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Characteristics of the use of novel psychoactive substances (NPSs) in Hungary

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1. RELEVANCE OF THE TOPIC

In the past decade, illicit drug market has markedly changed. With the growing popularity of web-based marketing and a decrease in the availability and purity of heroin, cocaine and ecstasy -accompanied by an increase in the price of these substances-, an era of novel psychoactive substances (NPSs) arrived. A reduction in heroin's, cocaine's and ecstasy's availability was significant not only in Europe but in Australia (Mattick et al., 2004) as well. This change had an enhanced impact on the substance use patterns of participants in the contemporary injecting drug scene, such as the clients of needle exchange programs or the patients of various opioid-substitution therapies.

Experts of addiction care and research rapidly realized the relevance of NPSs and in recent years, an increasing number of addiction conferences thematically dealt with the topic of these substances (e.g. Kapitány-Fövény, 2014). Although, it is now illegal to use the majority of these substances in Hungary and other parts of the world, users did not stop searching for further and further psychoactive substances. As it is delineated by recent findings (e.g. Ledberg, 2015), temporarily legal status of NPSs is a highly appealing characteristic for their users, as interest in these substances often significantly decrease around or after the time of classification. In many cases, users purchase NPSs via online drug shops. Besides being a risk factor for easy availability, web-based marketing and internet interest on NPSs can also be used as a potential epidemiological indicator as well as a useful tool for testing theoretical assumptions about NPSs.

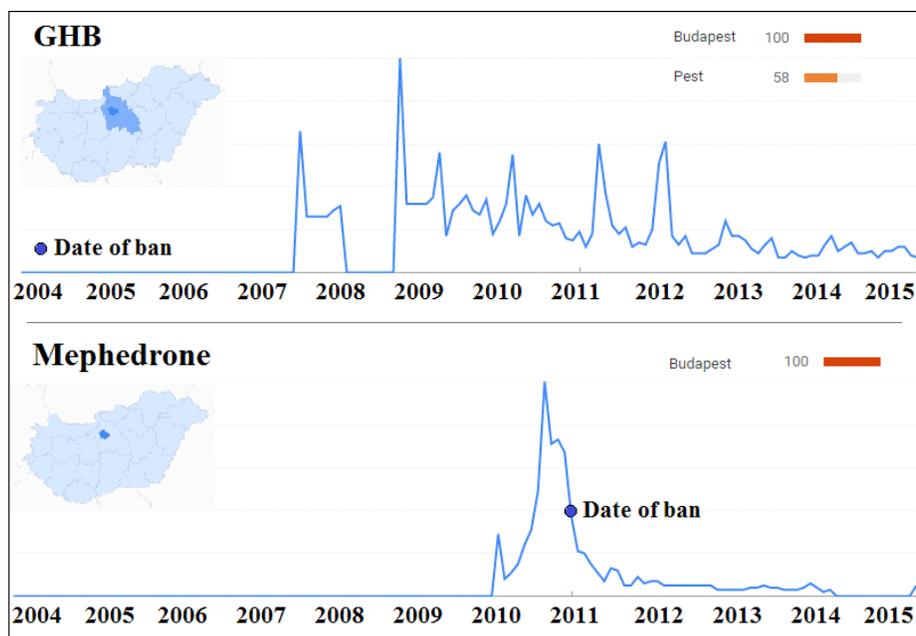
One of the many dangers of NPS use lies in the fact that users often do not know what they are consuming. Therefore, literature refers to NPS users as *human guinea pigs*, who experiment on themselves. This risky habit of NPS use, which frequently results in severe intoxications and sometimes fatal overdoses, may underline the need for studies that examine the subjective and somatic effects of these substances. Clinical evidence and epidemiological data (e.g. Nemzeti Drog Fókuszpont, 2012) both suggest that in the past decade synthetic cathinones and gamma-hydroxybutyrate (GHB) were the most popular NPSs in Hungary. For such reason, I decided to study these substances in my thesis.

2. INTRODUCTION

Between 2010 and 2012 the number of identified online shops, selling NPSs as products not intended for human consumption – such as bath salts, plant fertilizers or research chemicals – increased from 170 to 693 (EMCDDA, 2012). At present, illegitimate users still have the opportunity to order NPSs via online drug shops, even with an option of home delivery. Relative anonymity and perceived personal safety are further factors that make online purchasing an engaging option (Dick and Tarrant, 2010). With widespread availability of the internet, both drug users and traffickers started to obtain information about NPSs via online platforms, such as chat-rooms or various fora (Smith and Garlich, 2013). Internet became the primary source of illicit drug information, especially among adolescents and young adults (European Commission, 2008). Effective dissemination of NPS information is further supported by networking sites for *psychonauts* (i.e. persons who experiment with mind-altering psychoactive substances), such as Erowid, Dancesafe, Bluelight, Lycaenum (Smith and Garlich, 2013) or DAATH in Hungary (Móro and Rác, 2013). This new pattern of collecting NPS-related information as well as the phenomenon of ordering drugs via online drug shops brought a novel epidemiological method

into being: web search queries – provided by Google Trends - were found to be useful tools in predicting the prevalence of drug use and related harms (Figure 1). The rate of web search queries may reflect various interests of a social network.

Figure 1. Web search queries with search terms 'GHB' and 'mephedrone': Hungary (2004-2015)



Currently there are more than 450 NPSs being monitored by the EMCDDA with more than 100 NPSs reported for the first time in 2014, indicating that the market is still intensely transforming. Between 2008 and 2013 a seven-fold increase in the number of NPS seizures was reported across Europe (EMCDDA, 2015). The majority of seized substances were either cathinones, such as mephedrone (*4-methylmethcathinone*), pentedrone (*2-(methylamino)-1-phenylpentan-1-one*), methylone (*3,4-methylenedioxy-N-methylcathinone*), 4-MEC (*4-methylethcathinone*) and MDPV (*3,4-methylenedioxypropylvalerone*), or more recently synthetic cannabinoids, such as JWH-type products.

Mephedrone

Mephedrone's popularity as a commonly abused substance, started to spread in the recreational drug scene after 2007 (Psychonaut Web Mapping Research Group, 2009). Following the classification of MDMA as an illicit substance, a great number of synthetic and nonsynthetic substances have appeared on the recreational drug market as potential substitutes for MDMA but none of them reached or even approached the popularity of ecstasy (MDMA). Mephedrone, however, is the first substance in the past two decades that quickly gained a constant position on the illegal drug market. Mephedrone, as a stimulant substance, is often compared with other stimulants, such as ecstasy, amphetamine or cocaine (e.g. Schifano et al., 2010).

Besides its easy availability and capability to substitute MDMA and other entactogen stimulants, another possible reason for its popularity is that—according to users' reports—it can give a better quality high, than other stimulants (e.g. Winstock and Mitcheson, 2010). Followed by its ban in all the EU member states (e.g. in Hungary it was banned in January 2011) mephedrone was replaced with other cathinones.

In the new era of NPSs, opioid-dependent patients also started to substitute missing heroin and other opioids primarily and for a longer period with cathinones. High frequencies of injecting cathinone use were found among clients of needle exchange programs (e.g. Csák et al., 2013; Péterfi et al., 2014) and other low threshold harm reduction services (Van Hout and Bingham, 2012). The trend of cathinone injecting, however is rapidly forming. Following its decreasing popularity, mephedrone was first substituted with MDPV and then with pentedrone (Péterfi et al., 2014), while treatment seeking opioid-dependent users started to abuse new and basically unknown cathinones instead of heroin or methadone as a form of relapse. Furthermore, the intravenous use of mephedrone – compared, for instance to injecting heroin use – is typically associated with a much higher frequency of daily injecting (DrugScope, 2012), which might lead to the rapid damage of syringes and therefore to muscle and vein injuries as well as a greater risk of infections. As powder mephedrone is highly soluble in water, it can easily be dissolved and then injected intravenously or intramuscularly. Adverse consequences of cathinone injecting include skin erosion, localized infections, blood clots, burning sensation at the injection site and increases in HCV and HIV infection rates (Botescu et al., 2012).

GHB

A naturally occurring compound of mammalian central nervous system and peripheral tissue (Bessman and Fishbein, 1963), was first synthesized by Henri Laborit in 1960 (Laborit et al., 1960). Abuse liability of this chemical and the presence of a possible GHB dependence was empirically demonstrated (e.g. Galloway et al., 1997). Athletes and body-builders started to use GHB (or its precursor, GBL) in the 1980's (e.g. Michael and Hall, 1994) in order to improve their performance, as GHB may even double the secretion of growth hormone (Galloway et al., 1997; Van Cauter et al., 1997). However, widespread use of this substance as a recreational drug began in the 1990's (Kam and Yoong, 1998; Nicholson and Balster, 2001) and according to some more recent studies conducted in dance music settings, and in homosexual subpopulations, GHB is still popular recreational substance (Hillebrand et al., 2008). Despite its remarkable history both as a medication and an illicit substance, GHB is also considered to be an NPS as its popularity among recreational drug users arose in the 2000s, especially in Hungary, where it is frequently referred by its street name, Gina.

