Heroin Addiction and Related Clinical Problems

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Aggressive behaviour in heroin addicts at treatment entry

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Summary

Background: Few studies have focused on the difference between heroin-dependent patients and the general population. Methods: We evaluated the aggressive behaviour of 252 heroin-dependent patients (163 males and 89 females) at treatment entry, comparing them with the Italian general population (standardization sample). We also studied correlations between aggressive behaviour and the addiction history of our patients. We used the Buss-Durke Inventory (BDI) to assess aggressive behaviour and the Drug Addiction History Questionnaire for addiction history. Results: Overall, heroin-dependent patients scored higher than the general population. Specifically, the highest values were reached for the suspicion, resentment and assault dimensions; the lowest for irritability and verbal hostility. Feelings of guilt were higher than in general populations. Only 18.7% showed a low aggression profile; 3 out of every 4 patients were characterized by violent behaviour due to suspicion and resentment (type 2). With respect to the general population, a greater number of heroin-dependent patients showed an aggressive type 2 profile (OR=3.2). Addiction history and type and degree of aggressive behaviour showed a weak correlation (only found with altered mental status, legal problems, periods of voluntary or forced abstinence, social leisure activity). Conclusions: At treatment entry, heroin addicts showed more violent behaviour than the general population; this was related to altered mental status and weakly correlated with addiction history. Thus, studies correlating aggressive behaviour with other symptomatological states are needed.

Key Words: Heroin dependence; aggressive behaviour; addiction history

1. Introduction

In drug addiction, the risk of violence could depend on the type of substance that is being abused; for example, heroin abusers are hardly ever violent under the influence of narcotics, but they can be aggressive during withdrawal, while those who use stimulants are likely to be violent under the effects of those drugs, even in cases of episodic exposure. Violent crime is actually less frequent in heroin-dependent people than in alcohol and/or stimulant abusers [6, 11, 32]. Nevertheless, criminality appears to be an indirect, partial correlate of the aggressiveness displayed by heroin addicts, since the intersection between the two merely reflects acts of violent assaultive behaviour. In fact, offences perpetrated by heroin addicts can be divided into 3 major categories: crimes against 1) property, 2) people (assaultive violence) and 3) oneself (suicidality). Although drug users have always been regarded as a single violent social group [33, 39] and their involvement in crime is commonly reported [1, 2, 20, 33], their commitment to the criminal world is often related to the fact that heroin is expensive and illegal [20, 33]. In any case, many of the crimes committed by heroin addicts do not consist merely in drug selling or trafficking, but also involve other fields of criminal behaviour such as violent assaults. In particular, heroin addiction seems to be closely connected with offences against property, shoplifting, burglary and robbery [4, 23, 26, 32, 35].

To our knowledge few studies have focused on the difference between heroin-dependent subjects and
the general population regarding aggressive behaviour in general and violence in particular. Almost one study seems to suggest the existence of a more aggressive behavioural pattern in heroin-dependent subjects than in the general population; Gerra and co-workers suggested that in heroin-dependent patients during methadone or buprenorphine maintenance treatment. Using a laboratory task, the Point Subtraction Aggression Paradigm, it was possible to show that the enhancement of aggressive responses was higher in the heroin-dependent patient group (independently of the agonist treatment), than in the control group [19]. Even after long-term opiate discontinuation, heroin-dependent subjects showed a higher level of outward-directed aggressiveness than healthy subjects [17].

In this study, we evaluated the aggressive behaviour of heroin-dependent subjects at treatment entry, comparing them with the Italian general population (standardization sample). We studied also correlations between aggression indexes and addiction history of our patients.

2. Methods

2.1. Design of the study

This is a retrospective, observational, case-control study. The research study was implemented using a dataset from previous studies on MMTP carried out in Italy and used in previous published articles (Pisa addiction dataset: a database including anonymous individual information originally collected for clinical and research purposes).

The study included patients treated at Santa Chiara University Hospital, Department of Neurosciences, University of Pisa, Italy during the period 1994-2012. All patients gave their informed consent to the anonymous use of their personal data records for research purposes.

2.2. Sample

Patients included in the Pisa addiction dataset were selected on the basis of the following characteristics:

- Diagnosis of opioid dependence with physical dependence according to DSM-IV TR and various DSM criteria
- Patients for which a specific aggressive behaviour questionnaire was recorded (see below)
- Not receiving medications
- Be evaluated before entering treatment

We excluded patients:
- Using illegal methadone or other opioid agents at treatment entry

Patients using illegally obtained methadone or other opioid agents were excluded to limit the confusing effects of these medications on clinical psychiatric presentation [30].

We included in the study 252 consecutive heroin-dependent patients. The mean age of these patients was 25 ± 4 years old (18–42 ranged). 163 (64.7%) were male; 211 (83.7%) were single, 155 (61.5%) had less than 9 years of education, and 81 (32.1%) were unemployed. No differences were observed between males and females, apart from the finding that a significantly lower percentage of males (32.5% vs 49.4%) showed less than 9 years of education (chi²=6.93; p=.008).

As to drug addiction history, 158 (62.7%) patients reported physical complications; 209 (82.9%) had altered mental status; 155 (61.5%) showed work, 98 (38.9%) household, 94 (37.3%) romantic, 131 (52.0%) social leisure and 79 (31.3%) legal difficulties. 160 (63.5%) were poly-abusers (3 or more substances), 133 (52.8%) had experienced past treatment failures.

2.3. Instruments

2.3.1. Drug Addiction History Questionnaire (DAH-Q)

The DAH-Q [27] is a multidimensional questionnaire that comprises the following 8 areas: 1-demographic data, 2-physical health, 3-mental status, 4-social adjustment and environmental factors, 5-substances abused, 6-substance abuse modalities (heroin intake, modality of use, stages of illness, nosography), 7-treatment history and 8-addiction history (age at first contact, age at onset of continuous use, dependence length and age at first treatment). The questionnaire comprises 10 presence-absence items: 1-somatic comorbidities, 2-abnormal mental status, 3-work problems, 4-household problems, 5-sexual problems, 6-socialization and leisure time problems, 7-drug-related legal problems, 8-polysubstance abuse, 9-previous treatment, 10-combined treatments.

We encoded the modality of use as follows: 1-stables, 2-junkies, 3-two worlders, 4-loners according to Lahmeyer’s classification [25]. “Stables” are opioid addicts who espouse conventional values, hold legitimate jobs, are generally law-abiding and do not associate with other addicts. “Hustlers”, otherwise called “junkies” or “criminal addicts”, are
closely identified with an addict subculture, are not legitimately employed, and subsist on the proceeds of criminal activities. “Two-worlder” addicts engage in criminal activities and associate with other addicts, but are also legitimately employed. “Loner” addicts are not involved either in the addict subculture or the conventional culture. They are usually unemployed, and live on welfare benefits rather than on the proceeds of criminal activities. These uninvolved addicts may have severe psychological disorders.

The development of addiction may be considered to consist of three stages: 1-acute (immediate) drug effects (Honeymoon Stage); 2-transition from recreational use to patterns of use consistent with addiction (Increasing Dose Stage); and 3-end-stage addiction, which is characterized by an overwhelming desire to obtain the drug, a diminished ability to control drug-seeking and reduced pleasure from biological rewards (Revolving Door Stage) [22].

Considering the clinical typology, drug addicts can be divided into 1-reactive (presence of psychosocial stressors before using heroin), 2-selftherapeutic (presence of psychiatric stressors before using heroin), and 3-metabolic (no psychosocial or psychiatric antecedents) [31].

2.3.2. Substance use

Regarding toxicological urinalyses, we applied the routine analyses that are used for all hospitalized patients. The enzyme-multiplied immunotechniques for opiates, methadone, benzodiazepines, hypnotics, cocaine, amphetamines, hallucinogens, cannabinoids and inhalants were used. Problematic alcohol use was defined according to a lifetime history of frequent intoxication and/or negative consequences of habitual use on their social adjustment (work, family, social/leisure or legal issues).

2.3.3. Buss-Durke Inventory for Assessing Different Kinds of Hostility (BDI)

BDI defines the subclasses of hostility that are typically delineated in everyday clinical situations [7].

