each year and there is a lack of information about these substances. In absence of adequate pharmacological knowledge (mechanism of action, minimum effective dose, duration of effect, time of elimination etc.), appropriate criminal judgment and forensic assessment of crimes committed under the influence of these substances are also difficult. Similarly, alcohol is easier to detect in drivers, and the effects, prevalence, and consequences of drunk driving are well understood, with information on a wide range of legal consequences. Historically, driving under the influence of psychoactive drugs has received far less attention than drink driving. [64]

The aim of this work was to present and attempt to solve the major issues of forensic evaluation and criminal judgment of those who drive while under the influence of drugs. In Hungary, there is ***no compulsory guideline*** how to judge drugged driving, thus the practice can vary according to the knowledge of the experts. The cut-off limits and impairment legal limits were established about ten years ago (by agreement of the Hungarian toxicology laboratories), and they have been changed in many European countries since then. Consequently, the currently used forensic practice and legal background on drugged driving need reconsideration.

### 5.1 Legislation approach in the EU

***Within traffic safety,*** driving under the influence of drugs is a significant problem worldwide. Due to different cultures and laws, there are remarkable differences between the countries in respect of the determination of impairment caused by illicit drugs.

In EU countries, there are three main approaches are used for the determination of impairment [65]:

1. Legal limits, also known as **'per se' limits** based on a fixed substance blood concentration (similar to BAC levels) which still produces behavioral changes. The behavior-related cut-offs are the limits over which a drug affects the ability to drive. If the blood concentration of a substance reaches or exceeds the legal limit the driver is considered impaired. The legal limit

of the most common classical illicit drugs in Belgium, Luxembourg, Czech Republic, Denmark, Ireland, Norway, and the United Kingdom [66] are: THC: 1-2 ng/ml, amphetamine: 10-20-25-ng/ml, cocaine 10-20-25 ng/ml, morphine: 5-10-80 ng/ ml.

2. **Zero tolerance** law set legal limits to the laboratory limit of detection (LOD) or the lowest limit of quantification (LLOQ). Any driver with a detectable amount of a substance in the saliva or blood is considered impaired. This approaches are used in France, Poland, Portugal, Spain, Romania, Slovenia, and Sweden.

3. According to ***impairment legislation*** it must be proven that the skills of the driver were adversely affected by a psychoactive drug. Signs of impairment are usually observed and recorded by the police when they stop a driver. Most countries use a fixed testing protocol (Field Impairment/Sobriety Test) for the police to follow. It is not easy to prove scientifically that a person was under the influence at the time of driving, i.e. their skills were affected by any other reason/medical condition. This approach is used in Austria, Croatia, Cyprus, Malta and the Netherlands.

Each approach has strengths and weaknesses and their application depends on the existing legislative background of a given country.

In more countries per se limits are combined with the impairment approach called ***two-tier system***. For substances without impairment limit the impairment approach is used. In Germany a two-level system is used that allows a more sophisticated assessment. Lighter penalties are inflicted if the concentration of a substance is above the "per se limits" and more severe if the driving ability is actually impaired.

In most EU States police have the right ***to stop drivers*** randomly (for example to check the documentation) although in approximately half of these countries some suspicion of drugged driving is required for testing a driver for drugs. In more countries ***saliva*** is collected and tested on the spot, while in other countries the driver is ***assessed for physical or behavioral signs (Field Sobriety Test)*** by Horizontal Gaze Nystagmus Test, Walk and Turn Test and One-Leg Stand Test. Police forces are being trained to identify clinical signs of impairment based on a checklist. If three or more signs are identified, they can demand a saliva test. If it is positive, or negative but the driver produces the clinical signs of recent drug use, the police request a blood test. This is in line with the academic recommendations from the DRUID project. Nearly all countries require a ***confirmatory analysis*** performed in a toxicological laboratory and a forensic expert decides if the driver can be punished.

In the majority of EU countries drugged driving leads to ***withdrawal of the driving licence***, usually for a temporary period. Financial penalties range from a few hundred to several thousand euros. Some offences are not liable by penalties, while others are generally punished by prison (for example, fatal cases or accidents with personal injury) (EMCDDA).[67] [68]

## 5.2 Legal background in Hungary

According to te Hungarian Criminal Code drug use is punished. From criminological point of view traffic crimes belong to the category of crime as a consequence of drug consumption. [69]. Driving under the influence of drugs is punished with the same severity as drunk driving and is judged on the basis of the currently existing imapired state. The greatest difficulty in this process is to decide whether the driver was under the influence of drugs at the time of driving.

### The Hungarian Practice

Instruction No. 32/2014 (VIII. 29) issued by the Hungarian National Police Headquarters regulates the course of police action against drivers under the influence of drugs. If there is a suspicion of driving under the influence or if the person declares drug use a breath alcohol test is performed on the spot. Then the driver is taken to a medical ward for medical examination and taking a blood sample. By our experience, when the breath test is positive for alcohol, the police officers often does not continue to investigate any other substances.

During the medical examination, the measure of specific skills and general condition of the driver is assessed to reveal impairment. The tests can be divided into five main groups: eye examination (pupillary light reflex, pupillary size, nystagmus), divided attention psychophysical test (Romberg, modified Romberg, finger-nose test), cognitive tests (data communication, orientation, memory), vital signs (blood pressure, pulse), psychomotor (speech), and physiological (behavioural) tests. The driver is asked about the type, quantity, time and route of drug consumption, existence of diseases, medications used, and the time of the last meal. Using the above information and the toxicology results the forensic expert assesses whether the driver was under the influence of drugs during driving or at the time of an accident.

The weakness of this system is that no guideline for forensic medical professionals to determine how to assess the impaired state. Psychoactive drugs are ***difficult to define by impairment alone since different substances have different effects***. Some are sedating, which can lead to

drowsiness and lapses in attention, whereas others have excitatory effects which can increase alertness, confidence and impulsiveness. Despite numerous studies demonstrating the effects of psychoactive drugs on driving ability, there is no universal agreement on how best to measure the levels of impairment that psychoactive drugs cause to the driver. However, the overwhelming majority of psychoactive drugs have the same net effect, which is a decrease in the quality of mental and physiological effort dedicated to the driving task, which sees a decrease in performance and an increase in the risk of involvement in a collision [64].

The present practice is mainly based on the following recommendations of the DRUID project [67] (2008-2011):

<u>The forensic expert deems the driver impaired if:</u>

1. two or more active substances can be detected in the blood regardless of their concentration (including breath alcohol if its concentration exceeds 0.01 mg/l);

2. the blood concentration of a substance exceed the legal limit. The present legal limits are: amphetamine, methamphetamine, MDMA, cocaine, benzoyl-ecgonine (50 ng/ml), THC (2 ng/ml), morphine (20 ng/ml), GHB (30 µg/ml), breath alcohol (0.25 mg/l).

In the case of occasional medicine users, the impairment limit is the lower limit of the therapeutic range, for those who take them for medical prescription, the upper limit of the therapeutic range.

3. when an active substance without impairment limit is detected in the blood (NPS) and at least two of the clinical symptoms investigated are positive the driver is deemed impaired. The carboxylic acid metabolites of SCs are considered inactive, as their biological activity is not proved in man.

In the first two cases the clinical symptoms registered at the medical investigation are not considered in spite that according to law the condition “being influenced” has to be determined which is a mechanical process without the clinical symptoms.

## 5.3 The aims of the study

- To investigate whether there is a difference in ***age, gender, drug consumption distribution,*** and the prevalence of illicit and licit drugs between suspected DUID drivers and those who were involved in accidents and were suspected of drug use.

- To determine whether there are any symptoms that indicate impairment caused by the various drugs. What other tests or methods could be introduced in Hungary to improve the predictability of drug impairment?
- To investigate the connection between the clinical symptoms of impairment and the official ***legal limits***.
- To study the relationship between clinical symptoms, blood substance concentrations, and the time interval (between arrest/accident and sampling).

## 5.4 Materials and methods

In the present study the data of suspected drugged (sDUID) drivers and those who were responsible for traffic accidents (responsible drivers) were processed between 2016 and 2018 in Hungary. The sample represents nearly 85% of cases of the entire country. Blood and urine samples ***were analyzed*** for the request of the police at the Department of Forensic Toxicology of the Hungarian Institute for Forensic Sciences (HIFS) as described [70].

***Analytical data***, age and gender of the drivers, the time of arresting or accidents and sampling, and the results of medical investigation, were processed at the Department of Forensic Medicine, University of Szeged (DFM). All data were assigned to the drivers by a code for unanimous analysis, so we had no access to other databases. The sources of data were: the police order for toxicological analysis, analytical results of HIFS, and the sampling protocol sheet. The police order contains the time of arresting or accident, the observations of the officer, and the reason why analysis was requested, the sampling protocol sheet the time of sampling and the results of medical observation.

AM can be present alone or together with MA in the MA positive samples as its metabolite or as impurity, thus the positive findings of AM or MA were combined. MDA was seized only one occasion in the entire country during the investigation period, so it was evaluated as the active metabolite of MDMA. When impairment was evaluated the carboxy metabolites of SCs were regarded as inactive.

### 5.4.1 Statistical analysis

Statistical analysis was performed as described [70] setting the probability level to $p<0.05$.

Cohen's kappa coefficient ($\kappa$) statistic was used to measure agreement (strength of the relationship) between the observed clinical symptoms and blood concentrations of the single substances above and below the legal limit. 95% confidence intervals were also calculated for

the Cohen's kappa coefficient (κ) statistic. If there was no legal limit, then the proportion of positive sympthoms was investigated. 95% Clopper-Pearson exact confidence intervals were calculated for the proportion of positive sympthoms.

A p-value $p<0.05$ was regarded as statistically significant. The analysis was performed by IBM SPSS 26 software.

## 5.5 Results

### 5.5.1 Comparison of suspected DUID (driving under the influence of drugs) drivers and those who were responsible for traffic accidents

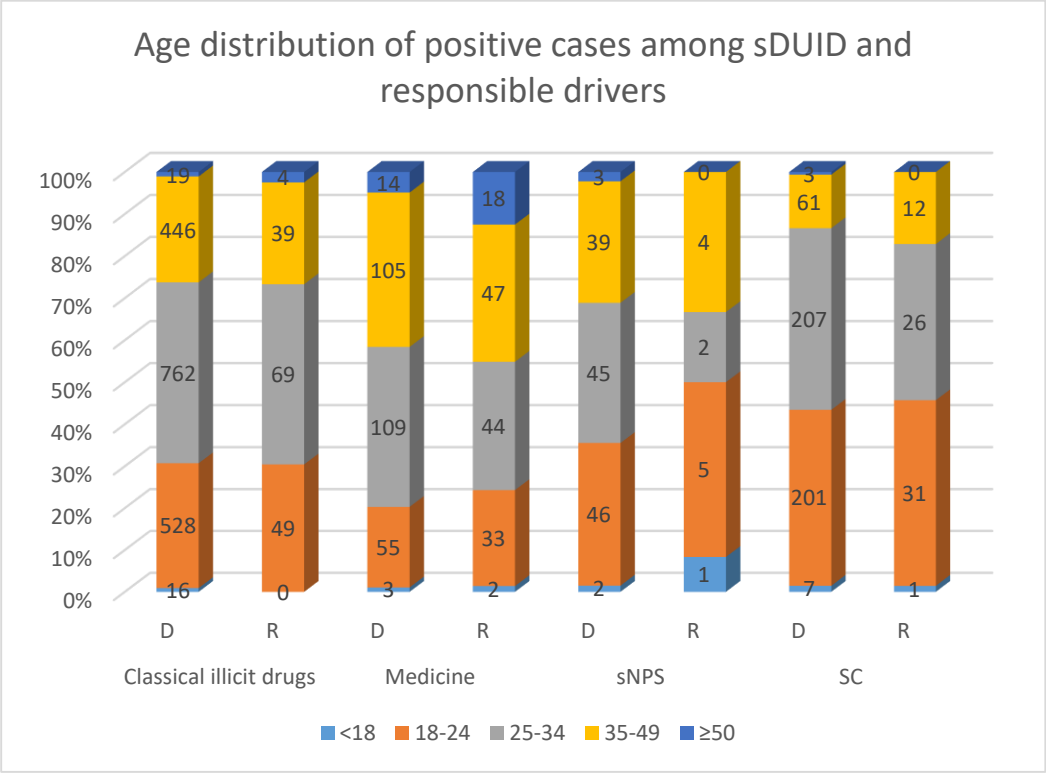
#### *5.5.1.1 Age and gender distribution*

*sDUID drivers*

In 2016–18 altogether 2369 sDUID drivers were sampled of which 2254 (95%) were tested positive (drug-positive cases) for at least one substance excluding those who used only alcohol. No significant difference was found in the gender and age distribution between the sample and drug-positive cases ($p > 0.05$ in all comparison). The age distribution of drug-positive cases was: 1% was < 18 years, 32% was 18–24 years, 42% was 25–34 years, 24% was 35–49 years, and 1% was ≥ 50 years. 97% of them were man with median age (quartiles 1st,3rd) of 28 (23,34) years, and 3% were woman with median age of 31 (24,38) years ($p = 0.017$). (Diagram B1)

The most frequent age group of classical illicit drug users was 25–34 years of those who took medicines was 35–49 years, of synthetic cathinon and SC users it was 18–24 years. The median age of classical illicit drug users was 29 years, of medicine users was 33 years, of synthetic cathinon users was 28 years, and of SCs users it was 26 years.

**Diagram B1:** Age distribution of positive cases among sDUID and responsible drivers




*Drivers responsible for accidents*

Between 2016 and 2018, a total of 451 suspected drug users were involved in traffic accidents. 75 drivers (16.6%) of them were negative for any substance investigated and 31 drivers (6.7%) were positive only for breath alcohol. 345 cases (76.5%) were positive for classical illicit drugs, medicines and for NPS.

In 302 cases (87.5%) the driver was responsible for an accident, and 43 (12.5%) were participant. ***Out of the 302 drivers 272 (90.1 %) were men with median age of 35 years, and 30 (9.9%) were women with median age of 42 years.*** The age distribution of drug-positive cases was: 1% was < 18 years, 28% was 18–24 years, 35% was 25–34 years, 27% was 35–49 years, and 7% was ≥ 50 years. The most prevalent age group was 25-34 years old. The median age of classical illicit drug users was 29 years, of medicine users was 34 years, of synthetic cathinon and SCs users was 25 years. The most frequent age group of classical illicit drug users was 25–34 years of those who took medicines was 35–49 years of synthetic cathinon and SC users it was 18–24 years. (Diagram B1)

### 5.5.2 Prevalence of the main substance groups in the two population

*Suspected DUID drivers*

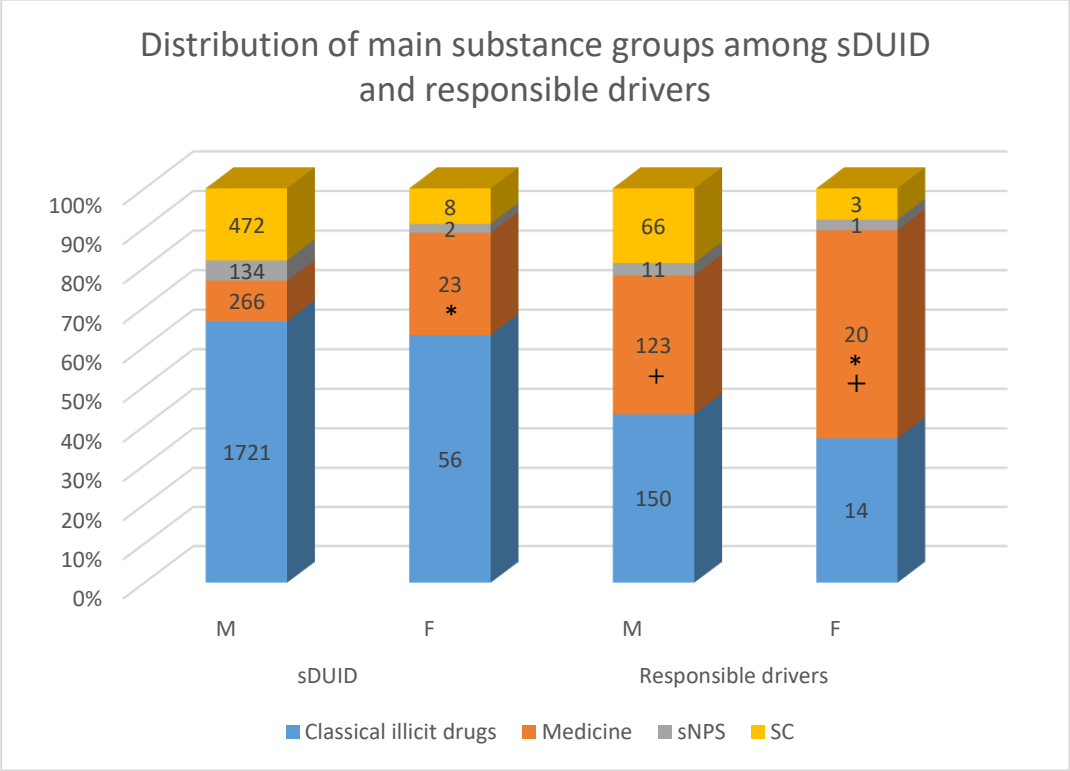
Among sDUID cases the proportion of drivers who used classical illicit drugs was 79% (n=1777). Within this group cannabis was the most prevalent (n = 1240, 70%) followed by AM/MA (n = 743, 42%), MDMA (n = 196, 11%) and cocaine (n = 180, 10%). The ratio of drivers who took medicines was 13% (n=289), the most frequently used medications were alprazolam (n = 188, 65%) and clonazepam (n = 83, 29%). The percentage of synthetic cathinon users was 6% (n=135), and in this group N-ethyl-hexedrone (n = 115, 85%) was the most prevalent. SCs were detected in 21% (n=480) of the drug-positive samples. During the three years 5 F-MDMB-PINACA (n = 267, 56%) was the most frequent followed by AMB-FUBINACA (n = 91, 19%), ADB-FUBINACA (n = 90, 19%), 5 F-MDMB-PICA (n = 34, 7%), MDMB- CHMICA (n = 20, 4%), and AB-FUBINACA (n = 15, 3%). AB-FUBINACA carboxylic acid (the common metabolite of AB-FUBINACA, AMB-FUBINACA, and EMB-FUBINACA) was detected in 246 samples of which only the metabolite was present in 200 cases. (Diagram B2) (App. Table B1)

*Responsible drivers*

Among responsible drivers the ratio of those who used classical illicit drugs was 54% (n=164). The most prevalent substances were cannabis (n=99, 60%), AM/MA (n=63, 38%), MDMA (n=29, 18%) and cocaine (n=16, 10%). Medicines were detected in 48% (n=145) of positive cases; the most frequent substances were alprazolam (n=80, 55%), clonazepam (n=35, 24%), and diazepam (n=12, 8%), the other benzodiazepines and zolpidem were detected in 10-10 cases (7-7%). Among synthetic cathinon (n=12, 4%) the most frequently detected substance was N-ethyl-hexedrone (n=7, 58%) while among SCs (n=69, 23%) AB-FUBINACA carboxy-metabolite (n=34, 49%), 5F-MDMB-PINACA (n=27, 39%), and ADB-FUBINACA (n=14, 20%), were the most frequent. (Diagram B2) (App. Table B1)

The NPSs changed year by year and the median blood concentration of NPS in the two populations does not show a significant difference. The drivers in DUID cases have lower benzodiazepin blood concentrations than the therapeutic, whereas the majority of cases in responsible cases have blood concentrations that exceed the therapeutic.

**Diagram B2:** Distribution of substance groups among sDUID and responsible drivers (M: male, F: female)




* p<0.05 between man and woman; + p<0.05 between sDUID and responsible drivers

*Multi-drug use in the two populations*

Among sDUID cases the proportion of ***multi-drug users*** was 49% (n=1102) significantly lower (p<0.05), than among responsible drivers (62 %, n=188). As the higher rate of multi-drug use among responsible drivers might be an indicator of the elevated accidental risk, we compared the most frequent drug-drug combinations (Table B2). According to the similar mechanism of action, we classify the substances and create 7 groups: cannabis (without THC-COOH – inactive metabolite), stimulants (AM, MA, MDMA, cocaine), benzodiazepines, SCs, synthetic cathinon, alcohol, and other drugs (LSD, morphine, GHB, methadone, EDDP).

**Table B2:** Combination of previously created substance groups

| **Number of created substance groups combination**[+] | **sDUID** | | **Responsible for accidents** | |
|---|---|---|---|---|
| | Absolute Number | % | Absolute Number | % |
| 1 | 1196 | 67,8 | 150* | 56,4 |
| 2 | 490 | 27.8 | 100* | 37,6 |
| 3 | 68 | 3,86 | 15 | 5,64 |
| 4 | 9 | 0,51 | 0 | 0.00 |
| 5 | 0 | 0 | 1 | 0,38 |
| **Total** | **1763** | | **266** | |
| | | | | |
| Multi-drug use<br>absolute number<br>% | <br>1102<br>48,8 | | <br>188<br>62,3* | |

*p<0.05 by chi-square test vs. sDUID cases. [+]No1 involves single drug use and the combinations of two or more substances within the same group, No2 means the combinations of substances from two different groups, etc.

The percentage of multi-drug users was significantly higher among the responsible drivers. The number of cases when only one substance was used or two or more substances were combined within one group was significantly lower among responsible drivers, but the percentage of cases in combination of two or more substances from two different groups was significantly higher among responsible drivers (Table B2). Combination of more than (created 7 substances) two created drug groups no longer increases significantly the accident risk - perharps because it is not suitable for causing a more serious effect/impairment.

App. Table B3 presents of only one substance group used and the combinations of two created substances groups more detailed. Their percentage is related to the frequency of one and the two substance group combinations (sDUID: 490, responsible drivers:100) respectively. As it is shown in App.Table B3, the single use of cannabis and stimulants is significantly higher in the sDUID group while the single use of benzodiazepines (single use, combination within each other) is significantly higher among responsible drivers.

Combinations of cannabis with stimulants, benzodiazepines with stimultants occurred in high number among the sDUID cases, but it was lower among responsible drivers. Although, the proportion of benzodiazepines combined with SCs, synthetic cathinon, alcohol and combination of alcohol with stimulants and SCs was higher in the later group.

### 5.5.3 Evaluation of driving under the influence of drugs

For this evaluation we joined the two databases according to the methodology/criteria presented in Table B4.