Main functionality of GHB use is characterized by its impact on human sexual behavior, either in the form of unintentional GHB intake (i.e. drug facilitated sexual assaults) or intentional and mainly recreational GHB use (i.e. a sexual enhancer). Studies examining GHB's role as a date rape drug, however, resulted in various and often contradictory conclusions (e.g. Scott-Ham and Burton, 2005; Du Mont et al., 2010). As such, professionals suggest to use the neutral term of 'alleged sexual assault' rather than 'date-rape' for several reasons (Németh et al., 2010), and they also emphasize the potential implications of GHB as well as other substances (i.e. alcohol, ecstasy, flunitrazepam, ketamine and marijuana) which may also be linked to such drug facilitated sexual assaults (Anglin et al., 1997; Simmons and Cupp, 1998; Woods and Winger, 1997; Jansen and Theron, 2006). As the first one to describe, Laborit identified four sexual-enhancing effects of GHB: disinhibition, heightened sense of touch (i.e. increase in tactile sensitivity), enhancement of male erectile capacity and more intense orgasm (Laborit, 1972). In the past decades mainly qualitative or observational studies have dealt with or mentioned the sexual correlates of the intentional and mainly recreational use of GHB (Palamar and Halkitis, 2006; Barker et al., 2007; Lee and Levounis, 2008).

3. AIMS AND SEQUENCE OF STUDIES

The studies included in my thesis had two main goals. As a first goal, I aimed to explore the characteristics of the first and current NPS use, including the social context of the use, the most frequently experienced subjective and somatic effects of mephedrone and GHB, and the psychiatric symptoms associated with their consumption. As part of this first goal, I also aimed to identify and test potential functions of the use of selected NPSs. In case of mephedrone, this function manifests itself in mephedrone's potential to be an effective substitute for not only MDMA and other psychostimulants but for opioids and other intravenously administered substances as well. Considering GHB, its main function lies in its impact on human sexuality.

My second goal was to test the adaptability of three psychological etiological model in explaining NPS use: a) self-medication hypothesis (SMH) (Khantzian, 1975, 1999), b) the impact of social context and c) the role of traumatic life events. When I hypothesized that users with more frequent or more intense (e.g. injecting) NPS use show elevated psychiatric symptom profiles (see Study 3), I mainly leaned on the basis of Khantzian's SMH. When I assessed traumatic life events among opioid dependent patients (see Study 4), I presumed that those who abuse NPSs show more intense emotional reactions to potential traumatic life events. And when I assessed social context of NPS use (see Study 3 and Study 6), I emphasized the relevance of user's social environment regarding both the onset and persistence of NPS use.

Study 1: The first study is analyzing web interest on mephedrone in order to assess the connection between mephedrone's legislative status and the rate of mephedrone-related web searches. This study also aims to explore the association between GHB-related web searches and GHB-intoxication cases. Therefore Google Trends is tested as a potential tool for predicting trends in NPS use and its adverse consequences.

Study 2: The second study is exploring mephedrone's main subjective and somatic effects in order to identify whether or not mephedrone can be an effective substitute for MDMA and other entactogen stimulants. The second and the third study analyzed the same sample of 145 recreational mephedrone users, recruited by snowball method.

Study 3: As the second study showed (Kapitány-Fövényi et al., 2013a), a relatively high rate of mephedrone users inject this NPS, which indicated a potentially more harmful pattern of mephedrone use. The third study therefore aims to assess the differences between injectors and non-injectors of mephedrone, with special emphasis of the severity of psychiatric symptoms. We also analyze the characteristics of first and current mephedrone use, and as such, we test the adaptability of the etiological model regarding the impact of the social environment on NPS use. Furthermore, alongside with the fourth study, we present mephedrone's substitutional potential as an intravenously administered substance.

Study 4: In the third study, we found a high rate of opioid users among mephedrone injectors (Kapitány-Fövényi et al., in press-a) and therefore discussed whether injecting mephedrone use or rather opioid use is associated with an elevated psychiatric symptom profile. In order to answer this question, we assessed NPS use and psychiatric symptoms among a clinical sample of 198 opioid dependent patients. The fourth study tested self-medication hypothesis by exploring the psychiatric symptoms and reasons of NPS use. As part of this study, we also examined the role of traumatic life events in NPS use as the third selected etiological model.

Study 5: The fifth study is exploring GHB's toxicity and its role in drug facilitated sexual assaults and acquisitory crimes. In this study we analyze a sample of 352 GHB-intoxicated patients (and altogether 408 intoxication cases), by assessing their medical reports. The main goal of this study is to test GHB's functionality as a potential date-rape drug and to compare intentional and unintentional cases of GHB intake.

Study 6: Finally, the sixth study is exploring GHB's sexual effects and behavioral correlates (Kapitány-Fövényi et al., in press-b). In the fifth study, we found that GHB facilitated sexual assaults are not as common as media reports might suggest and also that a significant proportion of the intoxicated patients are intentional users of this substance. Therefore, in this final study, we aimed to assess a sample of 60 recreational GHB users and test the assumption that one of GHB's main functions lies in its sexual enhancing effects. We also tested the role of the social environment in GHB use, as we did in the third study as well.

4. METHODS

4.1. SAMPLES

4.1.1. Recreational mephedrone users

Participants were recruited by snowball method. Twelve university students were involved and asked to find mephedrone users among their acquaintances, and have them fill out our questionnaire, while these subjects were also asked to help us in reaching further mephedrone users. The sample consisted of 145 mephedrone users (70.8% males, mean age= 24.1, SD= 5.6), who had taken mephedrone at least once in their lifetime. A total of 69.4% of the subjects were living in Budapest, the capital of Hungary, whereas 19.4% were resident in other cities and 11.1% in rural areas.

4.1.2. Opioid dependent patients

This sample consisted of 198 opioid dependent patients (70.8% males, mean age: 39.7, SD=6.8). The majority of the participants (72.6%) reported to live among average or better than average socioeconomic circumstances. With regard to their primary medication, 89.9% received methadone, whereas 10.1% were currently taking Suboxone as substitute medication. Patients were recruited at the drug outpatient center of Nyirő Gyula Hospital National Institute of Psychiatry and Addiction, the biggest drug outpatient center in Budapest, Hungary. Three university students from the Institute of Psychology (Eötvös Loránd University of Sciences) were involved in collecting data. Data was collected by face-to-face sessions with the participants between April and August, 2014. Subjects' answers were registered by the participating psychology students.

4.1.3. GHB-intoxicated patients

The sample consisted of 352 patients (54% males, mean age= 26.9, SD=10.2) who altogether induced 408 treatment cases. The youngest patient was 14 years old, the oldest one was 75 years old. In 182 cases (44.6%) a psychoactive substance was of fact detected, whereas in the other 226 cases (55.4%) either no serum or urine sample was analyzed, or the psychoactive compound has already been metabolised by the time of clinical intervention.

4.1.4. Recreational GHB users

The sample consisted of 60 GHB users (66.7% males, mean age=25.6, SD=4.6), recruited by snowball method. Fourteen university students were asked to find participants, who have used GHB at least once in their lifetime. Participants filled out the questionnaire and then often referred the researchers to other GHB users.

4.2. MEASURES

4.2.1. Web search queries (Study 1)

Google Trends presents percentages of total search queries regarding specific search terms during an adjusted time interval. Therefore it can be used to determine how many searches have been done for the given terms we enter, in comparison to the total number of Google searches done during the same time. We used the search term ‘mefedron’ as Hungarian equivalent of mephedrone. We analyzed web search queries within the time interval between January 2004 (as first available Google Trends date) and May 2015 (as current date of the analysis). The first ‘mefedron’ search query rate higher than 0 was dated on February 2010. Within the same time interval we registered the rates of ‘heroin’, ‘ecstasy’ and ‘kokain’ (as Hungarian equivalent of cocaine) related web search queries as well. We also registered all mephedrone-related web search results and arranged these into four groups: 1) mephedrone-related online written articles, including both newspaper articles and scientific materials (N=166), 2) mephedrone-related documentaries (short movies) (N=6), 3) mephedrone-related ads (to buy it online) (N=27) and 4) mephedrone-related forum or blog registries (users sharing their experiences with this substance) (N=23). In case of GHB, we used ‘GHB’ and ‘Gina drog’ as search terms. We analyzed Google Trends data between September 2009 and June 2013, the same period of the assessed GHB-intoxication cases. GHB-intoxication cases were registered in the Clinical Toxicology Ward of Péterfy Sándor Street Hospital Clinic and Casualty Centre.