- Assault: physical violence against others. This includes getting into fights with others, but not destroying objects.
- Indirect Hostility: both roundabout and undirected aggression. Roundabout behaviour like malicious gossip or practical jokes is indirect in the sense that the hated person is not attacked directly but by devious means. Undirected aggression, such as temper tantrums and slamming doors, consists of a discharge of negative affect against no one in particular; it is a diffuse rage reaction that has no direction.
- Irritability: a readiness to explode with negative affect at the slightest provocation. This includes quick temper, grouchiness, exasperation, and rudeness.
- Negativism: oppositional behaviour, usually directed against authority. This involves a refusal to cooperate that may vary from passive noncompliance to open rebellion against rules or conventions.
- Resentment: jealousy and hatred of others. This refers to a feeling of anger at the world over real or fantasized mistreatment.
- Suspicion: projection of hostility onto others. This varies from merely being distrustful and wary of people to beliefs that others are being derogatory or are planning harm.
- Verbal Hostility: negative affect expressed in both the style and content of speech. Style includes arguing, shouting, and screaming; content includes threats, curses, and being overcritical.

The variable of guilt was added because the relationship of guilt to the total score may be of clinical interest. Accordingly, items were compiled for a Guilt scale, with guilt being defined as feelings of being bad, having done wrong, or suffering pangs of conscience.

The items of BDI have been translated into Italian (QTA version) and then translated into English by a translator who did not know the English version. The accuracy of the translation and its conformity with the original version have been checked by a bilingual English expert native speaker, who confirmed the original meaning of the items of the QTA [8].

QTA was standardized in the Italian population (N=861) [28]; Standardized T points were corrected by gender and age (≤31yrs vs >31yrs). Factor analysis revealed two dimensions: without (type 1) and with (type 2) physical contact. The first dimension is characterized by verbal hostility, irritability, negativism and indirect hostility; the second one is characterized by suspicion, resentment, assault and guilt.

The ratio Guilt/Total QTA clustered subjects into (1) ego-dystonic and (2) ego-syntonic aggression groups.

Subjects obtaining T-QTA values higher than scores of 50 were considered to display highly aggressive behaviour; subjects who had scores of less
than 50 were considered to have a low level of aggressive behaviour with respect to the general population (standardization sample).

2.4. Data analysis

We used the following data analysis procedure.

To divide patients into the type 1 or type 2 aggression group, the two (i.e. without and with physical contact) factorial scores were standardized as z-scores to facilitate the comparisons between the scores recorded for the two factorial parameters. All the subjects were then grouped into different subtypes on the basis of the higher z-scores obtained for each aggression factor (dominant type of aggressive behaviour). This procedure opens up an opportunity to classify groups of subjects on the basis of their most statistically abnormal aggressive behaviour.

To divide patients into an ego-dystonic and an ego-syntonic group, we considered the same procedure by standardizing, as z-scores, Guilt and Total QTA scores and grouping on the basis of the higher z-score.

Using BDI T-total score we also divided the sample into patients with a high and low level of aggression.

We compared the aggressive behaviour factors of heroin-dependent patients to our standardization sample by applying the One-Sample T Test. We used the chi-square test to determine whether our subjects belonged to the aggression type 1 or 2 groups and the ego-dystonic or ego-syntonic groups. Lastly, type 1 versus type 2 heroin-dependent patients and high aggression (Total QTA T scores > 50) versus low aggression (Total QTA T scores ≤ 50) patients were compared, with reference to their addiction history.

All analyses were carried out using the statistical package of SPSS (version 20.0). Since this is an exploratory study, statistical tests were considered significant at the p <0.05 level.

3. Results

3.1. Aggressive behaviour profile

Figure 1 shows the BDI profile of our patients. Overall, heroin-dependent patients scored higher than the general population. Specifically, the highest values were reached for the suspicion, resentment and assault factors; the lowest for irritability and verbal hostility. Feelings of guilt were higher than in general populations.

205 (81.3%) patients showed a BDI total T-score >50 and were considered to have highly aggressive behaviour; 47 (18.7%) showed a BDI total T-score ≤50 and were considered to have a low level of aggressive behaviour.

60 patients (23.8%) showed a type 1 dominant
profile of aggressive behaviour characterized by verbal hostility, irritability, negativism, indirect hostility (aggressive behaviour without physical contact). 192 (76.2%) showed a type 2 dominant profile of aggressive behaviour characterized by suspicion, resentment, assault and guilt.

Aggressive behaviour was perceived as ego-dystonic by 140 (55.6%) patients and as ego-syntonic by 112 (44.4%).

3.2. Comparison with standardization sample

Table 1 shows comparisons with an Italian standardization sample. Significant differences were found for all factors and total score on the BDI. With respect to standardization sample, a greater number of heroin-dependent patients showed a type 2 dominant profile of aggressive behaviour (OR=3.2). No differences were found with regard to belonging to the ego-syntonic or ego-dystonic group (Table 2).

3.3. Correlations between addiction history and aggressive behaviour

Only the presence of altered mental status at treatment entry and unsatisfactory social leisure activity characterized aggressive behaviour type 2 patients (violence with physical contact). By contrast, patients with a low level of aggression showed fewer legal problems, were able to undergo periods of voluntary or forced abstinence lasting weeks to months, followed by period of relapse (Table 3 and Table 4).

4. Discussion

In our sample, heroin-dependent patients are more aggressive than the general population in all the BDI items, showing higher values for the suspicion, resentment and assault factors. In particular, a majority of the sample featured a type 2 profile (aggressive behaviour with physical contact), but there was no difference with respect to the general population on the question of its perception of aggressive behaviour. Regarding addiction history, type 2 patients are characterized by altered mental status and unsatisfactory social leisure activity. Patients with a low level of aggression have fewer legal problems, and more frequent periodic self-detoxifications.

The relationships between aggressive behaviour, inability to utilize and plan leisure time, the frequency of periodic self-detoxifications and the absence of differences related to the perception of aggressive be-

| Table 1. Aggressive behaviour of 252 heroin-dependent subjects at treatment entry, according to BDI. One group T-Test (referring to standardization Italian sample (N=861). T-score corrected for sex and age. |
|-----------------|-------|-------|-------|-----|
| Factors        | M     | SD    | T     | p   |
| 1. Assault     | 57.60 | 9.3   | 12.91 | .000|
| 2. Indirect hostility | 55.26 | 8.8   | 9.45  | .000|
| 3. Irritability | 51.98 | 7.7   | 4.10  | .000|
| 4. Negativism   | 53.55 | 9.1   | 6.19  | .000|
| 5. Resentment   | 58.58 | 11.4  | 11.96 | .000|
| 6. Suspicion    | 59.62 | 9.9   | 15.35 | .000|
| 7. Verbal hostility | 51.96 | 8.9   | 3.49  | .001|
| 8. Guilt        | 56.14 | 11.7  | 8.36  | .000|
| 9. Total score  | 55.51 | 6.5   | 13.54 | .000|

| Table 2. Dominant aggressive behaviour profiles in heroin-dependent patients with respect to standardization sample. |
|---------------------------------------------------------------|-------|-------|-----------------|-----|
| N=252                                                        | N=816 |
| N %                                                  | N %  |
| Aggressive behaviour type                                   |      |
| Type 1 (without physical contact)                           | 60   | 23.8 | 408             | 50.0|
| Type 2 (with physical contact)                              | 192  | 76.2 | 408             | 50.0|
| Aggressive behaviour perception                             |      |
| Ego-Dystonic                                                | 140  | 55.6 | 432             | 52.9|
| Ego-Syntonic                                                | 112  | 44.4 | 384             | 47.1|

chi p

53.64 0.000

0.52 0.529
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while the number of people who had committed property crimes showed a tendency to fall, but remained at quite high levels [24]. Heroin use is significantly associated too with other forms of aggressive behaviour, such as the perpetration of any severe intimate partner violence [11] and rarely with homicide [34].

Looking at these studies, heroin-dependent patients present a high level of aggressiveness characterized by physical contact, such as assault. These observations are in line with our results, in which a majority of the sample featured a type 2 dominant profile (aggressive behaviour with physical contact) with an OR of 3.2.