**Table B4:** Joined database of sDUID and responsible drivers according to the evaluation methodology/criteria (Total case number: 2769)

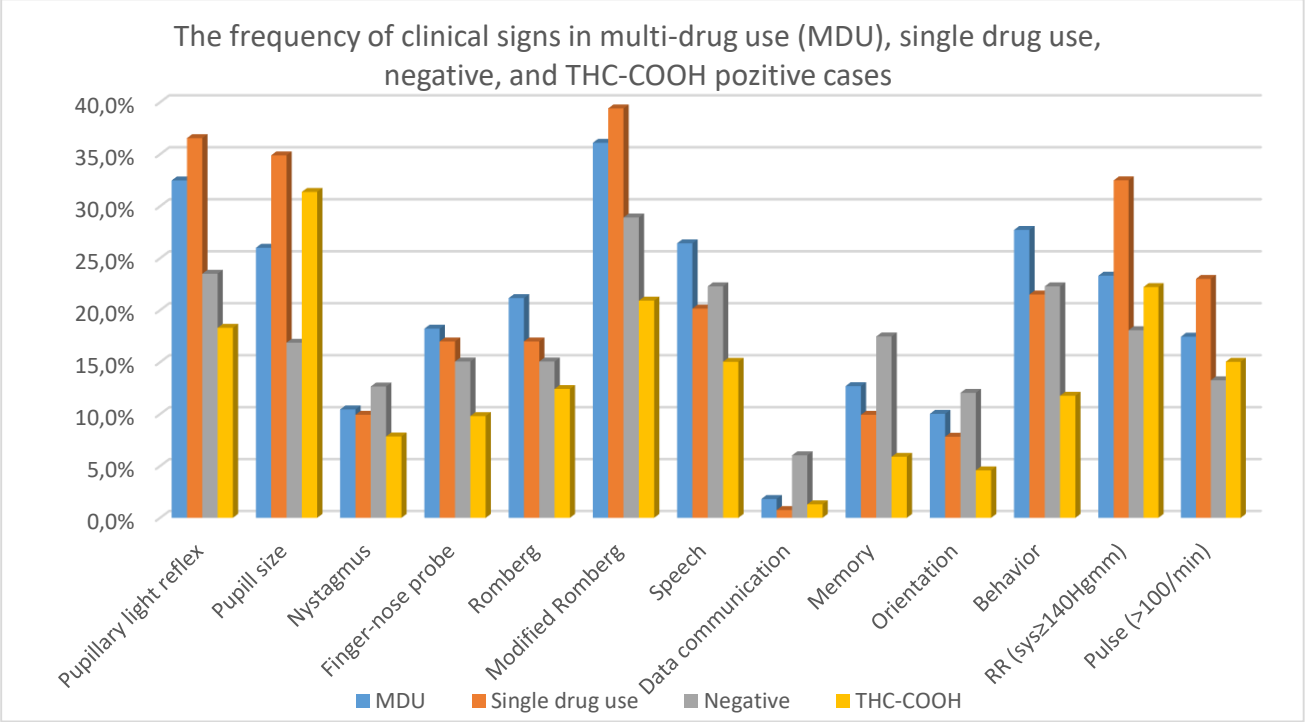
| | **Blood sample: 2510 cases (90.6 %)** | **Only urine sample: 259 cases (9.4 %)** |
|---|---|---|
| **Single drug use** | 987 (39.3 %) | 63 (24.3 %) |
| • **Classical drugs**<br>• **Medicines**<br>• **synthetic cathinon**<br>• **SCs** | • 759<br>• 90<br>• 38<br>• 100 | • 29<br>• 9<br>• 17<br>• 8 |
| **Multi drug use** | 1158 (46.1 %) | 135 (52.1 %) |
| **Negative for active substances** | 328 (13%) | 59 (23%) |
| • **Negative**<br>• **THC-COOH**<br>• **SC carboxy metabolites** | • 164<br>• 153<br>• 11 | • 9<br>• 46<br>• 4 |

Only breath alcohol was detected in 39 cases

We examined the recorded clinical symptoms at the time of blood sampling (App. Table B5). Cohen's kappa coefficients (κ) were below 0.2 in all of the cases and none of them reached statistical significance ( 95% confidence intervals contained 0). These results showed that there is no agreement (no relationship) between the observed clinical symptoms and blood concentrations of the single substances above and below the legal limit. If there was no legal limit (NPS, multi-drug use, negative) then the proportion of positive sympthoms were investigated. Although 60% of multi- drug users showed positive clinical symptoms, in absence of impairment limits this analysis (Cohen's kappa measure for agrrement) could not be performed for them. Based on the clinical symptoms 85 drivers out of the 166 negative cases could have been categorized as impaired. The App. Table B5 shows that there is a large overlap between the positive and negative case rates (and the 95% Clopper Pearson confidence interval) for substances without legal limit.

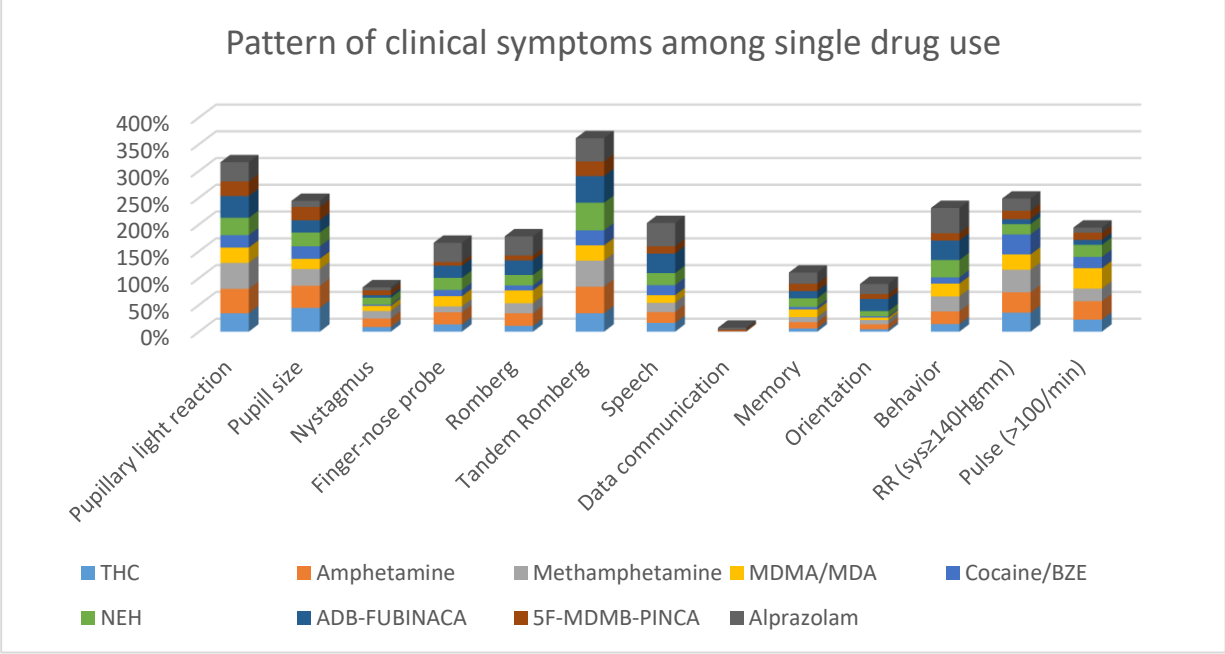
### 5.5.4 Examination of the clinical symptoms

**Diagram B3:** Pattern of the clinical symptoms among positive and negative cases




Except for the cognitive ones the pattern of the symptoms was similar to the positive and the negative cases. (Diagram B3)

**Diagram B4:** Pattern of the clinical symptoms among single drug use



Only 36% of single drug use cases (n=987) showed clinical symptoms. Clinical symptoms were almost similar among single substances, with the most pronounced clinical symptoms being ocular symptoms (pupillary light reaction, pupil dilatation), equilibrium symptoms (Tandem Romberg), behavior, blood pressure, and pulse. Only amphetamine, methamphetamine, and alprazolam had the most indicative symptoms. (Diagram B4).

### 5.5.5 Connection between clinical symptoms and blood concentration of drugs (App. Diagram B6)

App. Diagram B6 showes the presence and absence of positive clinical symptoms with increasing blood concentration in case of single drug use. The blood concentration of THC was between 2-10 ng/ml in majority of drivers. In this range the lack of clinical symptoms dominated, while below and above this limit their absence and presence were nearly equal. We did not find evaluable increase in the ratio of positive symptoms with the increasing blood concentration of AM, MA, MDMA and cocaine. Increasing ratio of positive symptoms with the blood concentration of alprazolam and N-ethyl-hexerone was found and the positive symptoms were dominant in all concentration ranges. The most sensitive parameters for alprazolam were finger-to-nose probe, tandem Romberg, speech, and behavior, for NEH Romberg, tandem Romberg, speech, behaviour, blood pressure and pulse. Although the number of cases was low a higher ratio of positive cases was found over 10 ng/ml concentration of ADB-FUBINACA. The most sensitive parameters were finger-to-nose probe, tandem Romberg, speech, and behaviour. Evaluable increase in the ratio of positive symptoms with the increasing blood concentration of 5F-MDMB – PINACA was not found.

### 5.5.6 Examination of clinical signs based on the time interval between the stop/accident and sampling (App. Diagram B7)

The average time period between the event and sampling was 161 minutes for sDUID and 191 minutes for accident cases. When the connection between the time period and the ratio of negative and positive cases was investigated, a decrease was found in case of cocaine and ADB-FUBINACA after 120 minutes. The ratio of positive cases was higher at all time period among those who used amphetamine, alprazolam or NEH.

## 5.6 Discussion

As compared the two populations the ratio of positive cases and the percentage of man was higher among sDUID drivers. In both populations the drug consumption was the most frequent in the 25-34 years age group. Regarding main substance groups (classical illicit drugs, medicines, synthetic cathinon, and SCs) the age group maximums were the same: NPS use was the most prevalent among the younger (18-24 years), medicine use among the older (35-49 years), while classical illicit drug use among the middle-aged (25-34 years) populations. The ratio and the median age of women among responsible drivers was higher than among sDUID drivers, and their majority consumed medicines and classical illicit drugs. Among them, the NPS use was the lowest in both populations. The age distribution of this population is shifted to the younger age groups, and remembers to the general drug user population rather than it is described by the Hungarian Central Statistical Office (CSO - 2015) for all drivers responsible for accidents [71]. The difference can be attributed to the higher degree of risk-taking behavior (e.g. drug use) in this population.

According to the absolute number of ***main substance groups***, the ratio of classical illicit drugs was lower among the responsible drivers but the ratio of medicines was much higher. This finding may relate to an increased accident risk of medicines, especially of benzodiazepines. It was also found that the accident risk of benzodiazepines may be higher than it was calculated in the DRUID project [67]. The frequency of NPS was practically the same in both groups, and their prevalence was much lower than of classical illicit drugs or medicines, so the drivers prefer the latter two substance groups. SC use was significantly more common among NPS than synthetic cathinone use.

Multi-drug use is prevalent in both populations, but it is significantly higher among responsible drivers; thus, drug frequency expressed in absolute numbers does not accurately reflect the actual frequency of drug use. The most common substances were classified based on their mechanism of action to investigate the possibility of an increased accident risk. As only the “within one group” and “between two groups” combinations differed significantly in the two populations, these two cases were analyzed more detailed. The single use of cannabis and stimulants is significantly lower while the single use of benzodiazepines is significantly higher among responsible drivers. Combinations of cannabis and stimulants occurred in significantly higher number among the sDUID cases. The frequency of all drug groups combined with alcohol or benzodiazepines was higher among responsible drivers.

Compared to a questionnaire survey, 7.4% of the Hungarian adult population has tried cannabis; the prevalence rate of ecstasy use (4%) is half that, but it is still impressive when compared to other substances. Synthetic cannabinoids (1.9%), amphetamines (1.7%), and designer stimulants (1.3%) trail behind the two most popular drugs.[29]

The last roadside survey in Hungary was performed in the frame of the DRUID projectBecause the drug market (due to the project's later appearance) and drug use habits have changed since then, our findings cannot be compared to them; instead, we compared data from responsible drivers to data from sDUID drivers. As this population is not an adequate control, we could only estimate the probability of accidents for some substances and combinations but the ***accidental risk could not be calculated.*** These results relate to a possible higher accident risk of benzodiazepines alone, the combinations of two benzodiazepines, and all drug groups combined with alcohol or benzodiazepines. Cannabis and NPSs may have only a slightly increased risk of accidents as they were less frequent among responsible than among sDUID drivers.

This finding is in line with the results of DRUID project [67]. The ***relative accident risk factor*** for some single drugs was estimated in the DRUID project: cannabis represents a low [72] [73], cocaine, opiates, benzodiazepines, Z-drugs a medium, while amphetamines and multidrug use represent a high risk [67]. However, legalized retail cannabis sales in Colorado, Washington, and Oregon were associated with a 5.2% higher rate of police-reported crashes when compared to neighboring states that did not legalize retail sales.[65] In concordance with the data in the literature [65] these combinations relate to an elevated risk of accidents after consumption of alcohol and/or drugs and medicines but in a different degree. For both fatalities and serious injuries alcohol is the riskiest substance and alcohol drug combinations are riskier then dugs in combination or drugs or alcohol singly. For medicinal drugs, it is important to distinguish regular therapeutic use, according to prescription, from abuse of these drugs. This plays a role for benzodiazepines and opioids. Most risk calculations based on epidemiological studies will measure the effects of both, and result in a much higher risk than regular therapeutic use. This is not surprising, as tolerance usually sets in after regular use, while recreational use is with the intention to get “high,” with high doses alternating with periods of abstinence. [65]

Table B6: Relative risk of getting seriously injured or killed for various substance groups (European Monitoring Centre for Drugs and Drug Addiction, 2012) [67]

| Risk level | Risk | Substance group |
|---|---|---|
| **Slightly increased risk** | 1-3 | Alcohol (BAC between 0.1 and 0.5 g/L)<br>Cannabis |
| **Medium increased risk** | 2-10 | Alcohol (BAC between 0.5 and 0.8 g/L)<br>Benzoylecgonine<br>Cocaine<br>Illicit opiates<br>Benzodiazepines and Z-drugs<br>Medicinal opioids |
| **Highly increased risk** | 5-30 | Alcohol (BAC between 0.8 and 1.2 g/L)<br>Amphetamines<br>Multiple drugs |
| **Extremely increased risk** | 20-200 | Alcohol (BAC≥1.2 g/L)<br>Alcohol in combination with drugs |

Z-hypnotics: zolpidem or zopiclone. As benzoyl-ecgonine forms from cocaine in vitro in the blood samples during storage, its presence in blood (without cocaine) can be associated with an increased risk.

***The literature on evaluating the efficacy of methods for determining driving under the influence of drugs is quite limited.*** Due to different evaluation methodologies in the European countries, the comparison is also difficult. In this thesis, we made an attempt to examine the effectiveness of the evaluation methodology used in Hungary based in the two databases.

The National Police Headquarters order the police to act according to the following instruction: "the driver of the vehicle should, if possible, be taken to a police medical service for blood and urine sampling and a medical examination should be performed at the same time to confirm intoxication, where clinical signs are accurately recorded". On the contrary, nearly 10% of drug impairment assessments fail due to ***insufficient sampling*** and/or registration of circumstances. Toxicological analysis of a urine sample is ineffective for determining impairment; it only demonstrates that the driver has previously used drugs (even if it was days or weeks ago).

Medication and other illegal substance urinary concentrations cannot be used to calculate blood concentrations. Some drivers also abuse medications by taking higher-than-recommended doses or combining multiple legal substances. In Hungary, the consumption of classical drugs (but not new psychoactive substances) is a criminal offense, but the traffic offense from the urine cannot be proven. (Act C of 2012 on the Criminal Code Section 178 (6) states).

According to Hungarian and European practice, if the concentration of a classic illicit drug in a ***single drug use*** exceeds a certain blood concentration (legal limit), the driver is deemed impaired regardless of the presence of clinical symptoms. Different impairment limits have been determined in the various European countries; the trend is to decrease these values to the possible lowest level. [64] Numerous studies have already confirmed that clinical symptoms are present in naive users at these blood concentrations (legal limit). In these cases, the drivers are tested using sensitive test methods in an artificial environment (e.g., simulator studies). [74] The contradiction observed in this study can be explained by the fact that clinical practice test methods are insufficiently sensitive, and the majority of car drivers are not typically naive consumers. Due to addiction, certain clinical symptoms cannot be detected even at higher blood concentrations. Difference in sample timing, severity of use, route of administration, psychiatric comorbidities, biological characteristics of the individuals, lifestyle differences, demographic background, genetic predispositions and environmental factors add complexity to measuring the impact of drug use in cognitive performances. [75] Moreover, the dose and time of drug consumption is not known and, if the time period is long enough, the acute symptoms may become less intense or even disappear. In addition, withdrawal symptoms may also occur below a given drug concentration what makes the evaluation more uncertain. Only for alprazolam did we find a significantly higher number of clinically positive cases exceeding the impairment limit, while the number of positive and negative cases for the other substances was nearly equal. These findings point to the current system of medical investigations have limited ability to determine impairment. But in the case of NPS, the impairment is only declared if there are concurrent clinical symptoms because there is no legal limit for NPSs due to a lack of available/reliable research information. Although the number of NEH and ADB-FUBINACA cases was low, the majority of positive cases also had positive clinical symptoms.

When negative toxicological results are accompanied by positive clinical symptoms, other acute/chronic neurological/psychiatric/internal illnesses or conditions may be to blame. (head trauma, stroke, diabetes, conjunctivitis, multiple sclerosis, cerebral palsy, actual behavior disorders, post-acute withdrawal syndrome, excited delirium). During the police checking the

driver is asked whether he/she suffers from any illness, takes medication regularly etc., but this is only an unofficial self-report. We have no further information on whether his/her condition necessitates additional medical attention following the traffic act. If so, the symptoms are most likely caused by the driver's health condition. Keep in mind that, according to self-reports, there are approximately 800,000 alcoholics in Hungary. If they do not consume alcohol, they may experience withdrawal symptoms. Alcohol consumption is also prohibited before driving, which is why withdrawal symptoms may occur frequently during police checks, or post-alcohol syndrome may occur as a result of consuming a large amount of alcohol the day before. The stressful situation of police control may also lead to misunerstandable clinical symtoms, like tremor slight vegetative signs of the stress, anxiety.

As a result, impairment is deemed for classical illicit drugs, medicines, and multi-drug use based on impairment limits, and the presence of positive clinical signs is ignored in 94.6% of cases. They are only relevant when impairment is suspected in NPS positive cases (5.4% of the population studied). If all positive cases were evaluated based on symptoms, impairment would be stated in fewer cases. It means that the impairment evaluation methodology is not uniform and fair because of the incompetent and delayed clinical examination.

Following alcohol consumption, with increasing ***blood concentration*** the structure of symptoms changes, and they also become more expressed. And while for alcohol there is a clear relationship between the concentration in blood and the crash risk, this concentration-effect relationship is much less clear for other drugs. In case of narcotic drugs, no correlation was found between blood concentration and symptom severity [75]. The lack of correlation can be explained primarily by the higher tolerance of moderate and regular drug users compared to naive users. There is growing evidence that chronic drug users drive more likely under the influence than moderate drug users [64]. Based on a self-reported questionnaire, approximately 5% of the general population, 15% of the young people, and about 85% of drug users state ever to have driven after having used drugs. [65]

Some correlation was found between blood concentration of THC and clinical signs, but several studies found that accidental risk is somewhat lower at higher concentrations. This could be explained by the hysteresis relationship between the concentrations of tetrahydrocannabinol (THC) in blood or plasma and the effects of cannabis. As a result, the effects are maximal when the concentration is already decreasing. In addition, THC concentration decreases very rapidly

(with a half-life of about 45–60 min) in the early phase after smoking, so the delay of 1–3 hr between the crash or police stop and the moment the blood sample was taken also plays an important role. In a driving simulator study, found that 8.2 and 13.1μg/L blood THC concentrations increased the standard deviation of the lateral position (SDLP), similarly to 0.5 and 0.8 g/L alcohol concentrations. In describing their reported dose effect, said 'The increase in odds was most apparent at higher blood THC concentrations. At 5 ng/ml and above the OR was 3.2 ($p = 0.01$), and at THC concentrations of 10 ng/ml and above the OR was 10 ($p = 0.03$) indicating that the odds of culpability increase with rising concentrations' [76]. Another study revealed the significant worsening of driving performance for occasional users but not for non-users and, as compensation, the daily users drove slower after cannabis use.[65]

Several studies have suggested that low doses of AM's could improve psychomotor skills, such as driving ability, even in fatigue subjects, but these investigations were performed under controlled clinical condition. Beside, AM's use significantly increases the risk of accidents due to their risk-taking behavior. High-doses may decrease traffic related performance, for instance by irrational behavior. [45] [75] [65] Chronic asbuse often involves high doses. According to another study there was a positive relationship between blood amphetamine concentration and impairment up to 270-530 ng/ml concentration. [77] In this thresis we found a relationship only in methamphetamine positive cases in the concentration range of up to 200 ng/ml.

Low doses of cocaine improve vigilance, arousal, and attention and enhances response inhibition and a speed component in psychomotor task. It has been stated that in the first 1-2 h of intake, cocaine induces impaired ability to react properly, poor concentration and judgements and over-confidence in driving skills which may increase taking risk. [75] In the present study we found that the clinical symptoms indicate influence in all cases above 300 ng/ml blood concentration.

In majority of cases, the blood concentration of alprazolam in drivers with positive clinical symptoms was above the therapeutic range.[45] This may indicate that alprazolam was not taken according to a doctor's prescription. Medicine consumption was within the therapeutic range in two-thirds of DUID cases, half of which involved the responsible driver. [78] [79]

Similarly, to the majority of classical illicit drugs, we were unable to identify a concentration of NPSs above which the frequency of positive clinical symptoms increases significantly. And it was not possible to find correlation between the concentraations of the NPS and the degree of impairment. [61] [80] The lack of a relationship could be attributed to the small number of cases

and the low reliability of clinical tests. The determination of NPS impairment/legal limit is not possible, according to the hungarian medical investigation panel.

The relatively ***long time interval between arresting and medical investigation*** raises the possibility of the complete metabolism of substances with short half-life [51] [81] [82]. If their metabolites are not monitored it can lead to loss of positive cases. Clinical symptoms, on the other hand, may disappear between arrest and medical investigation (approximately 3 hours on average), resulting in a false negative deem of impairment. Only when substances with a longer half life (AMs, long lasting benzodiazepines) are consumed do the psychoactive effects last longer.[74]

## 5.7 Limitation of the study

We had no information about the time of intake, the dose ingested, the pattern of use and drug history which can influence the clinical signs of impairment. The time interval between sampling and analysis was variable depending on the availability of the laboratory. During storage cocaine could be metabolized to benzoyl-ecgonine in the blood samples and some cathinones (e.g. 4-CMC) could decompose resulting in lower concentration or false negative result [59]. Chromatographic standards were only available weeks or even months after the appearance of a new NPS which likely resulted in missed positive cases.

## 5.8 Conclusion

The aim of this work was to compare the drug consumption of sDUID and responsible drivers and to evaluate the process of impairment determination.