4.2.2. Substance use characteristics (Study 2, Study 3, Study 6)

Regarding substance use data, a self-complete questionnaire was used that covered the following areas: demographics, substance use experience (past year and past month frequency data, first and current use, form of use, purchase of NPSs, social context of use and reasons of use). We generated a list of potential acute subjective and somatic (physical) effects of these NPSs on the basis of former findings, alongside with additional items based on the effects of similar substances. Subjects had to evaluate each acute effect on a 5-point Likert scale according to how often they experienced it as results of their NPS use (1 = never, 2 = sometimes, 3 = half of the cases, 4 = most of the time, 5 = nearly always/always).

4.2.3. Psychiatric symptoms (Study 2, Study 3, Study 4)

Psychiatric symptoms were assessed using the Brief Symptom Inventory (BSI) (Derogatis, 1975; Derogatis, 1993; Urban et al., 2014), a measure that assesses self-reported clinically relevant psychological symptoms. The 53-item questionnaire uses a 5-point Likert scale (from “not at all” to “extremely”). The BSI comprises nine symptom dimensions: Somatization, Obsession-Compulsion, Interpersonal Sensitivity, Depression, Anxiety, Hostility, Phobic Anxiety, Paranoid Ideation and Psychoticism. A summary score of General Severity Index (GSI)

can be applied to measure the intensity of general distress. Good reliability and validity has been found across various samples (Derogatis, 1975; Derogatis, 1993; Urban et al., 2014).

4.2.4. Negative life events (Study 4)

Emotionally intense life events (such as conflicts with significant others, loss of children, friends or parents, losing one's job, divorce, etc.) were assessed by the 28-item short version of the Life Events Scale (Paykel, 1991). Respondents were asked to score how intense emotionally was the specific event for them (from 0= "no emotional effect at all" to 5= "severe emotional intensity").

4.2.5. Medical reports of intoxicated patients (Study 5)

Data was collected by analysing patients' medical reports of the Clinical Toxicology Ward of Péterfy Sándor Street Hospital Clinic and Casualty Centre. Medical reports between the 14th of September, 2009 and the 13th of June, 2013 were reviewed. Every patient who admitted GHB use or of whom the clinicians presumed to had used this substance was administered in the database. Available data from medical reports consisted of epicrisis (the circumstances of the intoxication as the ambulance found the patients or the patient's own statement about the case); heart rate (pulse); serum and urine concentration of GHB, ethanol, amphetamines, cocaine, THC (Δ 9-tetrahydrocannabinol), benzodiazepines and opioids; scores of Glasgow Coma Scale and Poisoning Severity Score.

4.3. STATISTICAL ANALYSIS

Descriptive statistics, ANOVA with Bonferroni post hoc test, Mann-Whitney U tests, Independent Samples t-tests, Spearman's rank correlations, χ^2 tests and Fisher's exact tests were conducted by using SPSS 17 (SPSS Inc., Chicago, IL, USA). Path analysis with multiple regression analysis (structural equation modeling), explorative factor analysis with GEOMIN rotation, latent class analysis, multinomial regression analysis and binary logistic regression analysis were conducted by using Mplus 6.0 software (Muthén and Muthén, 1998-2007).

5. EMPIRICAL RESEARCH

5.1. Study 1

5.1.1. Goals of study

The main goal of this study was to explore the utility of Google Trends in predicting mephedrone-related trends and also in testing theoretical assumptions of the literature of mephedrone. More specifically, we aimed to test whether a decreasing interest in formerly banned substances – such as cocaine, heroin or MDMA – and the legislative status of mephedrone predict web interest about this NPS. We also aimed to examine the correlation between GHB-related web searches and the number of GHB-intoxications measured at the same month or one month later.

5.1.2. Results and discussion

Mephedrone

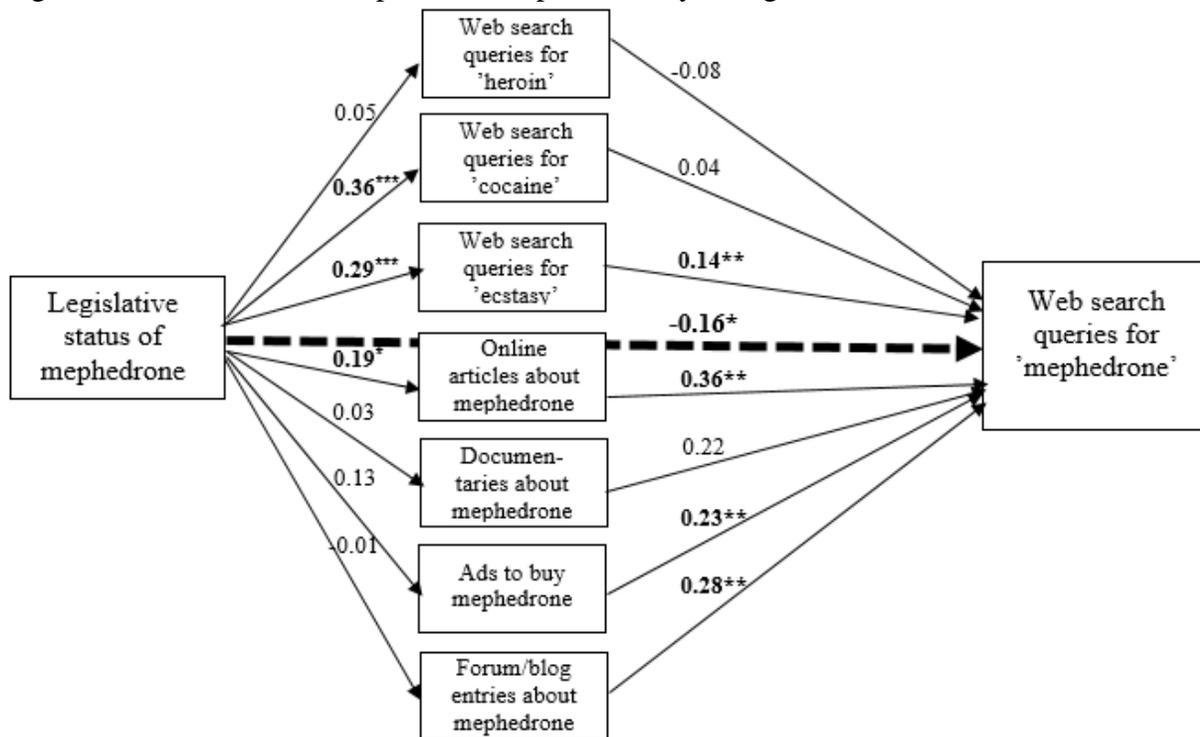
We found significant difference in mephedrone's, cocaine's and ecstasy's web search rates when we compared these in terms of pre-and post-legislative status of mephedrone. Web search rates of 'heroin' did not differ between these two stages of time. With regard to mephedrone related web entries, significant difference occurred only in the number of online published articles before and after the legislation of mephedrone. After mephedrone was banned, the number of articles dealing with this substance significantly increased.

Illicit status of mephedrone found to be a significant negative predictor of web search query rate regarding the term of mephedrone, indicating that web interest was higher when mephedrone was still legal (Figure 2). Based on this result we may conclude that followed by its legislation, mephedrone's popularity and social interest towards this substance significantly dropped. Users' interest changed and most possibly turned towards even more emerging NPSs, such as MDPV or pentedrone. Legislative status of this substance showed significant and positive connection with web search query rates for cocaine and ecstasy and the number of online articles about mephedrone. The connection between mephedrone-related web search query rate and legislative status of this substance was significantly mediated by ecstasy-related web search query rate, the number of online articles, ads and forum/blog entries about mephedrone.

The majority of the published articles contained mainly deterrent information about mephedrone (e.g. fatal overdoses or drug-induced psychotic states), whereas online advertisements were promoting mephedrone in order to increase its selling rate. Forum and blog entries contained both positive/confirmative and negative/deterrent information about mephedrone as these entries were mostly users' reports on their own experiences with mephedrone. Our result therefore indicate that web interest on mephedrone is independent of the content of published information. It might be the frequency of mephedrone being mentioned – in either positive or negative ways - which rather counts in evoking social interest.

The result that ecstasy-related web search query rate was a significant and positive predictor of the variability of mephedrone-related web search rate, might be explained by an increasing web interest regarding club drugs and especially stimulants in general. Furthermore, mephedrone is (or was) considered to be the most popular substitute for MDMA, thus web interest on these substances may be related.

Figure 2. Web interest on mephedrone as predicted by its legislative status



Notes: * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Correlations between mediator variables are not presented in the Figure. Significant correlations are boldfaced.

GHB

The search term "GHB" assessed in the same month showed a correlation of 0.31 ($p < 0.05$) with the number of GHB intoxication cases and a correlation of 0.18 ($p > 0.05$) when the date of intoxication cases were shifted with one month. Regarding the search term "Gina drog", a correlation of 0.18 ($p > 0.05$) was observed in the same month, whereas - when assessed with a one-month shift regarding intoxication cases - a correlation of 0.24 ($p > 0.05$) was detected. Although we only found moderate correlations, considering this result and the finding of Yin and Ho (2012), the analysis of web search queries regarding certain psychoactive substances might be a useful tool for estimating the rates of intoxication cases due to the overdose of the specific substance. Further research needs to be conducted in order to explore to what extent this marker can be used in the prediction of occurring intoxications.