Looking now at the relationship between aggressive behaviour and heroin addiction history, our results suggest a weak correlation between addiction history, and type and amount of aggressive behaviour, except for the presence of altered mental status and the fact of belonging to the type 2 aggressive behaviour profile. In the literature, there is general agreement on

Table 3. Correlations between addiction history and dominant aggressive behaviour type

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<tr>
<td></td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Gender (males)</td>
<td>252</td>
<td>36</td>
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<tr>
<td>DAHQ Factors</td>
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<td>01. Somatic compli-</td>
<td>251</td>
<td>37</td>
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<tr>
<td>variations (presence)</td>
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<td>02. Altered mental</td>
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<td>45</td>
</tr>
<tr>
<td>status (presence)</td>
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<td></td>
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<td>03. Occupation</td>
<td>248</td>
<td>39</td>
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<tr>
<td>(satisfactory)</td>
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<tr>
<td>04. Household</td>
<td>239</td>
<td>26</td>
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<td>(unsatisfactory)</td>
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<tr>
<td>05. Loving</td>
<td>214</td>
<td>25</td>
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<td>(unsatisfactory)</td>
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<td>06. Social leisure</td>
<td>226</td>
<td>25</td>
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<tr>
<td>activity (unsatisfac-</td>
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<td>tory)</td>
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<td>07. Legal problems</td>
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<td>08. Poly-abuse</td>
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<td>09. Never treated</td>
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Heroin abuse modalities

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<tr>
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</tr>
<tr>
<td></td>
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<td>5.6</td>
<td>-0.79</td>
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<td>223</td>
<td>22.89</td>
<td>5.7</td>
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<td>0.85</td>
</tr>
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<td></td>
<td>216</td>
<td>2.66</td>
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<td>2.83</td>
<td>3.5</td>
<td>-0.31</td>
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<tr>
<td></td>
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<tr>
<td></td>
<td>205</td>
<td>3.62</td>
<td>3.7</td>
<td>3.13</td>
<td>3.6</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Type 1 (without physical contact): Verbal Aggression, Irritability, Negativism, Indirect Aggression
Type 2 (with physical contact): Suspiciousness, Resentment, Assault, Guilt

The existence of a link between aggressive behaviour and legal problems is well documented. Generally speaking, offenders report higher rates of drug use, and drug users are more frequently found to be offenders. The number of heroin-related offences has increased in 16 reporting EU countries, while a decline was reported in Bulgaria, Germany, Italy and Austria over the same period (2003-2008) [13]. Even if heroin users are frequently involved in criminal behaviours [1, 2, 20, 33], and offences against property [32] such as shoplifting, burglary and robbery [4, 23, 26, 35], according to a longitudinal perspective (addiction history), the predominant type of illegal activities changes with an increase in the frequency of crime related to the circulation of illegal drugs. In that same period, the percentage incidence of violent crimes and acts of hooliganism decreased, while the number of people who had committed property crimes showed a tendency to fall, but remained at quite high levels [24]. Heroin use is significantly associated too with other forms of aggressive behaviour, such as the perpetration of any severe intimate partner violence [11] and rarely with homicide [34]. Looking at these studies, heroin-dependent patients present a high level of aggressiveness characterized by physical contact, such as assault. These observations are in line with our results, in which a majority of the sample featured a type 2 dominant profile (aggressive behaviour with physical contact) with an OR of 3.2.

Looking now at the relationship between aggressive behaviour and heroin addiction history, our results suggest a weak correlation between addiction history, and type and amount of aggressive behaviour, except for the presence of altered mental status and the fact of belonging to the type 2 aggressive behaviour profile. In the literature, there is general agreement on

behaviour of heroin addicts compared with the general population are hard to discuss. No studies, to the best of our knowledge, have faced these topics so far.
the higher risk of violence among people with severe mental illness (SMI) that is worsened by concomitant substance abuse, medication non-compliance, or lack of insight [37, 38]. Despite this, a recent report claimed that SMI alone was not statistically related to future violence behaviours [12, 41]. More precisely, the incidence of violence was only higher for people with SMI who had co-occurring substance abuse and/or dependence [3, 12, 36]. Of course, violence is further determined by the kind of diagnosis obtained by patients, [5, 9, 14, 15, 40].

The main result of our study remains the demonstrably higher T-scores of heroin addicts in all aspects of their aggressive behaviour, in accordance with the Gerra controlled study mentioned earlier [18]. However Gerra et al. concluded that in heroin addicts aggression seems to be related more to the premorbid personality than to addiction itself, partly because high levels of aggressiveness have been found in heroin-dependent patients treated with methadone [16, 21]. On the other hand, heroin-dependent patients with severe psychopathological features need a higher dosage of methadone to become stabilized. Contrary to expectations, when behavioural stabilization was pursued with no dose threshold, treatment-resistant patients with severe mental illness showed a better long-term outcome than treatment-resistant patients without psychiatric comorbidity [29]. Indeed, it is well known that methadone treatment, at blocking dosages, reduces levels of crime and violence [10]. Thus the knowledge that patients are in treatment only with methadone, without the certainty of blocking dosage use, cannot support the statement made by Gerra and co-workers. One possible alternative explanation is that patients’ still unstabilized opioid system, whether on the streets or during treatment, may be responsible for aggressive behaviour seen in our patients at treatment entry. Studies evaluating correlations between aggressive behaviour and withdrawal symptoms are needed.

### Table 4. Correlations between addiction history and patients with low and high levels of aggression

<table>
<thead>
<tr>
<th></th>
<th>Low-level Aggression</th>
<th>High-level Aggression</th>
<th>chi</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gender (males)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N</td>
<td>252</td>
<td>34</td>
<td>129</td>
<td>62.9</td>
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<tr>
<td><strong>QTA-Factors</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>01. Somatic complications (presence)</td>
<td>251</td>
<td>29</td>
<td>61.7</td>
<td>129</td>
</tr>
<tr>
<td>02. Altered mental status (presence)</td>
<td>250</td>
<td>37</td>
<td>78.7</td>
<td>172</td>
</tr>
<tr>
<td>03. Occupation (satisfactory)</td>
<td>248</td>
<td>33</td>
<td>71.7</td>
<td>122</td>
</tr>
<tr>
<td>04. Household (unsatisfactory)</td>
<td>239</td>
<td>16</td>
<td>36.4</td>
<td>82</td>
</tr>
<tr>
<td>05. Loving (unsatisfactory)</td>
<td>214</td>
<td>16</td>
<td>42.1</td>
<td>78</td>
</tr>
<tr>
<td>06. Social leisure activity (unsatisfactory)</td>
<td>226</td>
<td>20</td>
<td>48.8</td>
<td>111</td>
</tr>
<tr>
<td>07. Legal problems (presence)</td>
<td>242</td>
<td>9</td>
<td>20.9</td>
<td>70</td>
</tr>
<tr>
<td>08. Poly-abuse (presence)</td>
<td>247</td>
<td>26</td>
<td>59.1</td>
<td>134</td>
</tr>
<tr>
<td>09. Never treated</td>
<td>229</td>
<td>23</td>
<td>54.8</td>
<td>110</td>
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<tr>
<td>10. Requiring associated treatments</td>
<td>243</td>
<td>33</td>
<td>71.7</td>
<td>146</td>
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<tr>
<td><strong>Heroin abuse modalities</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Heroin intake (daily or more)</td>
<td></td>
<td>224</td>
<td>33</td>
<td>82.5</td>
</tr>
<tr>
<td>Modality of use (stable)</td>
<td></td>
<td>224</td>
<td>17</td>
<td>42.5</td>
</tr>
<tr>
<td>Periodic self-detox</td>
<td></td>
<td>216</td>
<td>36</td>
<td>92.3</td>
</tr>
<tr>
<td>Late phase of dependence</td>
<td></td>
<td>218</td>
<td>20</td>
<td>51.3</td>
</tr>
<tr>
<td>Typology (with psychosocial stressors at 1st contact)</td>
<td>207</td>
<td>20</td>
<td>52.6</td>
<td>84</td>
</tr>
<tr>
<td><strong>Addiction history</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>N</td>
<td>252</td>
<td>25.85</td>
<td>3.3</td>
<td>25.17</td>
</tr>
<tr>
<td>Age at first contact with heroin (yrs.)</td>
<td>225</td>
<td>16.23</td>
<td>3.3</td>
<td>16.78</td>
</tr>
<tr>
<td>Age at dependence onset (yrs.)</td>
<td>218</td>
<td>19.51</td>
<td>4.9</td>
<td>19.29</td>
</tr>
<tr>
<td>Dependence length (yrs.)</td>
<td></td>
<td>230</td>
<td>4.20</td>
<td>4.33</td>
</tr>
<tr>
<td>Age at 1st treatment</td>
<td></td>
<td>223</td>
<td>21.55</td>
<td>5.3</td>
</tr>
<tr>
<td>Abuse length (yrs.)</td>
<td></td>
<td>216</td>
<td>3.28</td>
<td>3.7</td>
</tr>
<tr>
<td>Treatment latency (from 1st use) (yrs.)</td>
<td>223</td>
<td>5.36</td>
<td>4.2</td>
<td>5.70</td>
</tr>
<tr>
<td>Treatment latency (from age at onset) (yrs.)</td>
<td>205</td>
<td>2.19</td>
<td>2.5</td>
<td>3.46</td>
</tr>
</tbody>
</table>
At treatment entry, heroin addicts showed more violent behaviour than the general population; this is related to altered mental status and is weakly correlated with addiction history, so inviting studies that aim to investigate the aggressive behaviour of heroin addicts as “state” conditions.