- The majority of drivers in both populations were man, the age group maximum of those who used drugs was 25-34 years. Classical illicit drug use was characteristic for the middle aged, NPS consumption for the younger, while medicine use for the older age groups, especially among women over the age of 35 years.
- The accident risk was estimated according to the frequency of the single substances and their combinations. We found that benzodiazepines alone and their combination was more frequent among responsible divers which may pose an increased accident risk. Similarly, combinations of alcohol or benzodiazepines with other substances also may increase the risk of accidents. The DRUID EU-6 project found a highly increased risk

of accidents for amphetamines, alcohol at the 0.8 – 1.2 g/L blood concentration interval, and for multiply drugs, while extremely increased risk for higher alcohol concentrations and for alcohol drug combinations. We found that benzodiazepines, both alone and in combination, may pose a higher accidental risk than we thought, especially when they are not taken according to medical prescription. The ratio of NPS use in the two populations was the same what relates to low accident risk.

- When the efficacy of clinical examinations was assessed, we discovered that for drugs with impairment limits, the ratio of positive to negative cases was nearly equal over and under the limits (the only exeption was alprazolam). This finding is related to the current system's weak strength, which can be explained, at least in part by some factors. The dose and time of drug consumption, as well as the drivers' level of tolerance (drug history), are unknown. Furthermore, the average time between arrest or accident and medical investigation is about 3 hours, during which the symptoms may simply disappear. Impairment limits for classical illicit drugs and medicines are established, but impairment caused by NPSs is assessed based on clinical symptoms. Because of the limited power of medical investigations, this method may result in impairment misjudgment.

## 5.9 Recommendations

1. Legal regulations: It is recommended that legal regulations be aligned with forensic expert practice. Primarily suggests determining the definition of "impaired state" used in legislation, as well as incorporating legal limits into legislation, as in the UK. This would avoid individual interpretations of the term "impairment," and the legal sanctions would be consistent across the country. A two-tier system is recommended for legal regulations. The combination of per se limits and an impairment approach allows for graded sanctions: a less severe sanction when drugs are present above the per se limit and a more severe sanction when the driver was impaired.
2. Improve ***roadside screening. Introduction of Field Sobriety Test*** (FST) in Hungary and ***training police officers*** to perform it correctly similarly to the Drug Evaluation and Classification (DEC) Program in the USA [83] [84] or in the UK [66] [85] [86]. The drug evaluation and classification process is systematic and standardized. Combining basic medical knowledge about drug pharmacodynamics with validated psychomotor tests, to determine whether a suspect is under the influence of alcohol and/or drugs and, if so,

by what category of drugs. It utilizes a variety of readily observable signs and symptoms that are accepted in the medical community as reliable indicators of drug influence. During examination the DRE officer (Drug Recognition Expert) takes the suspect's brief medical history and assesses the suspect's pulse, blood pressure, body temperature, pupil size and reaction to light, and psychomotor function. The DRE also examines the suspect's ocular tracking, smooth pursuit, and Horizontal and Vertical Gaze Nystagmus (HGN and VGN).

With this short investigation method, we could obtain information about the fitness to drive of the driver at the time of the act.

Monitoring the presence of drugs at the scene ***(OF, saliva rapid test)***[65]***:*** In contrast to alcohol that can be easily and reliably detected by breath analyzers, illicit drugs have to be detected by onsite drug screening devices. OF is offered as a non-invasive sample for roadside screening which enables direct supervision of the sampling; detection of compounds in the OF indicates recent consumption of drugs. The ***OF roadside tests*** focus on the classical recreational drugs (for example Dräger DrugTest 5000***)*** can detect up to eight substances/ substance classes with predefined detection limits (cutt-offs): amphetamines, benzodiazepines, THC, cocaine, methamphetamine, opiates, methadone, ketamine. This test is only suitable for qualitative testing, because for most drugs the OF/blood conversion factors are not satisfactory for all compounds. Thus, the blood concentration of a compound cannot be estimated well from the OF concentration. [87] The other disadvantage is that there is no OF road side test in use for NPSs and medications. [88] In our database the number of NPS (n=341, 12.3%) (SC alone (123) combined with itself (154), synthetic cathinon alone (55) combined with other synthetic cathinon (4), and GHB alone (5)) medication alone (n=101, 3.6 %) would show a negative result from the in situ saliva sample. In all other cases OF road side test would be suitable for fast and efficient roadside testing of drivers.

3. ***Reducing the time between police checking and sampling***: Because of the relatively long time delay between arrest and medical investigation, substances with a short half-life may be completely eliminated (NPS). Positive cases may be missed if their metabolites are not monitored. Clinical symptoms, on the other hand, may disappear between arrest and medical investigation (approximately 3 hours on average), resulting in a false negative deem of impairment. As a result of these uncertainties, we have no laboratory or clinical evidence to support the impairment of drugged drivers.

4. ***Further development of the medical examinations*** would be necessary introduced. Beside the structure of the currently used medical investigation in Hungary there are other factors leading to uncertain clinical diagnosis: (1) The degree of tolerance for a given substance depends mainly on the history of drug use: regular users need a higher dose to reach the desired effect, which is accompanied by a higher blood concentration; (2) The time-period between drug use and medical investigation, as well as the dose consumed is unknown. The pattern and severity of clinical symptoms of stimulant users depend on the phase of the effect: the most characteristic symptoms appear during the "bingeing" phase while in the "come down" phase resembles symptoms of fatigue [89]. Because the investigation requirements and checklist were designed for alcohol consumption, clinical diagnosis of impairment is difficult. Because there is no specific symptom of drug-impairment in general or of the drug consumed, the examining clinician must perform a complex evaluation of the non-specific symptoms. Additional tests could provide a more confidential diagnosis. The current system of medical investigations is inadequate for determining the degree of impairment and distinguishing between positive and negative cases, and it requires significant revision.
5. Forensic experts would need to develop a standardized method for assessing drug impairment. Furthermore, impaired driving regulations in all European countries should be harmonised.
6. Public campaigns must continue to spread simple information about driving under the influence. In general, young people aged 15 to 34 are the most likely to use psychoactive drugs, and males use them more than females. As a result, especially this age group should be better informed about the dangers of drugged driving. Legal psychoactive substance use, particularly benzodiazepines, is common among the elderly. Physicians and pharmacists should provide more detailed information about the effects of drugs prescribed/delivered, particularly their effects on driving fitness.

# 6 Comparison of the NPS blood concentrations of the not impaired, impaired, intoxicated person and fatal cases in two studies

The vast majority of NPS have only a few published cases, which may not be typical of DUID, drunk or fatal cases. Furthermore, it was not always present in all concentration ranges for some compounds. DUID concentrations overlap with those in intoxicated [51] and lethal cases. The presence of NPS confirms causation in our two lethal cases [46] [47] [48]. However, this is not true in every case because additional substances and thus drug interactions, individual variation, lack of drug tolerance, or involvement of additional diseases could all have contributed to the death. Based on existing clinical experience and laboratory findings, these data do not provide information on the ***impairement, toxic or lethal*** concentrations of the NPS because similar blood levels have been detected in asymptomatic not impaired, impaired, hospitalized, and deceased individuals. [61] We found no correlation between blood concentration and clinical symptoms when neither outpatient service physicians performed the clinical examination and sampling of the drivers nor experienced emergency ward psychiatrists diagnosed and treated the intoxicated patients.

***Further studies*** by eliminating all these shortcomings are needed to explain the exact relationship between blood levels and the severity of symptoms where consumer tolerance and the effects of any active hydroxyl metabolites should also be considered.

**Table C1:** Blood concentration of NPSs in the different groups of examined consumers (A: average blood cc., M: median blood cc., t: time interval between arresting and medical investigation)

| | Not impaired (ng/ml) | Impaired (ng/ml) | Intoxicated (ng/ml) | Lethal (ng/ml) |
|---|---|---|---|---|
| **5F-MDMB-PINACA** | **<0.1-3.2**<br>A: 0.74<br>M: 0.36<br>*t: 143 min* | **<0.1-1.19**<br>0.62<br>0.54<br>*140 min* | **<0.1 - 2.54**<br>0.23 ± 0.56 | |
| N: 61 | N:29 | N:14 | N:18 | |
| **5F-MDMB-PICA** | **0.25-1.76**<br>A:1.12<br>M:1.36<br>*t: 82 min* | **0.72**<br>*75 min* | **<0.1 - 8.21**<br>1.27 ± 2.05 | |
| N: 20 | N: 4 | N: 1 | N:15 | |
| **ADB-FUBINACA** | **<0.1-11.8**<br>A: 3.24<br>M.: 1.85<br>*t: 217 min* | **0.24-20.9**<br>10.9<br>10.8<br>*119 min* | - | |
| N: 22 | N: 11 | N: 11 | | |
| **AMB-FUBINACA** | **<0.1-0.5**<br>*T: 160* | | | |
| N:7 | N: 7 | | | |
| **MDMB-CHMICA** | **1.35**<br>*t: 528 min* | **0.24**<br>*110 min* | - | |
| N: 2 | N: 1 | N: 1 | | |
| **AB-PINACA** | - | **0.2**<br>*680 min* | - | |
| N:1 | | N: 1 | | |
| **CUMYL-4CN-BINACA** | **0.53**<br>*t: 340* | **-** | | |
| N: 1 | N: 1 | | | |
| **NEH** | **15-143**<br>A: 42<br>M:33.3<br>*t: 236 min* | **16-123**<br>53.2<br>31.6<br>*184 min* | **41.8-138**<br>102 | **285** [46] |
| N: 34 | N:15 | N: 16 | N: 3 | |
| **4-CMC** | | | **117** | |
| N: 1 | | | | |
| **4-CEC** | **12.6** | **14.8** | | |
| N: 2 | *t: 300 min* | *50 min* | | |
| **Mephedrone** | - | **32** | - | |
| N: 1 | | *108 min* | | |
| **Methylone** | | | | **272** [47 48] |
| N: 1 | | | | |

# 7 Final conclusion

In this thesis, we were unable to present a comprehensive comparison with the international literature because this type of clinical evaluation of consumption and impairment is not published. Some studies attempted to establish a link between the substance and clinical signs, but only weak correlations were found.

This thesis compared the relationship between blood concentration and clinical symptoms in three populations: drug-intoxicated patients, suspected DUID drivers, and drivers involved in traffic accidents. We focused on SC intoxications in drug-intoxicated patients and found no correlation between drug concentration in the blood and severity of intoxication (PSS, which may be due to the short half life of SCs). The majority of the symptoms reported in the hospital were not specific to the substances, which may be due to the short half-life of SCs. The most frequent symptoms were unconsciousness, bradypsychia, slow pupillary light reaction, conjunctival hyperaemia, and tachycardia.

Clinical symptoms (registered at the time of sampling) of NPS-positive drivers were also examined in connection with their blood concentrations to reveal whether it is possible to set impairment limit for them. As a first step, we had to determine whether the official set of medical investigations has the sensitivity and specificity required to detect driving impairment. For classical illicit drugs and medicines well defined impairment limits are available. Thus, we compared the frequency of positive clinical signs below and over the impairment limit but it was significantly higher over the impairment limit only for alprazolam. When the frequency of positive clinical signs was evaluated according to concentration ranges, it was significantly higher for alprazolam over 20 ng/ml, for N-ethyl-hexedrone up to the highest (≥50 ng/ml) concentration range, and for ADB-FUBINACA over 10 ng/ml. These findings indicate that the currently used official set of medical investigations is ineffective for determining driving impairment and requires strict revision. However, the weakness of this set of medical investigations can be attributed to more factors, including: the time interval between the arrest/accident and the medical investigation is approximately 3 hours in general, the dose and time of application of the drug used is unknown, and the users may have varying tolerance for the drug consumed. While impairment caused by classical illicit drugs and medicines is determined by impairment limits (or when multi-drug use was determined), the results of medical investigations are decisive for the new psychoactive substances.

Police officers generally stop drivers for abnormal or reckless driving, but in many cases they do not describe the drivers' symptoms. There suspicion is right in 85% of the cases so the field

sobriety test (at the time of police act) would be useful and effective for clinical impairment evaluation.

The current system of impairment determination could be improved by (1) training police officers to accurately predict symptoms and perform field sobriety tests on the spot, (2) revising the set of medical investigations, and (3) developing a legal framework of evaluation method for forensic experts.

## 7.1 Summary of results

- The majority of NPS users in both studies were men aged 18 to 24.
- Based on the anamnesis and clinical symptoms, it is not possible to clearly determine the substance/group of substances causing the intoxication.
- The intoxication symptoms caused by SCs show a large overlap.
- The relatively short half-life and toxicity difference of the two investigated SCs were previously published based on laboratory results; in our current work, these results were also confirmed based on clinical data.
- The clinical symptoms of the various substances are similar in the two examined groups of drivers, so the clinical symptoms cannot be used to draw conclusions about drug-induced impairment or drug type. Despite the clinical obscurity the police officers recognize the drug users with good effectiveness.
- The clinical examination results in 40-60 % are fals negative or fals positive so drug use and impairment must be proven by laboratory analysis and the rapid urine test are inadequate for this purpose.
- Those countries which use the zero-tolerance regulation limit this zero-tolerance onto the illegal drugs while some legal substances show higher risk in traffic accidents. The drug abuse problem incorporates the abuse of benzodiazepines and their multi-drug combination with other drugs among the drivers the benzodiazepines result a definitely higher risk of accidents. Especially when the blood levels show the signs of abusive use.
- Even though the NPS use is a severe problem their role in the accident risk seems to be weaker than the other investigated substances.
- The short half-life of some abusive substances results a quick recovery of the user and at the time of the sampling it is impossible to prove the

impairment/intoxication. From the point of forensic medical evaluation the police case can not be proven.

- Based on existing clinical experience and laboratory findings, these data do not provide information on the impairement/legal limit, toxic or lethal concentrations of the NPS.
- Reconsideration of the legislation is needed at least in three areas to lessen the drug use intoxication and drug-use-born accidents:
    - The benzodiazepines and other prescription drugs need new regulation when abusive consuming suspected.
    - Police officers should take part in special training to perform a field sobriety test by standardise protocols.
    - The mean interval between the police act and medical examination should be shortened because the present 3 hours results data-loss, that can be an obstacle during the criminal procedure.
    - The legalisation of natural cannabis in several countries makes a new situation from point of traffic accidents so the traffic regulations should incorporate the cannabis use-issuse.

# 8 Resume of the new findings

- The clinical symptoms and examination are insufficient for determining the substance/group of substances causing the intoxication, nor for determining drug-induced impaiment.
- The intoxication symptoms caused by SCs show a large overlap.
- The results of the clinical examination used to establish drug-induced impaiment give 40-60 % are fals negative or fals positive.
- The abuse of benzodiazepines and their combination with other drugs among the drivers result a definitely higher risk of accidents, the prevalence and the accident risk is much higher than in the case of illegal drugs, including the NPSs. It is even more definite when the blood levels show the signs of abusive use.
- The NPS's role in accident risk appears to be weaker than that of the other investigated substances.

- Because of the short half-life of some substances (NPS) it is impossible to prove the drug-induced impairment/intoxication, and there is only a short time for any medical observation and therapy during the short recovery.
- Based on existing clinical experience and laboratory findings, these data do not provide information on defining the impairement legal limit, toxic or lethal concentrations of the NPS.

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# 11 Author's publications related to the thesis

1. Institóris, László ; Kovács, Katalin ; Sija, Éva ; Berkecz, Róbert ; Körmöczi, Tímea ; Németh, István ; Elek, István ; Bakos, Ágnes ; Urbán, Ildikó ; Pap, Csaba et al. Clinical symptoms and blood concentration of new psychoactive substances (NPS) in intoxicated and hospitalized patients in the Budapest region of Hungary (2018-19) CLINICAL TOXICOLOGY 60 : 1 pp. 18-24. , 7 p. (2022) IF: 3.738 *
2. Institóris, László ; Hidvégi, Előd ; Kovács, Katalin ; Jámbor, Ákos ; Dobos, Adrienn ; Párosi, Ferenc ; Süvegh, Gábor ; Varga, Tibor ; Kereszty, Éva ✉ Drug consumption of suspected drug-influenced drivers in Hungary (2016-2018) FORENSIC SCIENCE INTERNATIONAL 336 Paper: 111325 , 9 p. (2022) IF: 2.676 *
3. Kovács, Katalin ; Kereszty, Éva ✉ ; Berkecz, Róbert ; Tiszlavicz, László ; Sija, Éva ; Körmöczi, Tímea ; Jenei, Nikolett ; RévészSchmehl, Hajnal ; Institóris, László Fatal intoxication of a regular drug user following N-ethyl-hexedrone and ADB-FUBINACA consumption: [Case Reports] JOURNAL OF FORENSIC AND LEGAL MEDICINE 65 pp. 92-100. , 9 p. (2019) IF: 1.302
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2. Pintér, Katalin Marietta, Katalin Kovács, and Éva Kereszty. 2019. “Ritkán Alkalmazott Sürgősségi Beavatkozás Alacsony Túléléssel - Sürgősségi Thoracotomia.” In FIOF 2019, 10–10.
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# 13 Appendix

**App. Table A1:** Seizure data in Hungary in 2016-18.

| | 2016 | | 2017 | | 2018 | | |
|---|---|---|---|---|---|---|---|
| | **N** | **%** | **N** | **%** | **N** | **%** | **Total N** |
| **Classical illicit drugs** | | | | | | | |
| cannabis | 3063 | | 4149* | | 3923# | | 11135 |
| amphetamine | 952 | | 1095* | | 1215# | | 3262 |
| MDMA | 442 | | 632 | | 760*# | | 1834 |
| cocaine | 319 | | 396 | | 416 | | 1131 |
| metamphetamine | 69 | | 83 | | 144*# | | 296 |
| LSD | 35 | | 62 | | 79* | | 176 |
| heroin | 52 | | 54 | | 64 | | 170 |
| other substances | 285 | | 259* | | 274* | | 818 |
| **Total** | **5217** | ***51.9*** | **6730** | ***61.8*** | **6875** | ***60.8*** | **18822** |
| **Cathinones** | | | | | | | |
| N-ethyl-hexedrone | 253 | | 622* | | 999*# | | 1874 |
| 4-Cl-α-PVP | 52 | | 147* | | 144* | | 343 |
| 4-CEC | 102 | | 79 | | 71* | | 252 |
| 4-methyl-N-ethyl-norpentedrone | 80 | | 141* | | 7*# | | 228 |
| 4-CMC | 143 | | 27* | | 17* | | 187 |
| pentedrone | 118 | | 16* | | 9* | | 143 |
| 4-Cl-PPP | 131 | | 7* | | 1*# | | 139 |
| α-PVP | 96 | | 4* | | 2* | | 102 |
| other substances | 285 | | 193* | | 104*# | | 582 |
| **Total** | **1260** | ***12.6*** | **1236** | ***11.4*** | **1354** | ***12.0*** | **3850** |
| **SCs** | | | | | | | |
| 5F-MDMB-PINACA | 252 | | 1038* | | 2052*# | | 3342 |
| AMB-FUBINACA | 936 | | 576* | | 327*# | | 1839 |
| ADB-FUBINACA | 1054 | | 496* | | 19*# | | 1569 |
| CUMYL-PEGACLONE | | | 318 | | 6# | | 324 |
| MDMB-CHMICA | 265 | | 26* | | 9*# | | 300 |
| 5F-CUMYL-PEGACLONE | | | 34 | | 248# | | 282 |
| CUMYL-4CN-BINACA | 205 | | 5* | | | | 210 |
| other substances | 718 | | 290* | | 343* | | 1351 |
| **Total** | **3430** | ***34.2*** | **2783** | ***25.6*** | **3004** | ***26.6*** | **9217** |
| **Other designer drugs** | 130 | *1.30* | 134 | *1.23* | 79 | *0.70* | 343 |
| **All seizures** | **10037** | | **10883** | | **11312** | | **32232** |

N: number of seizures; %: percentage of all seizures in the corresponding year; *p<0.05 vs. 2016, #p<0.05 vs. 2017 by chi-square test within the corresponding substance group;

**App. Table B1:** Frequency of substances and substance groups among the impaired, sDUID (N: 2254) and responsible drivers (N: 302) cases

| Classical illicit drugs | sDUID $N_1$=1777 (78.7%) | | | | $N_2$=249 | Responsible drivers $N_1$=164 (54.3%) | | | | $N_2$=122 | Concentration intervals DUID | | Resp. drivers | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **A** | **C** | **Sum** | **%** | **IMP** | **A** | **C** | **Sum** | **%** | **IMP** | **Blood (ng/ml)** | **Med** | **Blood (ng/ml)** | **Med** |
| AM/MA | 246 | 507 | **753** | *42.4* | 612 | 14 | 49 | **63** | *38.4* | 58 | 5.00-1954/ 5.10-1724 | 79.9/ 175 | 12.2-566/ 8.4-443 | 83.9 123 |
| Cannabis | 617 | 623 | **1240** | *69.8* | 874 | 26 | 73 | **99** | *60.4* | 37 | - | - | - | - |
| • THC | 397 | 277 | **674** | ***37.9*** | | 11 | 21 | **32** | ***19.5*** | | 1.10-53.8 | 5.50 | 1.10-12.9 | 4.57 |
| • THC-OH | 40 | 46 | **86** | *4.84* | | 1 | 6 | **7** | *4.27* | | 1.00-24.2 | 2.65 | 1.00-6.59 | 2.02 |
| • THC-COOH | 184 | 307 | **491** | | | 14 | 46 | **60** | | | 1.11-269 | 27.4 | 1.43-248.2 | 15.6 |
| MDMA | 17 | 179 | **196** | ***11.0*** | 163 | 5 | 24 | **29** | *17.2* | 26 | 9.25-980 | 104 | 11-1599 | 133 |
| Cocaine | 5 | 7 | **12** | *0.68* | 6 | 0 | 1 | **1** | *0.61* | 1 | 6.0-163 | 6.50 | 12 | - |
| BZE | 48 | 132 | **180** | *10.1* | 139 | 4 | 9 | **13** | *7.93* | 13 | 13.0-13900 | 149 | 28.8-2027 | 188.5 |
| GHB(µg/ml) | 5 | 12 | **17** | *0.96* | 16 | 0 | 7 | **7** | ***4.27*** | 7 | 28.0-412 | 65.0 | 26-174 | 90.0 |
| Methadone | | 9 | **9** | *0.51* | 8 | | 2 | **2** | *1.22* | 2 | 20.0-344 | 114 | 662.3 | - |
| Morphine | | 7 | **7** | *0.39* | 4 | 1 | 0 | **1** | *0.61* | 0 | 7.00-35.0 | 18.5 | - | - |
| Mirtagynin | | | | | | 0 | 1 | **1** | *0.61* | 1 | - | - | 0.35 | - |
| LSD | | 3 | **3** | | 2 | | | | | | 0.02-0.12 | 0.03 | - | - |
| Fentanyl | 2 | 1 | **3** | | 2 | 2 | 3 | **5** | | 0 | 0.33-1.06 | 0.40 | 0.28-7.32 | 0.74 |
| Ketamine | 6 | 15 | **21** | | 14 | 2 | 5 | **7** | | 0 | 22.6-962 | 139 | 42.2-895.6 | 164 |