5.2. Study 2¹

5.2.1. Goals of study

The present study aims to reveal the subjective and somatic effects of mephedrone in a systematic way in order to understand how this substance can serve as a potential substitute for

¹ This chapter is based on a published paper, titled 'Substitutional potential of mephedrone: an analysis of the subjective effects' (Kapitány-Fövény et al., 2013a)

entactogens. While doing so, we aim to provide an explanation for mephedrone's functionality and also its outstanding popularity among NPSs.

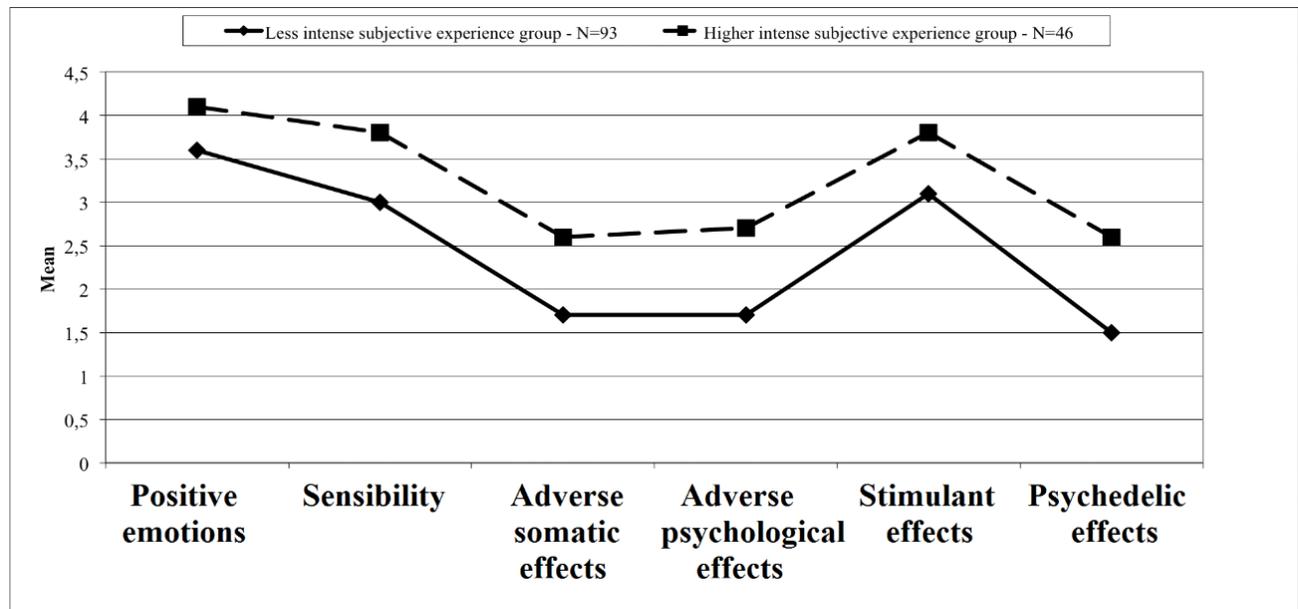
5.2.2. Results and discussion

Based on the model fit indices (RMSEA = 0.041, Cfit = 0.936 and CFI = 0.945) and interpretability of our exploratory factor analysis regarding self-reported mephedrone use experiences, a six-factor solution was retained ($w^2 = 728.3$ $df = 589$ $p=0.0001$). These six factors were positive emotions, sensibility, bodily symptoms, psychological symptoms, stimulant effects and psychedelic effects. The symptoms and effects of MDMA were found to be strongly similar by former studies (e.g. Peroutka et al., 1988; Davison and Parrott, 1997; Parrott and Lasky, 1998; Vollenweider et al., 1998).

The inspection of correlations between factors revealed a large correlation between the adverse somatic and psychological effects, which demonstrate that those who experience intense somatic effects also experience more intense psychological effects. Sensibility experience also correlates with positive emotions, stimulant effects and the adverse somatic effects.

Based on the perceived intensity or severity of the above mentioned six subjective experience factors, two latent classes of users were identified: 93 participants belonged to the first class, and 46 persons belonged to the second class (Figure 3).

Figure 3. Latent profiles of mephedrone use experience



When we compared these two classes, we found significant differences in the subjective judgement on mephedrone's addictive potential and an item referring to the stress reducing effect of mephedrone. A total of 86.7% of those who belonged to the second class and thus perceived more intense subjective and somatic effects during their mephedrone use considered mephedrone as an addictive substance, whereas in the other group, this proportion was only 68.5%. Similarly,

26.1% of members of the second class reported using mephedrone very often or nearly always in order to reduce stress, while that was only true for 6% of the members of the first class.

The most frequently reported effects of mephedrone were typical psychostimulant and entactogen symptoms as well as some adverse bodily experiences, indicating that mephedrone, similar to MDMA, is primarily popular for its psychostimulant and entactogen effects. Nine of the ten most frequently experienced symptoms belong to the factors of positive emotions, sensibility and stimulant effects. That means that, although the other three dimensions (adverse somatic effects, adverse psychological effects and psychedelic effects) also colour the experience of mephedrone use, the symptoms that belong to these factors are much less frequently experienced.

Finally, another topic that needs further analysis is definitely the phenomenon of the relatively high injecting rate. Approximately 12% of our sample administered mephedrone in an intravenous route. This rate is much higher than the rates reported by the UK studies (Newcombe, 2009; Winstock et al., 2011a, 2011b; Freeman et al., 2012) with a range from 0 to 1.2%. Furthermore, in the present study, those who injected mephedrone reported to use this substance almost exclusively this way.

5.3. Study 3²

5.3.1. Goals of study

In the previous study we found a high rate of mephedrone injectors. Using the same dataset, we therefore aimed to reveal potential differences between injectors and non-injectors of this substance, with special emphasis of psychiatric symptoms. We also aimed to explore the characteristics of first and current mephedrone use (including the social context).

5.3.2. Results and discussion

The mean age at the time of the first mephedrone use was 22.7 (SD=6). The majority of the sample (89 subjects; 65.4%) first received mephedrone for free. 131 persons (85.8%) received mephedrone from a close friend or from an acquaintance. Internet was the much less frequently mentioned source of mephedrone, with only 8 subjects (5.7%) reporting this source. A vast majority (134 participants; 93.1%) first used mephedrone with several friends or with one friend. The most frequently mentioned locations of first mephedrone use were discos and parties with 48 subjects (33.3%) reporting these locations. Regarding current mephedrone use, the self-reported mean dose of mephedrone consumed on a typical occasion was 1345.3 mg (SD=1211.7). 108 subjects (74.5%) buy mephedrone in 74.7% of all mephedrone use cases, while 108 (74.5%) subjects get it for free in 48.9% of all these cases. Close friends or acquaintances were still the most commonly reported sources of mephedrone. The majority of 127 subjects (87.6%) reported that they typically use mephedrone with friends or with acquaintances in 83.1% of all their mephedrone use, mostly in discos or parties, which locations were mentioned by 97 subjects (66.9%) as their typical location of mephedrone use. Intranasal use was the most commonly

² This chapter is based on a paper accepted for publication, titled 'Is there any difference in patterns of use and psychiatric symptom status between injectors and non-injectors of mephedrone?' (Kapitány-Fövényi et al., in press-a)

reported route of administration (123 persons, 84.8%), however, intravenous use was also reported by 11% (16 participants).

We found significant correlation between frequency of past month mephedrone use and psychiatric symptom severity as measured by GSI as well as the following BSI subscales: Somatization, Depression, Obsession-Compulsion. The typical daily amount of mephedrone (reported average dose: mg/day) showed significant correlation with GSI and all the BSI subscales, indicating that the more mephedrone is consumed a day the higher the BSI scores are.

Regarding the predictors of mephedrone use frequency – the grouping variable of occasional, monthly and weekly users - multinomial regression analysis indicated that when the predictors were age, gender and GSI, only GSI was a significant predictor of being a group member of weekly or daily users in comparison to occasional users with an odds ratio of 2.95. Males, compared to females, showed a 1.14 times higher odds ratio of being a weekly or daily mephedrone user. When monthly users were compared to occasional users, none of the predictors had a significant predictive value. Results of the second multinomial regression analysis - where distinct BSI scales were entered in the model as independent variables - showed that out of all the BSI scales, only Obsession-Compulsion had a significant predictive value on being a monthly user in comparison to being an occasional user. This finding might be explained by the common neurobiological impairment of OCD and stimulant dependence. In case of both disorders, functional connectivity of right inferior and superior orbitofrontal cortex was found to be abnormally reduced (Meunier et al., 2012). When weekly or daily users were compared to occasional users, the scales of Somatization and Phobic Anxiety had significant predictive values in the model, however Phobic Anxiety had a negative predictive value regarding mephedrone use frequency. A most likely explanation for this result is a psychometric limitation of this study, namely the possible impact of suppressor effect in our multivariate analyses (Tu et al., 2008) due to the relatively large correlations between psychiatric symptoms measured by BSI.