References


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Financial support for the implementation of this study was provided by internal funds.

**Contributors**

BL, JS, ML and JS designed the study and wrote the protocol. MP, LR, AGIM managed the literature searches and analyses. IM undertook the statistical analysis, and all the authors discussed the results. BL, ML, IM 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. IM served as consultant for Reckitt Benckiser Pharmaceuticals.

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Conclusions endorsed at the plenary session of May 27, 2012 during the 10th European Congress of the European Opiate Addiction Treatment Association, Barcelona, Spain, EU, May 25-27, 2012

- Opioid addiction(*) is a chronic relapsing disorder
- Detoxification should not be the primary goal, because of the high risk of relapse and lethal overdose
- There is no evidence for better outcome when leaving the general principles of treatment for chronic ill patients
- Addicted patients should be treated as normally as possible without stigmatizing regulations
- Long-term treatment with adequate dosage of an opioid should be started without delay - either buprenorphine, buprenorphine-naloxone or methadone. Dose should be individualized; split dosage may improve stabilization
- As patients in treatment may face intolerance to the traditional treatment, alternative opioid(s) should be offered
- Decentralized, full coverage of opioid treatment should be provided
- Polysubstance abuse is no contraindication to opioid substitution treatment

(*) Cfr : "Opiate Addiction Syndrome": International Classification of Disease (ICD10 F11.2) or DSM IV
Benzodiazepine misuse. Results of an Italian post-mortem study

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1 Department of Forensic Medicine, Forensic Service, University of Modena and Reggio Emilia, Italy
2 Department of Internal Medicine, Addiction Unit, Verona University Hospital, Verona, Italy

Summary

Benzodiazepines, which are typically used to treat insomnia and anxiety disorders, are widely prescribed in all medical fields. This widespread use has led to frequent, often inappropriate forms of consumption. Although benzodiazepines and illicit drugs are commonly associated, the rise in consumption outside the sphere of legitimate prescriptions, even in the general population, has been seriously underestimated. To better describe this phenomenon we assessed benzodiazepine prevalence and typology in 212 autopsy cases examined by the Forensic Medicine Department, University of Modena (Italy) in the three-year period from 2006 to 2008. The biological samples analysed for this study were central blood and urine. All the tests were performed using ultrasensitive liquid chromatography coupled with mass spectrometry in “tandem Mass Spectrometers”. After classifying the various causes of death, the study population was divided into the following groups: 70 deaths from natural causes (33%), 51 from accidental injuries (24%), 40 due to overdose (19%), 23 to homicide (11%), 23 to suicide (11%) and 5 from medical professional causes (5%). 30.8% of the females were BZD-positive, while that feature was identified in 25.9% of the males. The xenobiotics most frequently found were: Diazepam (29.6%), Delorazepam (22.5%), Flurazepam (14.1%), Lorazepam (12.7%), Alprazolam (11.3%) and Lormetazepam (11.3%). It is worth noting the total lack of Flunitrazepam, which is particularly prominent in the Drug Users group, because, worldwide, Flunitrazepam has been the most abused benzodiazepine among polydrug users. This finding tends to suggest that Flunitrazepam has been disappearing from the illegal market in Italy; it also seems to show that recent restrictions on its prescription in this country have already decreased its legal use or actually reduced it to zero.

Key Words: Benzodiazepines; forensic medicine; post-mortem; misuse; drug users; overdose.

1. Introduction

The search for benzodiazepines (BZDs) in body fluids is a typical example of routine analysis in forensic toxicology. This kind of interest is motivated both by reports of a rise in the consumption of these drugs and by the need to attain greater precision in defining the relation between major and contributory causes in determining death events [1].

The alarming spread of BZDs in Italy has been widely documented by the National Observatory on the Use of Drugs, which puts them in first place among the most frequently prescribed drugs for the central nervous system. In particular, Lorazepam and Lormetazepam are the 2 best-selling kinds of BZD in Italy [1]. Lormetazepam and Lorazepam were also found to be the most commonly abused BZDs in a large sample of patients who had been hospitalized for BDZ abuse in Italy [2].

In order to understand the reasons for the spread of the use and misuse of BZDs, we considered it useful to study the extent of this phenomenon on a post-mortem sample comprising various different causes of death.

2. Methods

The purpose of this study, was, therefore, to
evaluate the presence of BZDs in body fluids to obtain specific data (prevalence, type and combinations of the BZDs found) pertinent to the use and misuse of these substances in a large sample of subjects who had died from various causes of death. The combination of analytical techniques with judicial inquiry made it possible to carry out a precise investigation on the improper use of BZDs, which is a widespread phenomenon but has been largely overlooked by doctors and official bodies. In recent times, the development of techniques in liquid chromatography coupled with mass spectrometry in ‘tandem Mass Spectrometers’ (LC-MS/MS) has increased the feasibility, in a single step, of identifying drugs whose involvement was unknown, or had not been indicated in anamnestic or circumstantial findings [3-7]. These techniques have therefore made it easier to optimize screening by “Multi-Analyte procedures” and drug quantification of blood taken during autopsy, so making possible the simultaneous detection of multiple xenobiotics and, consequently, the causative or co-causative identification of compounds that exert a detrimental effect [8].

In this retrospective study, 212 autopsy cases were considered in all, by reviewing the observations of the Forensic Medicine Department, University of Modena and Reggio Emilia, in the three-year period 2006-2008 (55 cases in 2006, 77 in 2007 and 80 in 2008). Of all these subjects, most (160, 75.5%) were males; more precisely, 85% of them were aged between 22 and 60. We evaluated the various types of BZD used, amounting to a total of 29 analytes. All tests were performed using an ultra-sensitive LC-ESI-MS/MS method validated in our laboratory.

Investigations were required in order to determine the possible influence of drugs in causing damaging events, to document the appropriateness of drug therapy and, lastly, to exclude the detrimental influence of xenobiotics.

After classification of the various causes of death, the study population was divided into the following groups: 70 deaths from natural causes (33%), 51 from accidental injuries (24%), 40 due to overdose (19%), 23 to homicide (11%), 23 to suicide (11%) and 5 from causes that led to the investigation of medical liability (IML, 5%). 30.8% of the females were BZD-positive, while this feature was found in 25.9% of the males.

The biological samples analyzed for this study were central blood and, when present, urine; a total of 212 blood samples were tested, and 124 urine specimens. In all cases, in addition to the specific search for benzodiazepines by the methods described below, searches were also carried out for ethyl alcohol, narcotics and psychotropic substances. A ‘general unknown analysis’ was carried out with the aim of identifying the most suitable number of compounds of toxicological interest.

Standard Certificates of Alprazolam, Bromazepam, Brotizolam, Clobazam, Clonazepam, Clotiazepam, Delorazepam, Diazepam, Estazolam, Flunitrazepam, Flurazepam, Lorazepam, Lormetazepam, Medazepam, Midazolam, Nitrazepam, Nor-diazepam, Oxazepam, Pinazepam, Prazepam, Temazepam, Triazolam, 7-NH2-flunitrazepam, 7-NH2-clonazepam, OH-ethyl-flurazepam, Desmethyl-flurazepam, Desmetilflunitrazepam, OH-alprazolam, OH-triazolam at a concentration of 1.0 γ/μL or 0.1 γ/μL in methanol were obtained from the SALARS Company (Como, Italy).

Reagents were used with analytical grade RP-Carlo Erba SpA (Milan, Italy), β-glucuronidase enzyme; formic acid and ammonium acetate were obtained from the Sigma-Aldrich Company (St. Louis, MI, USA).

A liquid chromatograph (Agilent 1200 LC binary pump) was used, in combination with a mass spectrometer (API 4000 Q TRAP (Applied Biosystem) equipped with an autosampler.

Ion source TIS (Turbo Ion Spray) in positive ions was used, set at 450° C, with an ionization potential of 5,500 V. The chromatographic column used was a Synergi Polar RP (150 mm x 2 mm id, 4 µm Phenomenex) kept at a steady temperature of 40 °C and operating in the flow gradient elution at a 0.25 ml/min. flow.

The acquisition and processing of data were performed using Analyst software, version 1.4.1 (Applied Biosystems/MDS Sciex).