BZE: benzoylecgonine is the main metabolite of cocaine

| Medicines | sDUID $N_1$=290 (12.6%) | | | | $N_1$=251 | Responsible drivers $N_1$=145 (48%) | | | | $N_2$=113 | Concentration intervals DUID | | Resp. drivers | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **A** | **C** | **Sum** | **%** | **IMP** | **A** | **C** | **Sum** | **%** | **IMP** | **Blood (ng/ml)** | **Med** | **Blood (ng/ml)** | **Med** |
| Alprazolam | 30 | 158 | **188** | *64.8* | 156 | 24 | 56 | **80** | *55.2* | 70 | 5.00-939 | 30.2 | 6-547.1 | 60 |
| Clonazepam 7-amino clonaz | 11 | 72 | **83** | *28.6* | 75 | 3 | 32 | **35** | *24.1* | 35 | 5.00-505/ 5.00-1409 | 50.0/ 33.0 | 6-377/ 7-2016 | 46/ 58.5 |
| Diazepam | 1 | 12 | **13** | *4.48* | 12 | 0 | 12 | **12** | *8.28* | 11 | 10.0-619 | 40.1 | 6-553.9 | 83.6 |
| Other benzos | 4 | 12 | **16** | *5.52* | 13 | 0 | 10 | **10** | *6.89* | 10 | - | - | - | - |
| Zolpidem | | 2 | **2** | ***0.69*** | 2 | 1 | 9 | **10** | ***6.89*** | 10 | 406 | - | 0.52-1282 | 132.8 |
| Midazolam | | 7 | **7** | *2.41* | 7 | 0 | 8 | **8** | *5.51* | 0 | 5.00-414 | 81 | 5-499 | 69 |
| Carbamazepine | 2 | 8 | **10** | *3.45* | 9 | 2 | 3 | **5** | *3.45* | 3 | 37.8-18830 | 2760 | 160-9130 | 4994 |
| Citalopram | 2 | 13 | **15** | *5.17* | 12 | 0 | 4 | **4** | *2.76* | 4 | 7.00-112 | 22.3 | 12-48 | 24 |
| Mirtazapine | 1 | 5 | **6** | *2.44* | 5 | 0 | 3 | **3** | *2.07* | 3 | 5.00-72.0 | 17.0 | 14-373 | - |
| Tramadol | | 5 | **5** | *2.07* | 3 | 3 | | **3** | *0.49* | 0 | 38.5-997 | 91.7 | 32.6 | - |
| Tiapride | | 4 | **4** | *1.38* | 4 | | | | | | 4.00-1320 | - | - | - |
| Clozapine | | | | | | | 1 | **1** | | 1 | - | - | 11 | - |
| Buprenorphine | | 2 | **2** | | 2 | | | | | | 7.00 | - | - | - |
| Paroxetin | | | | | | | 1 | **1** | | 1 | - | - | 184 | - |
| Metoprolol | | | | | | 0 | 1 | **1** | | 1 | - | - | 24 | - |

**Other benzos**: (Lorazepam, Olanzapine, Clobazam, Nitrazepam, Medazepam, Cinolazepam); Z-drugs: Zopiclone, Zolpidem

| Synthetic cathinones | sDUID $N_1$=135 (5.98%) | | | | $N_2$=71 | Responsible drivers $N_1$=12 (3.97%) | | | | $N_2$=11 | Concentration intervals DUID | | | Resp. drivers |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **A** | **C** | **Sum** | **%** | **IMP** | **A** | **C** | **Sum** | **%** | **IMP** | **Blood (ng/ml)** | **Med** | **Blood (ng/ml)** | |
| NEH | 47 | 68 | **115** | ***85.2*** | **63** | 1 | 6 | **7** | ***58.3*** | **7** | 10.2-143 | 30.7 | 18.9-189 | 45.9 |
| Mephedrone | 1 | 3 | **4** | *2.96* | **4** | | 2 | **2** | ***16.7*** | **2** | 22.8-180 | | 30.1-260 | - |
| Pentedrone | | 2 | **2** | *1.48* | **1** | | 1 | **1** | *8.33* | **1** | 44-100 | | 54.47 | - |
| 4-CEC | 3 | | **3** | *2.22* | **1** | | 1 | **1** | *8.33* | **1** | 12.6-14.8 | | quantitative | - |
| NEP | | 3 | **3** | *2.22* | **2** | 1 | | **1** | *8.33* | | 10.6-298 | | quantitative | - |
| 4MENP | 2 | 6 | **8** | *5.92* | **4** | | | | | | 16.7-23.9 | | **-** | **-** |
| α-PVP | | 1 | **1** | *0.74* | **1** | | | | | | - | | **-** | **-** |
| 4Cl- α-PVP | | 2 | **2** | *1.48* | | | | | | | - | | **-** | **-** |
| 4-CMC | 1 | 2 | **3** | *2.22* | | | | | | | - | | **-** | **-** |
| 4Cl-α-PVP | | 2 | **2** | *1.48* | | | | | | | **-** | | **-** | **-** |
| EPh | | 1 | **1** | *0.74* | | | | | | | **-** | | **-** | **-** |

**4MENP**: 4-methyl-N-ethyl-norpentedrone; **NEP**: N-ethylpentylone; **NEH**: N-ethyl-hexedrone; **EPh**: ethylphenidate

| Synthetic cannabinoids | sDUID $N_1$=480 (21.3%) | | | | $N_2$=262 | Responsible drivers $N_1$=69 (22.8%) | | | | $N_2$=51 | Concentration interval DUID | | Resp. drivers | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | A | C | Sum | % | IMP | A | C | Sum | % | IMP | Blood (ng/ml) | Med | Blood (ng/ml) | Med |
| AB-FUBINACA M | 10 | 236 | **246** | 51.3 | 141 | 1 | 33 | **34** | *49.3* | 33 | 0.1-286 | 1.12 | 0.16-20 | 0.58 |
| 5F-MDMB-PINACA | 44 | 223 | **267** | 55.6 | 146 | 6 | 21 | **27** | *39.1* | 26 | 0.1-20.0 | 0.40 | 0.1-11.1 | 0.49 |
| 5F-MDMB-PINACA M | | | | | | 4 | 14 | **18** | *26.1* | 14 | 0.13-18.9 | 4.45 | 0.9-20 | 11 |
| ADB-FUBINACA | 20 | 70 | **90** | 18.8 | 60 | 2 | 12 | **14** | *20.3* | 14 | 0.11-23.4 | 3.78 | 0.13-26.4 | 3.2 |
| AMB-FUBINACA | 16 | 75 | **91** | 18.9 | 55 | 2 | 8 | **10** | *14.5* | 8 | 0.10-10.1 | 0.11 | 0.1-0.5 | - |
| 5F-MDMB-PICA | 6 | 28 | **34** | 7.08 | 24 | 1 | 8 | **9** | *13.0* | 8 | 0.10-11.8 | 1.36 | 0.1-0.25 | - |
| ADB-FUBINACA M | | | | | | | 5 | **5** | 7.25 | 5 | - | - | 4.57 | - |
| AMB-FUBINACA M | 5 | 7 | **12** | 2.50 | 5 | | 4 | **4** | *5.78* | 4 | 0.59-132 | 66.6 | 3.92-20 | - |
| 5F-ADB-PINACA | | 11 | **11** | 2.29 | 4 | | 4 | **4** | 5.78 | 4 | quantitative | - | quantitative | - |
| 5F-MDMB-PICA M | | | | | | 1 | 2 | **3** | *4.35* | 2 | 0.13-14.1 | 0.87 | 0.61-8.1 | - |
| CUMYL-4CN-BINACA | 5 | 8 | **13** | 2.70 | | 1 | 1 | **2** | 2.89 | 1 | quantitative | - | 0.53 | - |
| AB-FUBINACA | 0 | 15 | **15** | 3.13 | 9 | 1 | 1 | **2** | 2.89 | 1 | 0.29-1.58 | 0.58 | quantitative | - |
| MAB-CHMINACA M | | 1 | **1** | 0.21 | 1 | | 2 | **2** | 2.89 | 2 | 1.93 | | quantitative | - |
| MDMB-FUBINACA | | 2 | **2** | 0.42 | 2 | | 1 | **1** | 1.45 | 1 | quantitative | - | - | - |
| AB-CHMINACA | | 5 | **5** | 1.04 | 5 | | 1 | **1** | 1.45 | 1 | 0.38-2.38 | 1.03 | 0.2 | - |
| AB-PINACA | | 1 | **1** | 0.21 | 1 | | 1 | **1** | 1.45 | 1 | 0.88 | - | 0.61 | - |
| 5F-AMB M | | 14 | **14** | 2.91 | 9 | | 1 | **1** | 1.45 | 1 | 0.20-19.0 | 1.06 | - | - |
| 4 F-MDMB-BINACA | 1 | 3 | **4** | | 3 | | | | | | quantitative | - | - | - |
| 5 F-AMBICA | | 1 | **1** | | 1 | | | | | | quantitative | - | - | - |
| 5 F-AMB-PINACA | | 1 | **1** | | 1 | | | | | | 7.05 | - | - | - |
| 5 F-CUMIL-PEGACLONE | 2 | 7 | **9** | | 7 | | | | | | quantitative | - | - | - |
| ADB-CHMINACA | 1 | 1 | **2** | | 2 | | | | | | 0.45-9.8 | - | - | - |
| AKB-48 F | | 2 | **2** | | 2 | | | | | | quantitative | - | - | - |
| AMB-CHMICA | | 2 | **2** | | 2 | | | | | | quantitative | - | | |
| CUMYL-5F-P7AICA | | 1 | **1** | | 1 | | | | | | quantitative | - | | |
| CUMYL-CH-MEGACLONE | | 1 | **1** | | 1 | | | | | | quantitative | - | | |
| CUMYL-PEGACLONE | 2 | 5 | **7** | | 4 | | | | | | 0.25-4.01 | 0.34 | | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| CUMYL-5F-P7AICA | | 1 | **1** | 1 | | | quantitative | - |
| CUMYL-CH-MEGACLONE | | 1 | **1** | 1 | | | quantitative | - |
| CUMYL-PEGACLONE | 2 | 5 | **7** | 4 | | | 0.25-4.01 | 0.34 |
| EMB-FUBINACA | 2 | | **2** | | | | quantitative | - |
| JHW-122 M | | 1 | **1** | 1 | | | quantitative | - |
| MAB-CHMICA M | | 1 | **1** | 1 | | | 1.93 | - |
| MAB-CHMINACA | 3 | 2 | **5** | 2 | | | quantitative | - |
| MAB-CHMINACA M | | 2 | **2** | 1 | | | 0.38-5.77 | - |
| MAM-2201 | | 1 | **1** | 1 | | | quantitative | - |
| MDMB-CHMICA | 2 | 18 | **20** | 17 | | | 0.03-10 | 0.65 |
| MDMB-FUBICA | | 5 | **5** | 4 | | | quantitative | - |
| MDMB-FUBINACA | | 2 | **2** | 2 | | | quantitative | - |
| MMB-2201 | | 1 | **1** | 1 | | | quantitative | - |
| THJ-2201 | | 2 | **2** | 2 | | | quantitative | - |
| UR-144 | | 2 | **2** | 1 | | | quantitative | - |

*p<0.05 versus 2016, $^{+}$p<0.05 versus 2017 by chi-square test; **$N_1$**: number of drivers tested positive to any drug of the corresponding group, (%) percentage of the same drivers related to all positive cases; **$N_2$:** number of impaired drivers in the corresponding group, (%) percentage of the same drivers related to all positive cases;

**%:** frequency of the substances (Sum)/number of drivers tested positive in the corresponding substance group ($N_1$) x 100

**A**: alone **C**: in combination, **IMP**: prevalence of the substances among impaired drivers; **M**: all metabolites are of carboxylic acid type; **AB-FUBINACA M**: the common metabolite of AB-FUBINACA, AMB-FUBINACA and EMB-FUBINACA; **5F-AMB M**: the common metabolite of 5F-AMB-PINACA and 5F-AB-PINACA

App. Table B3: Frequencies of single use and combinations of two active drug groups (total number of only one group DUID: 1196; Responsible drivers: 150; total number of combinations of two drug groups: DUID: 490; Responsible drivers: 100)

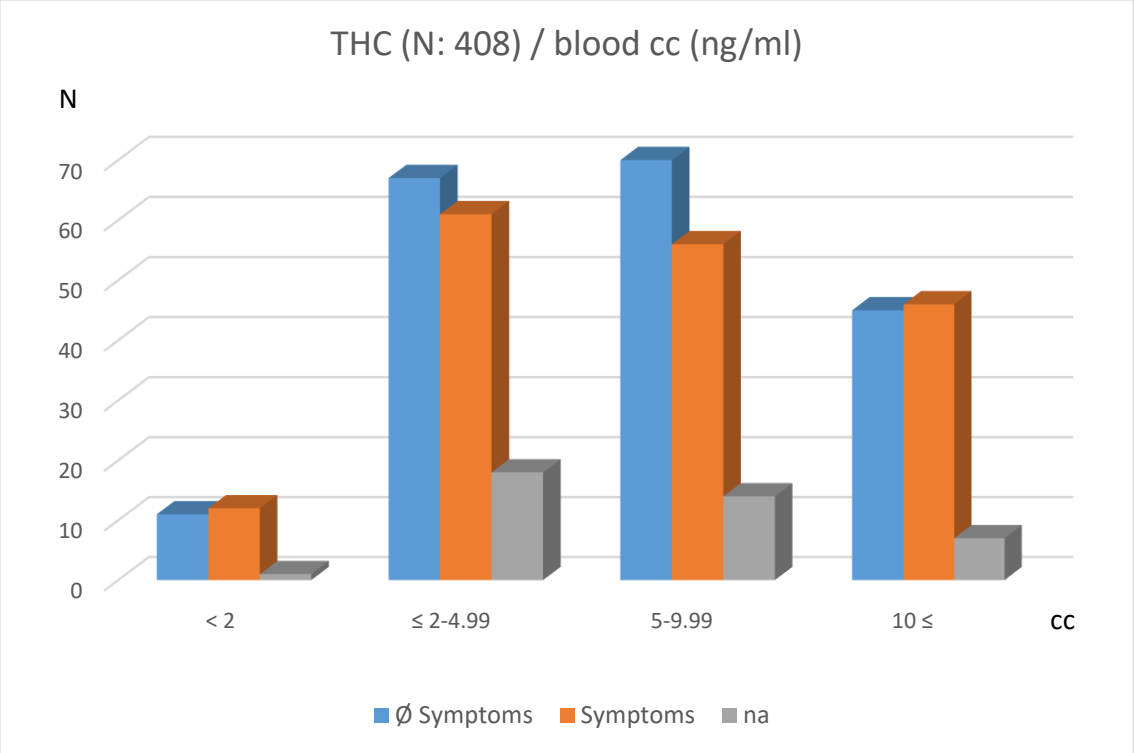
| | Cannabis | | Stimulants | | Benzodiazepine | | SCs | | sNPS | | Alcohol | | Other | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | D | R | D | R | D | R | D | R | D | R | D | R | D | R |
| One substance group | | | | | | | | | | | | | | |
| Single substances | 437* | 12 | 308* | 20 | 46* | 38 | 109 | 14 | 53 | 2 | 0 | 0 | 5 | 0 |
| % | ***36.5*** | ***8.0*** | ***25.6*** | ***13.3*** | ***3.85*** | ***25.3*** | 9.11 | 9.33 | 4.43 | 1.33 | | | 0.42 | |
| Comb. within the group | - | - | 61 | 4 | 13* | 7 | 143 | 11 | 4 | 0 | - | - | - | - |
| % | | | *5.1* | *2.7* | *1.09* | *4.67* | 11.9 | 7.33 | 0.33 | - | | | | |
| Combination of two substance groups | | | | | | | | | | | | | | |
| Cannabis | | | 208* | 8 | 17 | 5 | 22 | 0 | 3 | 1 | 20 | 5 | 1 | 0 |
| % | | | ***42.4*** | ***8.0*** | 3.47 | 5.00 | 4.49 | - | 0.6 | 1.00 | 4.08 | 5.00 | 0.2 | - |
| Stimulants | | | | | 33* | 6 | 29* | 4 | 10 | 0 | 36* | 15 | 6 | 3 |
| % | | | | | 6.63 | 6.00 | 5.92 | 4.00 | 2.04 | - | ***7.35*** | ***15.0*** | 1.22 | 2.27 |
| Benzodiazepine | | | | | | | 38* | 16 | 8* | 6 | 17* | 15 | 3 | 3 |
| % | | | | | | | 7.76 | 16.0 | 1.63 | 6.00 | 3.47 | 15.0 | 0.60 | 3.00 |
| SC | | | | | | | | | 19 | 0 | 5* | 5 | 1 | 0 |
| % | | | | | | | | | 3.88 | - | 1.02 | 5.00 | 0.2 | - |
| sNPS | | | | | | | | | | | 3* | 1 | 0 | 0 |
| % | | | | | | | | | | | 0.61 | 1.00 | - | - |

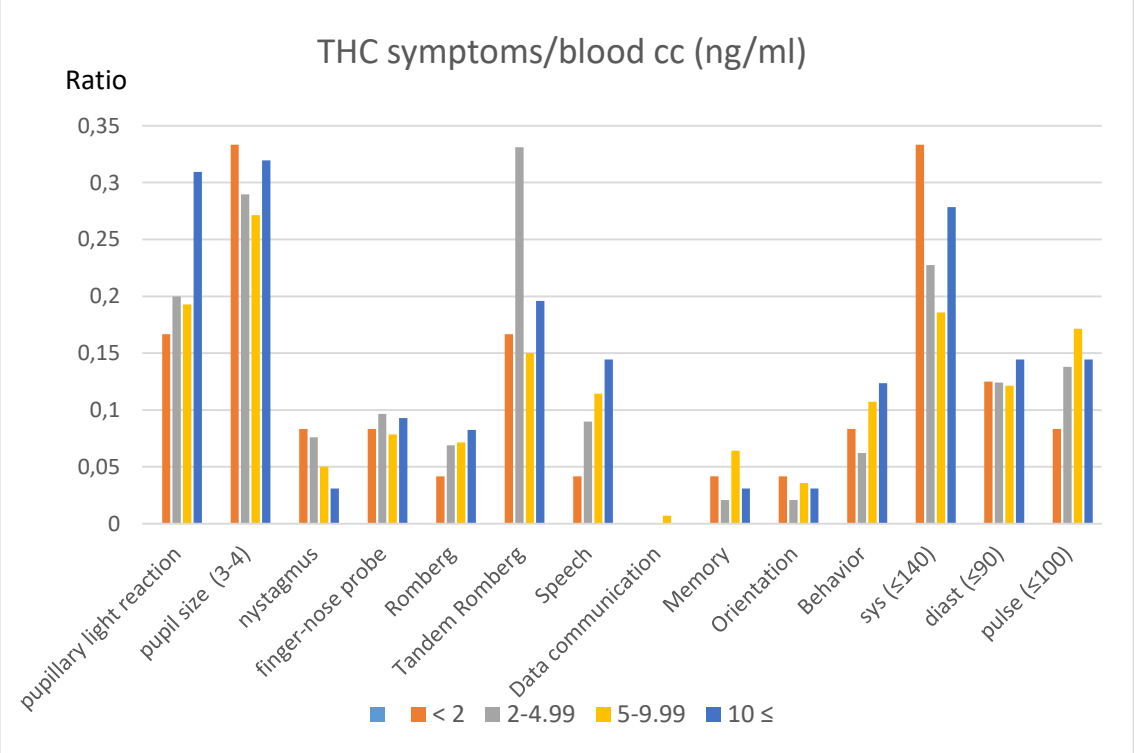
D- sDUID drivers; R – responsible drivers; Cannabis: THC, THC-OH, Stimulants – AM, AM, MDMA, Cocaine, SC- Synthetic cannabinoid; sNPS – Synthetic cathinones; Other – LSD, morphine, GHB, Methadone,

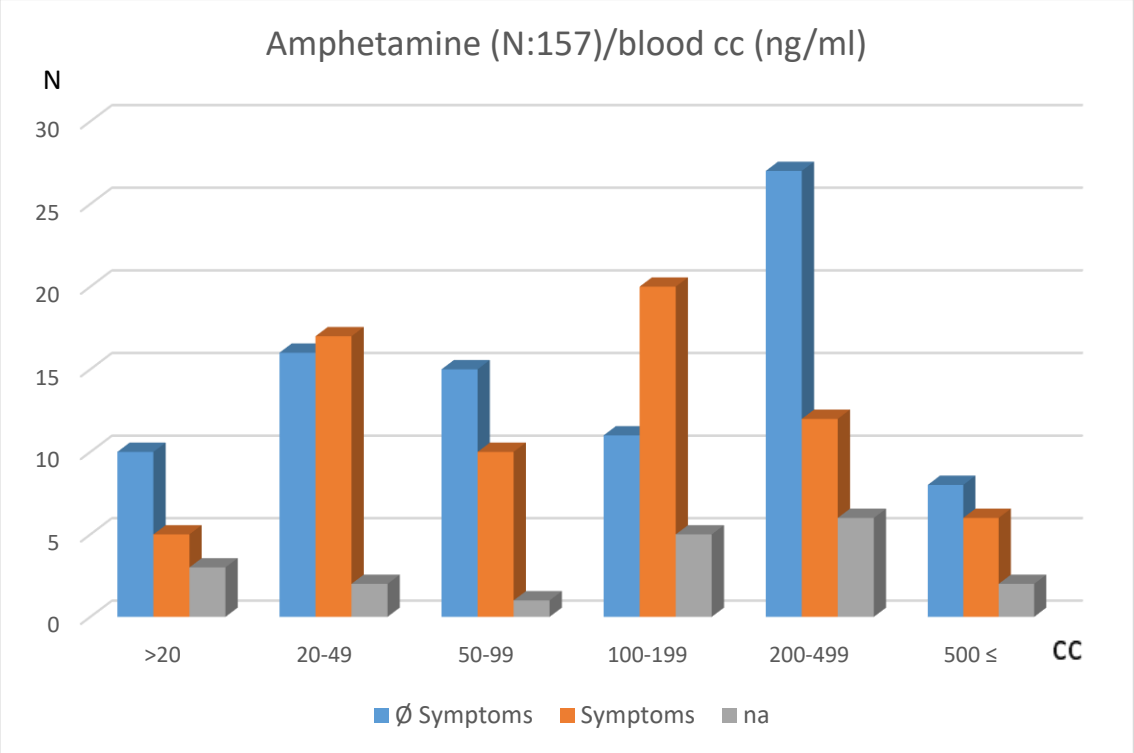
App. Table B5: Examination of clinical symptoms with and without the legal limit (single drug use) (NPS, negative, multi-drug use)

