Heroin Addiction and Related Clinical Problems

the official journal of

Europad

World Federation for the Treatment of Opioid Dependence

PACINI EDITORE

Vol. 20 • N. 3 • June 2018

ISSN 1592-1638 (print) - ISSN 2531-4122 (on line)

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</tr>
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<tbody>
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Cited in:  
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The second to fourth digit (2D:4D) ratios in patients with Heroin Use Disorder
Fatih Canan, Suna Sogucak, Servet Karaca, Cuneyt Tegin, Omer Gecici, and Murat Kuloglu 5

Novel psychoactive synthetic cannabinoids and synthetic cathinones: the never-ending story of potential clinical toxicity
Barbara Lovrecic and Mercedes Lovrecic 13

Relationship between self-mutilative behaviour and novelty seeking, the presence of antisocial and borderline personality disorders, and severity of psychopathology in a sample of male patients with Heroin Use Disorder
Cuneyt Evren, Vahap Karabulut, Iziği Ahniak, Gokhan Umut, Turan Cetin, Bilge Evren, and Ruken Agachanli 25

Impact of employment and marital status on lapse risk situations among addicted patients in Methadone Maintenance Treatment
Mohammadreza Abed 33

How to develop and implement an exercise programme in a heroin-assisted treatment setting
Livia Staub, Markus Gerber, Marc Vogel, Kenneth Dürsteler-Macfarland, Jonas Strom, Susanne Schoen, Uwe Pühse, and Flora Colledge 41

Diversion of buprenorphine: Scope of the problem and the measures taken to address it
Richa Tripathi, and Siddharth Sarkar 51
The second to fourth digit (2D:4D) ratios in patients with Heroin Use Disorder
Fatih Canan¹, Suna Sogucak¹, Servet Karaca¹, Cuneyt Tegin², Omer Gecici¹, and Murat Kuloglu¹

¹-Department of Psychiatry, Akdeniz University School of Medicine, Antalya, Turkey.
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Summary

Background: The ratio between the length of the second and fourth fingers (2D:4D ratio) has been linked with prenatal testosterone concentrations, but also with alcohol and tobacco misuse. Aim: We aimed to investigate any possible association between 2D:4D ratios and heroin use disorder, and whether such a relationship might be independent of impulsivity. Methods: A group of 150 men with heroin use disorder, consecutively admitted to a detoxification and therapy unit, completed the Barratt Impulsiveness Scale-version 11 (BIS-11) and had their 2D:4D ratios measured, along with a group of 266 male controls of similar age and education. Results: Men with heroin use disorder had lower 2D:4D ratios on their right hand when compared with those without heroin use disorder. Results from logistic regression indicated that 2D:4D ratios were not significant independent predictors of heroin use disorder when attentional and non-planning impulsivity were considered. Conclusions: These findings suggest that high prenatal testosterone levels, as measured indirectly by 2D:4D ratios, are not independently associated with heroin use disorder among males.

Key Words: Digit ratio; heroin use disorder; impulsivity; 2D:4D; men; testosterone

1. Introduction

The ratio of second to fourth digit length (2D:4D) is determined in the early development stage of the fetal period [16]. Digit growth is under the control of the Home box (Hox) gene [37] and is influenced by testosterone levels [17]. It has been suggested that the 2D:4D ratios are negatively correlated with in utero testosterone concentrations. In contrast, there is a positive correlation between 2D:4D and in utero estrogen levels [15]. Prenatal testosterone exposure leads to the development of masculine features in physiology, anatomy and behaviour [34]. As a consequence of in utero testosterone exposure, the 2D:4D ratio has a sexually dimorphic feature; men have lower values for the ratio than females [18].

Many psychiatric disorders are associated with variations in 2D:4D ratios. For example, ADHD [21] and autism [19] have been found to be negatively associated with 2D:4D ratios. Conversely, patients with schizophrenia [1], major depressive disorder [22], anxiety disorders [5], and eating disorders [29] exhibited higher 2D:4D ratios when compared with healthy individuals. Many stereotypically masculine traits such as hostility [8], aggression [26], risk-taking [4], and impulsivity [10] have also been shown to be significantly associated with 2D:4D ratios. In addition, both impulsivity and 2D:4D ratios are known to be correlated with antisocial behaviour [10]. Physical aggression, risk-taking, and antisocial behaviour are likewise commonly seen in patients with substance use disorders [23, 35], implying a link between 2D:4D ratios and substance use disorders.

There are only a few studies that have explored the association between addictive disorders and 2D:4D ratios [20, 12, 2, 9]. Most have shown low 2D:4D ratios in alcohol misuse [20, 12, 9] and high 2D:4D ratios in nicotine misuse. These findings suggest a complex relationship between in utero testosterone exposure, and substance-related and addictive disorders.

Impulsivity has been proposed as a causal factor in substance use disorders [31]. Individuals with alcohol and substance use disorders often exhibit high
levels of impulsivity [33]. Impulsivity has also been inversely associated with 2D:4D ratios [10], which may point to a link between addictive behaviours, impulsivity, and prenatal androgen exposure.

Despite a number of studies whose stated aim was to investigate the relationship between 2D:4D ratio and alcohol or nicotine misuse, to the best of our knowledge there are no studies so far that have investigated the association of other substance use disorders with 2D:4D ratios. Thus, we aimed to investigate the 2D:4D ratio in subjects with heroin use disorder by comparing them with those without heroin use. We also examined whether a potential relationship between heroin use disorder and 2D:4D ratios was related to impulsivity.

2. Methods

2.1. Sample

From January 2016 to May 2016, 150 consecutive heroin-dependent adult males who had been admitted to the detoxification and therapy centre of the Akdeniz University Hospital, Antalya, Turkey were recruited to our study. All patients fulfilled the DSM-5 criteria for opioid use disorder and were positive on urine drug tests, which are employed routinely in the centre. The diagnostic assessments and administration of self-report measures were performed after opioid withdrawal symptoms had been dissipated, as ascertained by a score of 4 or less on the Clinical Opiate Withdrawal Scale [3]. Heroin was the primary drug of abuse with all the patients who had been recruited.

266 healthy subjects with no history of dependence on any drug (except tobacco) were recruited as control group. Control subjects were recruited from the community, by word-of-mouth, after being contacted by the authors in the area. All the participants were of Caucasian origin. Candidate participants who had any finger deformity were excluded.

Heroin-dependent patients were excluded if they had any other substance use disorder (except tobacco use disorder). Exclusion criteria for all participants included a current diagnosis of psychosis, mania, mental retardation, current suicidal ideation, and major medical or neurological disease. Neither patients nor controls were excluded on grounds of moderate alcohol use (no more than 1–2 drinks per occasion, plus no intoxication or heavy drinking in the past year), caffeine use, or tobacco use.

This study was approved by the Committee for the Protection of Human Subjects of the Akdeniz University School of Medicine and conformed to the Helsinki Declaration of 2013. Every participant provided written informed consent prior to participation in the study.

2.2. Instruments

2.2.1. Addiction Profile Index (API)

The API [24] is a Turkish self-report instrument assessing various aspects of alcohol and substance use disorders. It consists of 37 items and five subscales (dependency diagnosis, characteristics of substance use, craving, the effects of substance use on the user, and motivation to quit using substances). The API was found to be reliable among alcohol and/or substance abusers with a Cronbach’s alpha coefficient of 0.89. Cronbach’s alpha coefficient for the subscales ranged from 0.63 to 0.86. This scale was administered only to the patients.

2.2.2. Barratt Impulsivity Scale-version 11 (BIS-11)

The BIS-11 [25] is a 30-item self-administered questionnaire that is widely used to evaluate the personality/behavioural construct of impulsiveness. It consists of three subscales: ‘attentional impulsiveness’ (eight questions reflecting a reduced ability to maintain attention toward a stimulus), ‘motor impulsiveness’ (11 questions measuring rapid action-taking and acting without forethought), and ‘non-planning impulsiveness’ (11 questions expressing a lack of planning and an emphasis on the present). The BIS-11 is a 4-point Likert scale; and item values range from 1=rarely/never to 4=almost always. Higher scores indicate greater levels of impulsivity. The Turkish version of the BIS-11 was found to be reliable among healthy students and also patients who had psychiatric disorders (Cronbach’s alpha coefficient: 0.78 and 0.81, respectively) [7].

2.2.3. Measurement of the 2D:4D ratios

The lengths of the 2nd (index) and 4th (ring) fingers were measured using a digital Vernier caliper (accurate to 0.01 mm). Participants were instructed to place their hands on the table with their palms facing up and stretch their fingers as much as possible. Digit length was measured from the crease most proximal to the palm of the hand to the tip of the finger, as described by Verster and de Haan [32]. For each subject, two consecutive measurements were performed by two different observers. Each measurement was averaged to obtain a definitive value. Interclass corre-
lation analysis was performed to assess the closeness of agreement between observers. The digit ratio was computed by dividing the length of the index finger by that of the ring finger.

2.3. Data analysis

IBM SPSS Statistics software version 20.0 (Armonk, New York, USA) was used to perform statistical analysis. Continuous variables were checked for normal distribution with the Kolmogorov-Smirnov one-sample test for appropriateness of fit. Only 2D:4D ratios were normally distributed. Thus, Student’s t-test was utilized to assess between-group differences with respect to 2D:4D ratios. The rest of the continuous variables (i.e. age and scale scores) were not normally distributed; to supersede this difficulty, they were analysed by non-parametric (Mann-Whitney U-test) tests. The correlation of 2D:4D ratios with patients’ sociodemographic data, clinical findings and other variables were analysed by the Spearman correlation test. Binary logistic regression was performed to estimate the effects of 2D:4D ratios, age, smoking status and impulsiveness subscales on a diagnosis of heroin use disorder. The χ² test was used to compare proportions between the groups. Binomial logistic regression was used to predict the outcome of a diagnosis of heroin use disorder. The final model was able to explain between 50.4% and 68.9% of variance. The model was found to fit the data adequately (Hosmer and Lemeshow’s χ² = 3.298, p = 0.914), and was able to predict heroin use disorder (Omnibus χ² (7) = 286.508, p < 0.001). Overall, the model was able to correctly predict 83.6% of all cases. Seven predictors were included in the model, using the Enter method. Only attentional impulsiveness and non-planning impulsiveness successfully predicted heroin use disorder status (squared Wald statistics are displayed in Table 2).

In correlation analyses, attentional impulsiveness, motor impulsiveness, and total impulsiveness scores were associated with low right-hand 2D:4D ratio than that of control participants. Furthermore, motor impulsiveness, non-planning impulsiveness, and total impulsiveness scores were significantly higher in patients than in control subjects.

3. Results

There was no significant difference in education levels between patients and the non-substance-using control group (χ² value = 3.957; p= 0.271). The prevalence of smoking, however, was higher in patients than in controls (100% vs. 33.9%, χ² value = 195.316; p < 0.001). Reliability of the two raters proved to be high, both for the right hand (2D: ICC = 0.991; 4D: ICC = 0.898; 2D:4D: ICC = 0.899) and the left (2D: ICC= 0.993; 4D: ICC= 0.897; 2D:4D: ICC = 0.912). Table 1 presents the means, standard errors, and minimum-maximum values for age, BIS-11 scores and 2D:4D ratios for patients and controls. Patients with heroin use disorder had a statistically significant lower right-hand 2D:4D ratio than that of control participants. Furthermore, motor impulsiveness, non-planning impulsiveness, and total impulsiveness scores were significantly higher in patients than in control subjects.

Binary logistic regression was used to predict the outcome of a diagnosis of heroin use disorder. The final model was able to explain between 50.4% and 68.9% of variance. The model was found to fit the data adequately (Hosmer and Lemeshow’s χ² = 3.298, p = 0.914), and was able to predict heroin use disorder (Omnibus χ² (7) = 286.508, p < 0.001). Overall, the model was able to correctly predict 83.6% of all cases. Seven predictors were included in the model, using the Enter method. Only attentional impulsiveness and non-planning impulsiveness successfully predicted heroin use disorder status (squared Wald statistics are displayed in Table 2).

In correlation analyses, attentional impulsiveness, motor impulsiveness, and total impulsiveness scores were associated with low right-hand 2D:4D ratios in patients with heroin use disorder (Table 3). Motor impulsiveness, non-planning impulsiveness, and total impulsiveness scores too were negatively correlated with left-hand 2D:4D ratios.

The relationships between the presence and absence of selected clinical and historical illness variables and 2D:4D ratios are shown in Table 4. Comorbid cocaine or alcohol use, having a history of

<p>| Table 1. Comparison between the study groups with respect to age, impulsivity, and 2D:4D ratios |
|-----------------------------------------------|-----------------------------------------------|----------------|-----------------------------------------------|</p>
<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Patients N=150</th>
<th>Controls N=266</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>22.8±4.2</td>
<td>23.0±4.7</td>
<td>0.371*</td>
</tr>
<tr>
<td>Attentional impulsiveness (BIS-11)</td>
<td>16.9±4.5</td>
<td>18.1±4.6</td>
<td>0.164*</td>
</tr>
<tr>
<td>Motor impulsiveness (BIS-11)</td>
<td>21.8±4.7</td>
<td>21.1±5.8</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Non-planning impulsiveness (BIS-11)</td>
<td>26.7±5.2</td>
<td>24.4±4.9</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Total impulsiveness (BIS-11)</td>
<td>64.7±11.3</td>
<td>59.4±11.1</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Right hand 2D:4D ratio</td>
<td>0.98±0.03</td>
<td>0.99±0.04</td>
<td>0.012**</td>
</tr>
<tr>
<td>Left hand 2D:4D ratio</td>
<td>0.98±0.03</td>
<td>0.99±0.04</td>
<td>0.055**</td>
</tr>
</tbody>
</table>
| BIS-11: Barratt Impulsivity Scale-version 11; 'Mann-Whitney U test; "Student’s t-test
suicide attempts, self-mutilation, or a criminal record, as well as the route chosen for administering heroin all turned out to be factors showing no association with 2D:4D ratios.

Table 5 displays a comparison of age, impulsivity, and 2D:4D ratios in control participants with and without daily tobacco use. Controls with daily tobacco use had higher motor impulsiveness, non-planning impulsiveness, and total impulsiveness scores than those without tobacco use. There was no statistically significant difference between tobacco users and non-users with respect to 2D:4D ratios.

4. Discussion

In this study, we found that patients with heroin use disorder had lower 2D:4D ratios on the right hand than those of non-drug abusing controls. This finding lends support to previous studies, which indicate that alcohol misuse may be related to more masculinized (lower) 2D:4D ratios [20, 12, 9]. In this connection, the present study can be said to extend previous work on the effects of impulsivity on the relationship between 2D:4D ratios and substance use disorders.

Prior studies revealed relatively consistent results with respect to 2D:4D ratios in patients with addictive disorders. For example, Manning and Fink [20], after collecting data from more than 150,000 participants via an Internet survey, concluded that, on both left and right hands, 2D:4D ratios were inversely associated with alcohol intake. In accordance with that study [20], Kornhuber et al. [12] and Han et al. [9] demonstrated similar findings, in particular by showing that that patients with alcohol use disorder had lower 2D:4D ratios on both their hands compared with healthy controls. Kornhuber et al. [12] evaluated 87 males and 44 females with alcohol dependence, whereas the patient group in the study by Han et al. [9] consisted entirely of males. In contrast, no relationship was found by Borowska and Pawlowski [2] between alcohol use and the 2D:4D ratio. They compared participants who regularly used both alcohol

Table 2. Logistic regression analysis of heroin use disorder diagnosis

<table>
<thead>
<tr>
<th>Predictor variable</th>
<th>Wald</th>
<th>df</th>
<th>P</th>
<th>Exp(B)</th>
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<tbody>
<tr>
<td>Age</td>
<td>2.120</td>
<td>1</td>
<td>0.147</td>
<td>0.958</td>
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<tr>
<td>Attentional impulsiveness (BIS-11)</td>
<td>21.633</td>
<td>1</td>
<td>&lt;0.001</td>
<td>0.807</td>
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<tr>
<td>Motor impulsiveness (BIS-11)</td>
<td>2.443</td>
<td>1</td>
<td>0.118</td>
<td>1.062</td>
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<tr>
<td>Non-planning impulsiveness (BIS-11)</td>
<td>12.648</td>
<td>1</td>
<td>&lt;0.001</td>
<td>1.132</td>
</tr>
<tr>
<td>Smoking status (Yes = 1)</td>
<td>0.012</td>
<td>1</td>
<td>0.993</td>
<td>0.001</td>
</tr>
<tr>
<td>Right hand 2D:4D ratio</td>
<td>1.722</td>
<td>1</td>
<td>0.189</td>
<td>0.002</td>
</tr>
<tr>
<td>Left hand 2D:4D ratio</td>
<td>0.064</td>
<td>1</td>
<td>0.800</td>
<td>2.914</td>
</tr>
</tbody>
</table>

HL: Hosmer and Lemeshow goodness of fit Model Cox & Snell R²=0.504; Nagelkerke R²=0.689; HL χ²=3.298 sig=0.914

Table 3. Correlation analysis for 2D:4D ratios, clinical variables, and impulsivity among patients with heroin use disorder

<table>
<thead>
<tr>
<th></th>
<th>Right hand 2D:4D ratio</th>
<th>Left hand 2D:4D ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>rs</td>
<td>p</td>
<td>rs</td>
</tr>
<tr>
<td>Age</td>
<td>-0.105</td>
<td>0.201</td>
</tr>
<tr>
<td>Average daily heroin dose (g/day)</td>
<td>-0.123</td>
<td>0.134</td>
</tr>
<tr>
<td>Age at moment of heroin debut (years)</td>
<td>-0.113</td>
<td>0.168</td>
</tr>
<tr>
<td>Attentional impulsiveness (BIS-11)</td>
<td>-0.190</td>
<td>0.020</td>
</tr>
<tr>
<td>Motor impulsiveness (BIS-11)</td>
<td>-0.210</td>
<td>0.010</td>
</tr>
<tr>
<td>Non-planning impulsiveness (BIS-11)</td>
<td>-0.099</td>
<td>0.228</td>
</tr>
<tr>
<td>Total impulsiveness (BIS-11)</td>
<td>-0.199</td>
<td>0.014</td>
</tr>
<tr>
<td>Characteristics of substance use (API)</td>
<td>-0.009</td>
<td>0.911</td>
</tr>
<tr>
<td>Dependency diagnosis (API)</td>
<td>0.074</td>
<td>0.368</td>
</tr>
<tr>
<td>Effects of substance use on the user (API)</td>
<td>-0.027</td>
<td>0.744</td>
</tr>
<tr>
<td>Craving (API)</td>
<td>0.072</td>
<td>0.383</td>
</tr>
<tr>
<td>Motivation to quit using substances (API)</td>
<td>0.097</td>
<td>0.240</td>
</tr>
</tbody>
</table>

API: Addiction Profile Index; BIS-11: Barratt Impulsivity Scale-version 11
and nicotine with a control group who used neither of them. There were no significant differences in the 2D:4D ratios between the two groups [2]. We have contributed to the existing literature by showing that a diagnosis of heroin use disorder was associated with lower 2D:4D ratios (i.e., elevated in utero testosterone levels).