Put briefly, blood samples and urine were subjected to a solid phase extraction (SPE) through the use of “Chromabond drug 200 mg” columns, after enzymatic hydrolysis by beta-glucuronidase for the urine matrix. The extracts were then subjected to analysis by LC tandem MS API 4000 Q Trap operating on positive ions with Multiple Reaction Monitoring (MRM) acquisition, using the transitions reported by Mueller [7]. Pinazepam was used as internal standard.

In accordance with the EURACHEM guidelines, the following parameters were considered to validate the method: matrix effect, selectivity, linearity, limit of quantification (LLOQ) and detection (LLOD). The extraction efficiency and matrix effect were studied by analysing three different sets of samples, as sug-
gested by Matuszewski [9].

The calibration curve was obtained by adding to samples of white urine or blood increasing amounts of the analytes involved. These samples were subjected to the extraction procedure, together with blank samples, and LC-MS/MS analysis [10]. Calibration curves proved to be linear within the range of interest (0.5 to 1000 ng/ml); the values of the correlation coefficients (r²) were all higher than 0.990. Both the limit of quantification (LLOQ) and limit of detection (LLQD) were estimated as the lowest amount of analyte with a signal to noise ratio (s/r) equal to 10 or greater than 3. LLOD and LLOQ values were estimated within a range of 0.1 ng/ml and of 0.3 ng/ml, respectively.

The study was approved by the appropriate ethics committee, and was carried out in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki.

4. Results

From toxicological investigations, which aimed to determine which BZDs were present in the biological samples under study, BZD positivity was found in 34.9% of the cases (74 cases out of 212). The age of the subjects was in the 20 to 83 year range, with an average of 43 years.

30.8% of female subjects were BZD-positive, while this feature was identified in 25.9% of the male subjects.

In determining the typologies of death in each case, the prevalence of positivity for BZDs was as follows: 62.5% in overdose cases, 45.4% in suicides, 40% in IML, 28.6% in deaths from natural causes, 23.5% in accidental events and 21.7% in murders (Table 1).

![Figure 1. Benzodiazepines most frequently found](image)

We would like to emphasize that the concentrations of BZD in the cases studied by us were within the therapeutic range in almost all cases, while we found toxic concentrations only in 2 cases of suicide (2.7%).

In 23 cases (31%), there was a simultaneous consumption of at least 2 different BZDs (only in 4 cases with a medical certificate); more than half (56.5%) of the cases in which there was polyconsumption of BZDs turned out to be DUs. The most frequently encountered BZD associations were: Alprazolam-Diazepam, Flurazepam-Clonazepam, Diazepam-Lo-

The analysis of the circumstantial case histories, which included a survey on the drug prescriptions in place at the time of death, showed that in only 32% of the cases were BZDs being taken on medical advice. This procedure allowed us to acquire information about the typology of subjects who showed a positive result for BZD. The category in which the use of benzodiazepines was highest was the one in which specific psychopharmacological therapies were unknown (50%), followed by drug users (DUs, 34%), chronic alcoholics (8%) and psychiatric patients (8%).

The xenobiotics most frequently found were: Diazepam (29.6%), Delorazepam (22.5%), Flurazepam (14.1%), Lorazepam (12.7%), Alprazolam (11.3%) and Lormetazepam (11.3%) (figure 1).

<table>
<thead>
<tr>
<th>Table 1. Cause of death and prevalence of BZDs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cause of death</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Overdose</td>
</tr>
<tr>
<td>Suicides</td>
</tr>
<tr>
<td>IML</td>
</tr>
<tr>
<td>Natural causes</td>
</tr>
<tr>
<td>Accidental events</td>
</tr>
<tr>
<td>Murders</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

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zolam (14%), Lorazepam (7%) and Clonazepam (7%).

It is worth noting the total lack of Flunitrazepam (FNZ), which has been particularly prominent in the DUs group because, worldwide, FNZ has been recognized as the BZD that is most frequently abused in this group [11,12,16].

5. Discussion

The comparison of results obtained from toxicological analysis with anamnestic/circumstantial data showed that the intake of BDZs is widespread, in many cases regardless of specific clinical indications and prescriptions.

Among the 74 cases that gave a positive result, 68% were not receiving any medical treatment, which confirms the idea that consumption often takes place in an arbitrary way; this phenomenon goes well beyond the category of illicit drug use.

Overdose cases have shown a higher rate of BZD use. This figures recorded in this study are comparable with those found in several previous reports in the literature (11-14).

The high prevalence of positivity for BZD (with all results above 20%), both in cases of natural death and of accidental trauma, was a more surprising finding.

Diazepam turned out to be the most prevalent BZD and this finding was confirmed again in the overdose cases; Lorazepam and Lormetazepam, the leading BDZs in Italy, were found less frequently than expected, even among DUs, as BZDs with a fast onset of action were those that were typically preferred [11,13,16].

The BZD levels we were able to observe in all subjects (except two cases of suicide where the abuses were probably due to the self-destructive act that led to death), turned out to fall within within the therapeutic range, so confirming the data that support the view that the abuse of high doses of BZD is limited to only a low percentage of patients [14-17]; in our study there were no high-dose users even among the DUs, where the prevalence of BZD abuse is usually described as considerable [13-16]. DUs have shown the frequent consumption of more than one BZD, almost always taking the form of an association of a short half-life BZD with one that has a long half-life.

The BZD positivity rate was found to be much lower in the overdose deaths of DUs that were not followed by an AC. The high prevalence of BDZs in the overdose deaths of DUs that were followed by an AC shows the high level of risk that is entailed by the prescription of these drugs, which is likely to make them unsuitable on account of their abuse potential [11,12,16].

Opioid users should be educated about the risks associated with polydrug intake. The administration of BDZs in heroin users is likely to raise the risk of accidental fatal overdose [18,19]. Prescribers should carefully consider types of pharmacological intervention that are alternative to BDZs, such as the adjustment of doses of long-acting opioid agonists, rather than prescribing symptomatic drugs like BDZs, when managing and treating opiate addiction.

Another element to be noticed is the absence of FNZ and its metabolite.

For a long time FNZ has been associated with antisocial behaviour and to a high frequency of attitudes that promote high-risk behaviours [17,18] but, in our study, it was absent even in all the recorded cases of violent death.

In a number of studies on the monitoring of BDZ, which involved thousands of BDZ users, FNZ still turned out to be the substance that had the highest abuse potential, and FNZ consumption is still considerable in some countries [11,21-23].

All these considerations led some countries, including Italy, to adopt serious selective restrictions in order to limit FNZ sales.

In Norway these restrictions of this kind, which were introduced in 2003, led to significant falls in FNZ sales [23,25].

Despite these changes, in the next few years, FNZ was found in 14% of Norwegian drivers involved in traffic accidents [26] - a phenomenon that was not encountered at all in our series - but was especially prominent as far as DUs are concerned.

In Italy, as in many other countries, FNZ was largely abused by DUs throughout the Eighties and Nineties [27]. To limit this phenomenon, specific regulatory barriers were put in place: drops were withdrawn from circulation to avoid injection misuse, and tablet dosage was halved to 1 mg. Similarly, the content of each packet was reduced by half. More recently, further specific restrictions regarding the prescription of FNZ became law in Italy. These regulatory barriers seemed to be effective in limiting the inappropriate use of FNZ, and data on the use of this drug are confirmed to have fallen to very low levels [1].

The total absence of FNZ in this sample, in particular among DUs, provides evidence not only of the disappearance of FMZ-containing drugs from the il-
legal market, but also of the likelihood that specific prescriptive restrictions may, in fact, have decreased its use or even eliminated it.

As a partial confirmation of this view, a recent Italian study reported that in a long series of patients who had been hospitalized for BDZ abuse, none of them had taken FNZ [28,29].

It would be unreasonable to suppose that such a successful measure, which is targeted at the limitation of FNZ misuse, cannot be applied with similar results to all BZDs, or at least to those that frequently show high risk of seizure. Flumazenil infusion to treat benzodiazepine dependence. J Clin Psychiatry 66:28-33.

These studies, if carried out by applying reliable methods, could make a useful contribution to the task of estimating the degree of use/misuse of BDZ, whether in the general population or among DUs.