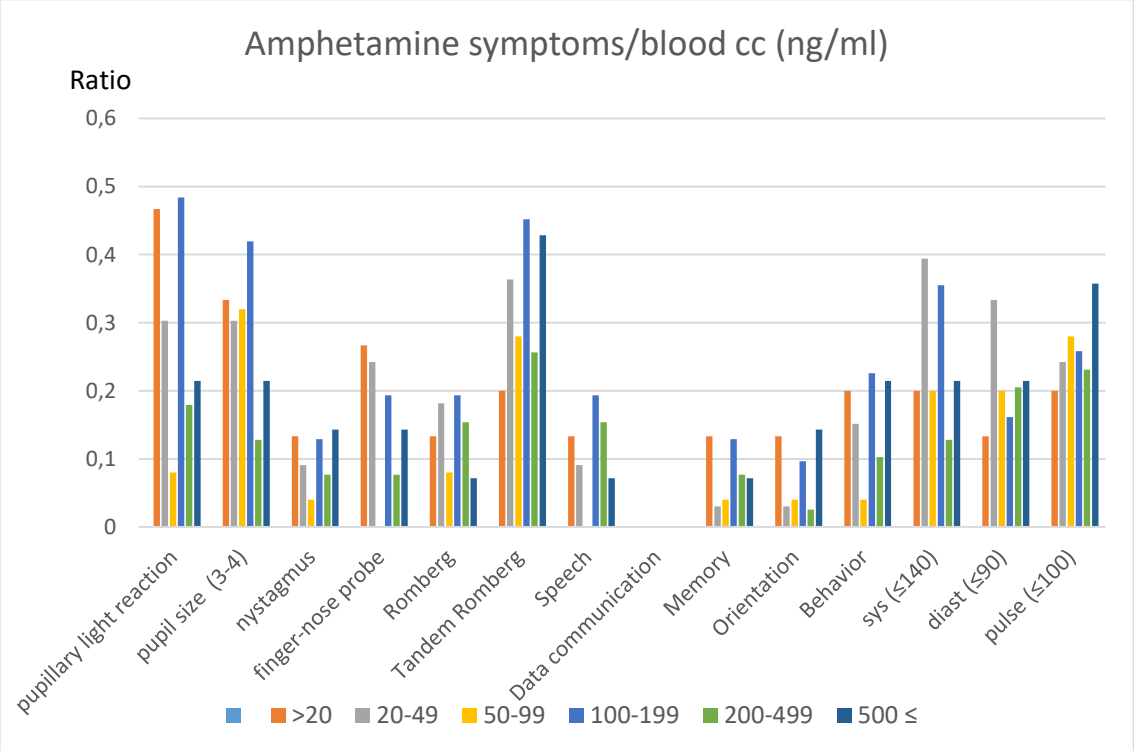
| SUBSTANCE | | | CLINICAL SYMPTOMS | | | | | COHEN'S KAPPA COEFFICIENT (95% CONFIDENCE INTERVAL) | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | N | Legal limit (ng/ml) | Under limit | | Above limit | | Not performed | Cohen's kappa coeffcient | Lower bound | Upper bound |
| | | | poz | neg | poz | neg | | | | |
| THC | 408 | 2 | 12 | 11 | 163 | 182 | 40 | 0,09316 | -0,00467 | 0,190993 |
| AMPHETAMINE | 157 | 20 | 5 | 7 | 65 | 61 | 19 | -0,02639 | -0,17199 | 0,119205 |
| | | 50 | 22 | 21 | 48 | 47 | | -0,00549 | -0,17325 | 0,162271 |
| METHAMPHETAMINE | 68 | 20 | 7 | 2 | 33 | 24 | 2 | -0,11075 | -0,39549 | 0,173994 |
| | | 50 | 24 | 17 | 16 | 9 | | 0,048908 | -0,18055 | 0,278368 |
| MDMA/MDA | 20 | 20 | 0 | 1 | 9 | 9 | 1 | 0,095238 | - 0,3336 | 0,524075 |
| | | 50 | 1 | 3 | 8 | 8 | | 0,150943 | -0,26045 | 0,562333 |
| COCAINE/BZE | 34 | 50 | 1 | 2 | 16 | 12 | 3 | 0,090293 | -0,28653 | 0,46712 |
| ALPRAZOLAM | 53 | 20 | 5 | 4 | 30 | 9 | 5 | 0,182482 | -0,17794 | 0,542901 |
| | | | | | | | | CLOPPER-PEARSON (95% CONFIDENCE INTERVALS) | | |
| | Without legal limit | | | | | | | Proportion | Lower bound | Upper bound |
| NEH | 31 | - | - | - | 21 | 10 | - | 0.6774 | 0.4863 | 0.8332 |
| ADB-FUBINACA | 15 | - | - | - | 12 | 3 | - | 0.8000 | 0.5191 | 0.9567 |
| 5F-MDMB-PINACA | 44 | - | - | - | 17 | 26 | 1 | 0.3953 | 0.2498 | 0.5559 |
| NEGATIVE | 166 | - | 85 | 69 | - | - | 12 | 0.5519 | 0.4698 | 0.6320 |
| MULTI-DRUG USE | 1158 | - | - | - | 636 | 439 | 83 | 0.5916 | 0.5616 | 0.6212 |

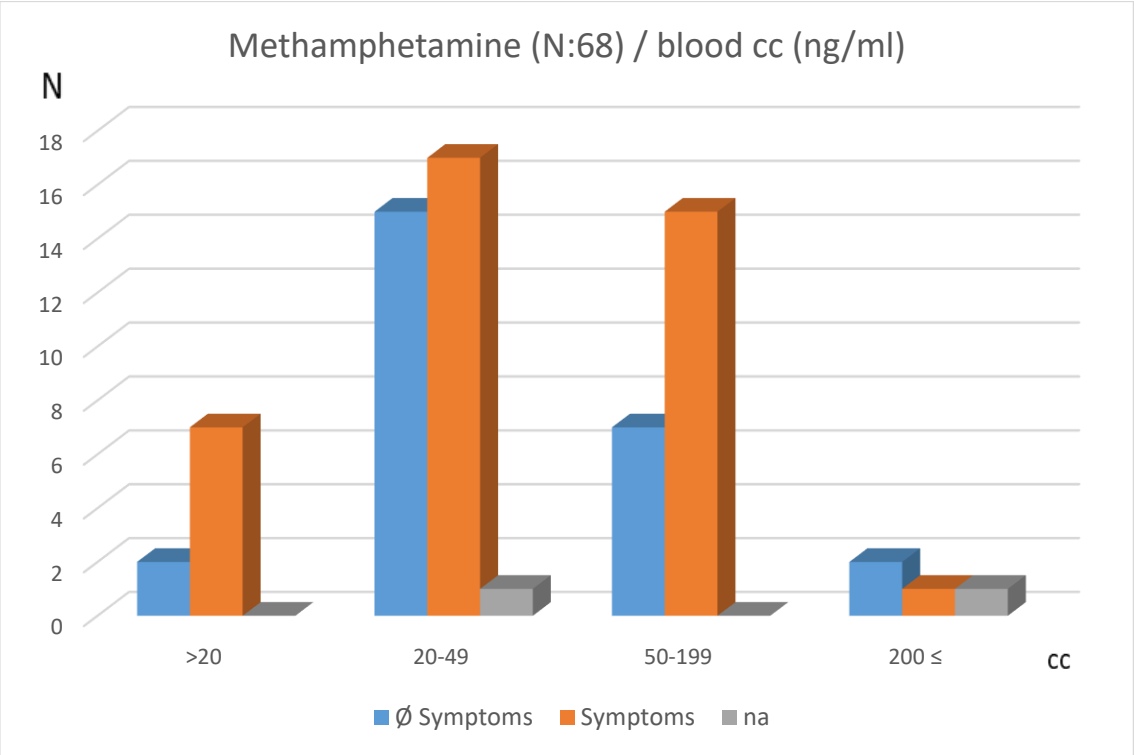
**App. Diagram B5:** Connection between clinical symptoms and blood concentration (cc) of different drugs (single drug use)

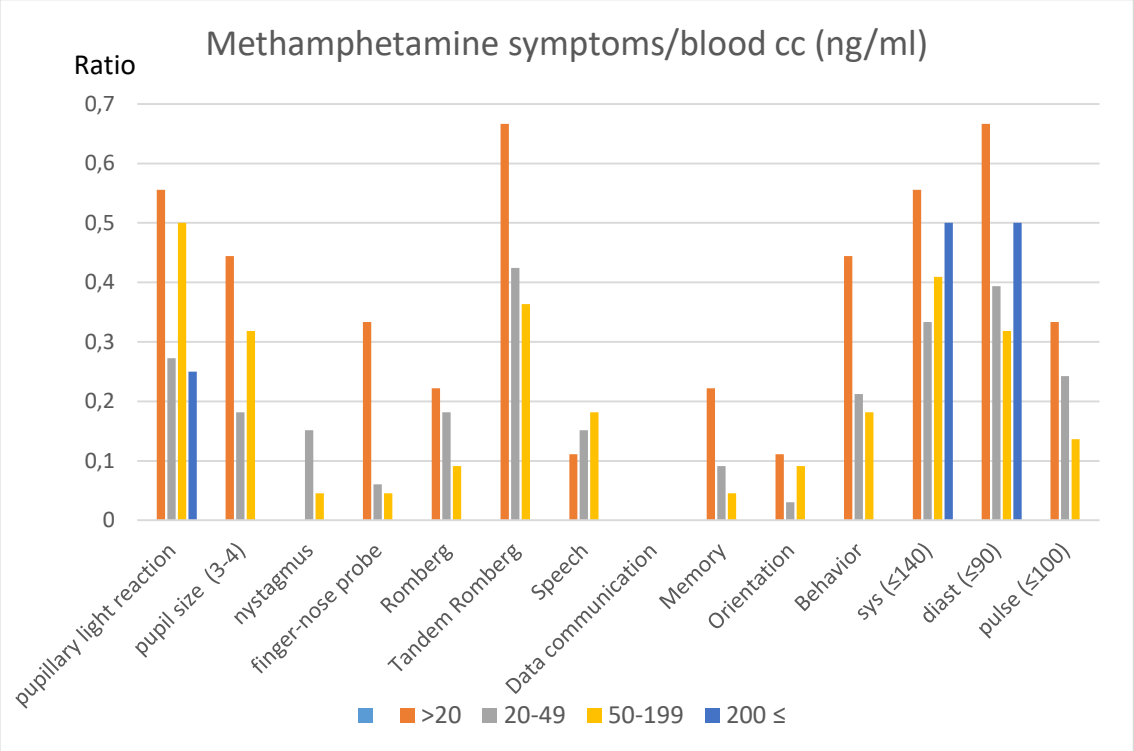


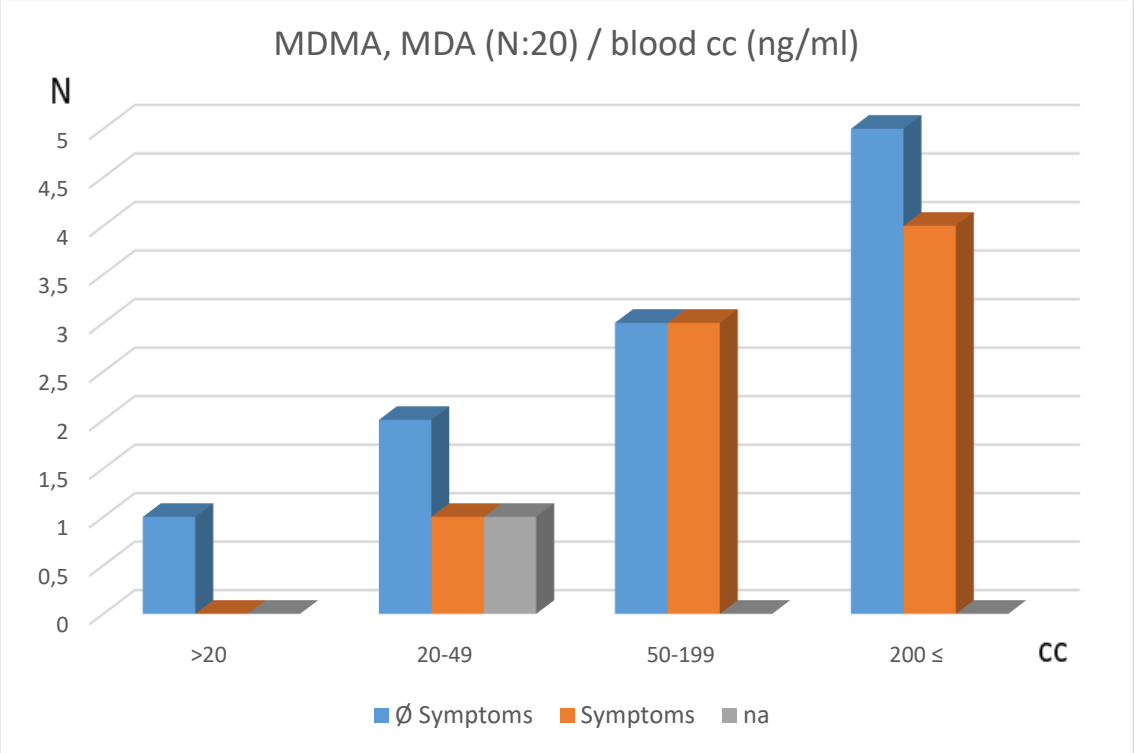



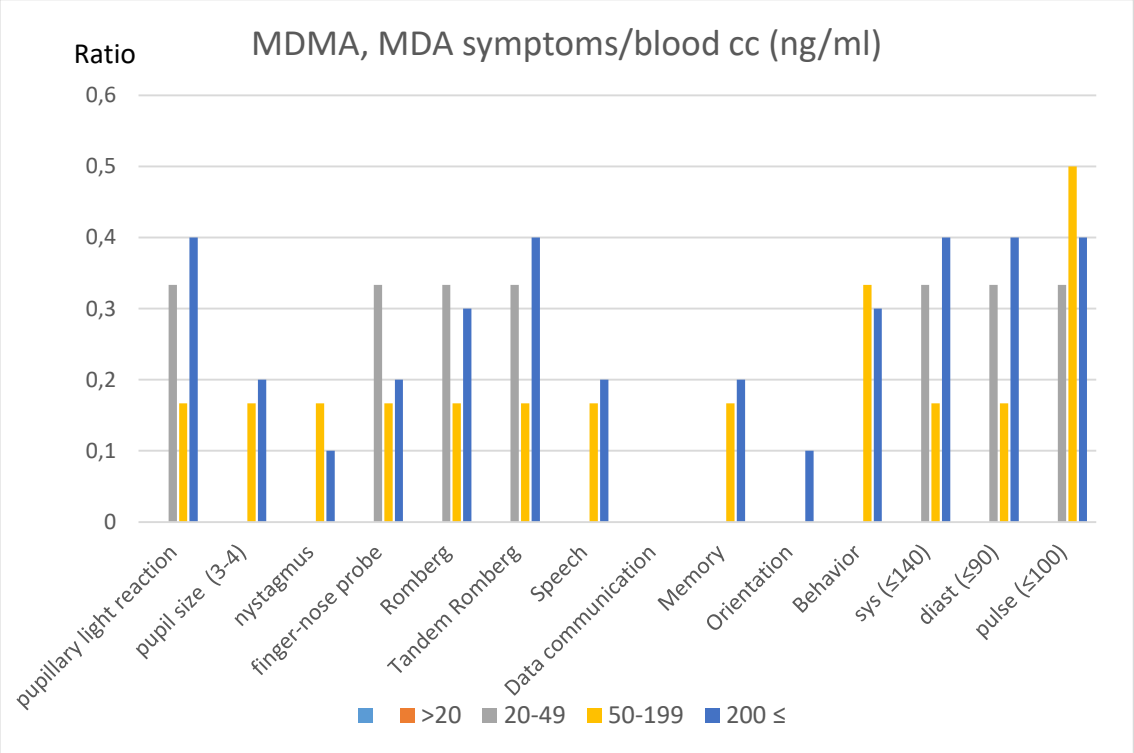

Amphetamine (N:157)/blood cc (ng/ml)
N
30
25
20
15
10
5
0
>20
20-49
50-99
100-199
200-499
500 ≤
CC
Ø Symptoms
Symptoms
na

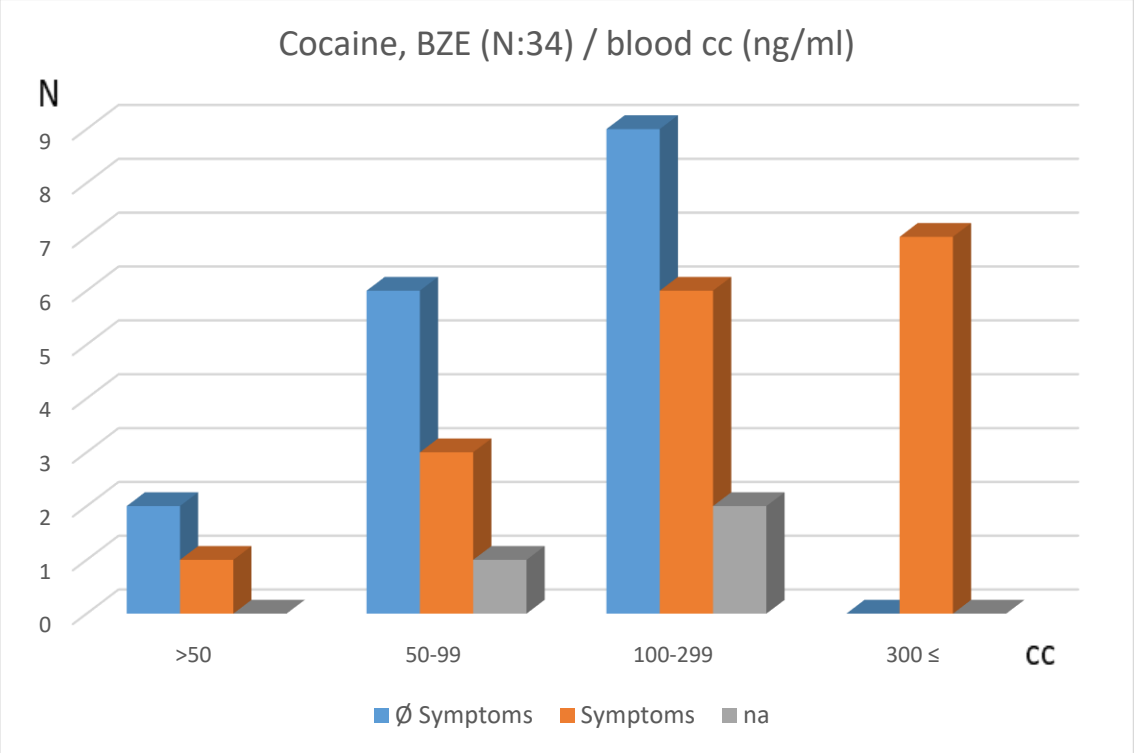

Amphetamine symptoms/blood cc (ng/ml)
Ratio
0,6
0,5
0,4
0,3
0,2
0,1
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
>20
20-49
50-99
100-199
200-499
500 ≤

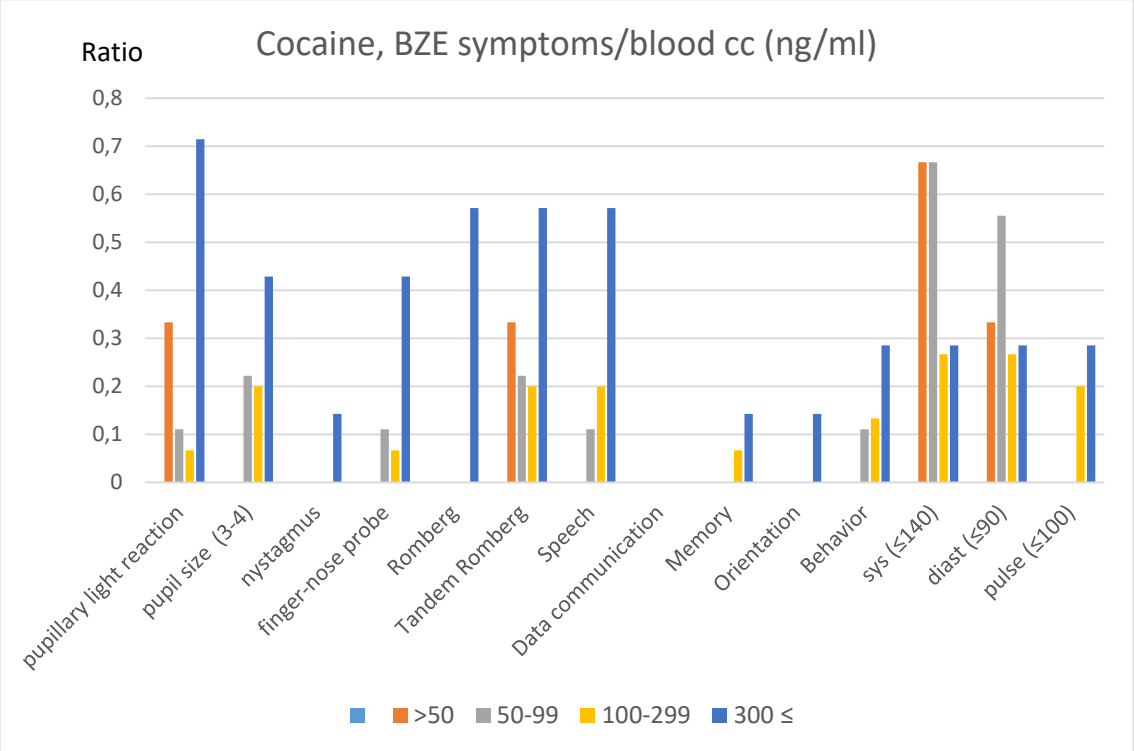

Methamphetamine (N:68) / blood cc (ng/ml)
N
18
16
14
12
10
8
6
4
2
0
>20
20-49
50-199
200 ≤
cc
Ø Symptoms
Symptoms
na

