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

Doctoral (Ph.D.) thesis

SUMMARY

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Content

1 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. These compounds are called designer drugs and new psychoactive substances (NPS). These designer drugs are structural or functional analogues of controlled substances and has been designed to mimic the effects of the original drugs. Typically, the new substances were synthetized to avoid the scope of legal regulation and to reduce their detectability during rapid toxicological tests. The modifications change the drug's pharmacokinetics, biological effects, and side 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.***

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 policymakers to target prevention and define law enforcement activities.

2 Introduction

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)***. Reliable information can be derived from seizure data and toxicological data measured from biological samples.

At the end of 2020, EMCDDA monitored approximately 830 new psychoactive substances, of which 46 appeared in Europe in 2020. Synthetic cannabinoids and cathinones take about 60% of all seizures, another 10% of seizures are arylcyclohexylamines (mostly ketamine) analogues. The NPSs appeared in the early 2000 years but their popularity raised from 2009 and reached their peak in 2014-2015 and declining trend is more definite in the Western European countries where the classic illegal drugs and the synthetic opiates started to raise. In Hungary the declination of the NPSs is also seen but they are still popular.

Between 2015 and 2018 the annual prevalence of NPS use ***among adults*** (15–64 years) ranged from 0.1% to 1.4%, with an average of 0.6%. According to the 2019 general population survey

in Hungary 7.9% of adults (between 18-64 years) and 14% of young adults (between 18-34 years) used some kinds of illicit drugs in their lifetime.

Legal background and judgment

The international regulation of narcotic drugs and psychotropic substances ***is based on three UN conventions, which are incorporated into the legislation also in Hungary.*** Several amendments to the substance lists of them are covering the new substances on the market. 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 ***abuse of new psychoactive substances is regulated by Act C of 2012 of the Criminal Code***. The ***export, import, production, transport, and possession*** of such materials can be punished by imprisonment as well as the trade of NPSs. Unlike classical drugs, the ***consumption*** of new psychoactive substances is not considered a crime. Hungarian legislation sets two different kinds of crimes: one is the drug consumption itself, the other is the driving under the influence of drug.

In Hungary, driving under the influence of drugs is punishable by law with the same severity as driving under the influence of alcohol. One of the biggest problems is the scientific proof of the driver's impairment by drugs during driving.

Backgroud for the new psychoactive substances

In this thesis, we focus on synthetic cannabinoids and cathinones (NPSs). The various types of NPS have a rapid turnover on the market; those with unpleasant 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 2006 new products, synthetic cannabis substances appeared in Europe and were sold as "legal" cannabis. In Hungary the highest number and quantity of SC seizures was in 2014. Since then, a gradual decrease has been observed followed by stagnation.

Little information is available about the recommended single, daily, occasional or regular doses of SCs. The consumer can get information from the dealer or from blogs. It can be dangerous when a new active substance with higher efficiency is introduced into the market because its toxic dose is lower than the previously distributed compounds.

Like THC synthetic cannabinoids bind to ***CB1 and CB2 receptors***. However, in many cases, the appearance of clinical symptoms and side effects are more severe than expected. The effect

of synthetic cannabinoids appears 1-5 minutes after consumption and lasts for 1-2 hours, but in some cases for 10-15 hours.

The psychological and behavioral effects are similar to THC, but the effect lasts for a shorter period of time, and is stronger. SCs ***cause addiction very quickly*** (even after a few uses), what was not experienced before. A ***withdrawal syndrome*** has been described among daily users.

The psychoactive symptoms and physical signs of ***acute SC-intoxication*** are described, but most published data on acute intoxication do not include toxicological results and are based on SC consumers' self-report.

Synthetic cathinones appeared as legal substitutes of illegal stimulants such as amphetamine, cocaine, and MDMA. In Hungary they were introduced into the black market in 2010. The first substance was mephedrone, since 2017, the most frequently seized substance was the N-ethylhexedrone.

Cathinons are often mixed with other synthetic cathinones or caffeine, lidocaine, and benzocaine. Synthetic cathinones have similar chemical structure to cathinone and methcathinone. It’s active substances (cathinone) is not stabile, it decomposes within two days. The desired effects of cathinons are euphoria, increased concentration and performance. The main side effects are agitation, panic attacks, paranoia. Cardiovascular effects and sudden cardiac arrest can also occur. Rhabdomyolysis, delirium, and multi-organ failure (MOF) occur in the most severe cases. Typical doses are between 5 and 30 mg, although users sometimes report taking doses of 50 mg or more.