References


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“A School for Life”. Monitoring of a multidisciplinary prevention intervention experience in four Neapolitan Schools

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Summary
Drug Addiction Unit No. 31 operating in the Centre of Naples for the city’s Local Health Authority (“U.O. Ser.T. 31, ASL Napoli 1 Centro”) has implemented the project called “A School for Life”. The project’s aims were to: 1) Get adolescent schoolchildren involved in the problems arising from exposure to psychoactive drugs”; 2) Monitor epidemiological data; 3) Evaluate the efficiency of the instruments used. Teachers, students and opinion leaders were involved. Workshops were set up to make the intervention more incisive. The programme was evaluated by teachers. 1,234 adolescents and 93 teachers participated; students took part in a course for peer-operators. Teacher evaluation showed an increase in project quality over time; an increase in cigarette and alcohol use emerged from the questionnaires administered to the schoolchildren; the use of alcoholic beverages and habitual drunkenness were seen. We recommend a policy of prevention that should be focused on the use of alcoholic beverages and drugs in Middle Schools.

Key Words: Prevention; school; substance abuse; alcohol; psychotropic drug

1. Introduction

The European Drugs Action Plan 2005-2008 looked forward to “significant prevalence reduction in the use of abusive substances in the population [...]”. The Action Plan listed 46 objectives that include: “furnishing reliable and comparable data relative to key epidemiological indicators, furnishing information on the diffusion of abused substance [...]”. With reference to alcohol consumption, the EU Action Plan recommends “keeping childhood alcohol free and delaying the onset of drinking”. The “European School Survey Project on Alcohol and Other Drugs” (ESPAD) questionnaire constitutes a valid instrument for achieving some of the objectives named above.

The effects of a prevention programme are hard to quantify in the short or the medium term, and there are many people who remain sceptical about the usefulness of preventive activity. In Italy, the prevention of abuse behaviour is one of the tasks attributed to drug addiction centres; the structure of these “Ser.T.” centres allows for the creation of multi-disciplinary activities to promote prevention. Without these activities, in many cases the work carried out in these centres has little clear purpose or outcome. The whole of Europe reveals the same problem in its various recognized systems that contribute to the fight against addiction.

Ser.T. 31, which works for Local Authority No. 1 within the central area of the city of Naples, proposed a 3-year prevention project entitled “A School for Life” in High and Senior, but also Middle Schools.
in certain neighbourhoods in the city. The project followed some indications for making prevention activity efficient that had been drawn up by the National Institute against Drug Abuse (NIDA) [10]. Knowledge of the most widespread abused substances in the city where intervention took place led to the choice of themes to be dealt with. In 2006 the local situation within Health District 31 was as follows: about 18,500 minors were under 18 years of age; 14,000 of these were under 13; about 500 people were receiving treatment through their local Ser.T.

Aims of this program were: 1) Making adolescents more actively involved in understanding the mechanisms found in the use of psychoactive substances. 2) Monitoring the epidemiological data in the study cohort. 3) Following the cohort through time in order to evaluate the efficiency and effectiveness of the project. 4) Studying teachers’ knowledge about substances. 5) Elaborating a model for policy makers who intend to implement prevention in schools.

2. Method

At the beginning of the project, the organization of personnel and the time schedules involved were predetermined; stimuli and strategies were declared; throughout the duration of the project, it was adapted to each single school through evaluation and necessary changes. The project lasted for 3 years, and comprised: a teacher training phase; training of students to become peer educators. Activation techniques like discussion groups held by students, role playing and the acting out of scenes were key parts of the project. Operators tried to facilitate communication between adolescents and their parents by involving the latter in workshops.

3.1 First year, 2007

Teachers: discussions were held between teachers and Ser.T. operators. The techniques used included lessons with the distribution of course notes, confrontation on beliefs and prejudices, teacher group activation on the main themes that emerged during discussions.

Students: the project began as soon as students enrolled for their first year of education at the schools involved. The techniques used were brief classroom lessons lasting 15-20 minutes, discussions on questions that were presented anonymously, student activation in creating in-depth group work and the acting out of that group work.

During the first year, students were given an anonymous questionnaire (the first), which had been prepared by the Ser.T. operators. The domains used were: family relationships; use of free time; use and knowledge of legal and illegal psychoactive substances; prejudices and stereotypes affecting attitudes towards the risks involved in substance abuse.

At the end of the school year, the project used a “key” to enter into an imaginary adolescent world; this took the form of a ‘party’ where the students involved acted out scenarios. Opinion leaders from show business and the sports world intervened in order to reinforce the message about healthy lifestyle behaviour.

Programme Test. Between the end of the first year and the beginning of the second, the programme was put to the test. Evaluation questionnaires were handed out to teachers dealing with critical points encountered in the organization of the project.

3.2 Second year, 2008

Teachers: once the questionnaire on quality had been prepared, it was decided to improve teacher formation by involving professionals who were considered to be experts in prevention activity in school settings. The results of the first set of questionnaires filled in by the students were distributed to their teachers.

Adolescents: student activation was achieved through role-playing and brainstorming.

A second anonymous questionnaire was administered. The domains examined were: family relationships; use of free time; verification of how much had been learned in the first year; use and knowledge of substances of abuse, cigarette smoking, alcohol and the self-administration of prescription drugs.

Message reinforcement: this took the form of a school party to allow meetings with opinion leaders, actors, famous people from the world of sport and representatives of institutions.

New test: between the end of the second year and the beginning of the third, the programme was once again put to the test by the teachers.

3.3 Workshops.

During its second year, the project included workshop activities organized under the title “Facts of Life” to combat the spread of addiction. In those workshops, groups of ‘peer-educators’ were formed to provide the actors and directors for 3 short films.
The adolescent students were guided by film professionals. Students participated in an in-depth phase focused on behaviour involving the abuse of various types of substance. Subsequently, they created a screenplay for three scripts during the course of 5 meetings held under the supervision of psychologists. The topics covered were: “addiction and prejudice”, “addiction and nutrition” and “alcoholism”.

The second workshop activity was “Images and Words”, a film club that was designed to include students’ parents, too. During the film club meetings, the following themes were addressed: how adolescents struggle with themselves, with love problems and with other members of their families; how real life and imaginary life may coexist, as long as one listens in real life, and how existential difficulties can be faced nowadays. Interesting discussions between parents and students followed the showing of films.

3.4 Third year, 2009

Teachers: the results of the second set of evaluation questionnaires administered to students were handed out to them. In order to obtain greater teacher involvement in this last year, a film was specially organized for them. As stimulation for discussion, films were shown on the theme of adolescence and the relationship between adolescents and teachers. As a series closure, the short film ‘Fatti... di vita’ (‘Facts... of Life’), which had been made by adolescent students throughout the workshop, was shown.

Students: The same film, ‘Fatti... di vita’, was shown to the students in order to stimulate free discussion in classrooms. Showing the film had the added aim of making the adolescents involved ‘famous’. This favoured mechanisms of projection and identification, while emphasizing the message contained in the film.

In addition, a semi-structural projective psychological test [14] was administered, during which students had to make up a story out of only partly structured images showing moments of ordinary life. In order to monitor the use and knowledge of psychoactive substances, the ESPAD questionnaire was administered. Data processing was done by members of the Section of Epidemiology at the Institute of Physiology of the Italian National Research Council (CNR) after they had eliminated the questionnaires that they assessed as failing to qualify as valid.

Meeting with opinion leaders: for this third year, too, a party was organized, with the inclusion of adolescents, teachers and a musical group.

4. Results

“A School for Life” involved a total of 1,234 adolescents in Middle School and three High/Senior Schools, together with 93 teachers.

4.1 Teachers

The interviews with teachers held during the first and second years about their evaluation of the intervention were centred on “efficiency in ways of intervening” and “reaching pre-established goals”; they showed that teachers had appreciated the efforts made to raise the quality of the intervention. The domains dealing with “method efficiency”, whether “the themes dealt with have been examined closely” and the “effect on students” were all evaluated positively by these teachers.

The domain “teachers’ involvement in the project” was implemented in the second year of intervention.

4.2 Adolescents

The first achievement was that of activating adolescents on addictions. About 150 works were shown during the course of the final show. The genres that were relied on most were paintings and various scenes that were acted out, followed by dances, songs, and a mural painted during one of the parties. 45 randomly selected students became peer educators.

4.3 Questionnaires

4.3.1 First year, 2007

The data collected came from questionnaires given out to students in High and Senior Schools; altogether, 399 were interviewed, 184 males and 215 females, with an average age of 14.

The most important point of reference within the family was the mother for 33.3% of these schoolchildren; it was a brother and/or sister for 23.1% of those interviewed, and the father of the family for 20.1%.

Healthy lifestyle: we asked what pastimes the students considered to be ‘healthy’: “sports” were identified as a healthy habit during free time by 48.1% and “music” was named by 25.4%. As many as 85% of these youngsters used a computer.

On the drinking of alcoholic beverages, 22.5% of those questioned associated drinking with socialization, while 39.8% of those youngsters said they
regularly drink alcoholic beverages.