All the patients who participated in our study were current smokers. As a secondary outcome, we compared the 2D:4D ratios of the control subjects with (n = 77) and without (n = 189) current tobacco use and found no difference, although there was a statistically significant difference between the two groups with respect to impulsivity scores. This finding contrasts with those of Borbowska and Pawlowski [2], who reported that 2D:4D on the left hand was positively related to smoking among females, and those of Manning and Fink [20], who found that 2D:4D ratios were positively associated with nicotine intake both in females and in males.

A meta-analysis of more than 100 studies [11] concluded that the 2D:4D ratio on the right hand should probably be considered a better indicator of prenatal testosterone exposure than the 2D:4D ratio on the left hand, so reflecting a consensus that, incidentally, offers a full explanation of why only right 2D:4D was associated with heroin use disorder in our study. Although most of the relevant studies in patients with alcohol or tobacco misuse have found significantly different 2D:4D ratios on both hands when compared with non-affected individuals [20, 12, 9], Kornhuber et al. [12] came to the conclusion that the detection of alcohol use disorder was most accurate using the 2D:4D ratios on the right hand.

Only Manning and Fink [20] investigated whether the relationship between 2D:4D ratios and

| Table 4. The relationship between clinical variables and 2D:4D ratios in patients with heroin use disorder |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Right hand 2D:4D ratio | Mean | SD | p value* | Mean | SD | p value* |
| Concomitant cocaine use | Yes (n=50) | 0.978 | 0.034 | 0.129 | 0.957 | 0.031 |
| No (n=100) | 0.987 | 0.036 | 0.984 | 0.034 | 0.119 |
| Concomitant alcohol use | Yes (n=48) | 0.981 | 0.039 | 0.523 | 0.979 | 0.028 |
| No (n=102) | 0.985 | 0.034 | 0.982 | 0.035 | 0.561 |
| Self-mutilation | Yes (n=62) | 0.981 | 0.035 | 0.297 | 0.981 | 0.034 |
| No (n=88) | 0.987 | 0.036 | 0.982 | 0.033 | 0.732 |
| History of suicide attempts | Yes (n=29) | 0.991 | 0.028 | 0.257 | 0.992 | 0.027 |
| No (n=121) | 0.982 | 0.035 | 0.979 | 0.034 | 0.059 |
| Criminal record | Yes (n=91) | 0.983 | 0.035 | 0.707 | 0.983 | 0.033 |
| No (n=59) | 0.985 | 0.036 | 0.979 | 0.033 | 0.461 |
| Route of heroin administration | Injected (n=41) | 0.986 | 0.037 | 0.717 | 0.981 | 0.031 |
| Smoked/chased (n=109) | 0.983 | 0.035 | 0.982 | 0.034 | 0.869 |

*Student’s t-test

| Table 5. Comparison between controls with and without tobacco use with respect to age, impulsivity, and 2D:4D ratios |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Characteristics | Controls with tobacco use (n=77) | Controls without tobacco use (n=189) | z-score or t-score | p value |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Age (years) | Mean | SD | Mean | SD | -0.536 | 0.592* |
| Attentional impulsiveness (BIS-11) | 18.1 | 4.6 | 16.4 | 4.5 | -1.012 | 0.312* |
| Motor impulsiveness (BIS-11) | 21.1 | 5.8 | 18.8 | 4.9 | -5.830 | <0.001* |
| Non-planning impulsiveness (BIS-11) | 24.4 | 4.9 | 22.4 | 5.0 | -6.396 | <0.001* |
| Total impulsiveness (BIS-11) | 63.6 | 11.7 | 57.6 | 10.4 | -5.817 | <0.001* |
| Right hand 2D:4D ratio | 0.991 | 0.036 | 0.996 | 0.044 | -0.850 | 0.396** |
| Left hand 2D:4D ratio | 0.986 | 0.056 | 0.991 | 0.041 | -0.797 | 0.426** |

BIS-11: Barratt Impulsivity Scale-version 11; *Mann-Whitney U test; **Student’s t-test
addictive behaviours is independent of other variables. In that study [20], 2D:4D ratios on both hands were found to be independently associated with alcohol intake when checking for sex, education, and nicotine intake. However, our logistic regression analysis suggested that 2D:4D ratios did not predict heroin use disorder in males, whereas attentional and non-planning impulsiveness were, indeed, found to be significant predictors. This authorizes us to put forward the hypothesis that the association between low 2D:4D ratios and heroin use disorder is not independent when impulsivity is taken into consideration. Furthermore, 2D:4D ratios were not related to clinical variables such as craving, average daily heroin dose, and concomitant cocaine use.

Prenatal hormonal environment has long been recognized as an important factor regulating brain development [6]. Few researchers, have, however, taken the trouble to address the effects of fetal androgen levels on the anatomy or function of the brain. A prospective functional magnetic resonance imaging (fMRI) study [13] has shown that fetal testosterone may influence the organization of reward-related regions, including the caudate, putamen, and nucleus accumbens. In another study, conducted on 28 healthy boys [14], prenatal testosterone levels were positively associated with grey-matter volumes, particularly in the right temporo-parietal junction/posterior superior temporal sulcus and left amygdala. Abnormal activation of the right temporo-parietal junction has also been reported among adolescents with marijuana and alcohol use disorders who were assigned a spatial working memory task [28]. Furthermore, amygdala volume has been shown to be associated with alcohol [36] and opioid [30] abuse. These studies suggest neural mechanisms for the relationship between prenatal testosterone levels and either alcohol or substance use disorders. Our study is consistent with the notion that testosterone levels and either alcohol or substance use are likely among males.

Although we recruited a relatively large sample of patients, and performed two consecutive measurements of 2D:4D ratios carried out by two independent assessors, several limitations should be noted. First, although using a digital Vernier caliper to measure 2D:4D is an acceptable method [27], a simultaneous scan of participants’ hands would offer an opportunity to conduct reliability analyses. Second, our patients and controls were men, with the consequent drawback that the results so obtained may differ from those obtained in women. Third, we examined 2D:4D ratios in patients admitted to a detoxification and therapy unit. Thus, our results might not be extendable to other patients with substance use disorder, including those who are not in treatment. Fourth, we did not evaluate other possible confounding factors such as ADHD [7] and depression [10], which could affect relationships between 2D:4D ratios and heroin use disorder. Fifth, although the two observers who measured 2D:4D ratios showed good agreement, it cannot be excluded that they might both be affected by experimenter bias, since they knew whether the participants were patients with heroin use disorders or else controls.

5. Conclusions

To our knowledge, this is the first study ever to have assessed 2D:4D ratios in patients with heroin use disorder. We observed that individuals with heroin use disorder had more masculinized (lower) 2D:4D ratios on the right-hand, which may qualify as a better indicator of in utero testosterone levels than 2D:4D ratios on the left-hand [30], when compared with non-affected individuals. It should definitely be noted that the relationship between 2D:4D ratios and heroin use disorder was no longer classifiable as one of mutual independence when logistic regression analysis was performed using attentional and non-planning impulsivity as factors. According to our findings, prenatal testosterone levels are not independently associated with the occurrence of a substance use disorder among males. Future studies using larger samples (if possible, including females) should evaluate the interaction between 2D:4D ratios and impulsivity in cases featuring substance-related and addictive disorders.

References


Role of the funding source

Authors state that this study was financed with internal funds. No sponsor played a role in study design; in the collection, analysis or interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors

All authors were involved in the study design, had full access to the survey data and analyses, and interpreted the data, critically reviewed the manuscript and had full control, including final responsibility for the decision to submit the paper for publication.

Conflict of interest

The authors have no conflict of interest to declare and are solely responsible for this article.

Ethics

All authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. All participants gave their informed consent to the anonymous use of their clinical data for this independent study. The study was approved by the Committee for the Protection of Human Subjects of the Akdeniz University School of Medicine.

Note

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Novel psychoactive synthetic cannabinoids and synthetic cathinones: the never-ending story of potential clinical toxicity

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Summary

Background: Over the last ten years, there has been an unprecedented increase in the use of new psychoactive substances (NPS) that are not yet under international control. This poses an emerging and demanding challenge to public health, clinical work and researchers worldwide. Synthetic cannabinoids (SCs) and synthetic cathinones (SKs) are the substances most frequently involved in producing states of intoxication; acute toxicity due to SKs is the most problematic prognosis from the viewpoint of public safety and health. Aim: To raise awareness among clinicians regarding NPS (especially SC- and SK-related) signs, symptoms and clinical toxicities. Methods: An electronic search was carried out on the Medline/PubMed and Google Scholar databases to find selected search terms with a particular focus on reporting acute toxicity and psychopathology. Results: Acute toxicity due to SCs and SKs has been implicated in the emergence mostly of neuropsychiatric and cardiovascular clinical manifestations. A majority of emergency medical problems are minor to moderate poisonings; however, severe intoxication can lead to life-threatening adverse effects and death. These substances cannot be detected by conventional drug screening methods. Clinicians should maintain a high level of suspicion of finding synthetic toxicity in patients presenting with unexplained agitation or cardiovascular symptoms, especially in cases of altered mental status with acute onset, excited delirium, renal failure or sympathomimetic symptoms. Conclusions: The acute and chronic toxicity of many NPSs is still unknown, as data from poison centres should be interpreted within their limitations (absence of analytical confirmation, secondary reporting of clinical features). There is a need for evidence-based treatment recommendations for cases of acute intoxication.

Key Words: New psychoactive substances; synthetic cannabinoids; synthetic cathinones; acute toxicity; psychopathology.

1. Introduction

According to UNODC, the emergence of novel psychoactive substances on the drug scene is not per se a new phenomenon, but this emerging problem has recently become a global phenomenon [67]. New psychoactive substances (NPSs) had been legally defined as a new narcotic or psychotropic drug, in pure form or in a preparation, which has not been scheduled either under the Single Convention on Narcotic Drugs of 1961 or under the Convention on Psychotropic Substances of 1971, but which may pose a public health threat comparable with that posed by substances listed in those conventions (Council of the European Union decision 2005/387/JHA), as people are seeking NPSs for use as intoxicants [67].

According to UNODC, the term “new” does not necessarily mean new molecules or inventions, and does not have to refer to the time when a substance was first identified or synthesized, but to when it emerged on the global market for recreational use, so that its true meaning comes close to “newly misused” (most of these substances were first created many years ago) [67]. Thus “new” substances are currently popular or available on the recreational drugs market [15, 30, 55, 66], whereas their use was barely known or completely unknown in those regions or countries.
Heroin Addiction and Related Clinical Problems 20(3): 13-24

Heroin Addiction and Related Clinical Problems 20(3): 13-24

Until one or at most two decades ago [67]. NPSs comprise a wide range of substances from research chemicals to products from previous pharmacological synthesis that have been newly re-discovered, with the production of new analogues or derivates designed to obtain effects similar to those of illicit drugs [15, 30, 66]. NPSs are marketed as if they were legal and are commercialized as alternatives to traditional illicit or banned drugs [36, 55]. Over the last ten years, the availability of, and the demand for NPSs have rapidly risen on global markets worldwide [15, 66, 67]; the total number of monitored NPSs in EU in 2015 was over 450 and, in 2015, on average one new NPS each week was recognized and monitored as having become available for sale [15].

In spite of the increasing numbers of NPSs, at present scientific knowledge about NPSs’ side-effects, toxicology, addiction potential or possible contraindications is still limited, on account of ever-new components or chemicals, and the absence of scientific research on their health consequences – especially long-term ones – in humans [10]. The recent literature on NPSs has dealt with their chemical compositions, their medical and neuropsychiatric effects and case reports [17, 34, 39, 46, 71, 73]. Data on clinical acute toxicity are limited to retrospective analysis, surveys and case reports, and are mainly reported by poison centres [31, 33, 51, 55].

The emerging toxicity of NPSs is usually expressed through neuropsychiatric and cardiovascular clinical manifestations; in rare cases severe, even life-threatening adverse effects have been known to occur [31, 51, 55]. The treatment of NPS toxicity is often limited to symptomatic and supportive care [31]. The long-term consequences of NPS use are currently unknown.

The purpose of this paper is to raise awareness among clinicians about NPSs by pointing out their clinical toxicity and the dangers of its manifestations, especially NPS-related acute psychopathological effects in specific cases of SC and SK use. Thus health professionals need to be aware of the acute psychopathology that is related to these substances.

2. Methods

We conducted an electronic search on the Medline/PubMed database for articles using the keywords “novel synthetic psychoactive substances” (n=91), “new synthetic psychoactive substances” (n=199), “synthetic cannabinoids, recreational use” (n=94), “synthetic cathinones, recreational use” (n=50), “new synthetic psychoactive substances, psychiatric disorders” (n=41), “new synthetic psychoactive substances, psychopathology” (n=2), “new synthetic psychoactive substances, acute toxicity” (n=8). An initial review of the titles and abstracts resulting from these electronic searches was followed by a more detailed assessment of pertinent articles, and an examination of the bibliographies of related reviews to identify other sources. In addition, the Google Scholar database was used for the same search terms. Titles and abstracts of the search results were inspected for their relevance. Government sources were also inspected for relevant information.

Papers were limited to those available in English, covering the period 2005-2016, and only if they were peer-reviewed, human reports focusing on acute toxicity and putting particular emphasis on psychopathology. In January 2017 a final search through the data available in electronic databases was conducted on SC- and SK-associated psychiatric manifestations.

3. Results

3.1. Common characteristics of NPS

The NPSs include substances with different chemical and pharmacological properties; each NPS could have a slightly different molecular structure, with unpredictable effects [67]. Based on their psychotropic effects, NPSs can be classified as stimulants, hallucinogens or empathogens/entactogens [33].

According to the UNODC classification, substances classified as NPSs include: SCs, SKs, phenethylamines, piperazines, ketamine, plant-based psychoactive substances (e.g. kratom [Mitragyna speciosa], khat [Catha edulis]), and other substances, including tryptamines, aminoindanes, phencyclidine-type substances [67], but also synthetic opioids, a wide range of prescribed medications; a long series of performance and image-enhancing drugs were included, too [55].

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The most widely used NPSs are the SCs (especially after 2008) and SKs (especially after 2009), while the most problematic for public safety and health seem to be the SKs [15, 67]. Most historically known NPSs appear to have been identified in Europe, but the total number of NPSs newly identified in the USA is twice the number recently discovered in the EU [67].

NPSs comprise chemical derivatives, chemical analogues (with one or only a few chemical modi-
fications; synthetics that slightly alter the structure of psychoactive substances) or mimetics (chemically different, but compounds that are designed to mimic, or that claim to mimic, the effects of banned, illicit, street drugs) [51, 55].

Most synthetic NPSs are mainly manufactured in chemical laboratories in Asia (China and India, in particular), in countries located in East or South Asia, and are then legally imported (as chemicals or as packaged products) into Europe, the Americas and other regions [33, 51, 67]. NPSs are produced without controls or mandatory standards applicable to the manufacturing process; hence, besides psychoactive components, NPS products contain contaminants (e.g. heavy metals, and additives that are subject to controls in some countries). In addition, no list of active pharmacological agents and no safety information are ever provided [9, 13, 36, 66].

NPSs are commercialized as “legal highs” or “smart drugs”, and are advertised as being “all natural” (e.g. “spice” or plant-based psychoactive substances), “safe to use” and as offering “safer”, “legal” alternatives to illicit or controlled drugs, but the truth is they are none of those things [51]. Suppliers advertise NPSs with effective marketing strategies, in ways that aim to escape detection and circumvent drug abuse legislation. NPSs are often labelled as “not for human consumption”, while further attempts to evade legal controls include package labels with visible indications of the contents such as: “herbal incense”, “for aromatherapy use only”, “air fresheners”, “bath salts”, “plant food” or “plant fertilizers”, “research chemicals”, “for novelty use”, “collectors’ items” or “use as directed” (without any directions for use on the package) [10, 33, 67]. NPSs are constantly changing in composition, in response to legal definitions and laws that change continually, with the creation of ever-new chemical variations. By constantly shifting their legal status so as to ‘stay legal’, new products may succeed in becoming legal, since they differ from a chemical structure that has been deemed illegal [15, 30, 66]. There is thus a continuous, dynamic and extremely rapid process that allows suppliers to circumvent drug controls by offering new alternatives to products that are restricted [67].

In contrast to illicit drugs, NPSs are sold in Europe either via the Internet (or by a ‘dealer’), while they are distributed in the USA through convenience stores, head or smart shops or gas stations [62] without any age restrictions, which makes them particularly attractive to children, adolescents and other vulnerable groups (e.g. young drug addicts) [9, 31, 36, 51, 55]. NPSs are commercialized with marketing strategies that are specifically designed to attract customers, mainly young people, with fun brand names, discounts and special offers by NPS retailers, who use colourful, professional packaging and wording that are often changed to adapt to new situations as the laws are amended [12].

Unprecedented growth in the number of NPSs on the illicit market and NPS misuse have been identified all over the world [15, 67, 72]; as a result, the number of young people who declare they have used NPSs has risen in recent years [15].

NPSs are attractive to users because of their easy availability, legal status, low cost, intense psychoactive effects and freedom from the risk of detection in routine drug screenings (users in prison or in the army, or people who drive after taking drugs) [33, 43].

3.2. Synthetic cannabinoids

3.2.1. Background

SCs, otherwise known as synthetic cannabinoids, are the most commonly used NPSs [18, 67]. SCs mimic the effects of the main active compound in natural cannabis, Δ9-tetrahydrocannabinol (THC) [36, 67]. Over the last 50 years SCs have been developed as pharmaceutical agents, and nowadays their structure comprises a few hundred molecules; however, in non-medical settings and in non-medical uses, it is hard to predict whether their desired properties will actually appear in a user [31, 51].