NPS issues and challenges in forensic practice

Urine is the most common matrix for testing drugs. 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. The ***analitical determination of metabolites*** may extend the detection window, it provides a reliable confirmation of consumption, when the parent compound is under the limit of detection.

Drug use affects fitness to drive, but it is difficult to determine to what extent. The Hungarian Criminal Code does ***not define the impairment***, the difference between legal and illegal drugs, among them the NPSs. Furthermore, it ***does not set any "legal impairment limit"*** for drug use. As lethal dose or blood concentration for NPS is not determined, a direct or indirect causative association between drug use and mortality should be taken into consideration after the autopsy findings and toxicological analysis.

3 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)

NPS are popular mainly among high school students, young adults, segregated people, and prisoners because of their easy availability, and low prise. Besides, they cannot be detected with the commonly used urine drug test. Unlike THC, SCs are full agonists of CB1 and CB2 receptors and can produce strong effect at low concentrations. In hospital care, there is no possibility to perform quantitative toxicological tests, patients are usually treated symptomatically.

3.1 Aims of the study

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***
- to determine the ***half-life*** of NPS following toxicological analysis of time-series blood samples taken at hospital admission.

3.2 Materials and methods

Patient selection at the DECT (1 April 2018 and 30 March 2019) 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.

116 patients suspected of NPS intoxication were selected by the above detailed criteria. EMS recorded the history of drug use as well as clinical symptoms. Intoxication was diagnosed by the EMS physician and by experienced emergency toxicology specialists. More detailed symptoms were registered upon admittance by the staff of DECT, and included Poison Severity Score (PSS). Medical history and prescribed medications were reported by the patients. Clinical laboratory tests were performed. Analysis of blood samples and data processing were performed at the Department of Forensic Medicine (DFM) at the University of Szeged. Both clinical data and blood samples were blindly assessed.

Analysis was directed to alcohol, 20 classical illicit drugs and medicines, 50 stimulant NPS, and 28 SCs. Illicit, licit drugs and stimulant NPS were analysed by GC-MS following liquid/liquid extraction and derivatization by MSTFA or HFBA. Blood samples were analysed for SCs by LC-MS/MS. Alcohol concentration was determined by head space method (GC-FID). 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 λZ is the first order terminal elimination rate constant. 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%.

3.3 Results

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

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. 30% (35 patients) of the total population used more than one drug.

The status and symptoms were evaluated separately at the scene, during transportation and at admission to the hospital. In majority of SC positive cases the witnesses described the condition as unconscious, "asleep". 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), epileptic seizure (n=2). Depressive state of consciousness was predominant. In psychotic cases, the history referred to pre-existing psychiatric disorders.

The transport time was less than 1 hour. During transportation the condition of almost one third of the patients improved, and only those with positive psychiatric symptoms required medication, the others received supportive therapy. Two thirds of them were already treated several times in the hospital with intoxication.

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, slurred speech, and confusion. Among somatic symptoms slow pupillary light reflex was found in almost all patients, hyperaemic conjunctiva in 27% and tachycardia in 24% of the cases.

We compared the PSS score for the two main SCs, 5F-MDMB-PINACA and 5F-MDMB-PICA 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. No patient in the study had a PSS = 3.

The initial 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, the blood levels of 5F-MDMB-PINACA and 5F-MDMB-PICA revealed an overall significant difference between the toxic concentrations of the 2 SCs. In addition, blood concentrations were significantly lower for patients with PSS = 1 for 5F-MDMB-PINACA than for 5F-MDMB-PICA, but not different in patients with PSS = 2 . ***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. According to our calculation the median half-life of 5 F-MDMB-PINACA was 2.50 hours, and of 5F-MDMB-PICA it was 2.68 hours. 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.
More than half of the patients left the hospital arbitrarily after feeling better. Most symptoms resolved within 12-13 hours an average (ranged from 1 to 27 hours).

Stimulant users: A male regular drug user consumed ***4-chloromethcathinon (4-CMC), with clinical symptoms.*** 3 patients were tested positive for ***NEH***. One patient combined NEH with 5F-MDMB-PINACA and produced sympathomimetic symptoms. The second patient produced serotoninergic and sympathomimetic symptoms. The third patient 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.