When we compared injectors and non-injectors of mephedrone, we found that injectors were significantly older, used higher doses of mephedrone on a typical occasion, showed higher frequencies of last month mephedrone use and higher rates of subjects who usually take other substances in order to ease potential adverse effects of mephedrone. Furthermore, a higher proportion of participants considered mephedrone as an addictive substance. Regarding proportions of subjects who used other substances in the past month, only the use of heroin or other opiates showed significant difference between the two groups. Among the group of injectors, a higher proportion of participants used heroin or other opiates in the past month. Finally, intravenous users of mephedrone showed higher scores on all the BSI scales and the Global Severity Index.

The predictors of injecting mephedrone use were also examined in a binary logistic regression model. Potential predictors were chosen by the significant results of the comparison of injectors and non-injectors: age, gender, GSI and heroin use. Out of these independent variables age, GSI and heroin use had significant predictive value on injecting mephedrone use, however, it was heroin use that showed the highest odds ratio (OR=25.42) of being a mephedrone injector. This may indicate that mephedrone injecting is most likely a continuous habit of former or current heroin injectors. Elevated psychiatric symptom profile of injectors may also be explained by the history of opioid consumption.

Although our sample was hardly big enough to draw further conclusion about the phenomenon of drug change and transition to injecting new synthetic substances, these results may still add to the understanding of these issues. The above mentioned findings are in line with the presumption that opiate users started to substitute opiates with other available (new synthetic) illicit substances in order to experience the desirable high, when the availability of heroin declined (Dickson et al., 2010; DrugScope, 2012; EMCDDA, 2012; Rácz et al., 2012; Csák et al., 2013).

5.4. Study 4

5.4.1. Goals of study

In the third study we found a relatively high rate of injecting mephedrone users, who also frequently showed a history of opioid use. These injectors showed an elevated psychiatric symptom profile in comparison to those who did not inject mephedrone or consumed opioids. Therefore, in the current study we aimed to assess psychiatric symptoms among a clinical sample of opioid-dependent patients in order to compare patients with and without a history of designer drug abuse, in order to examine whether designer drug use or rather opioid consumption shows association with elevated psychiatric symptoms.

Another goal of this study was to explore reasons behind the use of designer drugs and to examine potential predictors of designer drug use, including emotionally overwhelming life events. Finally, we aimed to study the impact of designer drug use on the perceived intensity of negative life events as well as to analyze whether or not this association is mediated by the severity of psychiatric symptoms. By using a cross-sectional design, our research could not aim to assess any causality.

5.4.2. Results and discussion

64 patients (32.3%) have tried any NPSs at least once during their treatment. Cathinones were found to be the most popular NPSs. Out of the 64 patients who abused any NPSs, 30 patients (46.9%) primarily abused pentedrone, 13 patients (20.3%) MDPV (often cited as “music”) and 12 patients (18.8%) mephedrone. Other substances such as biococaine, GHB or ketamine was chosen by only 1 or 2 patients as their primarily abused NPS. Regarding pentedrone as the most frequently consumed NPS, 36 patients (56.3%) used pentedrone in the last year, whereas 10 patients (15.9%) used it in the last month as well. Daily use of the chosen NPS occurred in the case of only 3 patients (4.7%). 40 patients (62.5%) of this subsample intravenously administered one or more designer drugs.

Out of the potential reasons of choosing a NPS instead of a more familiar psychoactive substance, the most typical reasons were curiosity, replacing other drugs and easy availability. As most of the participants abused cathinone-derivatives, these results may be interpreted as typical reasons for choosing a cathinone-type stimulant drug. However, relatively high mean scale score was found in case of the reason indicating the patient did not know what he/she used. In these cases, NPSs were presumably consumed by chance. There were no gender differences in how frequently the patients mentioned these reasons ($p > 0.05$). Age showed significant and negative correlation ($(r(64) = -0.26, p < 0.05)$) with the reason to substitute other substances, indicating that the older the patient was the less frequently he/she mentioned this reason. Educational level

showed significant negative correlation ($(r(64) = -0.28, p < 0.05)$) with the reason that NPSs are considered to be more natural. The assessed reasons of NPS use highlight the leading role of practical or economical aspects, irrespectively of the patient's gender. Psychopharmacological effects of NPSs (such as effect duration or intensity) were less frequently mentioned reasons.

Negative or traumatic life events that provoked the highest emotional intensity were loss of a child (mean= 4.9, SD= 0.32), death of the partner (mean=4.4, SD=1.21), death of a relative (mean= 4.3, SD=1.25), conflicts with parent(s) (mean= 4.1, SD=1.23), suicide in the proximal social environment (mean= 4.1, SD=1.5), miscarriage (mean= 4, SD= 1.33) and a severe chronic illness of a relative (mean= 4, SD= 1.29). Most frequently occurring adverse life event was the significant change in the patients' living standards, with 140 patients (70.7%) experiencing this life situation. With regard to the correlation between the perceived emotional intensity of negative life events and certain demographic variables, age showed significant correlation with emotional intensity of suffering physical abuse from a close relative ($(r(26) = 0.44, p < 0.05)$), whereas educational level did not show significant correlation with the perceived emotional intensity of any life events. However, gender was found to play a relevant role, as significant differences occurred between males and females with regard to the following life events: conflicts with the partner, raising child(ren) alone, pregnancy, own severe illness, the partner's job loss, suffering any violent crime, new member in the household and public proceedings. Females showed more intense emotional reactivity to all of these burdensome life situations.

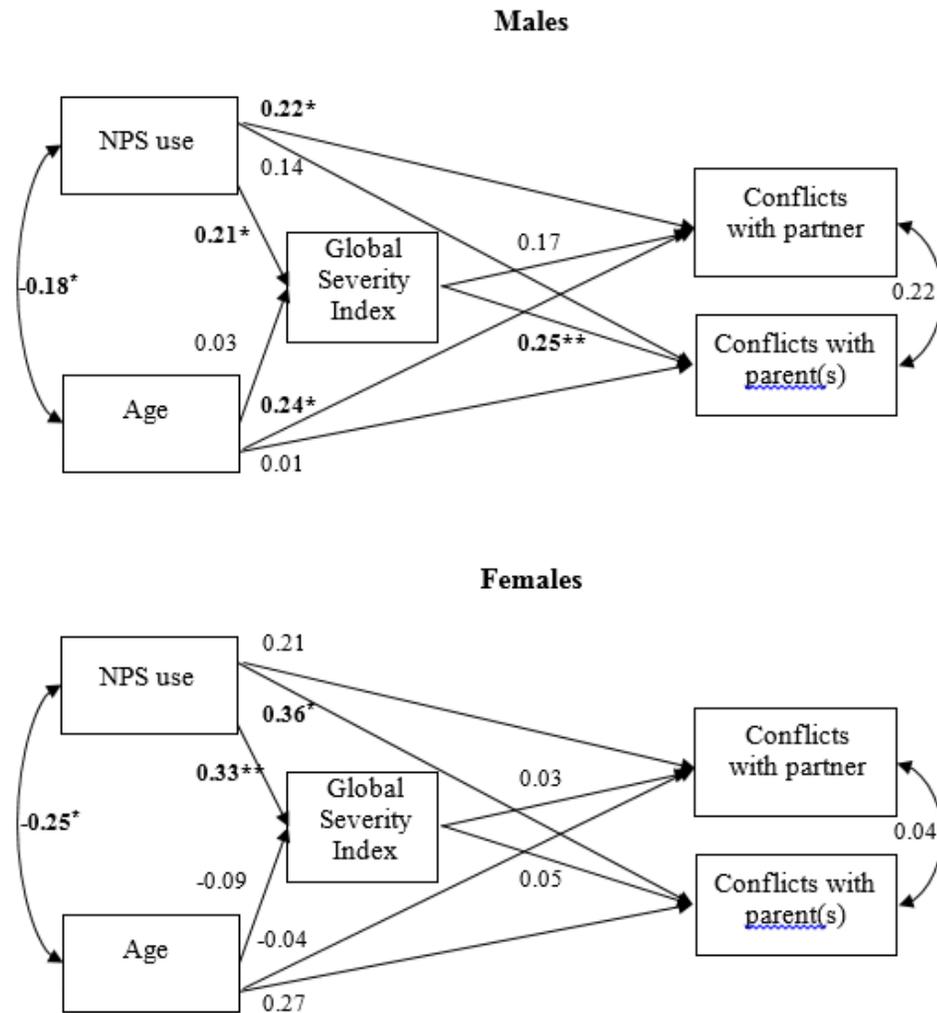
Patients with and without a history of NPS use were compared in terms of demographics, treatment indicators, life events and psychiatric symptoms. Regarding demographics, significant differences occurred in age as those patients who used any NPS at least once in their lifetime were younger than those without NPS consumption experiences. Regarding treatment indicators, patients who did not use any NPSs, were in treatment for a longer period of time. Out of emotionally overwhelming life events, we found significant differences in the level of emotional intensity in case of experiencing conflicts with the partner or the parents. For those, who used NPSs, these life events were emotionally more overwhelming. Finally, regarding psychiatric symptoms, with the exception of Somatization and Hostility, NPS users showed higher scores on each symptom scale. A higher Global Severity Index (GSI) was also found among this subgroup.