SCs are often mixed with herbal psychoactive mixtures and sold under the brand name Spice or K2, Moon Rocks, Yucatan Fire, Skunk and others (Table 1.). Herbal psychoactive products with added SCs appeared in Europe in 2004, and in the USA in 2008 [51, 55]; SCs sold as a cannabis-like drug, so-called “Spice”, began to appear in EU in 2008; after that their popularity increased dramatically [15, 16].

SC mixtures (“Spice products”, the term Spice being applied to all products containing SCs) are herbal mixtures and allow for variation within and between products through the addition of a wide variety of dried psychoactive plant material; they are commonly sprayed over with chemical additives including SC compounds [58]. The product is typically sold commercially as a mixture of plant materials and labelled “herbal incense”, “fragrance” or “potpourri”. In addition, SCs have also been documented to exist as tablets, capsules, powders [58] and even cigarettes.
SCs are mainly abused by smoking (alone or with marijuana), or prepared as a herbal infusion for drinking [34, 45, 68]. Besides herbal mixtures, also oral/e-liquid/injectable SC formulations for use in e-cigarettes or vaping are available. SC may be inhaled, ingested and injected [51] (Table 1.). There is substantial variability in product composition and wide concentration ranges for SC. Batches of SC preparations of the same brand may contain variable SC concentrations; the type and amount of SC may vary considerably from batch to batch even with the same product [8, 16, 55]. Within any given package, a range of different SC molecules and/or further psychoactive compounds can usually be identified; this fact alone is enough to make their effects unpredictable [19, 34, 47, 55].

Over 200 SCs have been reported to be available on the Internet [55]. The names of 140 chemicals associated with ‘legal highs’ were provided by detailed databases, and ‘Spice’ has been found to contain over 250 artificial chemical compounds, none of which are guaranteed to be safe for human consumption (e.g. HU-210 has been found to be between 100 to 800 times more potent than THC) [51, 55]. John W. Huffman with his academic team have synthesized over 450 cannabinoids (these substances bear the prefix “JWH”, e.g. JWH-018), the cannabinoids that were originally synthesized by Alexandros Makriyannis bear the prefix “AM” (e.g. AM-2201), while the prefix HU means designed at Hebrew University [16, 19, 31, 51, 57]. Most of the cannabinoids detected in Spice can be generally described as aminoalkylin-
Besides SCs, other psychoactive substances can be found in ‘Spice’ products, such as the synthetic opioid O-desmethyltramadol (active metabolite of the opioid tramadol) or non-cannabinoid ingredients such as cis-9, 10-octadecenoamide, which has cannabinoid-like activity and hypnotic properties [19].

One characteristic feature of Spice is its rapidly, indeed, continually changing composition, which is a consequence of the Narcotics Law in some countries that have banned all products containing SC compounds (e.g. Austria, Germany, France) [31, 51] or a result of the emergency scheduling enacted in 2011 in the USA, which temporarily scheduled several SCs (JWH-018; JWH-073; JWH-200; CP-47, 497; CP-47, 497 C8 homologue) in the Controlled Substances Act before putting them under regular control a year later [14, 67].

### 3.2.2. Neurobiology

Chemical structures of SCs differ from those of THC, while cannabidiol (with anxiolytic, antipsychotic and anticraving effects) is absent from SCs [33, 43, 45, 55]. Although the various SCs differ, they all possess a higher affinity with CB1 and/or CB2 receptors with a significantly higher dose-response efficacy than THC; SCs also tend to possess much more powerful and unpredictable effects, with higher toxicity and overdose potential than THC [16, 25, 33]. SCs lead to increased cannabinoid effects due to increased binding affinity and potency at the cannabinoid receptors than THC, showing full receptor agonism (THC is a partial agonist) and active metabolites [51]. SCs have a longer half-life, and their effects are more intense and longer lasting, bringing greater health risks than plant cannabis [5, 19, 61, 64]. SCs potentially pose a risk that is 30 times greater (so requiring emergency medical treatment) than natural forms of cannabis [72]. Some of the compounds also have metabolites that are themselves psychoactive. The likelihood, intensity and prevalence of adverse effects are greater than those of THC [33, 55]. SCs are thought to be associated with more severe psychosis, agitation and more sympathomimetic effects because they are more potent full receptor agonists [33, 43].

### 3.2.3. Toxicology and Adverse Events

Consumption of SCs may lead to rare but severe health consequences (see Table 1). The largest self-reported survey to be completed so far gathered data from over 22,000 participants from 123 countries. It revealed that those who were using SCs were thirty times more likely to need emergency medical treatment than users of traditional cannabis [72]. Among the adverse effects of SCs most commonly self-reported by users were panic and anxiety, paranoia, being scared, agitation, breathlessness, sweating, auditory hallucinations, chest pain, visual hallucinations, mood problems, being unable to talk, nausea, seizure, accidents, aggression, bladder problems; these symptoms were reported by a greater proportion of SC than cannabis users [72].

For 305 adolescents, like adults, when exposure to SCs was reported to the poison centre system, the most frequently reported adverse clinical effects were tachycardia, drowsiness/lethargy, agitation/irritability, vomiting, hallucinations/delusions, nausea, confusion, hypertension, chest pain and dizziness/vertigo.

---

**Picture 1.** Spice cigarette and dried herbal material with identified CP 47, 497 C8 (Slovenia, January 2009)
Acute SC intoxication is distinguished by agitation, anxiety and visual or auditory hallucinations, tachycardia, hypertension, mydriasis, hyperglycaemia, dyspnoea, nausea, vomiting and generalized tonic-clonic seizures [21, 26, 27, 51, 55, 61, 64, 68, 74]. Possible adverse effects also include violent behaviour, aggression, memory changes, sedation, psychosis, delusions, [18, 19, 26, 52, 54, 57]. Cases of severe intoxication may include stroke [23], encephalopathy [24], myocardial infarction [40, 64], ischemic stroke and emboli [64], acute kidney injuries [6, 38, 55, 64], excited delirium and physical violence emergencies; severe agitation can lead to rhabdomyolysis and the risk of renal failure, while seizures can lead to organ damage [25, 38, 64, 65]. Cases of accidental deaths, suicides and other causes of death have been related to SC [3, 48, 53-55, 65].

Patients also reported disorganized behaviour, mood alterations, intense suicidal ideation and behaviour [20, 21, 27]. According to Papaniti et al. [46] and to Schifano et al. [55], SCs can trigger the onset of acute transient psychosis in vulnerable individuals and/or the exacerbation of psychotic episodes in those with a previous psychiatric history and persisting psychotic disorders, the so-called ‘spicophrenia’, manic-like symptoms or relapse into a pre-existing bipolar disorder was also associated with SC use [36, 46, 55, 59].

Regular users may experience withdrawal and addiction symptoms, and a severe, prolonged withdrawal syndrome [33, 52, 55].

3.2.4. Management

In a majority of cases SC intoxications are clinically expressed by agitation, tachycardia, and nausea, and may not require inpatient treatment, usually symptomatic care alone with benzodiazepines, intravenous fluids and anti-emetics is sufficient [31, 64]. Most cases of SC intoxication(s) can be discharged from the emergency room after a short period dedicated to observation, monitoring and supportive care [31, 51, 64]. Less commonly, severe, life-threatening adverse effects or SC-related deaths appear, but estimates of incidence of are difficult to calculate, due to the lack of widely available, rapid laboratory confirmation, the great variety of SC compounds and the unknown number of individuals who are exposed to them [64].

Treatment of SC intoxication is supportive and symptomatic, as there is no antidote [20, 31]. Acute management consists of supportive care; benzodiazepines are indicated as the best way of controlling psychomotor agitation, anxiety, seizures [51, 31]. Antipsychotics are a possible alternative in combating agitation, psychosis and hallucinations [46, 51]. Antiemetics may be considered for nausea and vomiting [31]. Observation until resolution of abnormal vital signs, vomiting and psychiatric symptoms is recommended [7]. For persistent psychosis after SC intake, the use of neuroleptic medications (haloperidol, risperidone) has been reported [46].

3.3. Synthetic cathinones

3.3.1. Background

Synthetic cathinones (SKs) are central nervous system stimulants, analogues of natural cathinones derived from the active compound cathinone, which is present in the Catha Edulis plant (known as Khat or Qat) [36, 51, 67]. SKs are generally known as “bath salts” in the USA and as “plant food” in Europe [10, 31]. SKs mimic the hallucinogenic and euphoric effects of methamphetamine, cocaine or ecstasy [31, 51], and are β-keto-phenethylamines structurally similar to amphetamines/catecholamines [55], besides natural cathinones (cathinone, cathine), methyl derivatives, fluoro derivatives, methylenedioxy derivatives, pyrrolidine derivatives, and still more can be found on the drug market [62].

SKs are mainly available in the form of powder (white or light brown in colour), capsules and pills, in dosages ranging from a few milligrams to over 1 g [9, 51, 55]. Advertisements promote bath salt products by claiming they are safe, that they produce euphoria, and have sexual or energizing effects [9, 39].

SKs are sold under a variety of names (e.g. Ivory Wave, Purple Wave, Red Dove, Blue Silk) (Table 2). These products often contain various amphetamine-like chemicals, such as methylenedioxypyrovalerone (MPDV), mephedrone, pyrovalerone, butyline, dimethylcathinone, ethcathinone, ethylone, 3- and 4-fluoromethcathinone, methylene, pyrovalerone, but the complete contents of "bath salts" are largely unknown [9, 31, 36, 51].

According to Rech et al., the most frequent routes of administration include nasal insufflation (“snorting”) and oral ingestion; however, rectal, gingival, inhalation, smoking, parenteral (intravenous and intramuscular), “bombing” (wrapping powder in cigarette paper and swallowing it), intraocular, and “keying” (insufflating powder off the surface of a key) have been reported [51] (Table 2). The most common routes of administration differ by age; younger users
amine reuptake [36, 51]; each kind of SK displays subtle differences in its effects on neurotransmitters, but all the different kinds typically possess sympathomimetic/amphetamine-like effects [51, 55]. SKs present a high risk of liability to abuse and addiction [33, 60].

### 3.3.3. Toxicology and Adverse Events

Sympathomimetic adverse effects are common with exposure to SKs and most forms of toxicity are relatively mild [33]. Aggressive violent behaviour, paranoia and hallucinations are more frequently reported with SKs than with amphetamines [51]. SKs present a high risk of liability to abuse and addiction [33, 60].

#### Table 2. Common characteristics of synthetic cathinones: most famous brand (street) names, most popular active compounds, form on the market, means of use, neurobiology, acute adverse effects (psychopathology, others)

<table>
<thead>
<tr>
<th>NPS of abuse</th>
<th>Synthetic cathinones</th>
</tr>
</thead>
<tbody>
<tr>
<td>Most popular active compounds (chemical and alternative names) [9, 31, 33, 34, 51, 58, 62]</td>
<td>mephedrone (4-methylmethcathinone- 4-MMC, M-CAT), Methylene (bk-MDMA), 4-methylmethcathinone (4-MEC), Methyleneedioxyamfipiperadinovalerone (MDVP), Ethylone (bk-MDEA), Methedrone (bk-MPMA), Naphyrone, Flephedrone (4-Fluoromethcathinone - 4-FMC), 3-Fluoromethcathinone (3–FMC), Petylone, Uphedrone, 4PVP, Cathinone, Cathine, Methcathinone (ephedrine), Butylone (bk-MBDB), Brephedrone, Pyrovalerone, 3-MeOMC, 3-MMC; 4-BMC; 4-METO-PVP; 4-MEO-PBP; 4-MEO-PV9; 4-MPD; 4F-PV8; 4F-PV9; 4F-PVP; a-PBT; a-PHP; a-PVT; dibutylone; DL-4662; MDPPP; NEB; Pentedrone, PV-8, Dimethylcathinone, Ethcathinone,</td>
</tr>
<tr>
<td>Form on the market [51, 55]</td>
<td>tablets, capsules, powder</td>
</tr>
<tr>
<td>Means of use [31, 51]</td>
<td>peroral (tablets, capsules or solved in liquid), insufflation («snorting»), inhalation, smoking, powder wrapped in cigarette paper and swallowed («bombing»), dipping a key into the powder and insufflating («keying»), inserting into eye- intraocular («eye-balling»), injection (IM, IV), sublingual, gingival, rectal</td>
</tr>
<tr>
<td>Neurobiology [33, 36, 51, 55, 60]</td>
<td>dopamine, norepinephrine and/or serotonin reuptake inhibitors dopamine, norepinephrine release</td>
</tr>
<tr>
<td>Other acute toxicity [1, 2, 4, 7, 22, 28, 29, 31, 35, 37, 41, 42, 51, 56, 62, 69, 70, 75]</td>
<td>angina, palpitations, tachycardia, hypertension, mydriasis, tremor, hyperthermia, extremity vasoconstriction, chills, headache, motor automatism, rush, diaphoresis, nausea/vomiting, dizziness, drowsy, hyperventilation, dyspnoea, tachypnoea, hypotension, blurred vision, restlessness, chills, abdominal pain, rhabdomyolysis, electrolyte abnormalities, hypokalaemia, hyponatraemia, creatine phosphokinase elevation, liver function test elevation, metabolic acidosis, acute renal injury, renal failure, seizures, arrhythmias, coma, sudden cardiac death, death sympathomimetic toxidrome (involved agitation, mydriasis, diaphoresis, hypertension, tachycardia), serotonin syndrome</td>
</tr>
</tbody>
</table>

Tend to avoid injection, while older members of the population are more likely to inject [31].

The recreational use of SKs gained popularity around 2007, while their abuse in Russia and Eastern Europe had become widespread several decades earlier. In 2009 and 2010, the abuse of SKs (“bath salts” or “legal highs”) was reported in Western Europe and the U.S. [62]. SKs were first identified in 2008 by De Luca et al. [13, 55].

#### 3.3.2. Neurobiology

The main effects of SKs on the central nervous system are similar to those of other stimulants, mainly due to their action on monoamine reuptake and through functionally changing monoamine transporters [36].

Cathinone derivatives augment presynaptic concentrations of dopamine, norepinephrine and serotonin by stimulating their release and inhibiting monoamine reuptake [36, 51]; each kind of SK displays subtle differences in its effects on neurotransmitters, but all the different kinds typically possess sympathomimetic/amphetamine-like effects [51, 55]. SKs present a high risk of liability to abuse and addiction [33, 60].

#### 3.3.3. Toxicology and Adverse Events

Sympathomimetic adverse effects are common with exposure to SKs and most forms of toxicity are relatively mild [33]. Aggressive violent behaviour, paranoia and hallucinations are more frequently reported with SKs than with amphetamines [51]. Neuropsychiatric and cardiovascular toxicities are among the most common reasons for emergency medical treatment [22, 28, 35, 37, 51] (Table 2). A retrospective review of the Poison Data System on 1,633 patients seeking medical care due to SKs revealed that 15.5% of these cases resulted in
major outcomes, while 0.6% of patients died, and the most common clinical features were agitation, tachycardia, hallucinations, hypertension, confusion, creatine phosphokinase, drowsiness, mydriasis, tremors, electrolyte abnormalities, chest pain, fever, nausea, diaphoresis, hyperventilation, hypotension, vomiting, coma, liver function test elevation, rhabdomyolysis, creatine increase and seizures [69].

The most common clinical findings reported to poison centres include: agitation, aggression, tachycardia, hallucinations, hypertension, mydriasis, tremors, fever, confusion, psychosis, chest pain, nausea, palpitations, peripheral vasconstriction, headache, and convulsions [22, 28, 29, 35, 37, 49, 51]. The intoxicated patient often experiences vasoconstriction, so causing cold extremities and skin discoloration, skin rashes, and bruxism [31].

In some case toxicities can be severe, even life-threatening; exposure to SKs may precipitate a sympathomimetic toxidrome including hypertension, tachycardia, mydriasis, agitation, sweating, hallucinations, psychosis, dehydration, hyperthermia, seizures [33, 35, 51, 69]. Additional serious effects reported include rhabdomyolysis [4], electrolyte abnormalities [22], hypotension, acute renal failure [29], seizures, excited delirium (multiple case reports) [42, 44, 49, 70], suicide (single case reports) [56], sudden cardiac death (single case reports) [51]. There are several papers that describe deaths related to SK exposure [1, 2, 35, 37, 56, 75]: development of serotonin syndrome [41, 69], excited delirium syndrome [42, 44, 70], organ failure [2, 4]. Other case reports have shown paraspinal compartment syndromes due to injection [32] and Parkinson-like syndrome due to manganese contamination [63].

Psychopathological manifestations seen in patients presenting for medical intervention include agitation, psychosis, anxiety, paranoia, delusions, dysphoria, depression, suicidal ideation, confusion, short-term memory loss, tremors, seizures, and coma [31, 50]. SK users tend to develop increased aggression, including suicide [69].

Abusers report strong cravings and the urge to repeatedly use or increase their dose [31]. A significant proportion of SK users report tolerance, dependence or withdrawal symptoms [50].

3.3.4. Management

Acute management consists of symptomatic treatment and supportive care; benzodiazepines are the most likely agents of choice (at high dosages or with frequent re-dosing) [51, 55, 69]. Mechanical ventilation, intravenous hydration, hospitalization and intensive care could be required [28, 51].

Benzodiazepines are indicated to win control over psychomotor agitation, anxiety, seizures [51]. Symptoms of aggression and psychosis may be treated with sedation (benzodiazepines, propofol) and antipsychotics (haloperidol or atypical agents such as quetiapine or ziprasidone) [28, 51, 62]. Use of antipsychotics alone for agitation may further contribute to the acute toxicity effects of SKs [51, 55].

Observation should be continued until the moment of resolution of abnormal vital signs, vomiting and psychiatric symptoms [7]. No antidote is available [20].

4. Discussion

According to the review of Liechti, a majority (85-95%) of NPS (SC- and SK-) related emergency medical problems prove to be minor to moderate poisonings; however, severe intoxication by SCs and/or SKs can cause life-threatening adverse effects and death [33]. The incidence of severe toxicity is difficult to estimate, due to the lack of rapid laboratory tests to confirm exposure, the rapidly changing variety of NPS compounds and because of the unknown total number of exposed users [64]. Neither SCs, nor SKs can be detected by routine urine immunoassay screening for drugs of abuse, hence during the treatment of acute toxicity the identity of substances usually remains unknown, which leads to the further possibility of underrating SC- and SK-related toxicity, even if confirmatory clinical testing is available [65].