3.4 Discussion

Even though it would be important to make a correct diagnosis of SCs and cathinones, in most cases this is not possible in the clinical practice. Among patients who were suspected by NPS intoxication there were NPSs detected in 44% what indicates that NPS intoxication cannot be distinguish from other drug intoxications based on clinical symptoms.
The ***lower designer drug rate than expected*** could be due to several reasons. The ***patients self-reported*** (or may have misreported) what they have. In absence of specific symptoms or analytical results NPS cases are overrated. NPS intoxication produces non-specific symptoms which may overlap with the symptoms of certain ***psychiatric disorders***.
Beside NPS, the patients enrolled in the study also consumed alcohol, THC, benzodiazepines, 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. SCs in the current study did not lead to fatal or life-threatening outcomes, their PSS score never exceeded 2.
In this study, only two cathinones were detected. The intoxicated patients showed predominantly sympathomimetic and serotonergic symptoms, whereas noradrenaline-mediated effects were moderate or weak. The average onset of toxic symptoms typically resolves within half a day.
In our study, ***SCs were much more frequently detected than cathinones***. While SCs are stable for 1-2 weeks in stored blood samples, the concentration of some cathinone may have decreased

below the detection limit during storage leading to false negative results. 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. We did not find connection between blood concentration and severity of symptoms. Aside from consumer tolerance, the effects of active hydroxyl-metabolites should also be taken into consideration. The extreme half-life of the combination of the two SCs suggests competition for metabolism. 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.

3.5 Limitations

The study lacked information about the timing, dose, and form of administration of the drug. The EMS staff did not use the same standardized medical questionnaire at the scene, as at DECT

3.6 Conclusions

In the Budapest region, nearly half of the suspected illicit drug/NPS intoxicated patients used SCs, especially 5 FMDMB-PINACA and 5 F-MDMB-PICA. The symptoms caused by the different substances or substances groups like SCs and cathinones were not specific for the substance, differentiation was impossible even for the experienced clinicians. 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).

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

The aim of this work was to present the major issues of forensic evaluation of driving under the influence of drugs. In Hungary, there is no compulsory guideline to judge drugged driving, the currently used forensic practice and legal background need reconsideration.

EU countries use three main approaches for the determination of impairment.

1. Legal limits, also known as ‘per se’ limits based on a fixed substance blood concentration, the driver is considered impaired when that reached or exceeded.
2. Zero tolerance law set legal limits to the laboratory limit of detection. Any driver with a detectable amount of an active substance in the saliva or blood is considered impaired.

3. 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. It is not easy to prove scientifically that a person was under the influence at the time of driving.

In some countries per se limits are combined with the impairment approach called two-tier system. For substances without legal limit the impairment approach is used.

Nearly all countries require a ***confirmatory analysis*** performed in a toxicological laboratory and a forensic expert analyses the impairment.

4.1 Legal background and the practice in Hungary

Drug related impairment of the driver is punished with the same severity as drunk driving. The greatest difficulty is to decide whether the driver was impaired by drugs when driving.

If there is a suspicion of driving under the influence a breath alcohol test is performed on the spot. Then the driver is taken to a medical office for examination and taking blood and/or urine sample. The driver is asked about the drug consumption and medical history. The medical tests can be divided into five main groups: eye examination, divided attention psychophysical test, cognitive tests, cardio-vascular signs, psychomotor, and physiological tests. Psychoactive drugs are difficult to define by impairment alone since different substances may have colorful symptoms. There is no universal agreement on how best to measure the levels of impairment of the driver.

The forensic expert deems the driver impaired if:

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. 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.

4.2 The aims of the study

- To investigate whether there is any difference in the age, gender, drug consumption between suspected DUID drivers and those ones, who were responsible for accidents.

- To find any symptoms which indicate the impairment caused by the different drugs; and find new methods to increase the predictability of the drug impairment?
- To investigate the connection between the symptoms of impairment and the legal limits.
- To study the connection between the blood concentration of substances, clinical symptoms, and the time interval between arresting/accident and sampling.

4.3 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*** at the Department of Forensic Toxicology of the Hungarian Institute for Forensic Sciences (HIFS). ***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. The sources of data were: the police, analytical results, and medical protocol sheet.