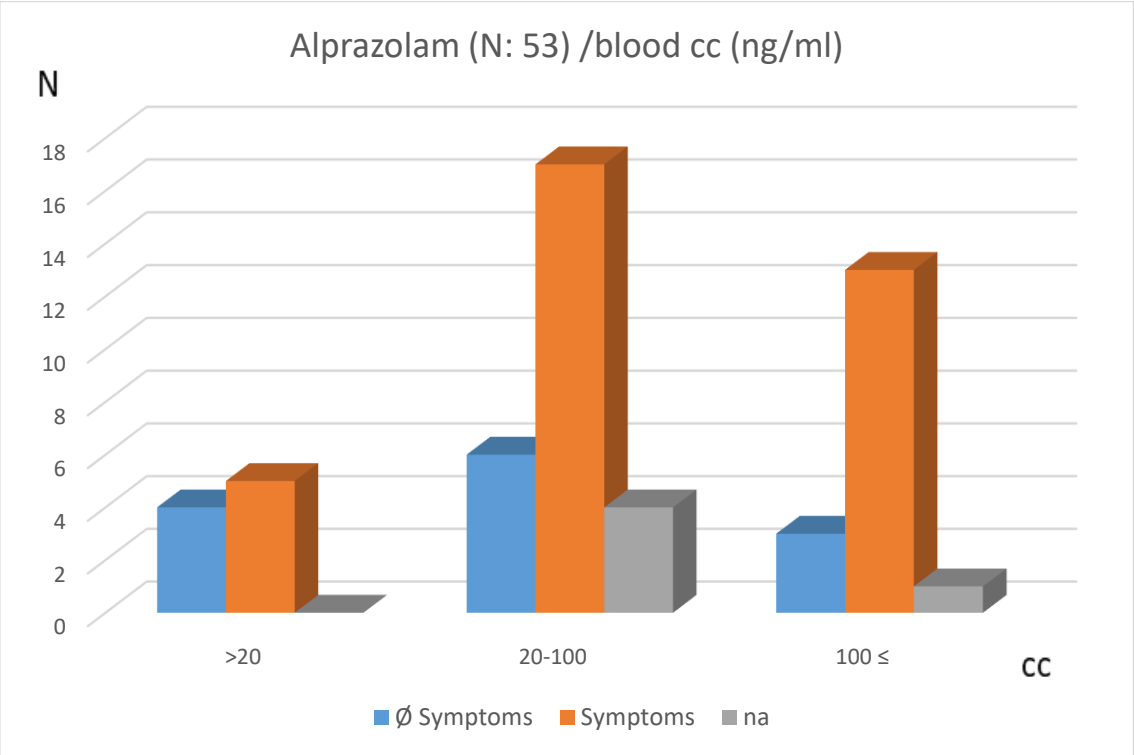

Methamphetamine symptoms/blood cc (ng/ml)
Ratio
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
>20
20-49
50-199
200 ≤

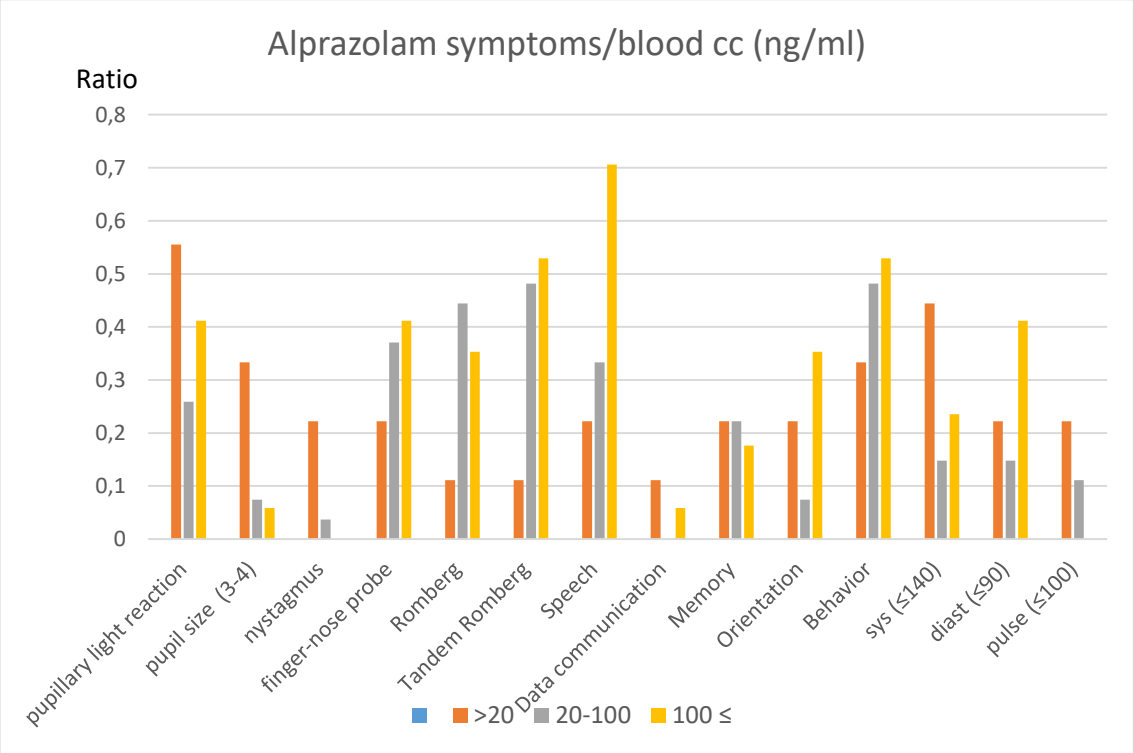

MDMA, MDA (N:20) / blood cc (ng/ml)
N
5
4,5
4
3,5
3
2,5
2
1,5
1
0,5
0
>20
20-49
50-199
200 ≤
CC
Ø Symptoms
Symptoms
na

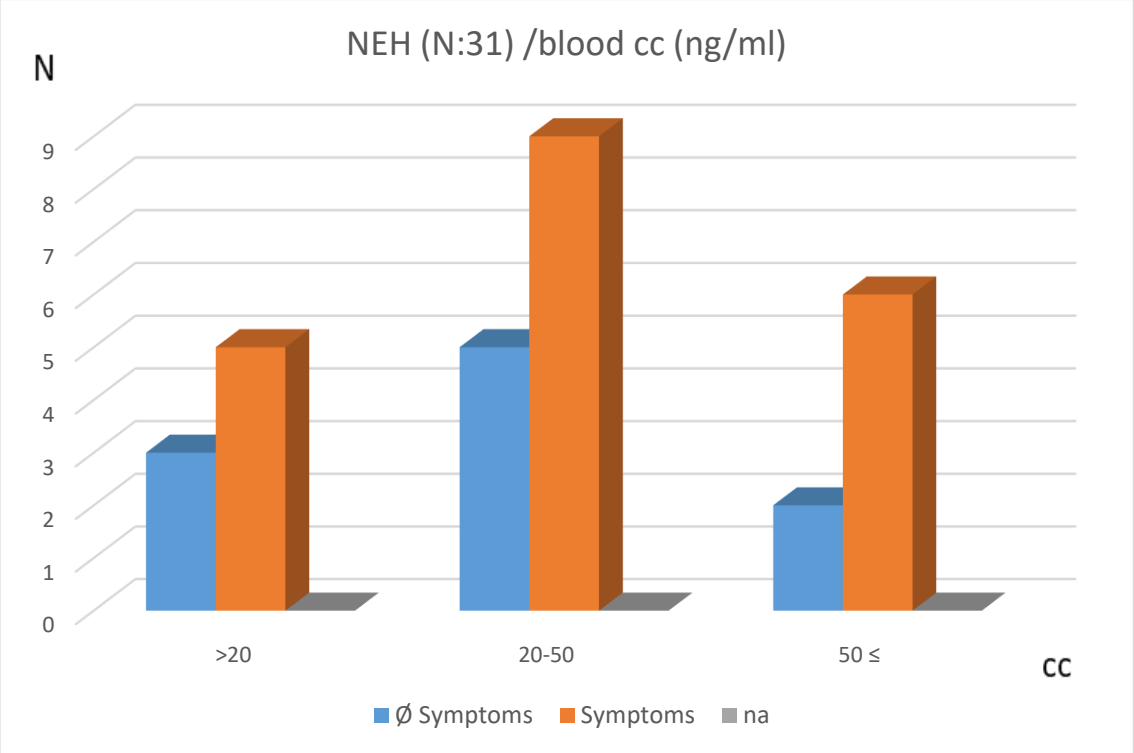

MDMA, MDA symptoms/blood cc (ng/ml)
Ratio
0,6
0,5
0,4
0,3
0,2
0,1
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
>20
20-49
50-199
200 ≤

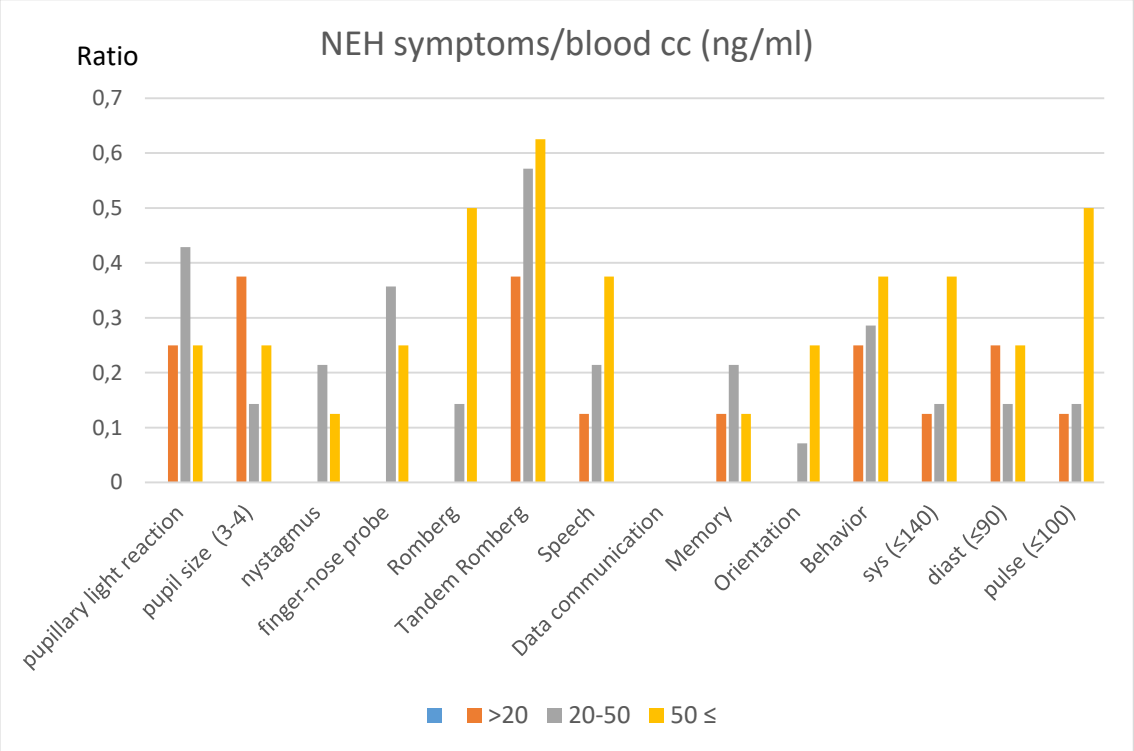

Cocaine, BZE (N:34) / blood cc (ng/ml)
N
9
8
7
6
5
4
3
2
1
0
>50
50-99
100-299
300 ≤
CC
Ø Symptoms
Symptoms
na

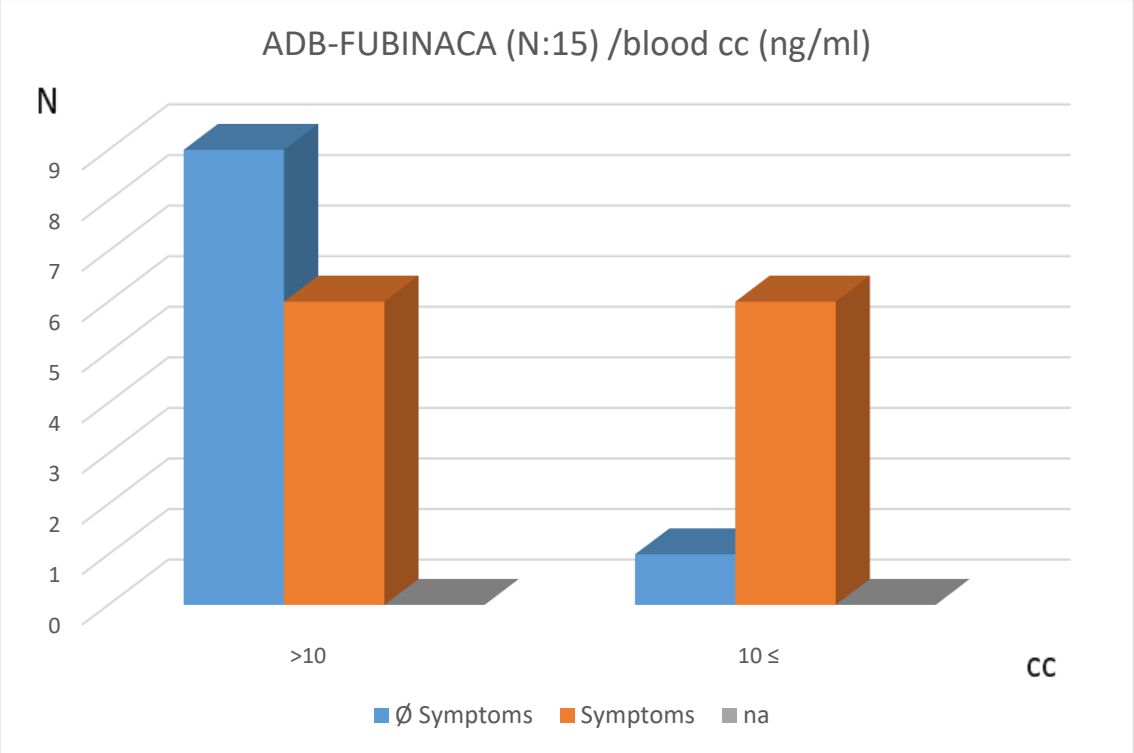

Cocaine, BZE symptoms/blood cc (ng/ml)
Ratio
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
>50
50-99
100-299
300 ≤

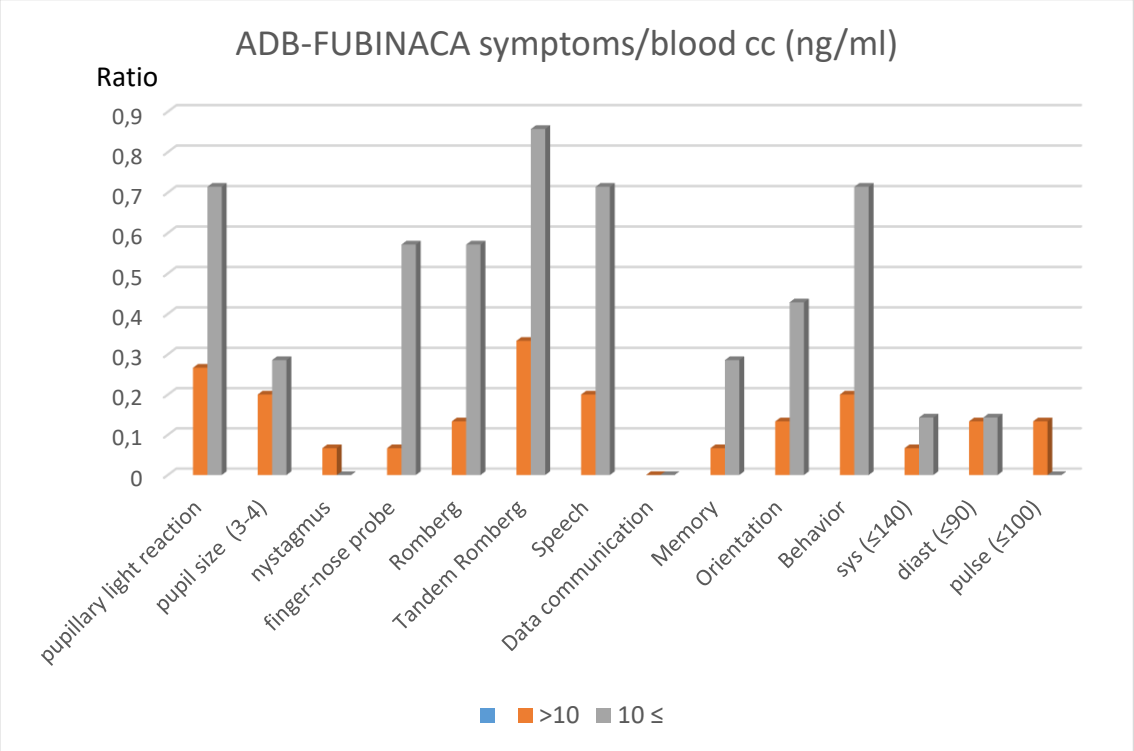

Alprazolam (N: 53) /blood cc (ng/ml)
N
18
16
14
12
10
8
6
4
2
0
>20
20-100
100 ≤
cc
Ø Symptoms
Symptoms
na

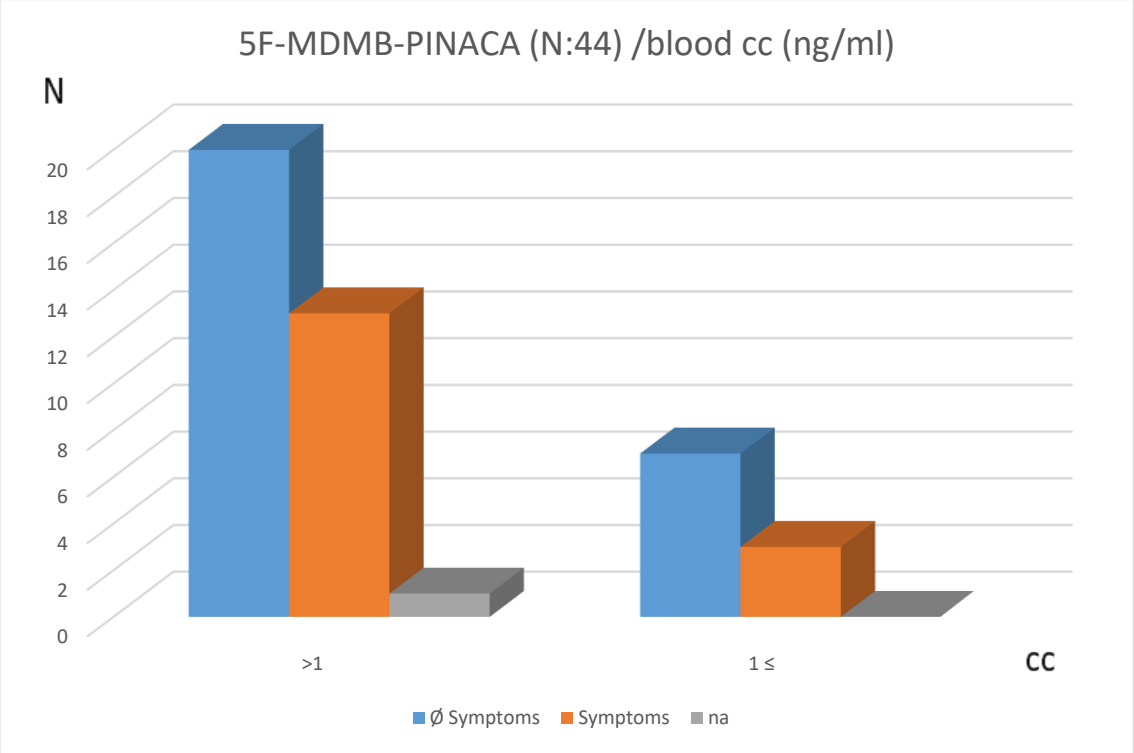

Alprazolam symptoms/blood cc (ng/ml)
Ratio
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
>20
20-100
100 ≤

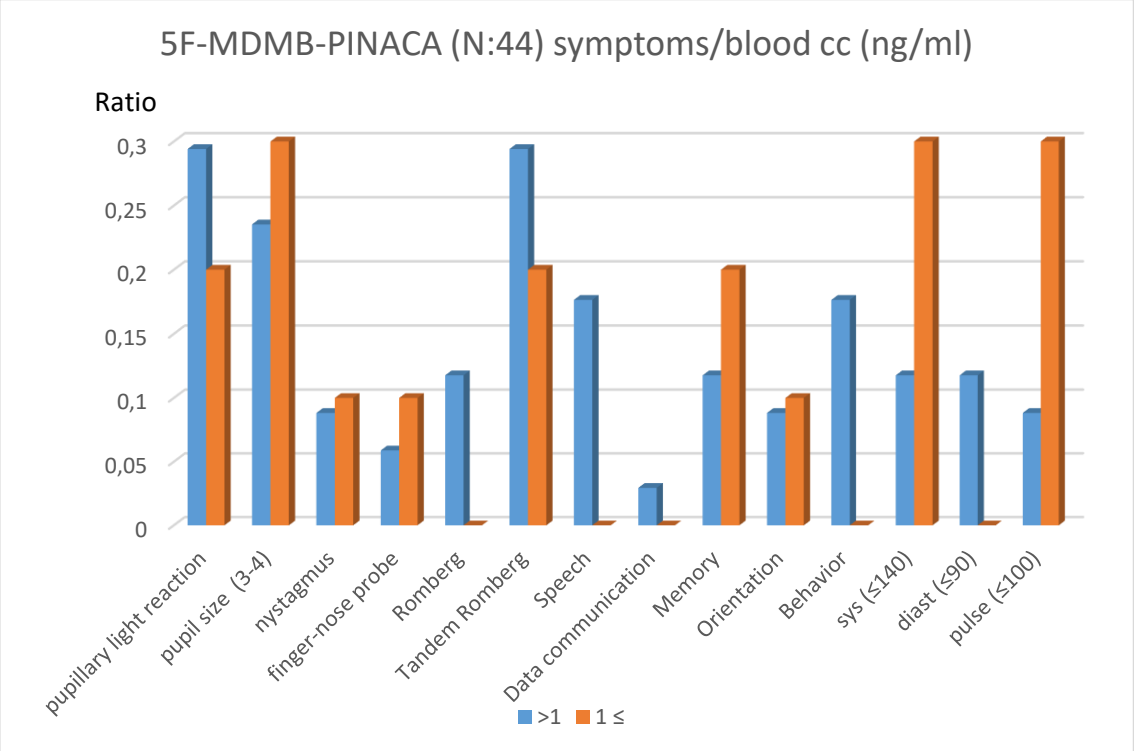

NEH (N:31) /blood cc (ng/ml)
N
9
8
7
6
5
4
3
2
1
0
>20
20-50
50 ≤
cc
Ø Symptoms
Symptoms
na


NEH symptoms/blood cc (ng/ml)
Ratio
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
>20
20-50
50 ≤