The management of intoxication is symptomatic and supportive, as antidotes are not available [20]. Heart rate, blood pressure and body temperature should be monitored in cases of acute toxicity [33].

Hypertension should be treated primarily with nitrates, while b-blockers should be avoided [33]. The combination of sedation, fluids and aggressive physical cooling (antipyretics are ineffective) may be required [20, 25, 33, 51, 69]. Benzodiazepines are the drugs of choice in cases of serotonin syndrome, excited delirium or/and sympathomimetic toxidrome [25, 31, 33, 51]. Rapid and aggressive sedation (with doses higher than normal, and frequent re-dosing); benzodiazepines should be indicated in these cases because of the presence of multiple effects, to protect against physical violence, decrease excessive heart rate and blood pressure, prevent seizures, reduce muscular hyperactivity, rhabdomyolysis and renal failure [31, 33]. Symptoms of aggression and psychosis may
be treated with sedation (benzodiazepines) and antipsychotics (haloperidol or atypical agents such as quetiapine or ziprasidone). The use of haloperidol without benzodiazepines is generally not recommended because seizure and dysrhythmia thresholds are lowered and negative drug-induced psychological effects including anxiety may increase [33]. After the medical stabilization of patients hospitalized for NPS toxicity, psychosis may persist, in which case dopamine blockage with neuroleptics is indicated [46].

SC- or SK-related toxicity should be considered by clinicians in cases where young adults show unexplained agitation or cardiovascular symptoms. An evaluation of substance use should be performed in patients with acute neuropsychiatric complaints, while SC or SK intoxication should be suspected in a patient with an acute onset of altered mental status, excited delirium, renal failure or sympathomimetic symptoms.

Acute behavioural disturbance is challenging because it is a potentially life-threatening clinical condition for each patient, and brings with it risks for patients, the general public, police and care providers, as it is extremely difficult to manage and is resistant to conventional interventions; in some cases emergency anaesthesia may be required.

5. Conclusions

The treatment of acute intoxication should be addressed by facing the issue of how best to target signs and symptoms. There is a need for further evidence-based treatment recommendations for acute intoxications. What is currently most worrying is the lack of evidence in support of treatment guidelines for prolonged treatment.

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Psychopharmacol. 12392)): 390-393

Acknowledgements
None

Role of the funding source
Authors state that this study was financed with internal funds. No sponsor played a role in study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication.

Contributors
The authors contributed equally to this manuscript.

Conflict of interest
None

Ethics
The technical work done in preparing this manuscript did not involve humans in any way, and therefore did not require IRB or other ethics committee approval, or informed consent.

Note
It is the policy of this Journal to provide a free revision of English for Authors who are not native English speakers. Each Author can accept or refuse this offer. In this case, the Corresponding Author accepted our service.

Received February 6, 2017 - Accepted May 18, 2017
Relationship between self-mutilative behaviour and novelty seeking, the presence of antisocial and borderline personality disorders, and severity of psychopathology in a sample of male patients with Heroin Use Disorder

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Summary

Background: Self-mutilative behaviour (SMB) is common among patients with heroin use disorder (HUD) and poses a severe threat to the safety and well-being of these patients. Aim: The main aim of the present study was to evaluate the relationship between SMB and novelty seeking (NS), while also carefully assessing the presence of antisocial (ASPD) and borderline (BPD) personality disorders and the severity of psychopathology in a sample of patients with HUD. Methods: Participants, in a group comprising 236 patients with HUD, were evaluated by applying the Symptom Checklist-Revised (SCL-90-R) and NS subscale of the Temperament and Character Inventory (TCI). In addition, BPD and ASPD were assessed with the Structured Clinical Interview for DSM-III-R-Personality Disorders (SCID-II). Results: Age, duration of education and marital status did not differ between those with a history of SMB (n=116, 49.1%) and those without (n=120, 50.9%). Age at first heroin use and percentage of those who were employed were lower among those with a history of SMB. Severity of psychopathology, ASPD, BPD and NS scores were higher among those with a history of SMB. In logistic regression analysis, high NS, together with the presence of both BPD and ASPD, together with severity of general psychopathology, in particular hostility, predicted patients’ history of SMB. Conclusions: These findings suggest that the history of SMB is related to the severity of NS, while the severity of psychopathology, particularly the hostility dimension, and the presence of BPD and ASPD may have additional effects on SMB among male patients with HUD.

Key Words: Antisocial Personality Disorder; Borderline Personality Disorder; Psychopathology; Heroin Use Disorder; Novelty Seeking; Self-mutilative Behaviour

1. Introduction

Although numerous studies have indicated that SMB predicts suicide [10], such behaviours are defined as “deliberate self-injury to body tissue without the intent to die” [5, 31]. SMB typically starts in adolescence and involves many episodes and a variety of methods, including cutting, burning, slapping, bunging, picking, and bone breaking [30]. Regardless of methods, SMB is a common and pervasive public health problem, particularly among those with substance use disorders (SUDs) [20, 21]. Young age [20], childhood physical abuse [20, 21], suicide-attempt history [20, 21], and having a personality disorder [21] have been proposed as determinants of SMB among male subjects with different types of SUD. Joiner [37] theorises that substance use helps individuals habituate to self-inflicted violence. Although there is no direct evidence for this conceptual explanation, there is strong evidence that individuals suffering from SUDs are more likely to self-mutilate [20, 21, 44, 48, 67]. The SMB rate ranges between 34.0% and 62.0% among treatment-seeking patients with SUD [14, 20, 21, 25, 26, 48]. Rates are even higher in patients with SUD (the risk of SMB was 3.1 to 8.8 times higher) than patients with alcohol use disorder (AUD) [20, 48].
Among different types of SUDs, patients with heroin use disorder (HUD) have the highest risk of SMB [14, 27, 45, 46]. Among the homogeneous groups of patients with HUD, the SMB rate ranged between 25% [46] and 88% [51]. Interestingly, SMB could be a consequence or even a cause of functional changes in the opioid system, on which heroin shows its mechanism of action [51]. Thus, SM is a prevalent behaviour problem in patients with SUD, particularly among those with HUD, yet in this population many fundamental aspects of SMB remain unknown. Despite the many uncertainties, what is clear is that this behaviour poses a severe threat to the safety and well-being of these patients [30].

Both epidemiological and clinical studies have reported a high prevalence of personality disorders in populations with SUD [62], particularly borderline personality disorder (BPD) and/or antisocial personality disorder (ASPD) of the B cluster [39, 54, 61]. These personality disorders were found to be associated with an increased risk of having the poorest overall outcomes in patients with SUD [7], such as early onset of SUD, regular intoxication, more extensive and severe substance use problems than those without diagnoses of these personalities [6, 39] consistently with this, a majority of the studies that have evaluated SMB so far have concentrated on BPD and ASPD [11, 42], and their results indicate that additional diagnoses of these personality disorders increase the risk of developing SMB among those with SUD [8, 13]. Studies conducted among patients with HUD showed that SMB is related to ASPD diagnosis (12.5 times higher risk) [22] and features of borderline personality [27, 46]. Thus, the relationship between SMB and, among personality disorders, ASPD and BPD in particular, is worth investigating in the population with HUD.

Specifically, when SMB is viewed through the lens of developmental psychopathology, it becomes apparent that early temperamental risk factors are associated with the risk of developing SMB and a range of highly comorbid conditions, such as BPD and ASPD [11]. Novelty seeking (NS) is a temperamental trait in Cloninger’s model of personality, and is considered moderately heritable, normally distributed, developmentally and situationally stable [9]. Individuals with high NS preferences tend to be quick-tempered, excitable, exploratory, curious, enthusiastic, ardent, easily bored, impulsive and disorderly [40]. There is considerable evidence that: highly motivated novelty seekers are at increased risk of using substances of abuse compared with those with low motivation [3, 64], NS functions as a vulnerability factor for SUD in general [32, 35], that it predicts early-onset SUD [36], is associated with the amount of substance used and severity of SUD [2] and constitutes a risk factor for dropping out of treatment [33]. NS also has been suggested to be a fundamental aspect of ASPD [50] and BPD [4, 38]. NS and ASPD are common findings in those who suffer from addictions, such as AUD [18] and SUD [50].

Although comorbidity is a common situation among those with SUD, when ASPD and/or BPD are present among patients with SUD, then the risk of comorbid psychopathology is even higher [43]. In this connection, BPD patients with additional depression have more SUD comorbidity, have higher NS and are more likely to engage in SMBs [4]. Thus, additional psychopathology seems to increase the risk of high NS and SMB among those with SUD [23]. Lastly, a few studies have evaluated and/or suggested a relationship between NS and SMB [4, 15, 23] – a topic that calls for further assessment, particularly in high-risk populations, such as patients with HUD.

The main aim of the present study was to evaluate the relationship between SMB and the severity of NS, while closely monitoring the presence of ASPD and BPDs in a sample of patients with HUD. Comorbid psychopathology is common among patients with HUD [19] and may be related to SMB [24, 25, 26, 47]. Thus a secondary aim was to monitor the effects of general psychopathology.

2. Methods

2.1. Design of the study

The study was conducted in Research, Treatment and Training Centre for Alcohol and Substance Dependence (AMATEM), Bakirkoy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery, in Istanbul. The procedures followed in the study were in accordance with the ethical standards of our local committee responsible for human experimentation and were compliant with the Helsinki Declaration (1975, revised 1983). Before procedures were implemented, the goal of the study was explained exactly to the participants and they were told not to hesitate if they wished to ask any questions. Then, after patients’ written informed consent had been obtained, a semi-structured sociodemographic form and the appropriate scales were applied to all participants. Interviews with the study group were conducted after a stabilization period, that is, 1 to 2 weeks after the last
day of heroin use.

2.2. Sample

As many as 236 consecutively admitted male patients (117 inpatients and 119 outpatients) with HUD participated in the study. Being a female was made a criterion for exclusion to avoid bias, since during the study period only five female patients with HUD were admitted to the clinic. Mean age of the total sample was 27.19±7.62 (26.91±6.22 for inpatients and 27.46±8.80 for outpatients). All participants met the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition) [1] diagnostic criteria for HUD according to the psychiatric interview conducted by an expert clinician.

2.3. Instruments

All patients were assessed by using a semi-structured sociodemographic form. In addition, the diagnoses of BPD and ASPD were evaluated with the relevant section of the Structured Clinical Interview for DSM-III-R-Personality Disorders (SCID-II) [60], Turkish version [59], conducted by a trained interviewer (CE).

2.3.1. Self-mutilative Behaviour Questionnaire (SMBQ)

Lifetime history of SMB was assessed during the clinical interview, and was rated on the semi-structured form designed previously by our group for this purpose [20]. SMB is defined as an act performed on oneself that is physically violent, intentional and purposeful, though not suicidal. These acts include cutting, burning, hitting oneself, inserting sharp objects into body orifices and pulling out body hair. This definition is similar to the superficial/moderate forms of SMB in Favazza’s classification [31]. Although differences in the various definitions given for SMB may account for the discrepancies between the results to be found in the literature, the definition used in the present study was the one appearing in previous reliable studies [20, 21, 55]. Responses were dichotomous (yes/no) for each type of SMB, rather than continuous; thus they failed to reflect severity. Those who had one or more incidents (episodes) of lifetime SMB were considered as a self-mutilator. Each incidence of SMB separate from any other was considered as an episode of SMB, which supplied information about the recurrence and the severity of SMB. Other than types of SM, age at onset of SMB, number of lifetime episodes of SMB and whether the patient was intoxicated with alcohol at the times when they self-mutilated (in most of the SMB incidents) were all evaluated too. After a detailed enquiry, all patients who had an affirmative answer were physically examined to better understand any sequelae of SM. This was done to gain otherwise unavailable information about the presence, severity and frequency of SM. Prompting events for SM were not assessed. Psychometric properties of this questionnaire were not evaluated, because these studies (including the present one) were not designed for this purpose [20, 21, 23, 25, 26, 27].

2.3.2. Symptom Checklist-Revised (SCL-90-R)

SCL-90-R is a self-report measure [16] used to assess psychopathological symptoms. It has 90 items rated with a 5-point Likert scale (1, no problem to 5, very serious) to assess the extent to which individuals have experienced the listed symptoms in the last 7 days. These 90 items were grouped into nine subscales, namely, somatization, obsessive compulsive, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychotism. It was suggested that the higher the scores on SCL-90-R is, the more severe the psychological distress that the individual has experienced. In the present study, the Turkish version of SCL-90-R was used [12].

2.3.3. Temperament and Character Inventory

For evaluation of NS, the TCI of Cloninger et al. [9] was used in the Turkish version, forced-choice, self-report scale [41]. NS is a 40-item multifaceted higher order temperament trait that consists of the following four aspects of lower order traits: Exploratory Excitability versus Stoic Rigidity (NS1) (11 items), Impulsiveness versus Reflection (NS2) (10 items), Extravagance versus Reserve (NS3) (9 items) and Disorderliness versus Segregation (NS4) (10 items). The reliability and validity of the Turkish version of the TCI were supported by its psychometric properties and construct validity [41]. In the Turkish version, Cronbach’s alpha was 0.74 for NS [41]. In the present study Cronbach’s alpha was 0.84.

2.4. Data analysis

The statistical package Statistical Packages for the Social Sciences (SPSS) 15.0 for Windows was used for all the analyses. Categorical variables were compared by means of the chi-square statistics. Odds ratios and 95% confidence intervals were calculated. We used Student’s t-test to compare the groups on
Taking SMB as a dependent variable, two logistic regression models were performed. For all statistical analysis, p values were two-tailed and differences were considered significant at p<0.05.

### 3. Results

Age, duration of education and marital status did not differ between those with the history of SMB (n=116, 49.1%) and those without (n=120, 50.9%). Age at first heroin use and employment rate both turned out to be lower among those with a history of SMB. Severity of psychopathology, ASPD, BPD and NS scores were higher among those with a history of SMB (Table 1). In the first logistic regression analysis, severity of general psychopathology predicted the history of SMB, whereas when subdimensions of SCL-90-R were entered into the analysis as independent variables instead of general psychopathology, hostility alone predicted SMB (Table 2). In the second logistic regression analysis, the presence of BPD and ASPD were entered in the analysis as independent variables, both of which predicted the history of SMB, together with the hostility factor (Table 2). Lastly, when NS was included in the analysis as an independent variable, the severity of NS predicted a history of SMB, together with hostility and the presence of both BPD and ASPD (Table 2).

### 4. Discussion

The SMB rate found in this study (49.1%) was in concordance with the rates found among patients with HUD in previous studies (25.0-88.0%) [14, 20, 21, 25, 26, 46, 48, 51]. Further, in a way similar to Oyefeso et al.’s [48] study (49.0%), half of the patients with HUD had SMB in the present study.

---

**Table 1. Sociodemographic and scale scores according to the presence of self-mutilative behaviour (SMB)**

<table>
<thead>
<tr>
<th></th>
<th>No SMB (n=120, 50.9%)</th>
<th>SMB (n=116, 49.1%)</th>
<th>t</th>
<th>(\chi^2)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>27.73 ± 8.45</td>
<td>26.66 ± 6.70</td>
<td>-1.076</td>
<td>0.283</td>
<td></td>
</tr>
<tr>
<td>Duration of education</td>
<td>9.09 ± 2.98</td>
<td>8.82 ± 2.68</td>
<td>0.741</td>
<td>0.460</td>
<td></td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
<td>2.185</td>
<td>0.335</td>
<td></td>
</tr>
<tr>
<td>Single</td>
<td>90 (75.0)</td>
<td>96 (82.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>20 (16.7)</td>
<td>14 (12.1)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Divorced</td>
<td>10 (8.3)</td>
<td>6 (5.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employment status</td>
<td></td>
<td></td>
<td>9.247</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Not working</td>
<td>71 (59.2)</td>
<td>87 (75.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Employed</td>
<td>36 (30.0)</td>
<td>16 (13.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Part-time employed</td>
<td>13 (10.8)</td>
<td>13 (11.2)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at first heroin use</td>
<td>20.88 ± 6.11</td>
<td>19.10 ± 4.11</td>
<td>2.632</td>
<td>0.009</td>
<td></td>
</tr>
<tr>
<td>Novelty Seeking</td>
<td>19.03 ± 4.66</td>
<td>21.39 ± 5.18</td>
<td>-3.680</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**SCL-90-R**

<table>
<thead>
<tr>
<th>Scale</th>
<th>No SMB</th>
<th>SMB</th>
<th>t</th>
<th>(\chi^2)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Somatic Complaints</td>
<td>1.29 ± 0.74</td>
<td>1.62 ± 0.74</td>
<td>-3.377</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Obsessive Compulsive</td>
<td>1.40 ± 0.90</td>
<td>1.81 ± 0.80</td>
<td>-3.754</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Interpersonal Sensitivity</td>
<td>1.42 ± 0.97</td>
<td>1.70 ± 0.88</td>
<td>-2.384</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Depression</td>
<td>1.57 ± 0.96</td>
<td>1.89 ± 0.91</td>
<td>-2.592</td>
<td>0.010</td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>1.17 ± 0.90</td>
<td>1.52 ± 0.83</td>
<td>-3.700</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Hostility</td>
<td>1.18 ± 0.95</td>
<td>1.72 ± 1.04</td>
<td>-4.163</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Phobias</td>
<td>0.66 ± 0.74</td>
<td>0.83 ± 0.66</td>
<td>-1.859</td>
<td>0.064</td>
<td></td>
</tr>
<tr>
<td>Paranoid Ideation</td>
<td>1.17 ± 0.91</td>
<td>1.52 ± 0.83</td>
<td>-3.112</td>
<td>0.002</td>
<td></td>
</tr>
<tr>
<td>Psychotic</td>
<td>0.87 ± 0.75</td>
<td>1.15 ± 0.78</td>
<td>-2.791</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>SCL-90 total score</td>
<td>12.42 ± 7.71</td>
<td>15.84 ± 7.20</td>
<td>-3.524</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

**Antisocial PD presence**

<table>
<thead>
<tr>
<th></th>
<th>No SMB</th>
<th>SMB</th>
<th>t</th>
<th>(\chi^2)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antisocial PD presence</td>
<td>43 (32.8)</td>
<td>72 (61.5)</td>
<td>20.490</td>
<td>&lt;0.001</td>
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</table>

**Borderline PD presence**

<table>
<thead>
<tr>
<th></th>
<th>No SMB</th>
<th>SMB</th>
<th>t</th>
<th>(\chi^2)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Borderline PD presence</td>
<td>13 (10.1)</td>
<td>32 (27.4)</td>
<td>12.247</td>
<td>&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Independent Samples t Test, Chi-square test, Odds Ratio (OR)=3.274, 95% Confidence Interval (CI)=1.944-5.515; OR=3.359, 95% CI=1.664-6.783. SCL-90-R: Symptom Checklist-Revised, PD: Personality disorder, Significance at p<0.05.
main finding of the present study was that higher NS scores predicted SMB among men with HUD, together with the presence of BPD and ASPD diagnoses and the severity of general psychopathology, in particular hostility. Consistently with these findings, severity of hostility [24, 25, 26] and the presence of BPD [11, 27, 45, 46] and ASPD [11, 22, 45] were found to be related to SMB in previous studies, whereas this is the first study to relate NS to SMB among patients with HUD.