Only 13.3% declared that cigarette smoking was part of healthy behaviour; of those questioned, 65.5% replied that they smoked “for the fun of smoking”.

In the first year of the project, students imagined that drugs were most commonly used in discos (26.3%), or in solitary places (19.9%). In order to define the opinions of these young students more accurately, they were asked “how do you imagine a person who uses drugs”; 69.2% described such a subject as “wild/problematic” (69.2%).

When asked whether they “would call a toll-free number to ask for help”, only 15.8% answered that they would, which showed they would prefer other forms of communication.

4.3.2 Second year, 2008

Of 380 students interviewed, 176 were males and 204 females, with an average age of 15. They were High or Senior School students.

Characteristics of these young students: 88.7% had a good level of dialogue with their parents, 97.5% were happy to meet with friends and 74.4% went out in groups. As for the use of psychoactive substances, 36.8% had recently drunk alcoholic beverages (males 43.2%, females 33.3%); 32.4% had smoked cigarettes (26.7% males, 40.4% females). 13.4% had tried smoking Delta-9 THC (males 16.5%, females 10.9%). Lastly, 3.9% had tried poppers (males 6.8%, females 1.1% males, 0.6% females).

When asked “if you drink, do you feel better when with others”, 11.9% of these students answered “Yes”. When asked: “if you smoke, do you feel better when with others”, 9.8% answered that they did.

Lastly, the use of prescription drugs in general presented worrisome characteristics: 36.4% took medicines without medical supervision (males 28.2%, females 46.9%).

4.3.3 Third year, 2009

In this case, 365 questionnaires were considered valid; they had been answered by 175 males and 190 females.

We administered the ESPAD questionnaire to Middle School students; 106 were interviewed (34% males, 66% females). Here we only report the results for alcohol and cigarette smoking:

Alcohol: the prevalence of its regular use was 55% (males 56%, females 46%). Its incidence during the previous 12 months was 51% (males 72%, females 40%). The incidence of alcohol use in the previous 30 days was 19% (males 28%, females 14%). Beer (81%) and wine (81%) were the easiest drinks to get hold of.

Cigarettes - Among extremely young students, the prevalence of smoking (a few days a week) was 6%; it was more common among females than males; this finding also applies to the use of cigarettes over the previous year.

High/Senior School Students (a group comprising 259 students): the sample group included 40.5% males (105) and 59.5% females (154), with an average age of 16.5. The students’ relationships with their parents were perceived as satisfactory in 92.6% of these cases; the family’s economic situation was defined as good by 87.7% of students and their perception of the attention they were receiving was considered good by 83.4%. 52.4% of these students practised a sport.

Among other characteristics: 89.4% had had problems because of fights; 44.7% had been to an emergency room, and 15.8% had been involved in unprotected sexual encounters. 10.3% of high school students declared they often took part in games costing money.

Alcohol - prevalence of alcohol use amounted to 91.9% (males 95.2%, females 89.6%). Its incidence, in the last 12 months, reached a total of 84.2% (males 91.4%, females 79.2%). The consumption of alcoholic beverages in the previous 30 days was recorded by 62.6% of the group.

Alcohol abuse prevalence, which was understood as getting drunk, was testified in 52.5% of those in the group (52.4% males, 52.6% females); over the previous 12 months, alcohol abuse was recorded in 38.2% (40.4% males, 36.7% females).

The beverage most often drunk was beer (57%), followed by wine (45%); the prevalence of the use of soft drinks amounted to 42%.

Cigarettes: among students, the prevalence of cigarette smoking (at least a few times per week) amounted to 54.6%; smoking was equally common in males and females; the same finding was true of substance use within the previous year. On the whole, cigarette use in the previous month amounted to 44.8% (males 47.7%, females 43.0%).

Delta-9 THC: a high percentage (44.8%) of the students interviewed spoke of having tried cannabis at least once in their lifetime; in this respect there was no difference between males and females. During the previous 12 months, the incidence of Delta-9...
The result was an activation of personal dynamics relative to the meaning that each adolescent attributed to the domain of addiction; it was followed by the making of films where students themselves worked as actors and technicians. This new experience gave them the feeling of actually creating the workshop activity, while allowing them to live out the plot of the story as stars. This outcome of making the participants stars in the perceptions of their schoolmates, was reinforced by the participants’ strong emotional involvement. This process constituted a significant moment in the formation of “peer-educators”. The climax of this workshop activity was the public showing of the movie.

The “Images and Words” workshop (organized by the film club) allowed parents and students to meet in a school environment. It included wide-ranging debates and confrontations on the topics explored in the films shown. On average, 50 scholars and 25 parents took part in each meeting.

5. Discussion

Using abuse substances is widespread among young people, and is associated with some types of psychological and/or social damage. The relationship between substance use and damage might not be casual \[9\]. To be able to identify a possible connection between adolescent substance use and damage, longitudinal studies or prevention interventions are necessary. Our study continued over a period of three years and tried to make adolescents more aware of the dangers of psychoactive substances during meetings.

In order to activate adolescents by giving them an understanding of the incisive mechanisms that come into play during contact with psychoactive substances, emphasis was put on the reinforcement of stimulating messages that aimed to induce the refusal of abusive substances. These messages directed adolescents towards favouring communication between parents and children, and between adolescents belonging to a variety of peer groups, while strengthening their social abilities. In parallel with the “A School for Life” project, which took place within the school environment, the “Images and Words” workshop took place within the family environment and it presupposed parental involvement.

The teachers who took part in the project evaluated the intervention as it unfolded; this led to a tendency for scores on the evaluation scale to rise over time.

Epidemiological data. At the end of the three-
A prevalence in the use of alcohol of 55%. The incidence was confirmed by the finding of the great importance of psychological analysis and of psychosocial precocious screening factors in a project of prevention. A correlation between psychosocial factors and delinquency; and running away from home; and substance abuse, based on their own personal experience. Discomfort indicators. Teachers interviewed indicated a low level of concentration, lack of control, apathy and sleepiness as indicators of possible substance abuse, based on their own personal experience. These ideas were first reported in a study on the consequences of Delta-9 THC use. Other connections with the use of Delta-9 THC were identified in difficult family relationships or those between friends. Little attention has been paid so far to antisocial personality characteristics and substance abuse in schools. Other studies on communities have identified the following symptoms: disturbances and antisocial personalities, learning disturbances and depression. About 1/3 of the people who are devoted to the use of substances present a psychiatric comorbidity that is under the threshold level. Other authors indicated a connection between substance abuse in adolescents and anxiety, antisocial behavior, delinquency; and running away from home. A correlation between psychosocial factors and substance use, in terms of intensity and frequency, was confirmed by the finding of the great importance of psychological analysis and of psychosocial precocious screening factors in a project of prevention.

Alcohol: with reference to the students attending the third year of Middle School, it is worth comparing them with the HBSC study. Our data reported a prevalence in the use of alcohol of 55%. The incidence during the course of the previous 12 months was 51.0% (males 72.2%, females 40.0%); the above data indicated that students attending the third year of Middle School used alcohol more than those attending the first year of Senior School; we can account for these data by referring to the selection process that students who are promoted from a Middle School to a High or Senior School have to go through. Lastly, during the previous 12 months, the incidence of alcoholic intoxication was 19% (males 27.8%, females 14.3%). In the HBSC study on Italy, the prevalence of 13-year-olds that drank at least once a week was 26% among males and 14% among females. The beverages most frequently consumed were beer (81%) and wine (81%). These age groups represent the onset of adolescence, a time of life that brings with it the challenge set by physical and emotional changes, and the intermediate years of youth, when important life and career decisions begin to be made. The percentage recorded for the consumption of alcoholic beverages in our population prompted the proposal that our research team would do well to begin a future project in Middle Schools.

According to ESPAD 2007, in the Campania Region and in the city of Naples, the prevalence of alcohol use, at least once in an individual's lifetime, was 93%; in the population examined by us, among those attending their third year at a High or Senior school, it was 92% (males 95.3%, females 89.7%). As to consumption within the previous 12 months in Naples and in region of Campania (of which Naples is the capital), the incidence was 88% (above the Italian average of 81%), while it proved to be 84% in the study target population (91.9% among males, and 79.4% among females). The cohort students in our study who reported having drunk alcohol in the previous 30 days had an incidence close to the Italian average (63%: ESPAD 2007). Beer (57%) and wine (45%) were the most commonly consumed beverages.

In Italy, the incidence of getting drunk during the previous 12 months was 27% (males 28%, females 27%), whereas in Naples, as also in the target cohort within our whole study cohort, it was 38% (40% males, 36% females). In other words, females got drunk a bit less often than males.