Statistical analysis

Statistical analysis was performed as described setting the probability level to $p<0.05$. The analysis was performed by IBM SPSS 26 software. Statistical method used for the most common classic drugs (Cohen's kappa coefficient (κ)) is a statistic that is used to measure inter-rater reliability (and also intra-rater reliability) for qualitative (categorical) items.

4.4 Results

In 2016–18 altogether 2369 sDUID drivers were sampled of which 2254 (95%) were tested positive for at least one substance excluding those who used only alcohol. No significant difference was found in the gender and age distribution between the sampling and drug-positive cases ($p > 0.05$). 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.

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. 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 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.

Prevalence of the main substance groups in the two population

Among sDUID cases the proportion of drivers who used classical illicit drugs was 79% (n=1777). Within this group cannabis was the most prevalent (70%) followed by AM/MA (42%), MDMA (11%) and cocaine (10%). The ratio of drivers who took medicines was 13%, mostly alprazolam and clonazepam use. The percentage of synthetic cathinon users was 6%, and the N-ethyl-hexedrone was the most prevalent. SCs were detected in 21% of the drug-positive samples. During the three years 5 F-MDMB-PINACA (56%) was the most frequent followed by AMB-FUBINACA (19%), ADB-FUBINACA (19%), 5 F-MDMB-PICA (7%), MDMB- CHMICA (4%), and AB-FUBINACA (3%). AB-FUBINACA carboxylic acid (the common metabolite of x-FUBINACA substances) was detected in 246 samples of which only the metabolite was present in 200 cases.

Responsible drivers

Among responsible drivers the ratio of those who used classical illicit drugs was 54%. The most prevalent substances were cannabis (60%), AM/MA (38%), MDMA (18%) and cocaine (10%). Medicines were detected in 48% of positive cases; alprazolam (55%), clonazepam (24%), and diazepam (8%), the other benzodiazepines and zolpidem were detected in 7-7%. Among synthetic cathinons (4%) the most frequently detected substance was N-ethyl-hexedrone (58%) while among SCs (23%) AB-FUBINACA carboxy-metabolite (49%), 5F-MDMB-PINACA (39%), and ADB-FUBINACA (20%), were the most frequent.

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.

Among sDUID cases the proportion of multi-drug users was 49% significantly lower ($p<0.05$), than among responsible drivers (62 %). We compared the most frequent drug-drug combinations. We created 7 groups: cannabis (without THC-COOH), stimulants, benzodiazepines, SCs, synthetic cathinon, alcohol, and other drugs.

The percentage of cases in combination of two or more substances from two different groups was significantly higher among responsible drivers. Combination of more than two drug groups no longer increases the accident risk significantly.

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. The proportion of benzodiazepines combined with SCs, synthetic cathinon, alcohol and combination of alcohol with stimulants and SCs was higher in the latter group.

Evaluation of driving under the influence of drugs

We found no correlation between the observed clinical symptoms and blood concentrations of the single substances above and below the legal limit. Although 60% of multi-drug users showed positive clinical symptoms, in absence of impairment limits this analysis 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.

Except for the cognitive ones the pattern of the symptoms was similar in the positive and the negative cases. Only 36% of single drug use cases showed clinical symptoms. Amphetamine, methamphetamine, and alprazolam had the most indicative symptoms.

The blood concentration of THC was between 2-10 ng/ml in majority of drivers. In this range the lack of clinical symptoms dominated. 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. A higher ratio of positivity was found over 10 ng/ml concentration of ADB-FUBINACA. Evaluable increase in the ratio of positive symptoms and the blood concentration of 5F-MDMB – PINACA was not found.

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.

4.5 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 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. 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. The frequency of NPS was practically the same in both groups, and their prevalence was much lower than of classical illicit drugs or medicines.

Multi-drug use is significantly higher among responsible drivers. The “within one group” and “between two groups” combinations differed significantly in the two populations. 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. 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.

For both fatalities and serious injuries alcohol is the riskiest substance, and alcohol drug combinations are riskier then drugs 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.

Clinical symptoms are generally present in naive users at per-se legal blood concentrations. The 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. In addition, withdrawal symptoms may also occur below a given drug concentration what makes the evaluation more uncertain. The current system of medical investigations has limited ability to determine impairment. Although the number of NEH and ADB-FUBINACA cases were 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. The stressful situation of police control may also lead to misunerstandable clinical symptoms. 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.

In case of narcotic drugs, no correlation was found between blood concentration and symptom severity. The lack of correlation can be explained primarily by the higher tolerance of 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. 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.