Few studies have so far evaluated SMB among homogeneous groups of patients with HUD, all of which included both males and females. Oyefeso et al. [48] suggested that the predominant function of SMB, in HUD patients, was affect-regulation and the secondary one, self-punishment. Pérez de los Cobos et al. [51] even suggested that SMB (88% had experienced SMB episodes) can provide useful criteria for subtyping patients with HUD. Maloney et al. [46] suggested that the presence of BPD is one of the main risk factors for SMB (25% had episodes of SMB) among patients with HUD. The study conducted among 188 therapeutic community entrants (34% had lifetime SMB) reported that the patients with HUD was significantly more likely than the cannabis group to have a history of SMB [14]. Lastly, a study conducted among inpatients with SUD suggested that those with SMB had significantly higher rates of HUD, personality disorder, and a greater number of substance use problems [45]. Thus, HUD seems to be closely associated with the risk of SMB [14, 27, 45, 46]. One possible explanation for this could be that heroin is a harder drug of abuse, as compared with other substances, and the number of behavioural problems, including SMB associated with HUD, is consequently higher among this group [17, 45].

The most commonly cited diagnosis in adult psychiatric inpatient self-mutilators is BPD [11, 49, 57, 66] and ASPD [11]. This relationship is even more apparent among patients with SUDs [27, 63], particularly among those with HUD [22, 46]. Consistently with this, ASPD and BPD were identified as unique predictors of SMB in the present study. Besides the self-harm criterion within the BPD diagnosis, one of the reasons for this association may be that individuals are trying to relieve their unpleasant feelings, which they have to cope with as a result of their personality disorders [46, 52]. Patients with HUD mostly use immature defense mechanisms (especially acting out and splitting), which are themselves correlated with NS, so suggesting that even heroin use itself may be recognizable as a maladaptive coping effort by these patients with high NS preferences, although the use of maladaptive defences might otherwise simply be one of the consequences of long term HUD [28]. Similarly, there is no clear cause-and-effect relationship between NS and SUD, which seem to be synergistically capable of influencing each other [65]. A relationship with this acting-out was higher in AUD patients who had a history of SMB (n=53, 44.92%) and predicted SMB in this group [29]. Thus, the NS trait is probably valuable not only for predicting individual vulnerability to SUD but also for generating successful treatment for patients with SUDs [65].

Possible links between SMB and hostility have been implicated in previous studies [34, 58]. In the study carried out among adolescent students, prior to SMB, feelings both of hostility and anxiety were described, which indicated support for the hostility model of SMB [53]. In a recent study conducted among male veterans with PTSD, it was found that SMB was related to hostility [55]. So too, although

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**Table 2. Predictors of high risk self-mutilative behaviour (SMB) in a logistic regression**

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>S.E.</th>
<th>Wald</th>
<th>df</th>
<th>p</th>
<th>Exp(B)</th>
<th>95% C.I. for EXP(B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Step 1a</td>
<td>SCL-90-R</td>
<td>0.065</td>
<td>0.019</td>
<td>12.089</td>
<td>1</td>
<td>0.001</td>
<td>1.067</td>
</tr>
<tr>
<td>Step 1b</td>
<td>Hostility</td>
<td>0.545</td>
<td>0.140</td>
<td>15.173</td>
<td>1</td>
<td>0.000</td>
<td>1.724</td>
</tr>
<tr>
<td>Step 2</td>
<td>Hostility</td>
<td>0.434</td>
<td>0.146</td>
<td>8.878</td>
<td>1</td>
<td>0.003</td>
<td>1.543</td>
</tr>
<tr>
<td></td>
<td>Antisocial PD</td>
<td>-0.911</td>
<td>0.287</td>
<td>10.050</td>
<td>1</td>
<td>0.002</td>
<td>0.402</td>
</tr>
<tr>
<td></td>
<td>Borderline PD</td>
<td>-0.870</td>
<td>0.401</td>
<td>4.718</td>
<td>1</td>
<td>0.030</td>
<td>0.419</td>
</tr>
<tr>
<td>Step 3</td>
<td>Hostility</td>
<td>0.320</td>
<td>0.155</td>
<td>4.288</td>
<td>1</td>
<td>0.038</td>
<td>1.377</td>
</tr>
<tr>
<td></td>
<td>Antisocial PD</td>
<td>-0.881</td>
<td>0.290</td>
<td>9.218</td>
<td>1</td>
<td>0.002</td>
<td>0.414</td>
</tr>
<tr>
<td></td>
<td>Borderline PD</td>
<td>-0.839</td>
<td>0.405</td>
<td>4.296</td>
<td>1</td>
<td>0.038</td>
<td>0.432</td>
</tr>
<tr>
<td></td>
<td>Novelty seeking</td>
<td>0.067</td>
<td>0.033</td>
<td>4.160</td>
<td>1</td>
<td>0.041</td>
<td>1.069</td>
</tr>
</tbody>
</table>

Nagelkerke R²: Step 1a = 0.073, Step 1b = 0.092, Step 2 = 0.185, Step 3 = 0.206, SCL-90-R: Symptom Checklist- Revised, PD: Personality disorder, Significance at p<0.05.
associations between SMB and high severity of general psychopathology were detected, hostility was the predictor of SMB in three different samples of inpatients with both AUD [24, 25] and SUD [26]. Lastly, Dell’Osso et al. [15] suggested that SMB is distinguished by high levels of hostility and NS.

4.1. Limitations

The present study has its limitations. First, because this study is cross-sectional, its findings are unable to indicate the causal relationships among the primary constructs of interest. Second, the assessment of SMB was dichotomous rather than continuous, which therefore failed to reflect severity. Also, psychometric properties of the questionnaire used to assess SMB in the present study were not evaluated, although they have been used successfully in several studies [20, 21, 24, 25, 26, 27]. Third, female patients may have a different profile concerning psychopathology, ASPD, BPD, NS and SMB. Indeed, current evidence indicates that there are notable gender differences in BPD, in particular, men with BPD have higher levels of NS [4], are more likely to display SUD, and to have treatment histories relating to SUD and ASPD than women with BPD [56]. Finally, the generalizability of the findings of the present study to the wider, non-treatment seeking, mixed-gender and general population samples of patients with SUDs now calls for further study.

5. Conclusions

From the clinical perspective, the fact that SMB occurs at extremely high levels among patients with HUD, and is strongly associated with NS, BPD, ASPD and hostility, needs to be borne in mind when assessing risk. Thus, to better understand SMB among patients with HUD, clinicians must carefully evaluate NS and hostility, together with the presence of BPD and ASPD in this population.

References

and correlates. Drug Alcohol Depend. 98(3): 227-234.

Acknowledgements

None.

Role of the funding source

Authors state that this study was financed with internal funds. No sponsor played a role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

C.E., V.K., I.A., T.C., B.E., R.A., designed the study and wrote the protocol. C.E., V.K., I.A., G.U., T.C., B.E., R.A., managed the literature searches and analyses. C.E., I.A., G.U., T.C., B.E., R.A., undertook the statistical analysis, and all the authors discussed the results. C.E., V.K., G.U., wrote the first draft of the manuscript. All authors revised the last draft. All the authors contributed to, and have approved, the final manuscript.

Conflict of interest

Authors declared no conflict of interest.

Ethics

Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study does not require ethics committee approval because the study was conducted according to a non-interventional protocol and whether patients participate to the study have not changed treatment to be applied.

Note

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Received May 30, 2017 - Accepted August 25, 2017
Regular article


Impact of employment and marital status on lapse risk situations among addicted patients in Methadone Maintenance Treatment

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Summary

Background: Identifying risk situations for lapses into substance abuse plays a central role in planning appropriate treatments and predicting the possibility of lapse and relapse. Methods: In the present study, 160 addicted male patients in Methadone Maintenance Treatment (MMT) were chosen from four randomly selected MMT centres in Isfahan. The inclusion criteria were being male opioid users who were in MMT treatment and were willing to participate in the study. Of these 160 participants, 82 were single and 78 married; in addition, 90 of them were employed and the other 70 unemployed at the time of the study. For data collection, patients were asked to complete the Inventory of Drug-Taking Situations (IDTS), a self-report questionnaire for risk situations. Results: The results of MANOVA analysis indicated that Physical Discomfort and Pleasant Times with Others were risk situations for the employed participants, whereas Pleasant Emotions, Urges and Temptations to Use, Social Pressure to Use and Testing Personal Control were the main risk situations for the unemployed ones. Considering marital status, Unpleasant Emotions, Physical Discomfort and Conflict with Others were the risk factors for the married participants, whereas Pleasant Emotions, Pleasant Times with Others, Urges and Temptations to Use, Social Pressure to Use and Testing Personal Control were the situations at risk for the single ones. Conclusions: Occupational activities are essential for lapse/relapse prevention, since they facilitate the establishment of non-substance abusing social networks; moreover, while married participants had fewer risk situations, it is likely that married life is open to influence from an addicted partner.

Key Words: Marital status; employment status; Methadone Maintenance Treatment (MMT); risk situations; addiction

1. Introduction

Various treatment strategies have been proposed to treat addiction. With regard to opioid addiction, the standard treatment is maintenance therapy with opioid agonists. Opioid agonist maintenance treatment, when correctly conducted, makes it possible to interrupt illegal narcotic drug use. The most commonly used medications are methadone and buprenorphine [47]. Due to its effectiveness, the World Health Organization included methadone in the list of “essential medicines for priority diseases” in 2005 [55]. Both Perry et al. [40] and Leece et al. [31], stated that for patients in treatment for opioid use disorders, methadone therapy ends in several better outcomes, such as retention in drug treatment and reduced opioid use. It is worth mentioning too that a wide variety of factors, such as education, employment status, gender, income, marital status, place of residence, age, and ethnicity, to name but a few, might be related to, and influence substance abuse [24, 53]. Among all these factors, the present study will delve into employment or occupational status, and into family or marital status. In any case, before opening the discussion on these two factors, a brief presentation of lapse, the main concern of the present study, seems crucial.

Lapse implies at least a single episode of use but not “severely re-initiating” substance abuse. The risk of a lapse event, despite ongoing pharmacological treatments such as methadone, implies the significant role of the situations that instigate drug seeking, along with behaviours associated with substance use [34, 17]. Situations directly related to these behav-
ours and to situations triggering emotional distress are equally lapse-inducing in opiate users [26]. As stated by Gossop et al. [18], lapse is a quite common addictive behaviour, so much so that it is frequently observed even among those who could manage to successfully quit substance abuse.

Smyth et al. [50] cite the assertion made by Ro- unsaville et al. [44] that lapse and relapse prevention have turned into a major challenge to clinicians and those who work with substance abusers. They found that two-thirds of the opiate users who participated in their study lapsed. In Iran, fifty percent of recovered substance abusers are inclined to re-initiate substance abuse [48]. This might support what is called by Gos- sop et al. [18] the “critical period” when the users are susceptible to lapse or relapse; it follows that preventive measures need to be taken in this regard. How- ever, Kenford et al. [29] take an extreme stance by claiming that all lapses eventually end in relapse.

As the first concern of the present study, the relationship between employment or having a job and substance abuse continues to be a major issue in political and scientific discussions [24]; this relationship is, moreover, complex and multifaceted, and it involves mutual influencing [19]. It is therefore a topic of intense interest among researchers today. After discussing the obstacles that impede the employment of people recovering from substance abuse, Shepard et al. [49] concluded that the inability to control substance abuse, family problems, poor social skills and work experience, together with the unwillingness of employers to hire the addicted, are among the major problems. In fact, substance abuse significantly limits the opportunities of the addicted for employment or beginning a career. As stated by Brewer et al. [8], unemployed individuals might continue using substances, either during treatment or after recovery, to a greater extent than those who are employed.

As the second concern of the present study, marriage has been reported to act as a protective factor against substance abuse; however, the relation between these two factors has not yet been fully un- derstood, especially during addiction treatment [22]. Merline et al. [37], a study of substance use among young adults, found that married individuals would be less likely to use cocaine than unmarried ones. Moreover, low marital satisfaction is closely correlated with poor treatment outcome [6, 36]; in this connection, little research has been done on the relationship between marital status and substance abuse during treatment [22].

Despite the importance of identifying factors that might increase the risk of lapse, there remains a paucity of evidence in this regard. The main aim of the present study has been to answer the two follow- ing questions:

1. Is there any significant difference between employed and unemployed substance abusers in MMT in experiencing lapse?
2. Is there any significant difference between single and married substance abusers in MMT in experiencing lapse?

2. Methods

2.1. Sample

160 male addicts in Methadone Maintenance Treatment (MMT) were chosen from four randomly selected MMT centres in Isfahan, Iran. The inclusion criteria were: being male opioid users who were in MMT treatment and were willing to participate in the study. Of these 160 participants, 82 were single and 78 married; in addition, 90 of them were employed and 70 were unemployed at the time of the study. Their age range varied between 22 and 50. Furthermore, by ‘married’ we mean those who were legally married and, by ‘singles’, those who were unmarried. It is worth mentioning that, considering the cultural norms of Iran, there are no cases of cohabiting with a partner without being legally married.

2.2. Instruments

The Inventory of Drug-Taking Situations (IDTS), developed by Annis et al. [2], is a 50-item self-report questionnaire that outlines situations in which a client has used alcohol or another substance. The situations are classified in the form of eight subscales, namely, Unpleasant Emotions (UE), Physical Discomfort (PD), Pleasant Emotions (PE), Testing Personal Control (TPC), Urges and Temptations to Use (UT), Conflict with Others (CO), Social Pressure to Use (SP), and Pleasant Times with Others (PT). Participants are requested to specify their frequency of drinking or substance use in each of 50 situations listed on a Likert scale ranging from “never” to “almost always.” The inter-rater reliability of categorizing items into subscales was high (.92-.96%) [3]. Pashaei et al. [39] investigated the reliability and validity of the Persian version of IDTS in Iran. The results indicated that all the IDTS subscales were reliable (Cronbach's alpha ranged from 0.7 to 0.81). The overall reliability of the questionnaire estimated by Cronbach’s alpha for the
The present study was 0.83.

2.3. Procedure

First, the participants’ consent to participating in the study was obtained and they were informed about the aims and purposes of the study. Then, the Persian version of the Inventory of Drug-Taking Situations (IDTS) was distributed among the participants and they were allowed to ask any questions in cases of ambiguity. It took around 30 minutes for the participants to fill in the questionnaire. To find answers able to meet the research objectives of the present study, multivariate analysis based on the variance (MANOVA) method of analysis was selected, taking into account the variables of the study.

3. Results

To find out whether employment status (employed vs. unemployed) influences the risk situations of lapse, considering the Inventory of Drug-Taking Situations (IDTS), a multivariate analysis on variance (MANOVA) was implemented.

MANOVA results indicated significant differences between the employed and unemployed participants in comparing their IDTS questionnaire scores. In particular, there was a significant difference between the two groups in five out of eight of the subcomponents of the IDTS questionnaire, namely, Physical Discomfort (employed: M=6.92, SD=2.13 and unemployed: M=3.18, SD=1.26), Pleasant Time with Others (employed: M=8.62, SD=2.84 and unemployed: M=3.95, SD=2.28), Pleasant Emotions (employed: M=2.15, SD=1.62 and unemployed: M=6.38, SD=2.48), Urges/Temptations to Use (employed: M=2.86, SD=2.77 and unemployed: M=7.8, SD=2.24) and, lastly, Testing Personal Control (employed: M=6.83, SD=3.82 and unemployed: M=8.14, SD=4.42) which is confirmed by the Wilk’s Lambda = .16, F (8,151) = 96.05, p = .000; therefore, the “Sig.” values (Table 1, last column) indicate statistically significant differences between the employed and unemployed participants, with a threshold level of .05.

To know whether marital status (single vs. married) influences the risk situations of lapse, another multivariate analysis on variance (MANOVA) was carried out on the data obtained from the Inventory of Drug-Taking Situations (IDTS). The results are presented in Table 2.

| Table 1. Effects of Employment Status in Inducing Emotional and Physical States in the Two Test Groups |
|-------------------------------|-----------------|-----|----------|-----|------|
| Dependent Variable           | Type III Sum of Squares | df | Mean Square | F   | Sig. |
| Unpleasant Emotions          | 1.042            | 1   | 1.042      | .081| .776 |
| Physical Discomfort          | 549.734          | 1   | 549.734    | 167.990| .000 |
| Conflict with Others         | .340             | 1   | .340       | .027| .869 |
| Pleasant Time with Others    | 856.917          | 1   | 856.917    | 125.361| .000 |
| Pleasant Emotions            | 704.586          | 1   | 704.586    | 168.569| .000 |
| Urges/Temptations to Use     | 1339.844         | 1   | 1339.844   | 337.578| .000 |
| Social Pressure to Use        | 98.414           | 1   | 98.414     | 5.059| .026 |
| Testing Personal Control     | 67.522           | 1   | 67.522     | 4.024| .047 |

| Table 2. Effects of Marital Status in Inducing Emotional and Physical States in the Two Test Groups |
|-----------------------------------------------|-----------------|-----|----------|-----|------|
| Source                                       | Dependent Variable | Type III Sum of Squares | df | Mean Square | F   | Sig. |
| Unpleasant Emotions                          | 1318.513         | 1   | 1318.513  | 290.714| .000 |
| Physical Discomfort                          | 59.025           | 1   | 59.025    | 9.254| .003 |
| Conflict with Others                         | 1253.294         | 1   | 1253.294  | 277.849| .000 |
| Pleasant Time with Others                    | 88.079           | 1   | 88.079    | 7.527| .007 |
| Pleasant Emotions                            | 247.599          | 1   | 247.599   | 35.011| .000 |
| Urges/Temptations to Use                     | 253.482          | 1   | 253.482   | 23.374| .000 |
| Social Pressure to Use                       | 2146.834         | 1   | 2146.834  | 330.905| .000 |
| Testing Personal Control                     | 1846.507         | 1   | 1846.507  | 334.540| .000 |
The results of the second MANOVA test indicated a significant difference between the single and married participants in their IDTS questionnaire scores. Furthermore, there was a significant difference between the two groups in eight of the subcomponents of the IDTS questionnaire, namely, Unpleasant Emotions (single: M=4.61, SD=2 and married: M=10.35, SD=2.25), Physical Discomfort (single: M=4.69, SD=2.71 and married: M=5.91, SD=2.3), Conflict with Others (single: M=3.81, SD=1.82 and married: M=9.41, SD=2.32), Pleasant Time with Others (single: M=7.3, SD=3.12 and married: M=5.82, SD=3.7), Pleasant Emotions (single: M=5.21, SD=3.18 and married: M=2.73, SD=1.95), Urges/Temptations to Use (single: M=6.64, SD=3.49 and married: M=4.12, SD=3.06), Social Pressure to Use (single: M=10.09, SD=2.8 and married: M=2.76, SD=2.23) and, lastly, Testing Personal Control (single: M=10.71, SD=2.59 and married: M=3.92, SD=2.06), which is confirmed by Wilks’s Lambda=.22, F (8,151)= 66.63, p=.000; therefore, the “Sig.” values (Table 2, last column) indicate statistically significant differences between the employed and unemployed participants, with a threshold level of .05.