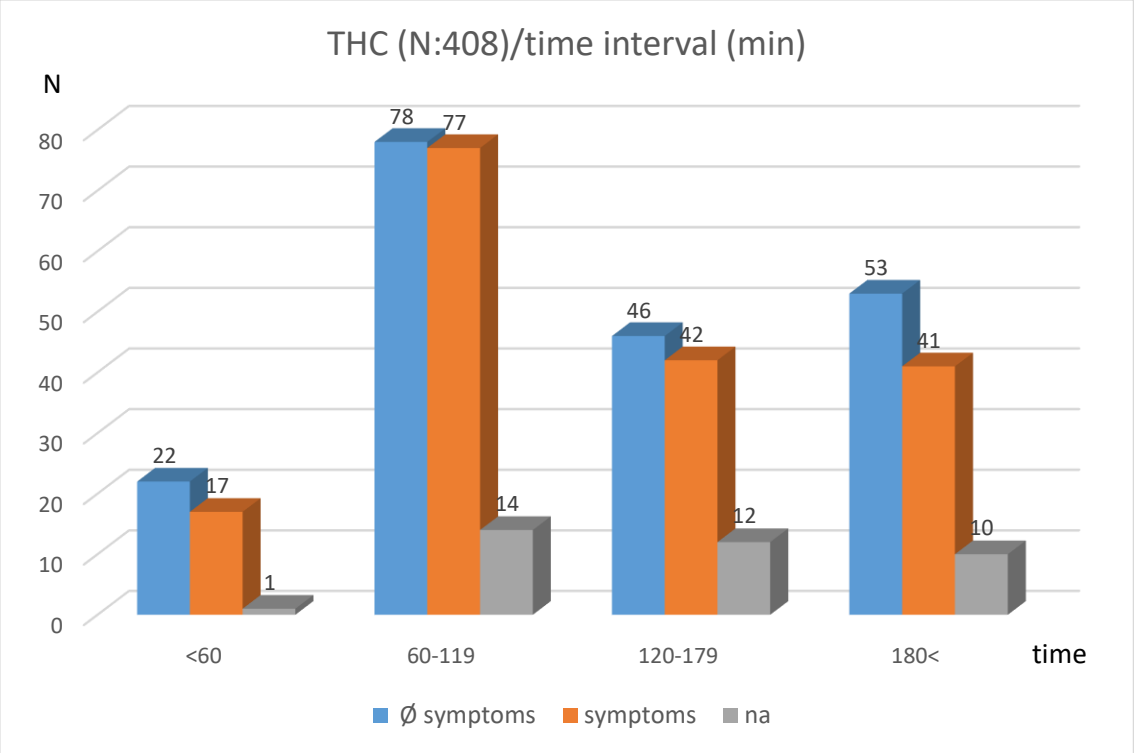

ADB-FUBINACA (N:15) /blood cc (ng/ml)
N
9
8
7
6
5
4
3
2
1
0
>10
10 ≤
cc
Ø Symptoms
Symptoms
na

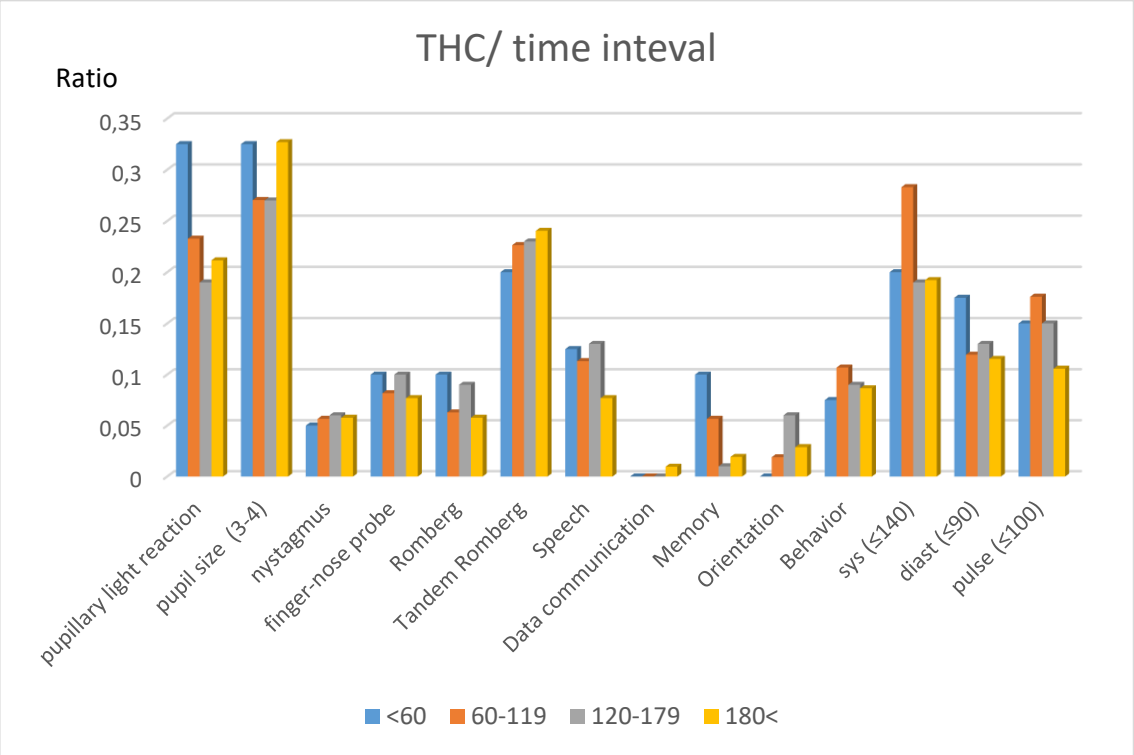

ADB-FUBINACA symptoms/blood cc (ng/ml)
Ratio
0,9
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
>10
10 ≤

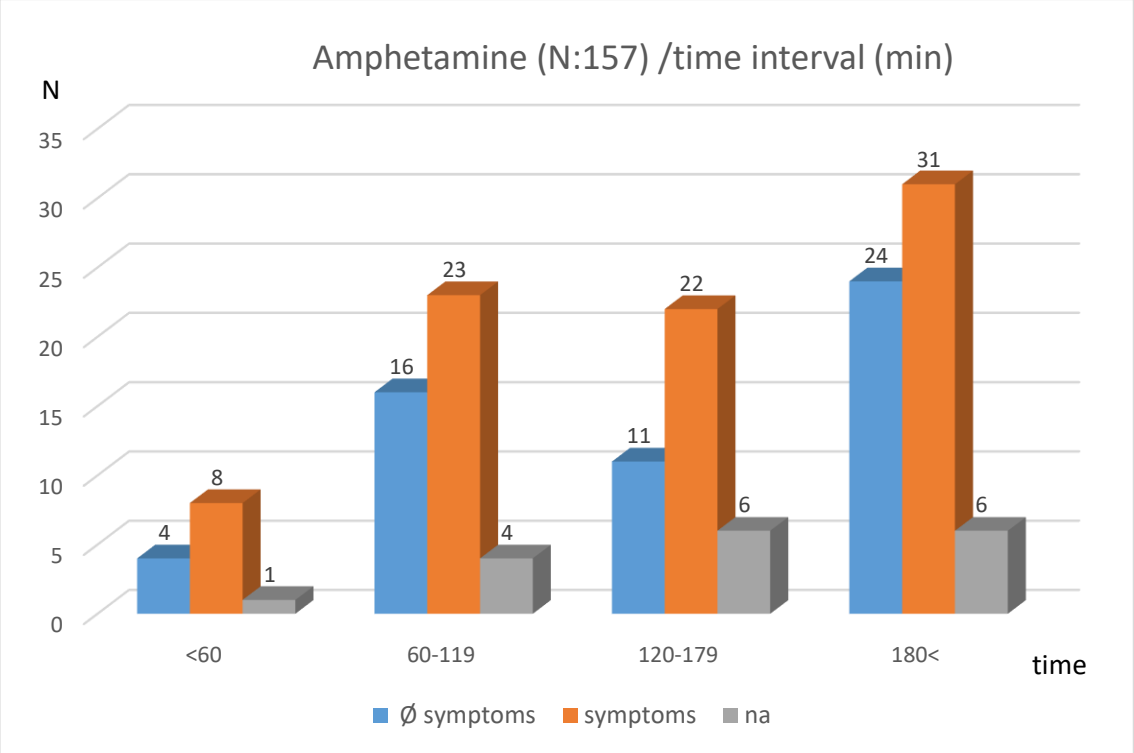

5F-MDMB-PINACA (N:44) /blood cc (ng/ml)
N
20
18
16
14
12
10
8
6
4
2
0
>1
1 ≤
CC
Ø Symptoms
Symptoms
na

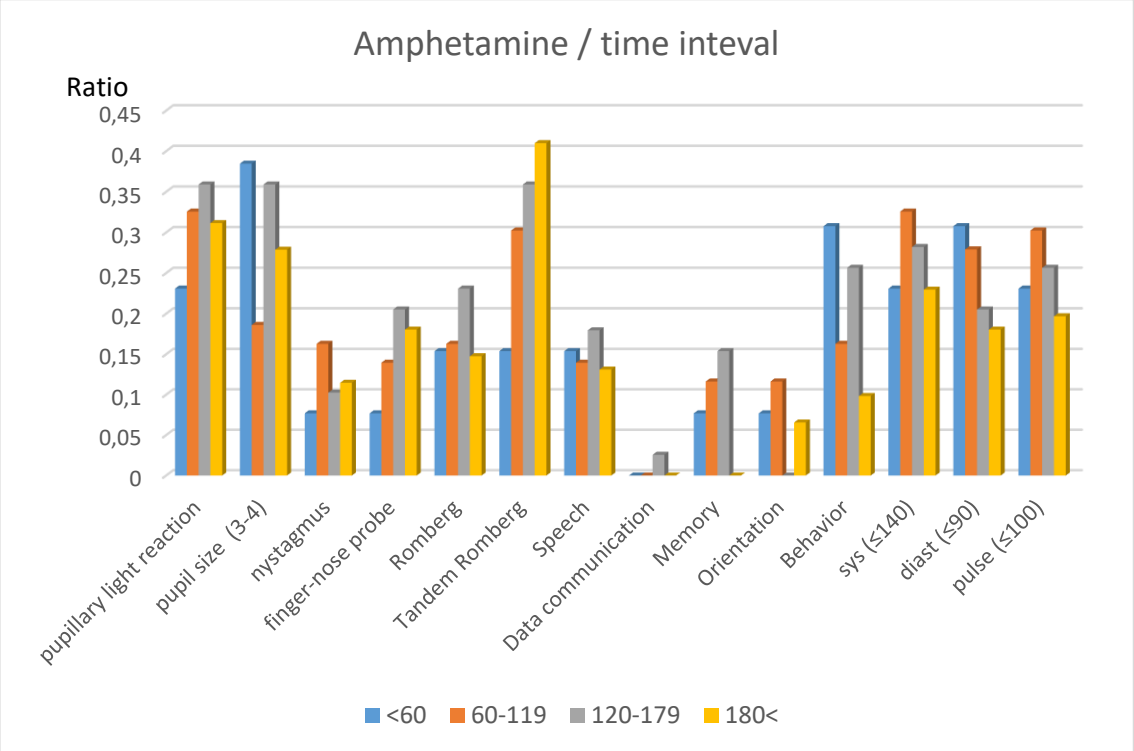

5F-MDMB-PINACA (N:44) symptoms/blood cc (ng/ml)
Ratio
0,3
0,25
0,2
0,15
0,1
0,05
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
>1
1 ≤

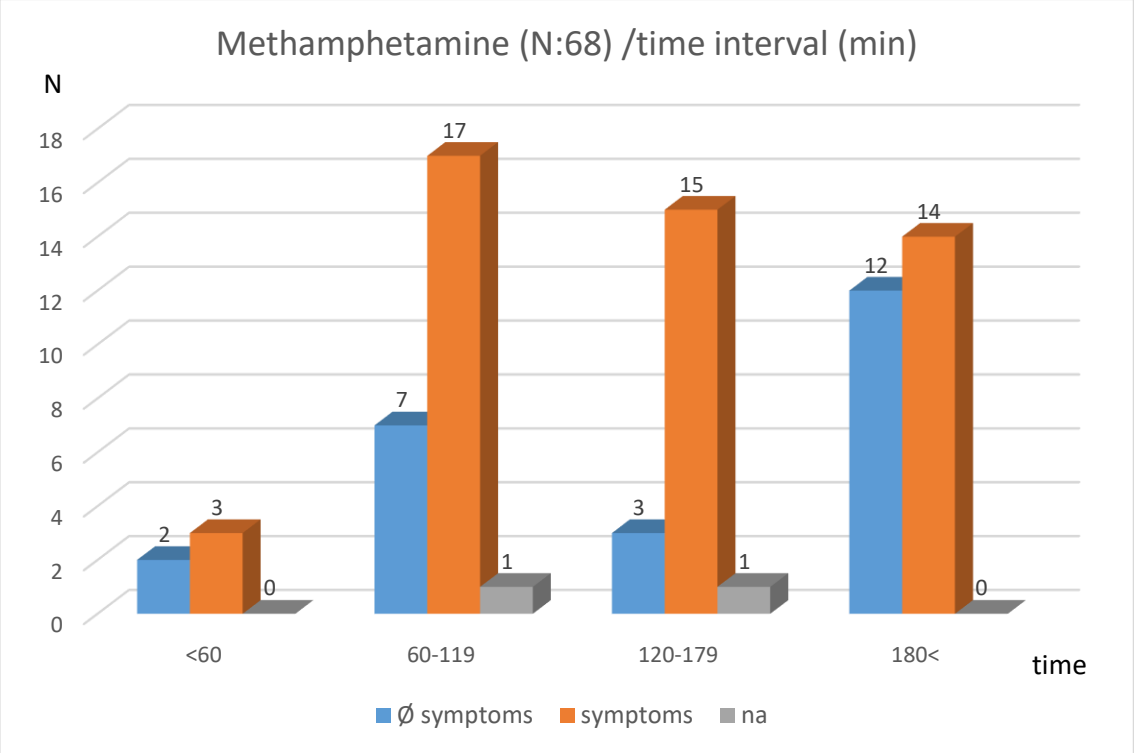
**App. Diagram B6:** Drug impairment (single drug use) judged by clinical symptoms in the time interval (between arresting and medical investigation) distribution (na: not available)

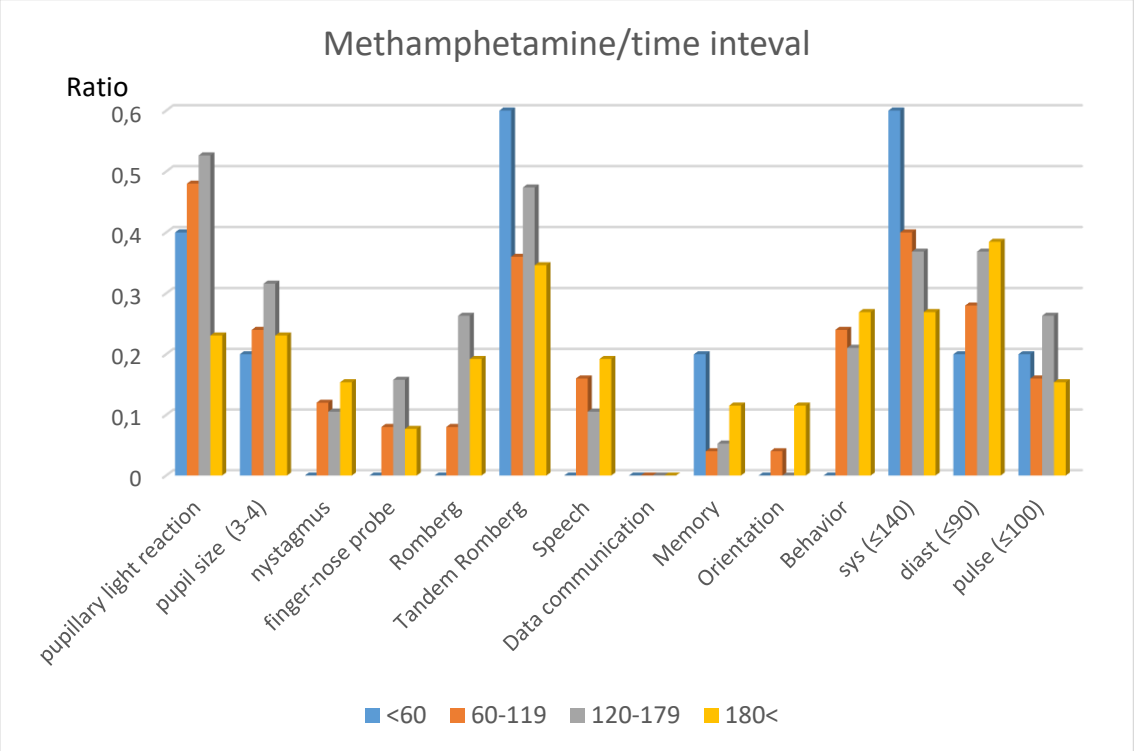


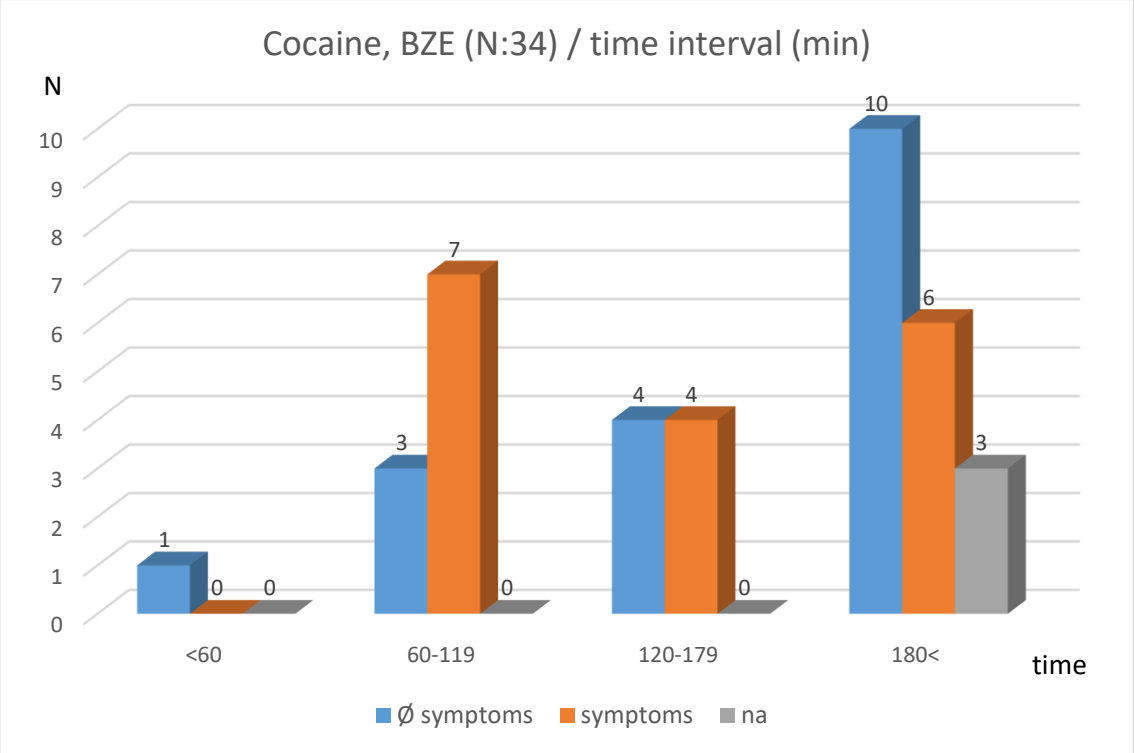



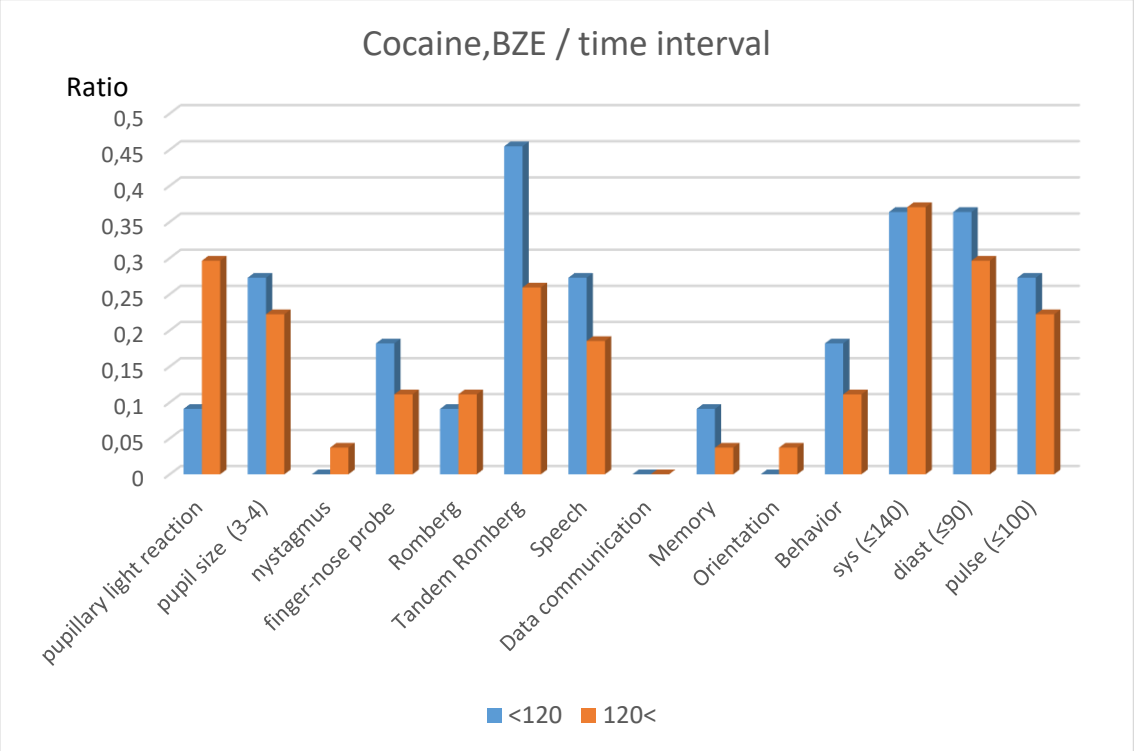

Amphetamine (N:157) /time interval (min)
N
35
30
25
20
15
10
5
0
4
8
1
16
23
4
11
22
6
24
31
6
<60
60-119
120-179
180<
time
Ø symptoms
symptoms
na