Several studies refer low doses of AM's improving psychomotor skills, such as driving ability, high-doses may decrease traffic related performance. Chronic abuse often involves high doses. We found relationship only in methamphetamine positive cases in the concentration range of up to 200 ng/ml. In the first 1-2 hours of intake, cocaine induces impaired ability to react properly, clinical symptoms indicate influence in all cases above 300 ng/ml blood concentration. The blood concentration of alprazolam in most drivers with symptoms was above the therapeutic range. We were unable to identify a concentration of NPSs above which the frequency of positive clinical symptoms increases significantly. The determination of NPS impairment/legal limit is not possible by the present medical investigation panel.

4.6 Limitation of the study

We had no information about the time and dose of intake and drug history which can influence the clinical signs of impairment. Chromatographic standards were available only weeks or even months after the appearance of a new NPS which likely resulted in missed positive cases.

4.7 Conclusion

We found that benzodiazepines alone and their combination were more frequent among responsible drivers which may pose an increased accident risk. Similarly, combinations of alcohol or benzodiazepines with other substances also may increase the risk. This benzodiazepine related risk, both alone and in combination, seems to be higher than we thought, especially when they are used not by the medical prescription. The NPS use in the two populations was the same what relates to low accident risk.

We discovered that for drugs with impairment limits, the ratio of positive to negative cases was nearly equal over and under the limits (except alprazolam). The average time between police act/ accident and medical examination is about 3 hours, during which the symptoms may simply

disappear. The limited power of medical investigations, the symptom based NPSs evaluation may result in impairment misjudgment.

4.8 Recommendations

- *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. A two-tier system is recommended for legal regulations.
- *Improve roadside screening*: Introduction of Field Sobriety Test (FST) in Hungary and training police officers to perform it correctly.
- *Monitoring the presence of drugs at the scene* (OF, saliva rapid test): The OF roadside tests focuses the classical recreational drugs (for example Dräger DrugTest 5000), can detect up to eight substances/substance classes: amphetamines, benzodiazepines, THC, cocaine, methamphetamine, opiates, methadone, ketamine. This test is only suitable for qualitative testing. There is no roadside test in use for NPSs and medications. In our database the number of NPS (12.3%) would show a negative result from the in situ saliva sample.
- *Reducing the time between police checking and sampling*: Because of the delay between arrest and medical investigation, substances with a short half-life may be completely eliminated (NPS). To avoid the data-loss metabolites should be monitored, too.
- *Further development of the medical examination protocols* would be necessary. The present checklist was designed for alcohol influence examination, for drugs it is needed a different examination. The clinician must perform a complex evaluation of the non-specific symptoms.
- Forensic experts would need to develop a standardized method for assessing drug impairment.
- *Public campaigns* must continue to spread information about driving under the influence. In general, young people aged 15 to 34 are the most likely to use psychoactive drugs, especially this age group should be better informed about the dangers of drugged driving. Physicians and pharmacists should provide more detailed information about the effects of legal drugs prescribed/delivered, particularly their effects on driving fitness.

5 Comparison of the NPS blood concentrations of the not impaired, impaired, intoxicated person and fatal cases

The majority of the NPS have a small number of published cases, which may or may not be typical DUID, intoxicated, or lethal cases. It was not possible to present concentrations in all ranges for some compounds. DUID concentrations overlap with those in intoxicated and lethal cases. Based on existing clinical experience and laboratory findings, these data do not provide information on the impairment, toxic or lethal concentrations. We could not find correlation between the blood concentration and clinical symptoms neither sampling of the drivers, nor when experienced emergency ward physicians diagnosed the intoxicated patients.

6 Final conclusion

The relationship between blood concentration and clinical symptoms was compared in three groups: drug-intoxicated patients, suspected DUID drivers, and drivers responsible for 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. The majority of the symptoms reported in the hospital were not specific to the substances.

When the frequency of positive clinical signs was evaluated according to concentration ranges, it was significantly higher for alprazolam, N-ethyl-hexedrone, and for ADB-FUBINACA. These findings indicate that the currently used medical examination is ineffective for determining driving impairment and requires strict revision.

Police officers generally stop drivers for abnormal or reckless driving, their suspicion is right in 85% of the cases so the field sobriety test would be useful for further clinical evaluation.

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

7 Overall 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.

9 Scientific research related to the thesis

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