4. Discussion

The first research question posed by the present study aimed at finding the risk factors or situations that tend to increase the risk of lapse in employed vs. unemployed patients under methadone treatment. The results indicated that the two situations of Physical Discomfort and Pleasant Time with Others raised the risk of lapse for the employed participants.

Back et al. [4] reported pain as one of the major reasons among the addicted for taking opioids. In other words, somatic concerns mainly influence lapses in addicted patients undergoing MMT. Besides pain, physical discomfort might stem from other health issues. For instance, in a 33-year follow-up study of 108 male heroin users that had completed medical tests, Hser et al. [25] mentioned several indicators of poor health among heroin users. They reported that more than half of the participants had high blood pressure and abnormal liver function, were overweight, with about one fifth of them showing high glucose levels. The reason that physical discomfort was the risk situation for the employed participants in the present study might be justified, after considering the employment conditions and the job itself: long working hours, doing repetitive kinds of work, tensions in the workplace and about job performance, burnout, boredom and sleeplessness due to physical fatigue [1] – in some cases, even malnutrition.

The second lapse risk situation for the employed participants was Pleasant Time with Others. To the best knowledge of this researcher, very few, if any, studies have dealt with this aspect of risk situations among employed addicts; the point to be made is that spending pleasant time with others might be a possible response to the previous risk situation, that is, physical discomfort. Due to the considerable pressure imposed on an employed addict undergoing treatment, he might be interested in finding a way to relieve this pressure, enhance intimacy or escape a routinized lifestyle; individuals in this predicament may well prefer to spend time with friends or others, some of whom might be their addicted friends – a situation likely to trigger a lapse into substance abuse.

Of the eight risk situations, four of them, namely Pleasant Emotions, Urges/Temptations to Use, Social Pressure to Use and Testing Personal Control, were the probable lapse risk situations for the unemployed participants in the present study.

The first lapse risk situation for the unemployed participants was experiencing Pleasant Emotions. As stated by some scholars [5,27], substance abuse is often triggered by fairly positive motives and emotions, such as excitement seeking and curiosity, since these substances exert sedative psychopharmacological effects [23]. Moreover, a positive mood would heighten the ability of the appetitive thought to draw forth reward, since positive emotions, aroused by substance abuse, share a “hedonic tone” along with the pleasant aspect of reward [42,43]. In other words, positive feelings will be aroused because of their accentuation of pleasure or relief after using drugs or thinking about them [28]. Moreover, the positive evaluation that substance abusers commonly make about the benefits of consumption, such as fun, relaxation states, and disinhibited behaviour, might trigger lapse or relapse [16]. Looking at the issue of unemployment from the perspective of pleasant emotions, since the unemployed individuals have more free time and experience no special job-related tensions, they might return to substance abuse during their MMT treatment as a way to feel pleasure.

The second factor influencing the unemployed was Urges/Temptations to Use. Temptation and intention to use substances might stem from various situational cues [38]. For instance, Laberg et al. [30] claimed that individuals might be tempted to lapse or use substances simply by revisiting places where sub-
stance use took place, or by a change in internal mood state. Cue reactivity is commonly explained through classical conditioning, either due to withdrawal sensations or to previous consumption [52]. As stated by Bruehl et al. [9], the cues might be the substance itself, individuals related to substance abuse such as dealers or substance-using friends, or being in a place previously used for using substances. As mentioned earlier, the unemployed participants, unlike the employed ones, are not commonly in the position of having to face job-related tests and controls targeting the health issues of employees. An employed person in addiction treatment might attempt to resist the urges/temptation to succumb to lapse or relapse thanks to job commitments and conditions, while this is not the case for an unemployed person; therefore, unemployed people under treatment might be more susceptible to succumbing to lapse temptations.

Social Pressure to Use was the third risk situation for the unemployed participants. Establishing relationships with peers who use substances is a risk situation because of the influence that peers exert [20], not only considering substance abuse behaviour itself, but also with reference to other problematic behaviours [14,51]. Furthermore, Dishion et al. [13] indicated that substance use appears to influence the selection of friends and that attachment to deviant friends might lead to deviant behaviours such as lapse or relapse into substance abuse. Due to having more free time, and spending more time with peers and friends, unemployed individuals undergoing MMT may experience more social pressure and, as a result, a higher probability of lapse.

Testing Personal Control was the last risk situation for the unemployed participants. As stated by Savickas [46], the self-concept that is substantiated in the “pejorative lens” of addiction will disrupt an individual’s effort to integrate by accepting social roles such as employment. Furthermore, Comerford [11] made the claim that “substance misuse and work dysfunction have similar roots in self-efficacy, or the belief in one’s ability to solve problems, be successful, or to positively effect change in one’s life” (p. 250). The unemployed individuals might lack confidence and, to regain their confidence and test their personal control over substance abuse, might be tempted to return to abuse even during MMT.

The second research question posed by the present study sought to discover whether marital status impacts the eight drug taking situations; in other words, the aim of this question was to find the situations that trigger lapse for the substance abusers who are receiving methadone. The MANOVA result indicated that, among the eight situations, having Unpleasant Emotions, Physical Discomfort and Conflict with Others all raise the risk of lapse in married substance abusers.

According to Blumstein et al. [7], individuals who are in a close relationship, due to marriage, (for instance, with others such as family members), become more interdependent, so the behaviours and actions of one will impact others, since they get involved in a substantial shift from individualistic values to interdependent values brought into play by their new role as a spouse. However, considering the role incompatibility theory [54], socially deviant behaviours such as substance abuse are incompatible with roles such as parenthood or marriage. It can thus be predicted that substance abusers may experience difficulty in carrying out their roles and, as a result, the dissatisfaction of others may lead to conflicts. In connection with the participants in the present study, the wives of the addicted men under treatment were dissatisfied with their partners’ addiction; however, they were informed about the addiction treatment process and encouraged their partners to follow the treatment; that development, however, did not mean that they had no further conflicts, and those conflicts were, in fact, among the factors triggering relapse.

Due to the occurrence of conflicts, substance abusers may find themselves isolated from their families [10]. This might be the reason why the married participants in the present study experienced more unpleasant emotions such as loneliness. Reilly et al. [41] listed a number of interaction patterns that are likely to be found in families that include a substance abuser. The first one is negativism, i.e. the family communication pattern takes the form of criticism, expressing displeasure and complaints, and such negativity might reinforce lapse. The second pattern is parental inconsistency in rule setting and enforcement, which ends in the confusion of children and might end in conflicts between parents and children. The third factor is suppressing anger, i.e. the parent(s) might use substance or have a lapse as a strategy for managing the suppressed anger in the family.

Self-medication is another pattern that is employed to deal with mental and physical pains and types of discomfort. Moreover, according to Heartwell et al. [21], opioids are commonly prescribed to relieve pains; therefore, the use of opioids as a pain-killer is only to be expected. In other words, substances can work as a medicine to alleviate these pains [35]. Moreover, as already stated for the employed
individuals, the married ones among them might experience more physical discomfort from working long hours and, sometimes, doing repetitive things, tolerating workplace tensions and the fear of losing their jobs. In other words, they have to work hard to make ends meet. In conclusion, the married substance users who experienced several relapses mainly had to deal with unpleasant emotions such as feeling lonely, angry, stressed and depressed, and physical discomfort, such as suffering from pain or feeling sick, but also conflict with others, in cases like an inability to express feelings, or get along well with others, fights at home and feeling pressure – situations that may have acted as the main triggers of a lapse.

The other five risk situations, namely, Pleasant Time with Others, Pleasant Emotions, Urges/Temptations to Use, Social Pressure to Use and Testing Personal Control were more significant for lapse probability in single participants receiving MMT.

Being single and having no strong commitment to family or married life may pave the way to situations where single substance abusers are able to spend time with friends, go to parties and use substances, which, in turn, might end in a higher chance of lapse or relapse in single individuals. Therefore, Pleasant Time with Others was a more significant risk situation for the participants who were still single.

Considering Pleasant Emotions, Robinson et al. [43] argue that the “hedonic hypothesis”, in which substances are, at first, consumed because of their pleasurable effects, then taken compulsively to prevent withdrawal symptoms, is an evident explanation for this risk-taking situation; moreover, the individuals who experience higher levels of positive emotions such as relaxation, fun and happiness in response to substance abuse may also become more likely to use these substances for hedonic reasons. Single individuals might be tempted more by experiencing pleasant emotions, since they are less constrained by family and job-related issues and have more free time; they may therefore seek to return to substance use to experience pleasant emotions.

With regard to Urges/Temptations to Use, Cooney et al. [12] stated that the presence of substance-related cues could cause the abuser to think positively about reusing the substances. These substance-related cues might include thinking about substances or being in a place that had been used previously for using substances. In other words, these cues trigger the urges/temptations to reuse and, as a result, a lapse occurs. As stated before, being single and having no family life commitments make the single participants more susceptible to a lapse due to urges and temptations.

The next risk situation that influenced single participants in the present study was Social Pressure to Use. In the words of Lowman et al. [33], social pressure to use substance or resume drinking is one of the most important high-risk situations for lapse/re-lapse. Moreover, when the lapse data are analysed in greater detail, it is evident that most lapses occurred in the company of other users or in the home of another user [18]. Being in close contact with personal friends, some of whom are substance abusers, may increase the risk of a lapse in singles, compared with married individuals.

Testing Personal Control was the last risk situation for the single participants. The concept of personal control implies a person’s ability and competence to cope with difficult situations and whether he/she possesses enough ability and confidence to refrain from engaging in such situations [32]. As stated by Salah et al. [45], substance abusers possess poor self-efficacy, which might be due to their isolation from, or being rejected by society. Therefore, testing their personal degree of control, e.g. by proving to themselves that drugs are not problematic for them or that they are capable of using those substances moderately, will improve and increase their self-efficacy.

5. Conclusions

In general, considering both employment status and marital status, substance abusers need help and training to be able to improve their problem-solving abilities, learn negotiating strategies, and enhance general communication skills, which usually exert a positive influence on treatment response and outcome by helping to prevent risk situations that could lead to a lapse or relapse [15]. Moreover, as employment and marital status are important aspects of the private life of the addicted people under treatment, clinicians are required to take into account the private life of addicted individuals during treatment to lower the chances of possible relapse.

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Received August 10, 2017 - Accepted September 4, 2017
How to develop and implement an exercise programme in a heroin-assisted treatment setting

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Summary

Background: Individuals in treatment for substance dependence suffer more frequently from a variety of psychiatric and physical comorbidities in comparison with the general population. In the past, it has been shown that exercise can be beneficial as an adjunct therapy in the treatment of these diverse comorbidities; however, in substance dependence treatment, compliance with exercise programmes is inadequate. Aim: The aim of this study was to gather the perspectives of patients on how an exercise programme should be developed and implemented in an outpatient setting dedicated to treating substance dependence. Methods: The study was carried out in a clinic offering heroin-assisted treatment (HAT) in Switzerland. A survey, focus group and interviews were administered before and after a 3-month exercise programme. Results: Participants in the focus group (n=12) and survey (n=28) reported that they were eager to participate in an exercise programme, and recognized that it would be beneficial for their well-being. The exercise programme was adapted to offer parallel sessions for differing ability levels. Feedback from the programme indicated that a varied multisport programme was most favoured, and that special attention was required to ensure that participants would not lose touch with each other through miscommunication. Final interviews (n=14) indicated that patients wanted the programme to become a fixed part of treatment. Conclusions: It is essential to take patients’ views into account when implementing an exercise programme in an outpatient substance use treatment setting. Clear and repeated communication, programmes which adapt to patients’ abilities, and continuous assessment of the programme are important in motivating participation.

Key Words: Exercise; heroin-assisted treatment; sport

1. Introduction

Heroin-assisted treatment (HAT) has been implemented in Switzerland since 1994, and has become a recognized treatment modality for long-term opioid-dependent individuals who have been unable to successfully remain abstinent or tolerate methadone agonist treatment [34]. HAT refers to the prescription of diacetylmorphine, which patients may inject, typically in a supervised clinical setting. Following the success of Swiss trials suggesting that HAT leads to reductions in illicit drug use, criminal activity and health complaints, as compared with pretreatment levels [18], other countries have held trials, and now offer the treatment. In 2013, approximately 1,600 opioid users were enrolled in HAT in Switzerland [11]. Individuals who have been dependent on opioids for two years, are over the age of 18, and have had two previous unsuccessful treatment attempts (at least one of them with methadone) are eligible.

Many of these patients suffer from psychological and physical comorbid diseases, and a higher mortality risk than the general population [16]. The mean age of Swiss HAT patients is approximately 42 years, an increase of over 7 years in the past decade. Age-related diseases such as osteoporosis, malnutrition, chronic infectious disease, liver failure, cardiovascular disease and cognitive dysfunction appear at an earlier age in this population [4]. The emergence of health problems associated with an unhealthy life-
style (such as COPD due to cigarette smoking, and metabolic disorders) has also been documented [14].

One mid- to long-term goal of HAT is to reduce the negative health consequences of illegal heroin use and lower social discrimination [28]. In the “Handbook for heroin-assisted treatment” published by the Swiss Federal Office of Health, participation in physical activity and exercise is explicitly cited as a constitutive part of this goal [5]. Exercise participation has been shown to be an effective adjunct therapy for COPD [23], cardiovascular disease [31], osteoporosis [3], cancer [10], depression [9], and many other psychological disorders and cognitive dysfunctions [27, 33]. It has also been shown to play an important role in the prevention of numerous diseases [25, 24].

There is now strong evidence that regular physical activity may improve physical and psychological functioning and reduce mortality and morbidity [15, 30].

To date, there have been few high-quality studies examining the effects of exercise participation during substance use treatment; while initial results have been promising, they require cautious interpretation [19, 12]. Positive outcomes include improved social integration, increased fitness, higher self-esteem, reduced cravings, improved mood regulation, reduced stress, and a greater ability to cope with stressful life events [12, 35, 37, 26, 17, 7, 29]. A number of these studies were, however, plagued by low rates of compliance and high numbers of dropouts during the intervention phase [12, 35, 17, 29].

A variety of non-exclusive hypotheses for the mechanisms by which exercise may improve health in substance-using individuals have been posited. They include physiological factors, such as an elevated release of certain neurotransmitters, or the induction of neurogenesis [32]; psychological factors, such as reduced stress and anxiety [37]; and sociological ones, such as improved social integration through team sports [6].

To summarize, the current literature suggests that exercise may be effective in improving the health and well-being of substance-using individuals. The problem is that individuals with a long history of substance abuse in outpatient treatment rarely have any opportunity to participate in structured exercise programmes. Based on the information presented above, it can be hypothesized that an exercise programme could provide a valuable form of adjunct therapy in a HAT setting. To date, the majority of studies assessing exercise in substance use treatment have been carried out in inpatient facilities; an outpatient setting could act as an even greater challenge for inclusion and compliance with an exercise protocol. It is therefore essential to address the most effective way to implement an exercise programme, by enlisting the views and experiences of the patients directly involved.

The aim of this paper is to report on the experiences of patients who took part in a 12-week pilot study on an exercise programme in a HAT setting. A number of articles in recent times have reported on study protocols, rationales, and points to consider in this field, reflecting a growing interest in exercise as an adjunct treatment, and the recognition that care and experience is required in implementing exercise programmes for this population. Data were drawn from a survey and focus group before the programme started, and from semi-structured interviews upon completion. Based on these reports, we offer a list of points to consider in the development and implementation of an exercise programme in outpatient substance use treatment.

2. Methods

2.1. Participants

Participants were recruited from a HAT clinic in Basel, Switzerland. The clinic treats approximately 160 patients. A study team of four investigators were assembled in the waiting room of the clinic, through which all patients must pass when they arrive, to inform patients about the study, and administer the survey (described in detail below). During the survey, participants were informed about the further steps of the study, and invited to participate. Posters with information about the various steps to be taken during the study were placed in the waiting room.

A mixed methods approach was employed in order to elicit information about the planning, implementation and critical appraisal of the exercise programme [20]. The study was carried out in conjunction with a randomized trial of the effects of 12 weeks of twice-weekly exercise. In order to ensure participant anonymity, names were not recorded during the survey or the focus group meetings, and code numbers replaced names for the intervention and subsequent interviews. Consequently, we are unable to report what percentage of survey participants took part in the focus group or intervention.

2.2. Survey

First, a survey was carried out to determine patients’ exercise history, interest in participation, and
their wishes about how to improve programme implementation. The survey consisted of 26 open, closed and hybrid questions. Participants were offered a drink and small snack as a reward for their participation. The survey was carried out in the waiting room of the clinic over three three-hour sessions, and all individuals passing through the waiting room were invited to take part. All surveys were administered face-to-face by an investigator, who then recorded the responses in a computer.