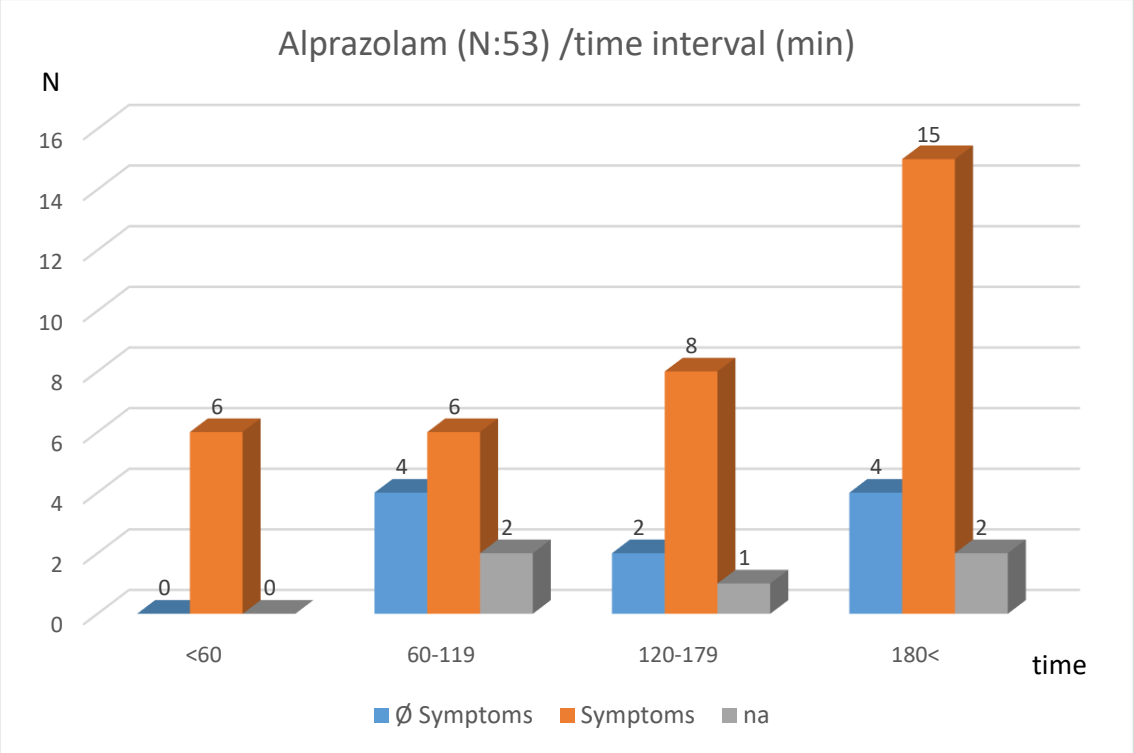

Amphetamine / time inteval
Ratio
0,45
0,4
0,35
0,3
0,25
0,2
0,15
0,1
0,05
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
<60
60-119
120-179
180<

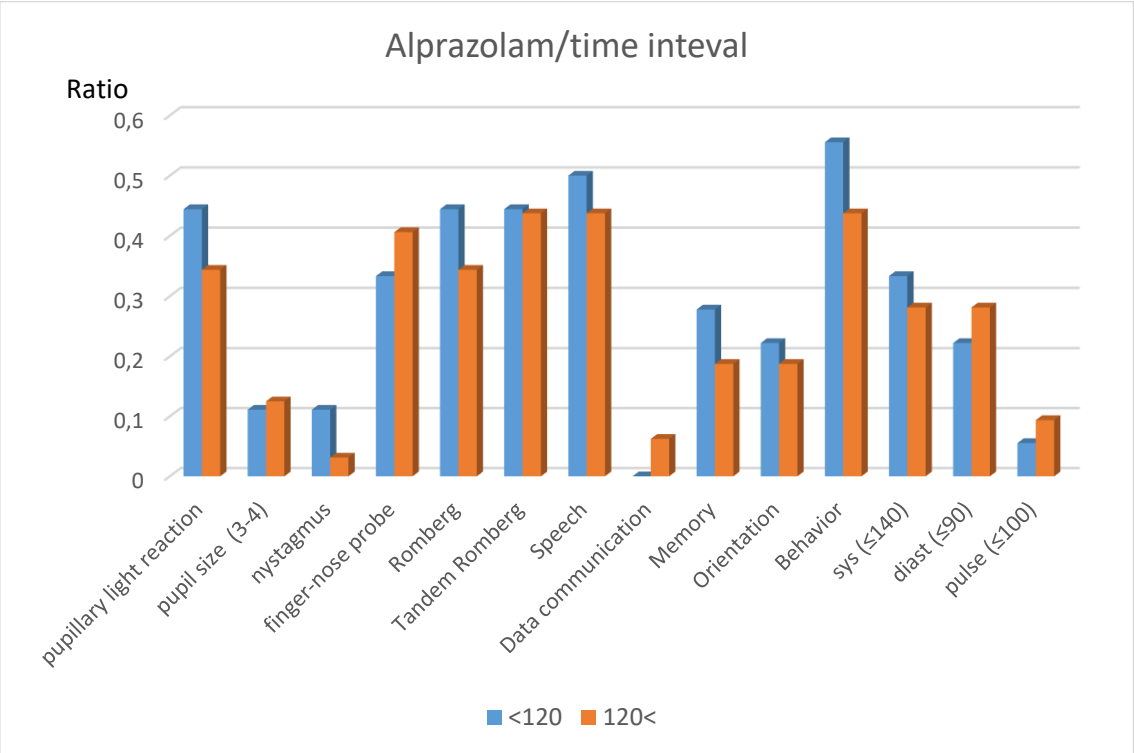

Methamphetamine (N:68) /time interval (min)
N
18
16
14
12
10
8
6
4
2
0
2
3
0
7
17
1
3
15
1
12
14
0
<60
60-119
120-179
180<
time
Ø symptoms
symptoms
na

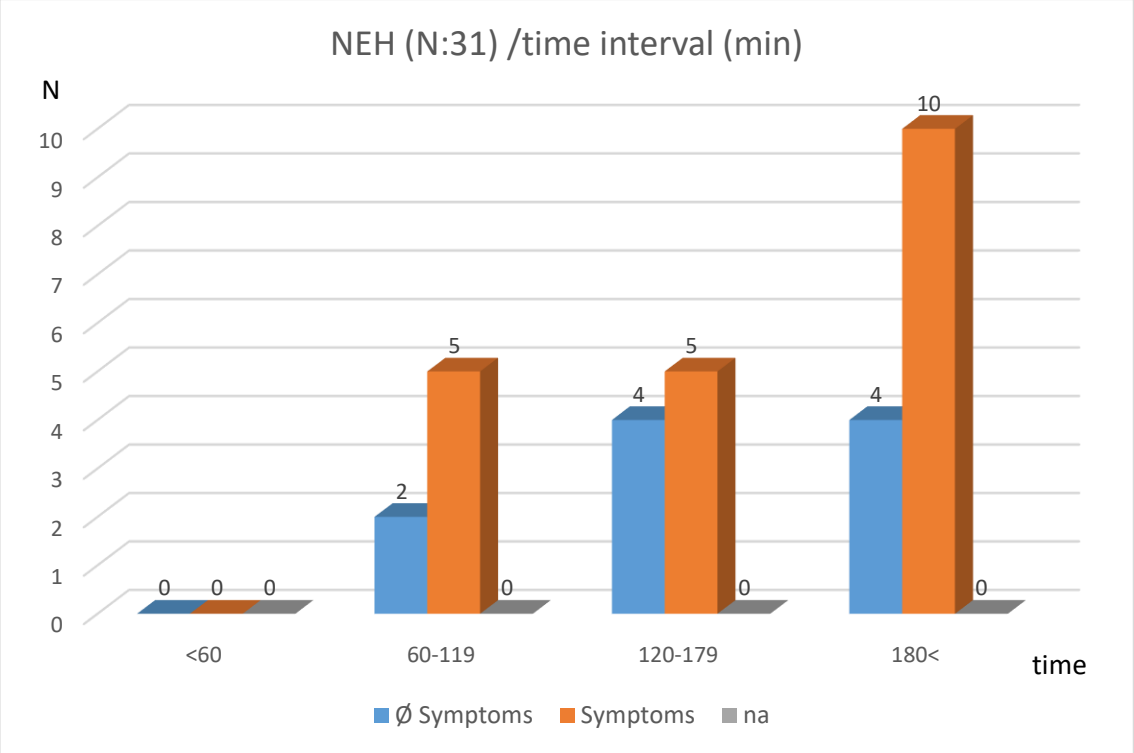

Methamphetamine/time inteval
Ratio
0,6
0,5
0,4
0,3
0,2
0,1
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
<60
60-119
120-179
180<

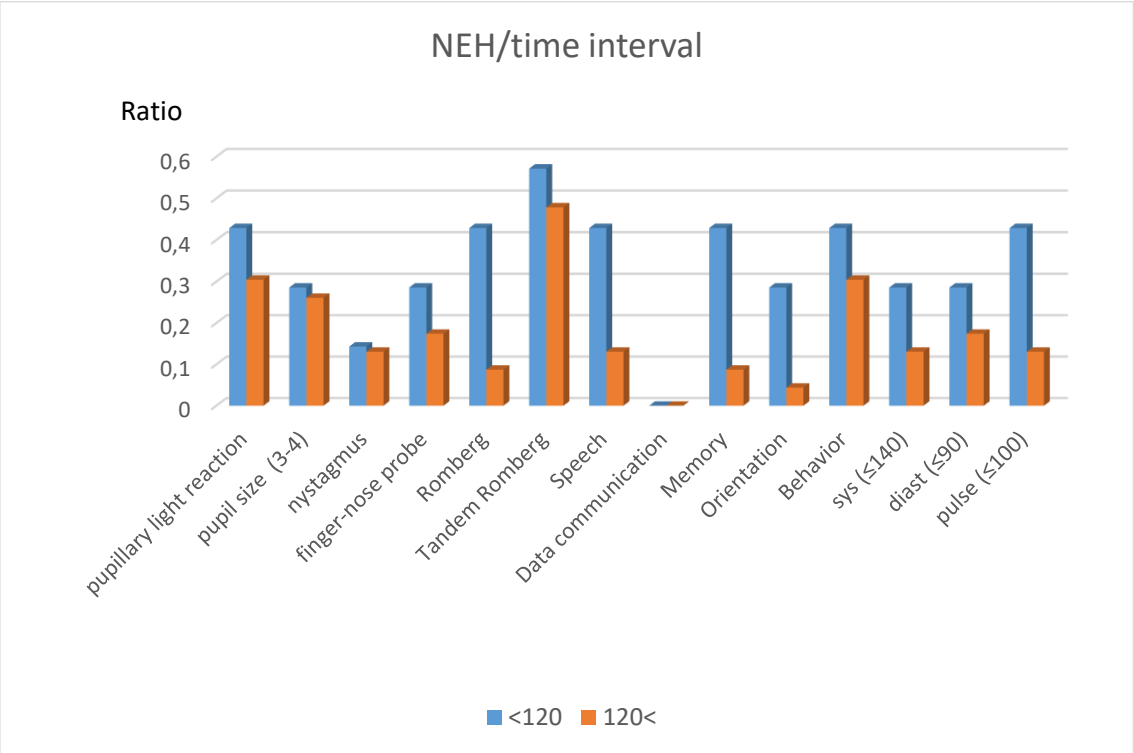

Cocaine, BZE (N:34) / time interval (min)
N
10
9
8
7
6
5
4
3
2
1
0
1
0
0
3
7
0
4
4
0
10
6
3
<60
60-119
120-179
180<
time
Ø symptoms
symptoms
na

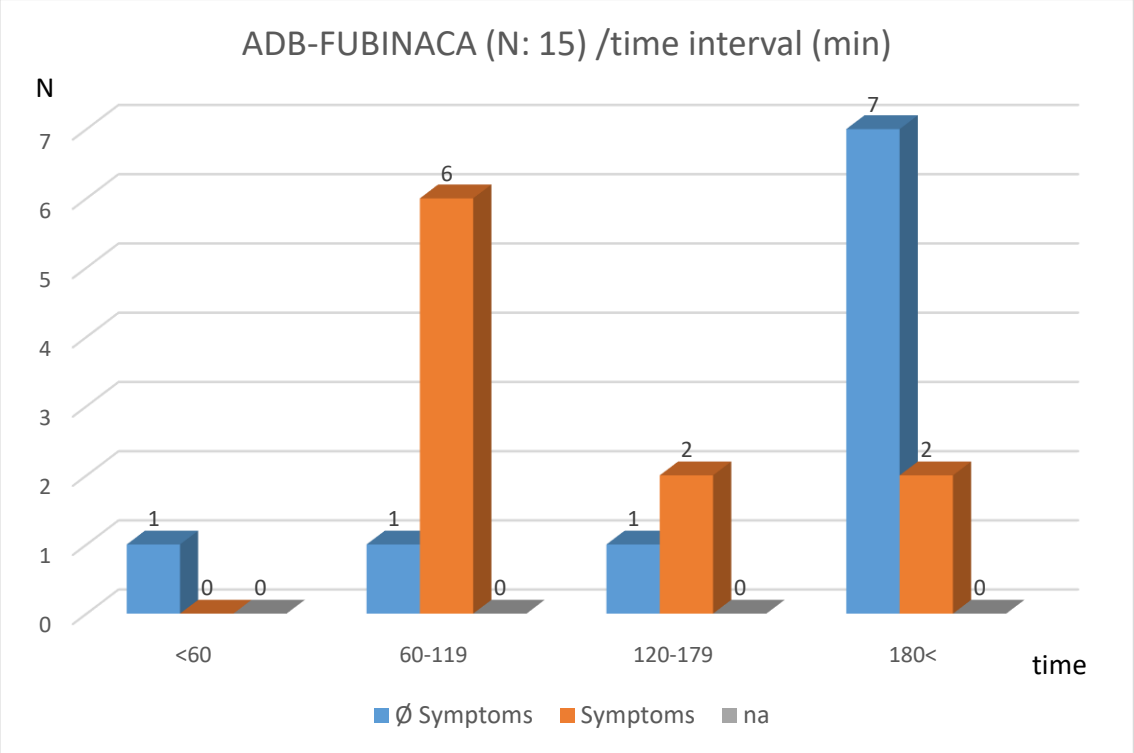

Cocaine,BZE / time interval
Ratio
0,5
0,45
0,4
0,35
0,3
0,25
0,2
0,15
0,1
0,05
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
<120
120<

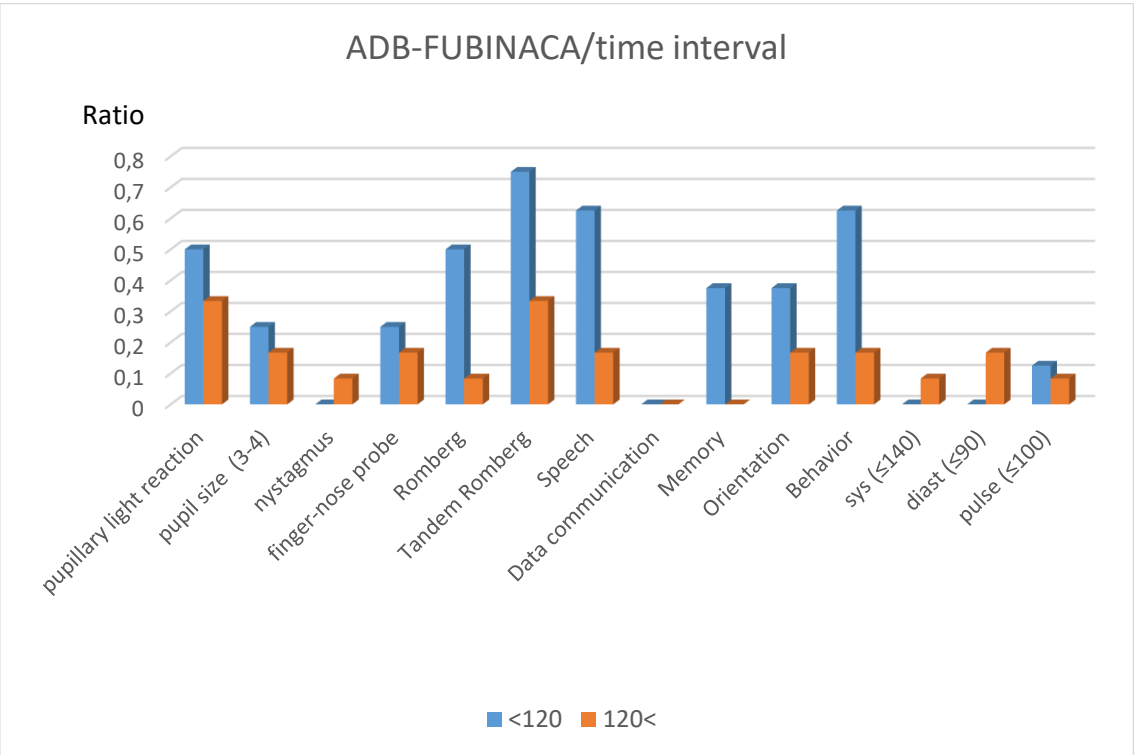

Alprazolam (N:53) /time interval (min)
N
16
14
12
10
8
6
4
2
0
0
6
0
4
6
2
2
8
1
4
15
2
<60
60-119
120-179
180<
time
Ø Symptoms
Symptoms
na

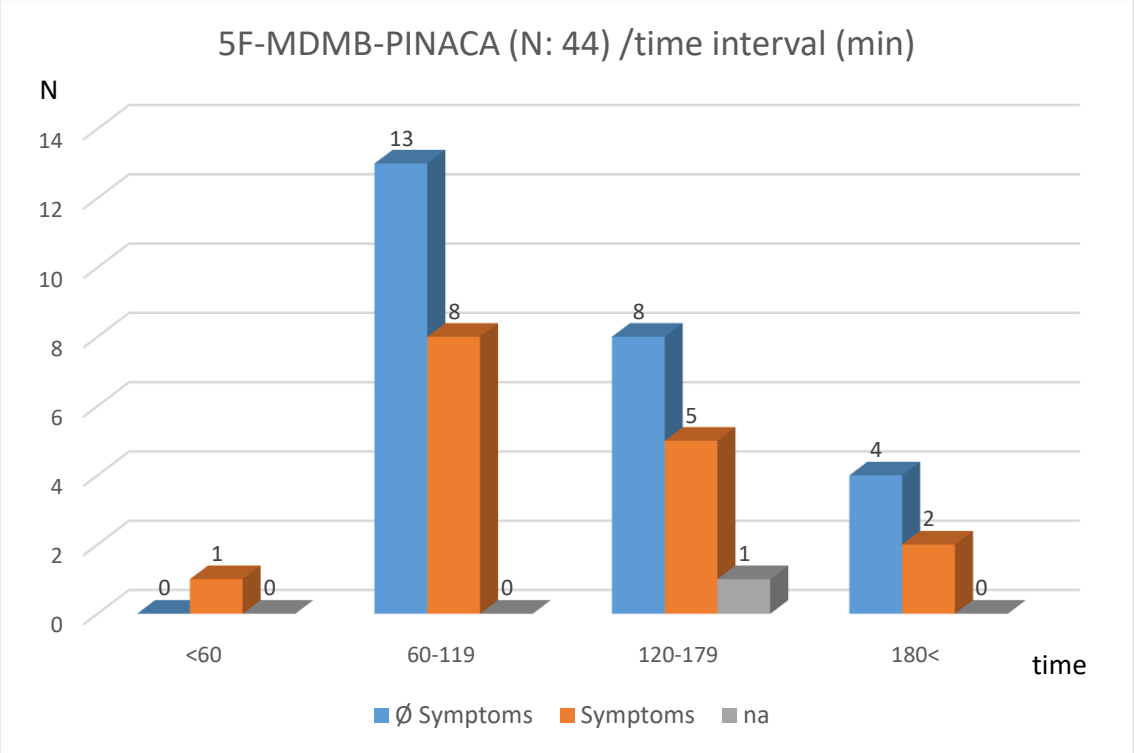

Alprazolam/time inteval
Ratio
0,6
0,5
0,4
0,3
0,2
0,1
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
<120
120<

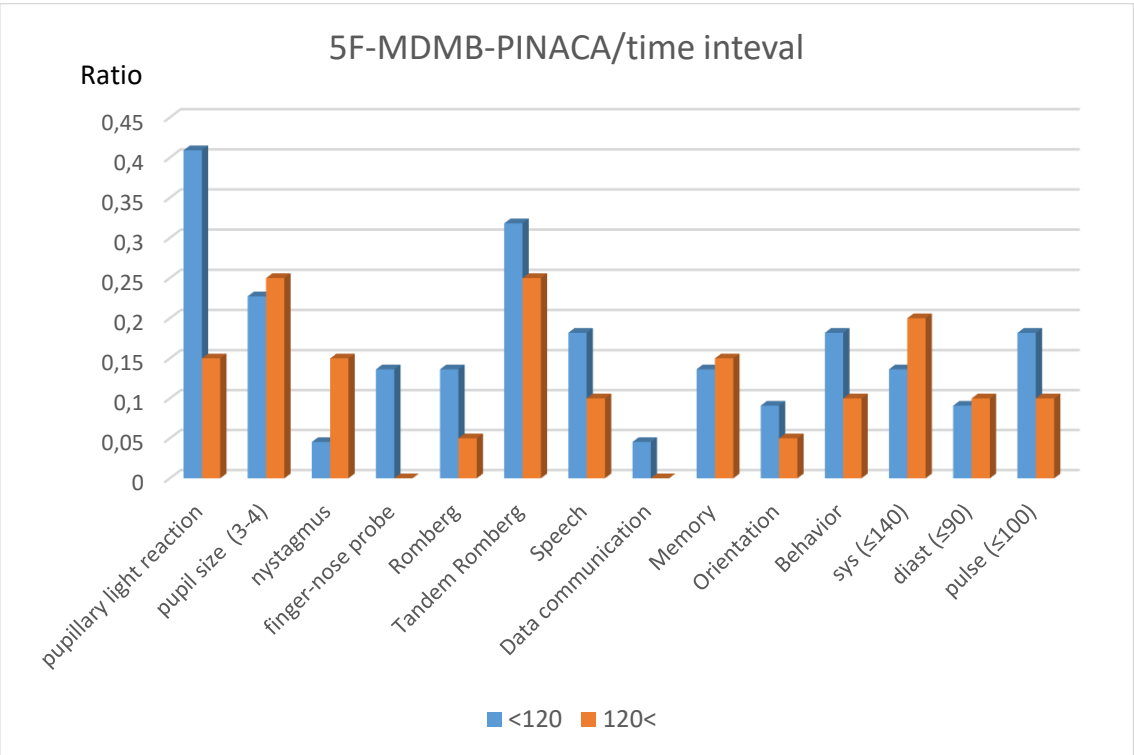

NEH (N:31) /time interval (min)
N
10
9
8
7
6
5
4
3
2
1
0
0 0 0
2 5 0
4 5 0
4 10 0
<60
60-119
120-179
180<
time
Ø Symptoms
Symptoms
na


NEH/time interval
Ratio
0,6
0,5
0,4
0,3
0,2
0,1
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
<120
120<


ADB-FUBINACA (N: 15) /time interval (min)
N
7
6
5
4
3
2
1
0
1
0
0
1
6
0
1
2
0
7
2
0
<60
60-119
120-179
180<
time
Ø Symptoms
Symptoms
na


ADB-FUBINACA/time interval
Ratio
0,8
0,7
0,6
0,5
0,4
0,3
0,2
0,1
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
<120
120<


5F-MDMB-PINACA (N: 44) /time interval (min)
N
14
12
10
8
6
4
2
0
13
8
8
5
4
2
1
0
1
0
0
1
0
<60
60-119
120-179
180<
time
Ø Symptoms
Symptoms
na


5F-MDMB-PINACA/time inteval
Ratio
0,45
0,4
0,35
0,3
0,25
0,2
0,15
0,1
0,05
0
pupillary light reaction
pupil size (3-4)
nystagmus
finger-nose probe
Romberg
Tandem Romberg
Speech
Data communication
Memory
Orientation
Behavior
sys (≤140)
diast (≤90)
pulse (≤100)
<120
120<