As a next step, we used the indicators where these two subgroups showed significant differences as potential predictors of NPS use in a binary logistic regression model. Age, conflicts with partner and conflicts with parents were found to be significant predictors of being a NPS user. Conflicts with partner showed the highest odds ratio (OR=12.79), indicating that those patients who face conflicts with their partner as well as they perceive this life event as an emotionally intense experience, has approximately 13 times the odds to at least try NPSs. This result emphasizes the relevance of both pair-and family therapy in addiction treatment. Providing services to not just the addicted individual but the whole family is proved to improve treatment effectiveness (Center for Substance Abuse Treatment, 2004). Regarding age, our result indicates that being younger is also a risk factor for being a NPS user.

As it was based on a cross-sectional design, this research did not assess causality between NPS use, stressful life events and psychiatric symptoms. However, based on former findings (e.g. Franken et al., 2001), it can be hypothesized that the significant association between NPS use and the level of perceived emotional intensity of previously presented interpersonal conflicts is mediated by the severity of psychiatric symptoms. In other words, perceived emotional intensity

of interpersonal conflicts can be interpreted as a risk factor for NPS use as well as NPS use itself might have an impact on the perceived emotional level of these life events. Therefore, we finally examined a path analysis model in which NPS use was entered as a predictor variable with age as a covariate, GSI as a mediator variable and conflicts with either the partner or the parent(s) as outcome variables. We analyzed this model separately for males and females (Figure 4). In case of males, being a NPS user was associated with higher perceived emotional intensity of having conflicts with the partner. More severe psychiatric symptoms as potential mediators predicted higher perceived emotional intensity regarding the conflicts with the parent(s). Age was also found to be a significant predictor of higher perceived emotional intensity with regard to conflicts with the partner and there was a significant and negative correlation between NPS use and age. In case of females, being a NPS user predicted higher perceived emotional intensity of having conflicts with the parent(s) and also more severe psychiatric symptoms. Psychiatric symptom severity did not predicted higher emotional intensity regarding interpersonal conflicts. Age and NPS use showed significant and negative correlation.

Figure 4. Psychiatric symptom severity as a mediator between NPS use and the perceived emotional intensity of interpersonal conflicts



Notes: *p<0.05; **p<0.01; ***p<0.001.

The overall elevated psychiatric symptom profile of NPS using patients confirms the assumption of our former study, namely that the use of cathinone-derivatives may be related to highly impaired mental states, and this psychiatric impairment cannot be solely explained by the history of opioid use. Furthermore, the fact that not distinct psychiatric disorders – such as anxiety, mood disorders or OCD – but rather a general psychopathological severity characterizes these cases, may underline the pronounced need of inpatient psychiatric care even more.

5.5. Study 5

5.5.1. Goals of study

This study aimed to assess the frequency of not only drug facilitated sexual assaults but acquisitory crimes as well as a comparison between intentional and unintentional GHB consumption cases. We also aimed to compare cases with sole GHB consumption with polysubstance use cases in terms of the level of their neurocognitive impairment.

5.5.2. Results and discussion

The upward and downward trend of GHB's popularity demonstrated by former studies (e.g. EMCDDA, 2014) is delineated by our results as well, although we did not assess a representative sample. 2011 was the year with most GHB-related cases (29.9% of all the cases) followed by a decrease in GHB's popularity and resulted in only 40 cases (9.8% of all the cases) in 2013. Some authors describe a rising abuse of GHB in 2014 as well (e.g. Brennan and Van Hout, 2014), indicating that an other upward trend of GHB use may arise. Others highlights that after the ban of GHB, users switched to the use of it's precursor and legal alternative, GBL (γ -butyrolactone), which is now gaining a growing popularity (van Amsterdam et al., 2014).

We found that GHB intake either in itself or with a co-ingested substance may usually result in minor poisoning. The frequency of severe poisonings did not differ between cases of GHB detected alone and GHB with co-ingested substances detected, however we found gender differences in poisoning severity ($\chi^2=8.85$, $p<0.05$). Considering that among males both moderate and severe poisonings occurred more often which was found to be unrelated to GHB's serum or urine concentrations, and yet females showed higher rates of blackouts or memory losses, we might state that males seems to be more capable of retaining consciousness under more severe states of poisoning.

The frequency of enduring either GHB facilitated sexual assaults or acquisitory crimes under the presumed influence of GHB and other concomitantly consumed psychoactive substances were compared between cases of intentional (111 cases) and unintentional (46 cases) GHB intake. We found significant difference in both the frequency of sexual assaults (Fisher's exact test, $p=0.024$) and acquisitory crimes (Fisher's exact test, $p=0.0001$) between the two groups as these offences were only observed among unintentional GHB intake cases. Among female patients the frequency of cases of unintentional GHB consumption was higher than among male patients ($\chi^2=33.66$, $p<0.001$).

GHB facilitated sexual assault occurred in 11 cases (2.8%), while acquisitory crimes occurred in 38 cases (9.6%). The rate of sexual assaults is in line with the findings of former similar studies in which GHB was detected in 1 to 5% of all drug facilitated sexual assaults (ElSohly and Salamone, 1999; Varela et al., 2004; Du Mont et al., 2010). With regard to the 11 cases (11 different patients) of drug facilitated sexual assaults, 9 patients (81.8%) were females,

the youngest patient was a 17 year-old girl, whereas the oldest one was a 53 year-old male (the mean age was 28.9, SD=12.21). GHB was only detected in 2 patients (18.2%) and in 2 other patients (18.2%) only ethanol was detected. 6 patients (54.5%) had blackouts and 3 patients (27.3%) had memory loss.

Among those cases of self-reported unintentional GHB intake we found a higher rate (6.5%) of endured GHB facilitated sexual assaults as among intentional GHB use cases, no sexual assaults occurred. Our result that among victims of drug facilitated sexual assaults there were male patients as well cannot be mentioned as an unusual finding, since victims of both childhood and adulthood sexual abuse are often men, although it is the female gender which was found to be a risk factor for the increased likelihood of sexual victimization (e.g. Xu et al., 2013). The validity of our result might also be impacted by the potential underreporting of sexual offences. Fear of stigmatization, feeling of shame and humiliation, fear of being judged as gay, isolation, negative schemas about the self and denial are the most typical consequences of sexual victimization that also lead to underreporting these assaults in case of both male and female victims (Lisak, 1994; Sable et al., 2006).

In the 38 cases (38 different patients) of acquisitory crimes the majority of the victims, altogether 26 cases (68.4%) were males, the youngest patient was a 14 year-old male, whereas the oldest patient was a 75 year-old female (the mean age was 31.5, SD= 14.18). In 25 cases (80.6%) the poisoning severity was minor, moderate poisoning occurred in 2 cases (6.5%). None of these patients needed intubation as the lowest GCS total score was 9, represented by 2 patients (5.4%). Blackouts occurred in 15 cases (39.5%), memory losses occurred in 19 cases (50%). GHB was detected in 9 cases (23.7%), out of which GHB was solely detected in 6 cases (15.8%). Only other psychoactive substances were detected in 5 cases (13.2%) out of which only ethanol was detected in 2 cases (40%), ethanol with other psychoactive substances (amphetamine, cocaine, THC and benzodiazepine) were detected in 2 cases (40%), whereas in 1 case (20%) only THC was detected.

Both our and former results (Németh et al., 2010) indicate that the use of GHB as a date-rape drug is a factual but not as frequent threat as media report might suggest. It is rather voluntary GHB use that shows linkage with drug-influenced sexual behavior as users intentionally tend to consume GHB in order to enhance their sexual experience (Laborit, 1972; Palamar and Halkitis, 2006; Barker et al., 2007; Lee and Levounis, 2008).

5.6. Study 6³

5.6.1. Goals of study

As the results of our former study indicated that the use of GHB as a date-rape drug might be less frequent than it is suggested by media reports, we considered intentional GHB use to show a stronger linkage with drug-influenced sexual behavior, as users rather intentionally tend to consume GHB in order to enhance their sexual experience. Therefore, the aim of this study was to focus on and measure the sexual correlates of such GHB use, the possible impact of this substance on users' sexual experiences and related risky sexual behaviors. We also aimed to

³ This chapter is based on a paper accepted for publication, titled 'Enhancing sexual desire and experience: An investigation on the sexual correlates of gamma-hydroxybutyrate (GHB) use' (Kapitány-Fövényi et al., in press-b)

confirm sexual enhancing effects of GHB described by former qualitative and observational studies within the confines of a quantitative study. Our final research goal was to explore potential gender differences in GHB's sexual effects and correlates.