2.3. Focus Group

During the survey, participants were informed that a focus group would be formed, and were invited to participate. The focus group was moderated by an investigator who had a set of seven guide questions designed to instigate discussion about the logistical and organizational development of the exercise programme. Patients were informed in advance that snacks, drinks, and a financial reward of 20 CHF would be provided during the focus group. The focus group meeting lasted approximately one hour. The proceedings were recorded and transcribed verbatim.

2.4. Exercise intervention

During the 12-week exercise intervention (described in detail in Colledge et al. [8]), all individuals, after being randomized as to the exercise condition, rated each training session on a scale of 0 (very poor) to 10 (excellent), and were also able to give feedback by writing in the “Comments” section. Participation in the study was rewarded with a maximum of 100, and a minimum of 36, Swiss Francs, depending on frequency of participation. Prior to beginning the study, participants signed a contract stating that they recognized that missing more than a certain number of intervention sessions would result in a reduction of 4 Swiss Francs per subsequent absence. As individuals in HAT attend the clinic at least once per day, reminders were programmed into the dispensation system, so that all study participants were personally reminded by clinical staff, at the time of dispensation, that the exercise programme was taking place on that day.

2.5. Interviews

During the final week of the intervention, an investigator interviewed all the study participants who had been randomized to the exercise condition. Three semi-structured interview guides were developed for participants, who were categorized as: compliant (at least 18 out of 23 sessions attended); semi-compliant (between 17 and 5 sessions attended); and non-compliant (4 sessions or fewer attended), respectively. Compliance and non-compliance therefore equated to approximately 80% (or more) and 20% (or less) attendance, respectively. The broad semi-compliant category was deemed the best way to represent the irregular attendance displayed by certain participants; given the small sample sizes in this study, more detailed compliance categories were deemed inappropriate. The interviews addressed participants’ experiences of the exercise intervention, their recommendations for improvements, and, where relevant, their reasons for infrequent participation or non-participation. Participants were offered a drink and small snack to show gratitude for their participation. Each interview was recorded and transcribed verbatim.

The entire study was approved by the Ethik Kommission Nordwestschweiz (EKNZ). All patients provided informed consent, separately for the survey, focus group and intervention-related assessments. The study was carried out in accordance with the principles of the Declaration of Helsinki.

3. Results

3.1. Survey

28 (16 male; age 25-35 = 14 %, age 35-45 = 40%, age 45-55 = 46%) individuals took part in the survey. 93% indicated that they felt they would benefit from regular participation in an exercise programme. Most participants reported having been physically active in childhood and adolescence. Accordingly, they reported enjoying exercise, but that the effort to begin a new regime alone felt like too much of a challenge. The great majority of participants reported that they would therefore be keen to participate in an exercise programme offered by the clinic, as a number of hurdles, including cost, organization and accountability, would thereby be removed. Further preferences are reported in Table 1.

Lastly, a third of respondents indicated that they felt they would need reminders to participate in the programme.

3.2. Focus Group

12 individuals took part in the focus group. Age and gender of the participants were not recorded. Par-
participants reported that they were keen to begin with the exercise programme.

“We need a start, and this study is perfect for us.”

“I always wished the hospital would provide a service like this.”

Participants again reported a wide variety of exercise and sports they found attractive, and an equally varied list of those they would not wish to participate in, with both lists frequently overlapping. Participants also reflected that they were likely to have very different physical abilities, and that they were concerned that a group environment might cause some individuals to feel unable to participate, whilst others would be bored by a slower pace. Importantly, patients stressed that such negative experiences were likely to cause them to lose motivation very quickly. It was suggested that two groups, covering different ability levels, could be offered.

Participants agreed that they would like to meet for sessions at the clinic, as they had to visit this location daily, and would thus avoid excessive and potentially confusing travel and meeting arrangements. As it was anticipated that some sessions might take place at locations far from the clinic, the possibility of meeting other patients at the clinic, and then travelling as a group by public transport, was addressed, too. Establishing an ideal time for the session to take place involved much discussion, as participants had a wide variety of family and job-related commitments.

Some individuals emphasized that a lack of financial resources meant that they had no clothing or shoes to participate in sports, and suggested that help in this domain might be an important facilitator to participation.

Participants indicated that they felt they would need reminders about the exercise programme, with some emphasizing that clinic patients might underestimate the frequency with which they should be reminded. All agreed that being reminded on the day of the exercise session at the clinic while receiving their medication, and fliers in the waiting room, would be helpful to their participation.

Lastly, it is important to emphasise the value patients placed on having a respectful, supportive training environment, and understanding training staff.

“When it comes to interpersonal dealings… We expect the same of you as you do of us.”

## 3.3. Post-session feedback

Feedback following the training sessions indicated that all the sessions were enjoyed by all 14 (10 male, mean age= 42.9, SD= 6.2) participants, who were randomized to the exercise condition; a majority of the scores given were 8 or 9. Three exercise types (offered on more than three occasions) were scored with 10s by all participants who took part; climbing (5 and 6 participants); badminton (2 participants) and coordination training (4 and 6 participants).

### Table 1: Responses and response rates given during survey addressing attitudes to exercise programme

<table>
<thead>
<tr>
<th>Popular sports</th>
<th>Unpopular sports</th>
<th>Barriers</th>
<th>Expectations of the training instructor</th>
<th>Positive aspects of exercise</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endurance/ Walking/ Running</td>
<td>Long-distance running</td>
<td>Pain, health issues</td>
<td>Enjoy their job</td>
<td>Doing something good for myself</td>
</tr>
<tr>
<td>39%</td>
<td>21%</td>
<td>32%</td>
<td>79%</td>
<td>68%</td>
</tr>
<tr>
<td>Swimming</td>
<td>Competitions/ group games</td>
<td>No interest</td>
<td>Are kind and motivated</td>
<td>Feeling my body is working</td>
</tr>
<tr>
<td>32%</td>
<td>14%</td>
<td>25%</td>
<td>79%</td>
<td>61%</td>
</tr>
<tr>
<td>Climbing</td>
<td>Martial arts</td>
<td>Tiredness</td>
<td>Understand me and my situation</td>
<td>Forgetting worries</td>
</tr>
<tr>
<td>29%</td>
<td>14%</td>
<td>21%</td>
<td>54%</td>
<td>57%</td>
</tr>
<tr>
<td>Dance</td>
<td>Dance</td>
<td>No time</td>
<td>Take my wishes seriously</td>
<td>Letting off steam</td>
</tr>
<tr>
<td>29%</td>
<td>14%</td>
<td>18%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Fitness/ Strength training</td>
<td>Swimming</td>
<td>Don’t want to see the others</td>
<td>Don’t force me to do anything or push too hard</td>
<td>Giving everything and winning</td>
</tr>
<tr>
<td>21%</td>
<td>14%</td>
<td>14%</td>
<td>50%</td>
<td>49%</td>
</tr>
<tr>
<td>Badminton, Football or other group games</td>
<td>Ice Skating</td>
<td>No motivation</td>
<td>Are funny and authentic</td>
<td>Enjoyment and fun</td>
</tr>
<tr>
<td>21%</td>
<td>14%</td>
<td>11%</td>
<td>46%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Note: N=28. Respondents could select/report as many responses as desired.
“Comments” section was used infrequently; however, some participants complained about the lack of shower facilities and small rooms at one training location.

3.4. Interviews

All 14 individuals who were randomized to the exercise condition took part in the semi-structured interviews at the end of the 12-week intervention. All participants who were compliant or semi-compliant with the protocol reported that they had enjoyed the exercise programme, and would like it to continue as an integrated part of treatment. Many reported enjoying the agreeable feeling of tiredness, improved sleep, an increase in strength, and improved mood following training. Many also reported that participating in the programme provided a rare opportunity to focus entirely on their own well-being. They were also pleased to discover that they could overcome their tiredness or lack of energy, and add some structure to their daily lives.

A number of individuals emphasized that in HAT there was no focus on the promotion of physical well-being, so the exercise programme was a welcome way to fill this void. Some participants felt that the clinic staff could play a role in motivating patients to participate in such a programme, by recommending it as a health-promoting element of treatment. Furthermore, although they enjoyed the programme, a majority reported that they would have difficulties in carrying out regular exercise training on their own, without the structure afforded by a clinic-based programme.

Interviewees who had participated in the training sessions reported that the engagement and support of the exercise trainers was a motivating factor, and they particularly valued the options and structure of the programme, stating that the aim of including participants of all ability levels had generally been met. It was also appreciated that the exercise trainers had a background in sports science, and could give advice about physiotherapeutic exercise, while showing vigilance about excessive training loads. Lastly, the small reward of a snack and drink was seen as a positive factor which might foster motivation, and some patients suggested that occasional outings would be likely to foster a cohesive group environment.

Participants reported that they valued the fact that their input had been sought during the planning and implementation phases of the project, and that they appreciated having their views taken seriously. They appreciated the opportunity to become active after, in many cases, long periods of little activity, and also mentioned with positive emphasis the opportunity to make new acquaintances with other clinic patients. One patient reported that the realization that, despite years of substance use and little physical activity, it was still possible to participate in sport, was extremely gratifying.

Some participants complained that certain training locations were a long way from the clinic, and consequently that time was lost walking to the location. A further point raised by numerous participants was that the room used for exercise should be designed for this purpose. Due to time constraints, a seminar room and neighbourhood meeting room were used for some training sessions; while these were large enough for exercise to be carried out safely, patients made it clear that they felt these rooms were not suitable for serious exercise, and offered no options for taking a shower after the session.

Several participants emphasized that frequent reminders were necessary to ensure regular participation, and to raise awareness of the programme within the clinic. Importantly, it was made clear that these reminders should be given through a variety of media; posters and flyers in the clinic waiting room, announcements on the electronic screen, individual reminders at the point of medication dispensation, and the frequent presence of training personnel in advance of a session. Participants reported that using only one reminder method was simply not enough, as it could too easily be overlooked or forgotten, particularly in a population that had a less than clear daily schedule.

In line with this point, some participants also reported that motivation and trust in such a programme could be very quickly lost if training sessions were missed, either due to miscommunication with staff, or because the patient was unable to attend for other reasons for a period of time. A number of patients reported being unsure that they would be allowed to continue attending after missing some sessions (despite the fact that they had been informed at the start of the study that this would not be the case), and some also reported that they lost trust in the staff after a miscommunication on timing resulted in a session being missed.

The issue of trust in the trainer was highlighted by the complaint that, during one session, the trainer did not participate in the strength exercises being carried out. This was perceived negatively; some participants explained that the collegial atmosphere of the session had been damaged, and that they were being asked to do exercises that were too challenging for
their level.

Those participants who frequently missed sessions, or who missed all or nearly all sessions, reported that health issues had stood out as a major barrier to their regular participation. Some spent periods in hospital or suffered from acute medical problems, while a small number complained of general physical pain. Further reasons cited for missing one or several sessions were: forgetting the sessions, having other appointments, incarceration, family duties, illicit substance consumption, and lethargy caused by the consumption of diacetylmorphine. Respondents tended to report that motivation was not a problem for them, but that they believed this to be a problem that had to be faced by other participants who missed sessions.

Those individuals who missed all or nearly all sessions expressed frustration with themselves that they had let a good opportunity go by. They acknowledged that they had been frequently reminded to participate, and had equally given assurances that they would, but nevertheless found themselves unable to do so. One participant reported that this non-participation was “inexplicable […] I like to do something, then I get the chance to do something, but in the end I don’t do it.”

4. Discussion

Individuals attending this outpatient HAT clinic were keen to see an exercise programme integrated into the treatment structure, despite the majority not currently engaging in any exercise. This suggests that a structured, trainer-led environment may be a means to bring individuals in outpatient substance use treatment to regular exercise. Through collaboration with the patients, a programme was developed and continuously assessed, in order to determine the factors which contribute to the success of such a programme. A positive overall response to the programme, and a number of constructive criticisms, were documented.

The HAT patients felt different positive physical, mental and social health outcomes resulting from participation in the programme, and stated that they felt it could help them to establish a healthier lifestyle and an improved daily structure. As stated in the meta-volitional-model, structural or organizational changes are frequently required to modify the health behavior of single individuals [36].

Based on the above findings, the following section outlines the key factors which emerged as important in the development and implementation of an exercise programme in a HAT setting.

1. Assessing the exercise experience and preferences of patients is essential to creating a training environment that they will appreciate. In this study, as in a previous investigation of exercise preferences amongst substance users [1], the preferred exercise forms and physical abilities of the participants were wide-ranging, and this was taken into account as far as possible in the exercise programme. Where possible, continuous assessment and feedback about the training sessions should be used in planning future sessions.

2. Locations and instructors play an important role in the implementation of the programme. Rooms which are not suited for exercise, and instructors who are not prepared for the particular needs and wishes of this population, can negatively affect the programme in a way so severe that it may lead to reduced participation. In particular, trainers who are willing to participate and adapt their sessions may be especially valuable in this setting. Where possible, large rooms or sports facilities with at least one changing room should be used, and trainers with a background in exercise science or physiotherapy should be engaged. As budgetary constraints may make this ideal situation challenging or impossible, compromise solutions showing respect for the wishes of participants should be sought (e.g. working with sports science master students on an internship basis, carrying out training outdoors when possible). While Weinstock and colleagues note that, in some instances, it may be preferable to introduce unsupervised training sessions [35], the patients in this clinic generally expressed a desire for supervision, to optimize training but also to increase motivation. In particular, training staff play an integral role in the success of such a project, as they will shape the training environment. Respect for every participant, an understanding of their abilities and wishes, and special attention dedicated to the physical and psychological situations faced by substance-using patients, are all crucial. Good communication between the clinic staff and trainers, to ensure that participants are continuously informed about the programme and supported in their par-
in individuals under HAT, it is reasonable to suppose that this group would not display markedly lower rates of delay discounting than those found in other studies of heroin-dependent individuals. Consequently, it may be supposed that the necessarily distant rewards of participating in exercise are a particular challenge for this group. As there is evidence that treatment for opioid dependence reduced delay discounting rates [22], it may be that an exercise programme would be more widely accepted in other treatment settings, although the integration of the patients in the treatment programme must also be borne in mind. In light of this, our participants’ reports that small incentives were valuable motivators should also be emphasized, as these small immediate rewards may be essential in supporting individuals who struggle with the challenges of an exercise programme; the importance of making the programme itself a ‘fun experience’, and not simply focused on a distal goal such as greater cardiorespiratory fitness, must be considered too. In their description of a contingency management system in supporting exercise in substance-using populations, Weinstock et al. also emphasize the importance of strict adherence to a system of regular rewards [35]; particularly in the early phase of an exercise programme, physiological benefits may be slow to emerge, so alternative reinforcers are of particular importance.

4.1. Limitations

The findings of this study must be considered in light of certain limitations. First, individuals from a single clinic took part in the study, so regional and national variations are not represented here. Second, the daily structure of a HAT clinic in Switzerland is particularly conducive to supporting participation in a regular programme, as patients must attend at least once a day. These findings cannot therefore be generalized to other outpatient substance use clinics. Third, a selection bias at all stages of the study is likely to have occurred, as participants with no interest in exercise are unlikely to have participated—with almost certain exclusion beyond the survey stage. Lastly, the final interview was carried out by a trainer who had supervised the exercise intervention. It is possible
that participants may have developed a rapport with this investigator, and therefore tended to answer questions in a way which they felt, consciously or unconsciously, might be more pleasing or socially desirable to this individual.

5. Conclusions

Patients in this study reported interest in participating in a clinic-based exercise programme, and, following their participation, reported positive experiences and a desire to continue. Based on participant feedback, clear and transparent organization, frequent personal contact, and respect for patients’ abilities and wishes, emerged as key elements to address in the development of an exercise programme in an outpatient substance use clinic.

References

Acknowledgements
None

Role of the funding source
Financial support was provided by Infodrog, the addiction research branch of the Swiss Federal Office of Public Health (grant number 5025/14/BS/Substitution-Sport)

Contributors
M.G., M.V., K.D.M., J.S., S.S., U.P., F.C., designed the study and wrote the protocol. L.S., M.G., F.C., managed the literature searches and analyses. L.S., M.G., M.V., K.D.M., J.S., S.S., U.P., F.C., undertook the statistical analysis, and all the authors discussed the results. L.S., F.C., wrote the first draft of the manuscript. All authors revised the last draft. All the authors contributed to, and have approved, the final manuscript.

Conflict of interest
Authors declared no conflict of interest.

Ethics
Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects. This study has ethics committee approval. All patients gave their informed consent to the anonymous use of their clinical data for this independent study.

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It is the policy of this Journal to provide a free revision of English for Authors who are not native English speakers. Each Author can accept or refuse this offer. In this case, the Corresponding Author preferred not to use our service.

Received January 17, 2017 - Accepted September 1, 2017
Diversion of buprenorphine: Scope of the problem and the measures taken to address it

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Summary

Background: Opioid dependence is a matter of public health concern globally. Opioid agonist treatment (OAT) is recommended as one of the most effective treatment strategies to manage opioid use disorder. As a partial opioid agonist, buprenorphine is widely used all over the world for OAT. Clinical use of buprenorphine is often coupled with instances of diversion and misuse of this medication. There can be multiple reasons and motives for diversion. Methods: In this paper, we assess the various reasons for, and the effects of diversion, along with the range of mitigation strategies adopted to reduce that diversion. Results: The potential methods that can be utilized for reducing diversion include improving medication adherence, adequate dosing, supervision of dosing, being cautious of possible diversion at clinical visits, termination of treatment in selected cases, provision of confidential treatment in specific situations, random urine screening, prescription monitoring, utilizing alternative formulations of buprenorphine, and scaling up of OAT. Conclusion: The concerns often expressed about diversion should not be allowed to become a deterrent against the rational use of buprenorphine for OAT, though reflective and corrective measures are needed once diversion has been detected.

Key Words: Drug dependence; drug problematic use; opiate; substance problematic use

1. Introduction

The World Drug Report, 2015 suggests that there are about 32.4 million opioid users worldwide [47]. Globally, opioids constitute the second most commonly used illicit drug after cannabis. Opioid use is associated with a considerable medical and social burden. Opioid use disorders are linked with increased rates of mortality, transmission of blood-borne viruses, criminality, and loss of productivity [24, 33, 50]. Several treatment approaches have been demonstrated to be effective for the treatment of opioid use disorders. Among them, Opioid Agonist Treatment (OAT) has become a standard practice in many regions of the world due to its efficacy [4, 34].

The concept of OAT is intertwined with harm-reduction. Simply put, OAT aims to replace illegal, impure opioid substances (such as heroin) with legal medication of known purity and potency, taken through a safer route and administered under medical supervision. Bearing in mind that OAT as a harm reduction approach is complex and multi-faceted, its overriding aim should be focused on the non-judgmental and non-coercive facilitation of services to reduce the use of substances and pave the way to patients’ integration in society. OAT facilitates the passage from the rewarding-addictive use of substances to the non-rewarding, non-addictive use of medications. The common medications used for OAT are buprenorphine and methadone. Replacement with methadone and buprenorphine decreases illicit drug use, criminal activity and risk of overdose, and in its turn achieves improvement in physical, psychological, and social functioning [52]. OAT also reduces mortality, drug-associated crimes and HIV risk. Of late, office-based buprenorphine treatment has become popular, and annual prescriptions of buprenorphine have increased [44].
Though buprenorphine has been widely used for the treatment of individuals with opioid dependence, concerns have been raised about its diversion. Diversion of buprenorphine has been reported across the globe \[12, 15, 28\]. Diversion of medications used for OAT is a pragmatic concern, as it creates a sense of alarm among policy makers about OAT, and a sense of mistrust among clinicians towards potential diverters. This review discusses the misuse and diversion of buprenorphine, their many consequences, and the strategies utilized for mitigation. Prior to further discussion about diversion, it would be prudent to take into account a brief overview of the varied terminologies pertaining to use and diversion (box 1), and to understand the buprenorphine formulations as presented in the next section.

2. Buprenorphine formulations and their pharmacology

Buprenorphine is a partial agonist at µ-opioid receptor, an antagonist at the kappa opioid receptor and a partial agonist at the nociceptin receptor \[11, 18\]. Being a partial agonist, its intrinsic activity can be defined as a less than full opioid agonist like methadone, so it has a ceiling effect on the upper end of the dose response curve. This leads to buprenorphine’s superior safety profile with respect to respiratory depression and overdose. This superiority probably explains the lower rates of buprenorphine overdose than those of methadone \[23\]. Death rates attributable to buprenorphine were found to be three times lower than those of methadone \[6\].

Being a partial agonist, buprenorphine probably has a lower abuse liability than full µ-opioid receptor agonists. Yet it has been seen that buprenorphine can produce acute effects similar to those of methadone \[51\]. This propensity to exert acute effects makes buprenorphine liable to both misuse and diversion. Soon after approval of oral buprenorphine for OAT, the problem of diversion had surfaced, including the use of buprenorphine through the injectable route. Naloxone was added to the oral buprenorphine formulation to prevent misuse through that route. Naloxone has minimal absorption when taken by the oral route, but has high bioavailability when it is injected. When taken by injection, it prevents the action of buprenorphine by blocking the µ opioid receptor. However, there is some evidence to suggest that buprenorphine to naloxone in a ratio of 4:1 in the present formulations may be insufficient to completely block the subjective effects of injected buprenorphine \[3, 17\]. Research studies have also found that subjects prefer a full µ opioid receptor agonist to partial ones like buprenorphine, and buprenorphine preparations are preferred over buprenorphine-naloxone combinations \[19, 43, 49\].

### Box 1. Terminology related to diversion [from ref. 5, 19, 32]

- **Use**: Any use of the drug, with no restrictions as to purpose or legality
- **Abuse**: Repeated intentional improper or incorrect use of a drug for the purposes of experiencing psychotropic effects (e.g., to get high), which is difficult to control and that may cause harm to the user or others
- **Misuse**: Intentional improper or incorrect use of a drug for reasons other than to get high. It also includes taking medication in a manner, by route or by dose, other than prescribed
- **Non-medical use**: Includes both abuse and misuse
- **Diversion**: Unauthorized rerouting or misappropriation of prescription medication to someone other than for whom it was intended
- **Prescription drug diversion**: Unlawful channelling of regulated pharmaceuticals from legal sources to the illicit marketplace

### Box 2. Methods of diversion

- Illegal sale of prescriptions
- Doctor shopping to obtain multiple prescriptions
- Forgery of prescriptions
- Theft of medications/prescriptions
- Alteration of prescriptions by health care workers and patients
- Giving away/selling medications to others
- Secretly removing medication from mouth for later use
3. Buprenorphine diversion: Methods and contributing factors

Diversion of buprenorphine occurs in many ways (Box 2). It can take the form of: illegal sale of prescriptions; doctor shopping to obtain multiple prescriptions; and theft, forgery, or alteration of prescriptions by health care workers and patients [22]. It can otherwise occur in the form of giving away or selling medications to others from one’s dispensed stock of medications. Diversion may even occur when patients take their sublingual medications through an injectable route. When there is no supervision of the doses of medications provided through OAT, patients may over-report their dose requirement, and then divert away a fraction of the medications already dispensed to them.

Numerous factors contribute to the diversion of buprenorphine. These include both demand- and supply-related factors. The demand-related factors for diversion may include underdosing of the medication, alleviation of opioid withdrawal, craving for a ‘high’, and relief from negative affective states [32]. Some individuals may be reluctant to come for treatment due to issues of stigma, and may react by procuring diverted medications for their self-treatment. Patients may divert away their medication to help addicted family members or friends, to use the money received from diversion to get more potent substances (like heroin), or make economic gains. The supply-related factors include the availability of buprenorphine in the healthcare system, the policies of regulation and prescription of this medication in the service, the price of buprenorphine, and the degree of supervision over its use. Sometimes, theft of medications can occur when precautions over the safe storage of buprenorphine cannot be ensured.

Several reasons and motives have been documented as having contributed to buprenorphine diversion, some of which are shown in box 3. In discussing the reasons for diversion, Olivier et al., [42] found that, once buprenorphine-naloxone has been diverted, it is consumed by people with opioid dependence to get high. Poor access to local, affordable treatment is another important cause of buprenorphine-naloxone diversion. Price is a further factor accounting for the increasing diversion of buprenorphine, as buprenorphine is cheaper than heroin when obtained through prescription or even when illicitly purchased on the streets [2].

Studies examining buprenorphine diversion and illicit use have identified additional motivations other than euphoria and alleviating withdrawal symptoms. In a study in Singapore, a false belief among intravenous drug users was that intravenous administration of buprenorphine might enhance erection [14]. In a study in India, buprenorphine users believed that there is less threat of getting harassed and arrested by the police if they possessed buprenorphine rather than heroin [25]. In another Indian study, the rampant use of buprenorphine as choice of injection compared with heroin was associated with lesser interference of regulatory bodies like the police [41].

The type of opioid available in a region determines the types that individuals experiment with. Hence, if buprenorphine is commonly available on the unregulated market, it might become the first opioid of use in some patients. Novel opioid users experimenting with buprenorphine would thus become an alarming issue [20, 30]. Buprenorphine being the first drug of dependence in some patients with injecting drug use has thus become a priority concern [40]. On a similar note, the introduction of buprenorphine has contributed to polydrug use among injecting drug users [30].

The source of the buprenorphine that is diverted to patients can be varied, and may include friends, acquaintances or dealers [27]. Among out-of-treatment intravenous drug users who had received diverted buprenorphine, the authors found that friends were the most common sources of buprenorphine and buprenorphine-naloxone, followed by other acquaintances and dealers. Apart from these considerations, some brands of buprenorphine have been found to be

<table>
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<tr>
<th>Box 3: Reasons for diversion</th>
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<tr>
<td>• To get high</td>
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<td>• To prevent withdrawal</td>
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<td>• To share it with peers who can’t find treatment</td>
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<td>• Lack of access to local affordable treatment</td>
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<td>• Belief that self-treatment is effective</td>
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<td>• To enable the self-treatment of opioid dependence</td>
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<td>• Unwillingness to engage in treatment</td>
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<td>• To make financial gains</td>
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more appealing to patients than others [38].

4. Intravenous misuse by patients and out-of-treatment opioid users

Use of Intravenous injection of buprenorphine has been reported worldwide. Whether buprenorphine has been bought for pain control or for OAT, it can reach its destination through means of diversion. A survey carried out in the United States between 2005 and 2007 on 1000 individuals presenting for prescription opioid abuse treatment found that 6% of participants had injected buprenorphine and 37% had injected other prescription opioids (e.g., oxycodone) for euphoric effect [16]. Data emanating from Australia suggested that the self-reported injection of the medication was significantly lower among patients whose prescriptions were for buprenorphine-naloxone rather than for buprenorphine [19]. The reasons most commonly expressed for intravenous use include self-treatment to combat withdrawal or addiction, and to produce euphoria [3, 9, 36, 49].

It is generally seen that when a pure opioid agonist like heroin is easily available, it is preferred to buprenorphine. One different scenario, however, that was discovered in Finland and Malaysia has raised a number of serious concerns. In Finland, the numbers of daily intravenous buprenorphine users rose towards the end of the 20th century, as soon as the supply of heroin from Afghanistan had fallen [48]. By that time, buprenorphine had become the most commonly abused opioid among people seeking addiction treatment in Finland. Stringent rules for access to opioid maintenance treatment were probably the leading risk factor for continued diversion and misuse. Unable to enter treatment for opioid use disorders, the individuals misusing opioids had probably switched their type of usage to diverted buprenorphine.

In Malaysia, the injection of buprenorphine emerged shortly after its introduction in 2002, as in most cases it was initially prescribed by general practitioners who had received no prior training [49]. Dispensing was incentivized, and the quantum of payment made to physicians was linked to the volume of medications dispensed. Buprenorphine-naloxone was launched in Malaysia in 2007 to overcome the problem of diversion through drug use by injection. But, shortly after buprenorphine-naloxone became available, it began to be taken by opioid users through injection. The most common source was the dispensed medications prescribed by private practitioners. The Malaysian experience suggests that significant intravenous buprenorphine use can arise when buprenorphine is provided in large supplies (i.e., enough to last 2-4 weeks) to injecting drug users in treatment settings that have incentives for providers.

Given the two above examples, the question of whether the extent of diversion will rise or fall according to less restrictive policies or more stringent ones does not yet have a clear answer. A cautious, public health-oriented approach with checks and balances has good credentials as the right way forward to promote the responsible clinical use of buprenorphine and, at the same time, minimize diversion.

Use of diverted and injected buprenorphine is associated with some health hazards. There are reports of uncommon fungal infections like ocular candidiasis when buprenorphine is kept in the mouth for later injections and is subsequently injected with contaminated solutions [1, 13]. There have been case reports of severe liver pathology after injection use, and co-infection with hepatitis B and/or C [10, 21]. Even sudden deaths have been reported after buprenorphine injections [6].

On a positive note, it has been seen that non-medically supervised buprenorphine reduces HIV risk behaviour, in a way similar to supervised buprenorphine [7, 25]. Illicit buprenorphine injectors

Box 4: Methods to reduce diversion

- Improving medication compliance
- Adequate dosing
- Shifting to full agonists like methadone
- Supervision of dosing
- Assessing possible diversion at clinical visits
- Termination of treatment in selected cases
- Provision of confidential treatment in specific situations
- Random urine screening
- Alternative formulations: Buprenorphine-naloxone film, implant or patches
- Scaling up of opioid agonist treatment
- Prescription monitoring
proved to be less likely to share injection equipment and had fewer drug-using members in their social networks than heroin users, probably contributing to a reduction in the risk of HIV transmission.

5. How can diversion be reduced?

Several approaches can be used to address the issue of diversion of buprenorphine (box 4). Currently there are no specific guidelines on how to handle the issue of diversion. Even so, certain efforts in clinical practice may result in a lesser extent and fewer instances of buprenorphine diversion.

Medication diversion in a way reflects non-compliance with treatment. In the case of opioid dependence, non-adherence lowers treatment effectiveness and raises the chances of illicit opioid use, or recourse to diverted medications [46]. Hence, supervising the treatment and optimizing the dose of buprenorphine or a buprenorphine-naloxone combination would be the first step in addressing the issue of diversion. The clinicians and health-care providers may address the withdrawal symptoms and unremitting craving by optimizing the buprenorphine dose. In a study of Finnish maintenance treatment patients, lower doses of buprenorphine were associated with diversion [29]. Hence, the initial aim of clinicians should be towards optimal dosing. Some patients may not perceive the full effect of opioids with buprenorphine, because buprenorphine is only a partial µ-receptor agonist. In such patients, methadone, which, by contrast, is a full µ-receptor agonist, may be tried, where the programme allows for methadone dosing.

Whether the clinician should inquire about diversion during routine clinical encounters is a challenging issue to be addressed. The patient may either be a source or a recipient of diverted medication. In cases where a patient reports acquiring diverted buprenorphine naloxone from other sources, then the dose requirement may be assessed, and upward titration of the dose of medication may be implemented in deserving situations. However, a clinician may feel doubtful whether the increased dose being prescribed is actually required. Clinically supervised dosing, in which at least one dose is supervised, may be helpful in assessing the dose requirement, as the patient would appear sedated when the doses given are higher than required.

In case the patient reports that he/she has been diverting away his/her own prescribed medications, then the situation needs to be evaluated on an individual basis. Continuation of treatment after warning with first time offenders may be considered after weighing the risks and benefits of treatment continuation/discontinuation. Treatment termination may be considered for repeat and recalcitrant offenders, or those who present as a threat to staff and other patients. Law enforcement agencies may need to be involved in cases where individuals snatch away other patient’s medications, or break into the stocks and supplies of the treatment facility. Treatment termination may be required in response to the fact that such actions will only increase the chances of the patient’s relapse into taking illicit opioids, with a consequent increase in morbidity and mortality [35].

Some individuals take recourse to diverted medications as they would not like to present themselves as ‘addicts’ at a treatment facility, and would prefer to keep their identity as a secret. In such patients the option of confidential treatment services may be considered, or the treatment provided by general practitioners or general adult psychiatrists.

The quantum of medication prescribed needs to be reasonable. It has also been seen that take-home medications are associated with an increased risk of diversion [54]. Hence, as far as possible, daily dispensing of the buprenorphine dose may be preferred. It may, however, be inconvenient for some patients to take dispensed medications daily, given their pursuits towards social and occupational rehabilitation after leaving street drugs, and may result in treatment discontinuation. Hence, on a pragmatic note, some patients would need take-home medications during the course of OAT, putting them at a risk of getting involved in diversion. Family and other care givers should be involved in the treatment process in such situations, and their help may be sought in observing the quantum and intake of buprenorphine being prescribed.

Apart from this, random urine screens may be helpful in ascertaining whether the patient is using buprenorphine in any form. In a cross-sectional study in India, 14% and 34% of patients receiving buprenorphine-naloxone and buprenorphine, respectively, tested negative for buprenorphine on random observed urine testing [8]. It must be recognized that urine drug testing has limited practical utility in detecting intermittent non-compliance. A clinician may clarify to the patient at the initial appointment that assessment and monitoring are a part of treatment, and a urine screen may be requested at any time to check adherence.

Change in the formulation of buprenorphine-naloxone has been tried as a means of limiting diversion.
In some areas, buprenorphine-naloxone is provided in the form of a sublingual film which is muco-adhesive and dissolves more quickly than a tablet. This feature makes it difficult to remove the film from the mouth and use it for diversion [31]. However, the diversion of such buprenorphine-naloxone films has actually been documented [28]. Buprenorphine implants is another option, as these provide steady levels of buprenorphine over long periods of time, so obviating the need for frequent or daily doses of buprenorphine [53]. Buprenorphine transdermal patches may additionally help patients receive buprenorphine sans oral route.

At a policy level, provision of OAT on a larger scale might reduce the demand aspect of diversion. Easy access to OAT, with a minimal entry barrier, would provide care to a larger number of people, who would be benefited by OAT and reduce the demand for diverted buprenorphine. At the same time, safeguards are needed to allow the implementation of the rational use of buprenorphine and monitor current dispensing practices.

In addition, prescription monitoring may be utilized to track suspected cases of diversion. In situations where prescriptions can be tracked at a national level, individuals receiving multiple prescriptions can be identified. Electronic monitoring has been tried in Finland by using a device that registers the time and date of tablet removal. The technology was well accepted there, and the diversion of buprenorphine was lowered by using this method [45]. Such technologies are resource-intensive and may not be feasible in resource-limited settings.

6. Diversion in a pragmatic context

While there are several concerns relating to the diversion of buprenorphine, some benefits to the individual taking it may also be construed. In many instances, individuals using illicit buprenorphine may be doing so in an attempt to decrease the illicit use of other opioids, self-treat opioid dependence, manage or mitigate withdrawal symptoms [12, 20, 37, 42], or reduce the level of harm associated with injection drug use [25]. Thus it is probable that a diversion may function as a pragmatic solution for tiding over a crisis in a few selected individuals. In a wider context, however, occurrences of diversion should probably be viewed as a systemic failure either in reaching out to care for those in need, or in regulating access to buprenorphine at the societal level. Thus, stringent control or monitoring policies need to be coupled with parallel efforts to increase access to OAT for individuals with opioid dependence.

7. Conclusion

To conclude, the complete cessation of diversion may not be feasible for a medication with considerable abuse potential, such as buprenorphine. However, cognizance of the extent, reasons and means of diversion would help the team of healthcare professionals and policy makers to take corrective actions. Concerns about diversion should not be allowed to act as a deterrent against the rational use of buprenorphine for OAT in the clinical setting, as such OAT makes possible several positive outcomes. In any case, reflective and corrective measures would be in order whenever diversion is detected.

Longitudinal research is needed to understand the long-term implications of diverted buprenorphine use. Another matter calling for clinical research is how much benefit intermittently prescribed buprenorphine can bring to patients who aspire to abstain from illicit opioid use but are not able to enter formal treatment. Also, more clinical research is needed to gain a better understanding of the diversion of novel forms of buprenorphine such as transdermal patches and film-based preparations. The motivational specifics behind injecting buprenorphine need to be explored further to allow such drives towards diversion to be properly addressed.

References

vending machines, needle exchange programs and legal pharmacy sales in Marseille, France. Eur Addict Res. 7(1): 40-45.


Acknowledgements
None

Role of the funding source
Financial support for the implementation of this article was provided by internal funds.

Contributors
All authors were involved in the review of the literature, critically reviewed the manuscript and had full editorial control, and final responsibility for the decision to submit the paper for publication.

Conflict of interest
Authors declared no conflict of interest.

Ethics
Authors confirm that the submitted study was conducted according to the WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects.

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