5.6.2. Results and discussion

As we have seen it in the case of mephedrone as well (Study 3), both the first encounter with GHB and persisting consumption usually occur within the social context of peer substance use (mostly with friends). The majority got GHB for free, most frequently from a close friend. Typical locations for first and current GHB use are discos, parties and hops. Regarding current use, the role of unknown individuals and the internet as potential sources of the drug were found to be more relevant than in the case of the first encounter with GHB. The majority of the sample usually consumes GHB in the form of liquid. The mean age of the first GHB use experience was 22.1 (SD=4.9).

42 participants (70%) has used GHB in the last year, and half of them has used GHB at least once in the last month as well. With regard to other substance use in the last month, 33 subjects (55%) has smoked cannabis at least once, 16 (27.1%) used MDMA, 14 (23.7%) used cocaine, while 2 persons (3.5%) used heroin or other opiates, 2 (3.5%) used LSD or magic mushroom, and only one used any inhalants. The majority (96.7%) drank alcohol at least once in the past month.

The ten most frequently rated subjective and somatic effects of GHB were the following: pleasant mood and euphoria mentioned by 35.6% and 35.1% as nearly always or always experienced when using GHB, followed by the feelings of ease, tranquility, feeling of being close to others, feelings of being drunk, and experiencing stupor. Increased sexual arousal, sharpened perception, and hyperactivity were also among the ten most frequently experiences symptoms. Males experienced euphoria and hyperactivity more frequently than females. As we can see, among the ten most frequently mentioned symptoms of GHB, we found both stimulant and depressant effects. This result can easily be explained by GHB's dose dependent characteristics as it might bind to GHB-specific receptor at low doses and by inhibiting presynaptic dopamine release it evokes stimulant-like effects (Feigenbaum and Howard, 1996), while at higher doses, GHB stimulates GABA_B receptor resulting in an increase in dopamine levels and inducing depressant effects (e.g. Xie and Smart, 1992). Futhermore, GHB seems to function as a stimulant substitute especially for males as they more frequently experience hyperactivity as a result of their GHB use.

Specific sexual effects of GHB were also assessed (Table 1). Every fourth respondents (25.4%) reported an intense attraction towards the sexual partner when using GHB. On the other hand, 84.5% said that they never had an unsatisfactory sexual experience when using GHB. Sexual disinhibition (28.8), heightened sense of touch (13.8), and more intense orgasms (12.3) were also relatively often experienced effects of GHB. Regarding gender differences, males more frequently experienced intense orgasms as a result of their GHB use. Average daily dose (mg/day) showed significant and positive correlation with all specific sexual effects, indicating that those participants who never felt these effects, usually consumed lower doses of this substance. Therefore, sexual effects of GHB may be interpreted as reinforcing effects with a possible impact on further and repeated GHB use as well.

Table 1. Specific sexual effects of GHB

	Never N (%)	Sometimes N (%)	Half of the cases N (%)	Most of the cases N (%)	Nearly always/ always N (%)	<i>Zero order Spearman correlations between sexual effects and average daily dose of GHB (mg/day)</i>
More intense attraction towards sexual partner	14 (23.7)	12 (20.3)	5 (8.5)	13 (22)	15 (25.4)	0.54**
Sexual disinhibition	18 (30.5)	9 (15.3)	7 (11.9)	8 (13.6)	17 (28.8)	0.49*
Heightened sense of touch (tactility)	15 (25.9)	11 (19)	10 (17.2)	14 (24.1)	8 (13.8)	0.42*
More intense orgasm	27 (47.4)	8 (14)	7 (12.3)	8 (14)	7 (12.3)	0.47*
Sex becomes more boring this way	49 (84.5)	5 (8.6)	3 (5.2)	0	1 (1.7)	0.15
Gender differences						
			Mean scale score (SD)		Mann Whitney U test	Effect size r
			Males (N=40)	Females (N=20)		
More intense attraction towards sexual partner			3.2 (1.6)	2.8 (1.5)	U= 325.5	r= 0.13
Sexual disinhibition			3.1 (1.7)	2.6 (1.5)	U= 317.5	r= 0.15
Heightened sense of touch (tactility)			2.9 (1.5)	2.7 (1.2)	U= 356.5	r= 0.07
More intense orgasm			2.7 (1.6)	1.6 (0.9)	U= 230*	r= 0.39
Sex becomes more boring this way			1.4 (0.9)	1.1 (0.2)	U= 317	r= 0.22

Notes: *p<0.05; **p<0.01; ***p<0.001. Significant correlations are boldfaced.

Our results also showed that more than half of the subjects (54.2%) do have sex under the influence of GHB, and 18.7% does so at least in the half of the cases. Interestingly, while 39.1% exclusively and another 19.6% most typically have sex with his/her partner when using GHB, others prefer to have sex with friends or even strangers under the influence of this substance. Almost half of the respondents (44.8%) reported to have sex with friends or acquaintances when using GHB, and more than one third (34.5%) reported to do so with strangers. Establishing sexual intercourse with strangers under the influence of GHB was more common among males than females. Our result that sexual disinhibition is one of GHB's most typical sexual effect also needs to be taken into consideration with regard to the role of GHB in risky sexual behavior. Additionally, GHB use itself had already been found to have a strong relation with both syphilis and HIV infection (Bellis et al., 2002).

The most frequently reported reason of GHB use was to reach an altered state of mind (reported by 25.9% as being a motive always or nearly always), where everything else ceases to

be (17.2%), or to exclude everyday problems and situations (15.5%). With regard to the correlation between specific reasons of GHB use and the frequency of either last month use or self-reported mean dose of GHB, reaching an altered state of consciousness showed the highest correlation with self-reported mean dose of GHB ($r=0.73$, $p<0.001$). Though, 'enhancing sexual experience' was not an often reported reason of GHB use (only 3.4% mentioned this reason as being a motive of GHB use always or almost always), this reason showed the highest correlation with last month frequency of GHB use ($r=0.41$, $p<0.01$) and a significant gender difference was found only in the case of this reason as males more frequently reported using GHB in order to enhance their sexual experience than females ($U=255.5$, $p<0.05$).

6. DISCUSSION

6.1. Exploratory results

Web search queries

Our result that web interest on mephedrone is independent of the content of the published information and rather associated with the number of mephedrone being mentioned, holds important implications for drug prevention programs. This finding indicates that providing a) deterrent information and b) using only information delivery strategies in prevention might be a double-edged sword, as it may either provoke reluctance or even pique the target population's interest towards psychoactive substances. Former studies also emphasized potential disadvantages and ineffectiveness of providing only deterrent information in prevention programs (e.g. Rácz, 2000).

We demonstrated that legislative status of mephedrone predicts web interest on this substance. Most recently, Ledberg (2015) presented similar results, as he found that the activity on an internet discussion forum related to NPSs was significantly decreased around the time of classification. The impact of legislation regarding further NPSs needs to be tested with Google Trends as well, in order to find out to what extent this tool can be utilized. A potential function of Google Trends might be the analysis of time-dependent changes in the rates of web searches in relation to specific events (as an analogue for *event-related potential* in electroencephalography).

Mephedrone: substituting other substances

Substitutional potential of mephedrone was confirmed by our studies (Study 2, Study 3, Study 4). On the basis of its psychopharmacological effect, mephedrone can be a substitute for MDMA and other entactogen stimulants. Whereas on the basis of its intravenous administration, it can also function as a substitute for frequently injected drugs, such as amphetamines, cocaine or opioids. Based on our findings, we can also interpret mephedrone use as a maladaptive coping strategy, as we found that those who perceive more intense subjective and somatic effects (i.e. members of the second latent class in Study 2) when taking mephedrone, may use this substance as an instrument to reduce stress. These users also consider mephedrone to be more addictive. In case of other psychostimulants, perceived effect intensity was linked to decreased cerebral blood flow in the right amygdala and hippocampus (Carhart-Harris et al., 2014), indicating not only psychological but also neurobiological differences between SUD individuals.

Injecting use of mephedrone and other cathinones was found to be a still existing problem, associated with riskful correlates, such as a higher average dose of mephedrone consumed, a

more frequent monthly use of this substance, the consumption of other substances in order to ease mephedrone's adverse effects, a history of opioid use and more severe psychiatric symptoms.

GHB and sexuality

Gender differences in both intentional and unwanted GHB intake need to be addressed. In line with former findings (e.g. Kim et al., 2007), male gender was found to be a risk factor for experimenting with GHB's sexual enhancing effects and also for engaging in potentially risky sexual activities. Furthermore, GHB was found to be a stimulant substitute especially for males as they more frequently reported hyperactivity as one of the relevant psychopharmacological effects of GHB. GHB's capability to increase the intensity of orgasm was also more inherent among males. Considering the involvement in GHB-facilitated crimes, male gender was also found to be a risk factor, indicating that in this case gender differences might be overemphasized, especially in media reports.

Based on our results, GHB's impact on human sexuality is considered to be a significant function of this substance. Intentional use of GHB seems to be more relevant than GHB being a date-rape drug, however, comparable with former studies (e.g. Goullé et al., 2003), we also empirically proved that GHB is truly used as a roffie in some cases. As such, recent studies reported novel methods to detect GHB in various drinks, like the use of fluorescent sensor, which exhibits GHB's fluorescence quenching property (Zhai et al., 2014), or other color-change reagent tests that were also tested within real life circumstances (Quest and Horsley, 2007).

6.2. Adaptability of etiological models

NPSs and self-medication

Results that support the hypothesis:

Our multinomial regression analysis (Study 3) indicated that the severity of psychiatric symptoms predict mephedrone use frequency with an odds ratio of 2.95 to consume this NPS on either a weekly or daily basis, in comparison to occasional users. We also found that injectors of mephedrone with more severe psychiatric symptoms, tend to use mephedrone more regularly. Among opioid dependent patients (Study 4) we found that NPS – primarily synthetic cathinone - users are characterized by an elevated psychiatric symptom profile, in comparison to those patients who did not use NPSs. Finally, experiencing stressful life events, such as interpersonal conflicts, also predicted higher odds of using NPSs. As we saw in our path analysis model (Study 4), the severity of psychiatric symptoms could also be interpreted as a mediator between NPS use and the perceived emotional intensity of interpersonal conflicts.

Results that contradict the hypothesis:

Among opioid dependent patients, we found that the severity of psychiatric symptom was not a significant predictor of NPS use (Study 4). Furthermore, among the most frequently mentioned reasons of NPS use, we identified practical or even economical – like availability and substituting other drugs – and psychosocial reasons – like the impact of friends – and not psychopharmacological preferences. Similarly, when we assessed potential reasons of GHB use

among recreational users, we found that the reasons ‘to reduce tension and stress’ was one of the least frequently mentioned reason. This reason- which might be a potential way of self-medication – did not show significant association with GHB use frequencies either.

Based on these findings, we state that Khantzian’s hypothesis is still one of the most relevant etiological model of substance use, however, we cannot fully support its utility regarding the etiological explanation of NPS use.

NPSs and negative life events

Those life events of traumatic nature – i.e. the exposure to actual or threatened death, serious injury or sexual violation as described by DSM-5 (American Psychiatric Association, 2013) -, such as the loss of a child, the death of a partner or a relative, a suicide in the social environment evoked higher emotional intensity among SUD patients, compared to stressful but not traumatic life situations, like divorce, break-up, retirement or job loss.

Gender was found to have a relevant impact on the perceived emotional intensity of the assessed life events. Being a female seems to be a significant risk factor regarding the emotional reactivity to interpersonal conflicts, pregnancy and parenting, illnesses and crime-related experiences. This result is also comparable with former findings (Breslau et al., 1997), indicating that women are more vulnerable to traumatic life events. In case of NPS using males, emotional reactivity to interpersonal conflicts was mediated by the severity of psychiatric symptoms, whereas psychiatric symptoms among female patients did not play a relevant role in the mediation between NPS use and emotional reactivity related to negative life events. This finding may denote that the neurobiological (e.g. Bianchin and Angrilli, 2012) and psychosocial (e.g. Bramston et al., 2000) differences between men and women in emotional sensitivity might be reduced by psychiatric symptoms. Furthermore, the connection between age and emotional reactivity was significant only among males. Hence, we may assume that age also reduce the above mentioned differences in emotional sensitivity between men and women. These gender differences may hold important implications for tailored interventions, developers of such programs are thus advised to consider gender-related specificities.

Social environment of NPS use

With regard to the onset of NPS use – the first encounter with the assessed NPSs – the impact of friends was found to be most relevant. Users most frequently tried NPSs with their acquaintances for the first time, as well as they purchased NPSs from them, usually for free. Social context of NPS use remained similar in persisting NPS use. The significance of peers in NPS use was affirmed by others as well (e.g. Lea et al., 2011). Majority of our recreational NPS users – and not our opioid dependent patients – were in their twenties. As the impact of friends and acquaintances on substance use is usually linked to adolescence and early adulthood (e.g. Nation and Heflinger, 2006), our results are in line with former ones. Mean age of the first NPS use was around the age of 22. Based on this finding, we emphasize the importance of prevention programs for not just adolescents but young adults as well.

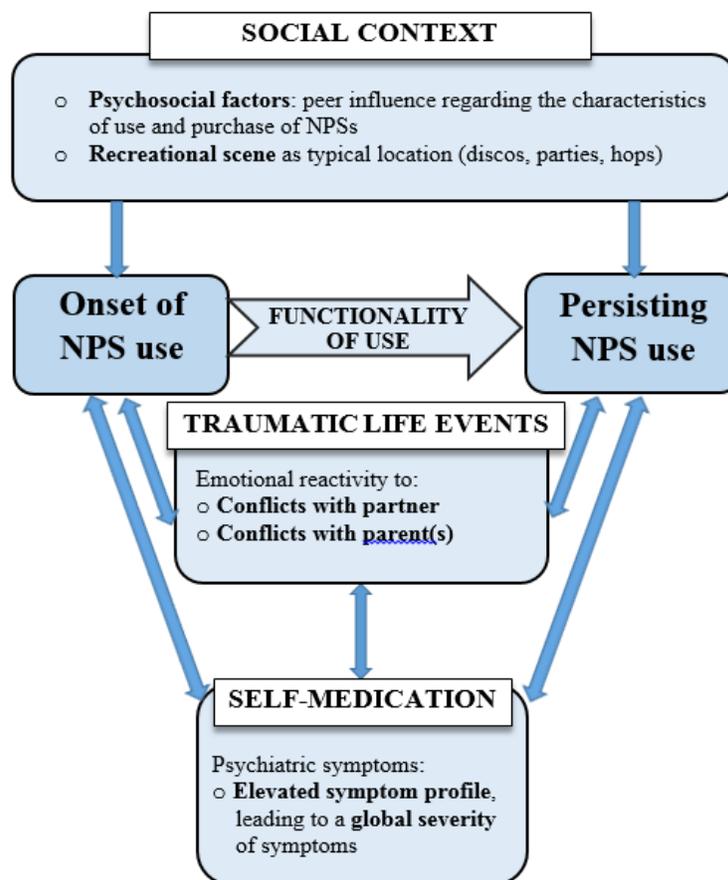
Slight differences occurred between mephedrone and GHB users. In case of mephedrone, the role of the internet as a potential source of purchase was more relevant than in the case of GHB. In comparison to the former findings of Dargan and colleagues (2010) and Matthews and Bruno (2010), our results indicate that online obtainment of mephedrone was less inherent. With regard to the reported locations of NPS use, house parties/hops were more frequently mentioned

among GHB users. In terms of prevention, hops are hardly monitored, as it is a challenging if not impossible goal to conduct effective programs at these recreational events. Furthermore, these locations may help users in remaining a hidden population.

7. CONCLUSION

As an effort to summarize our findings, I finally present an integrated model of the three cited psychological etiological theories, in relation to our results regarding the onset and persistence of NPS use (Figure 5).

Figure 5. Interrelatedness of tested theoretical assumptions in connection to the results of presented empirical researches



Considering both the onset and persistence of NPS use, psychosocial factors (mainly peer influence on the characteristics of use and purchase of NPSs) and the recreational scene as the setting for trying and later using NPS play a relevant role. Psychiatric symptoms, including the global severity of these symptoms showed correlational (two-sided) connection with both the onset and persisting use of NPSs. This association was interpreted as a supporting evidence for self-medication hypothesis, although the design of our studies did not allow us to confirm causality. Thus, vica versa, we might also presume that the use of NPSs can result in elevated psychiatric symptoms. Similarly, in case of the impact of negative life events, and emotional reactivity to them, these stressful experiences (emotional intensity as induced by interpersonal

conflicts) were considered to either predict NPS use (in this case we did not differentiate between the onset and persistence of use, therefore we may hypothesize that negative life events have a significant impact on both), and NPS use was also tested as an explanatory variable for higher levels of emotional reactivity to these life situations. Furthermore the connection between NPS use and negative life events was found to be mediated by the severity of psychiatric symptoms among male opioid dependent patients.

I interpret the functionality of NPS use to play a significant role in persisting NPS use. In case of mephedrone and other synthetic cathinones, their capability to substitute various previously banned psychoactive substances, and in case of GHB, its sexually enhancing properties might have an impact on the persistence of NPS consumption.

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