Trends: young people who declared that they had drunk alcoholic beverages at some point in their lifetime increased during the three-year period covered by our observations, from 38% to 73% (between the first and second year), reaching 92%, in their third year. This behaviour reflects the evolution of a stu-
dent who tries to insert him/herself in more structured groups, where drinking is considered to be synonymous with growing up.

The data for Naples on the incidence of alcohol consumption showed 11 percentage points over the Italian average (38% vs. 27%). This result should stimulate us to promote more effective prevention action; binge drinking can determine undesirable or dangerous actions, or even life-threatening ones. as has been reported in England [2].

On the whole, 65.1% of youngsters had expectations about drinking that had negative connotations (health damage, disorientation, an incapacity to quit), while 34.9% of the answers given reflected positive expectations (fun, happiness, friendly behaviour).

Cigarette smoking. This too showed an increase between the first and third year of monitoring; from the first to the third year, the proportion of youngsters who declared that they smoked rose from 13% to 54%.

Even with our intervention, it had to be recognized that there was a sharp increase in the incidence of cigarette smoking and alcohol during the course of school attendance. This could have been determined by: the age of these subjects; a wish and a tendency to join social groups and a consequent desire to fit in with a peer group. It might even be due to the greater sincerity of the answers given to the questionnaires handed out by us. The percentage of students that had smoked within the previous 30 days (45%) was higher than the national average (37%). In Italy and in Europe, females smoked more than males (39% vs. 34%), although, in our study, this relationship was reversed (48% males vs. 43% females). In any case, daily smoking was perceived as a dangerous habit by 85% of those interviewed.

Delta-9 THC. In our cohort, 45% of youngsters stated that in their lifetime they had tried Delta-9 THC, and the incidence during the course of the previous year was reported at about 32%; it was greater in males (37.0%) than in females (27%). These findings demonstrate the much more frequent use of Delta-9 THC in Naples than in Italy (23%) as a whole, and in Europe (14%).

The data just reported highlight the role of behavioural and contextual variables, and support the importance of reinforcing social skills by organizing preventive programmes [4].

Epidemiological evidence of a high level of Delta-9 THC use makes it evident that prevention intervention is a necessary measure in combating the use of substances, especially considering that the use of Delta-9 THC may worsen the educational performance of young people. It is likely that this reflects the pressures of the social context that lead to the use of Delta-9 THC rather than any direct effect of Delta-9 THC on cognitive ability or motivation.

Ecstasy: High School students did not report the use of ecstasy, while Senior Art School Students showed a prevalence of 4.2%, double that of the whole Neapolitan area; use during the previous 12 months was 3.5%; during the previous month, it was 2.8%.

Cocaine: in the third year of High/Senior School, the use of cocaine at least once in a lifetime was reported by 4.7% of students; its incidence during the previous 12 months was 3.6% (males 6.4%, females 1.8%) and, during the previous month, 1.4% stated that they had used it. In this case too, use by Art School students was about double that of the whole Neapolitan area (the incidence in Art School students during the previous 12 months was 6.6%, against 3.3% and 3.1% for the city of Naples and for its County, respectively).

Heroin: in general, a use of heroin at some point in the subject’s lifetime was reported in 3.9% of the target group (males 5.5%, females 2.9%), while its incidence during the previous year was 2.4%. In the case of heroin smoking, Senior Art School students reported a use that was double that of the whole Neapolitan area: for use at least once in a lifetime, 6.3% against 2.7% and, for the previous year, 4.9% against 1.7%.

Use of prescription drugs: 21.5% of youngsters took prescription drugs, in most cases without a medical prescription. In particular, in taking tranquillizers, as has been reported in the ESPAD, Italy and Lithuania are the two European countries where such drugs are used without having to obtain a medical prescription. Prevalence in Naples was 4.4% (males 4.9%, females 3.9%); incidence during the previous year was 3.0% (males 3.8%, females 2.1%). Even if the use of tranquillizers in our cohort seems to have been less than half the Italian average, the use of prescription drugs in general seems to be a cause for concern, so much so that it seems to make clear the need for new areas in which to intervene.

6. Conclusions

We tried to work out a model for policy makers that would be applicable to the development of prevention in schools by examining the epidemiological data collected in an adult population receiving treatment at our Ser.T., where a prevention project was im-
implemented (data not yet published) among those being treated at that Ser.T., where the number of cocaine addicts was strongly on the rise. In addition, relative to the educational level reached by patients, only 26% had failed to complete their Middle School education. On that basis it is reasonable to conclude that intervention involving students who are attending a High/Senior School may actually be unlikely to reach more than a quarter of the population receiving treatment from the Ser.T in the city centre of Naples. This problem is a common one in European countries, so much so that it places an analytical limit on the corresponding value of the questionnaire, which will not reach youngsters who drop out of school. It seems advisable, therefore, to focus on intervention to promote prevention during the course of Middle School education by trying to create alliances with teachers and with members of students’ families, with special reference to the use of alcoholic beverages and cocaine.

References


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Drug-related mortality in Slovenia. Differences between deceased treated and untreated illicit drug users

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Summary

In this study we assessed, in a three-year follow-up, Drug-Related Deaths (DRDs) in Slovenia and compared mortality and causes of death in deceased subjects who had been treated for addiction (DT) in specialized centres in Slovenia with those who had not been treated (DNT). A total of 223 DRD cases were found; in 60.1% of these, the cause was directly drug-related, and in 39.9% the cause was indirectly drug-related. 37.7% of DRDs were accidental, 27.4% were intentional and 35.0% were undetermined. The percentage of DT patients that were female was remarkably low. The treated patients who survived had a much lower mean age that patients in the DT and DNT cohorts; the DNT group was the one that had the highest mean age. Direct DRDs were more frequent in DNT than in DT patients. No differences were observed regarding the type of intentionality of death. Intentional poisoning by narcotics was less well represented in DT patients. On the whole, our data confirm the importance of agonist treatment in preventing narcotic-related deaths. In fact, the cause-of-death profile of deceased addicts in treatment is closer to that of the general population than that of deceased non-treated addicts.

Key Words: Agonist Opioid Treatment; Drug-Related Death; Addiction; Addiction Services; Opioid Maintenance; Overdose

1. Introduction

The mortality of a population and its particular groups is an important health indicator, because death rates derive directly from the most critical diseases, injuries and poisonings. Drug-related mortality, as a special part of mortality, is a complex phenomenon that accounts for a considerable percentage of deaths among young people.

The cause of a drug-related death (DRD) can be defined as a morbid condition or disease process, abnormality, injury or poisoning that leads, either directly or indirectly, to death. DRDs have been classified by the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) in a way that involves their separation into two groups: the first group comprises direct DRDs that arise while the illicit drug is present in lethal concentrations in the body and is directly responsible for death. This includes deaths that appear to be due to intentional intoxication (poisonings) by an illicit drug/drugs, unintentional intoxication, or deaths due to an undetermined intention. According to WHO rules, in direct deaths the underlying cause is known to be drug intoxication, and these direct deaths are registered as such in the General Mortality Register (GMR). The second group includes indirect deaths, meaning those that occurred while the illicit drug was not found in toxic concentrations in the body; the condition of substance addiction is associated with the underlying cause of death, and has
accelerated that death [16-18, 30].

The most frequent type of DRD in Europe is direct DRD (i.e. overdose); this accounts for up to 50-60% of all deaths among injectors in countries with a low prevalence of HIV/AIDS [19]. Overdose with heroin is the major cause of death between illicit drug users in the EU as a whole [12, 19], where a majority of the victims are men aged between 20 and 40 [19]. Unintentional drug overdose remains a primary cause of illness and premature death among illicit drug users worldwide [24, 26, 28, 38, 40]. In addition, a substantial number of deaths have been considered to be related indirectly to drug use (e.g. traffic, accidents, suicides, homicides, HIV/AIDS) [1, 19, 21].

Increased mortality is found in those who use opioids – so much so that between 10% and 23% of mortality among those aged 15 to 49 could be attributed to illicit opioid use (heroin, opium and the illicit use of pharmaceutical opioids outside the recommendations of health professionals) [1, 7, 13, 15, 25, 37, 39, 41, 42, 44, 51]. It has been estimated that opioid addiction is associated with a mortality rate approximately 13 times higher than that for the general population of the same age and sex [20, 27]. In most cases heroin users run a risk of death that is at least 15 times higher than that of young adults aged 15-44 in the general population, and this kind of risk could account for over 10% of young adult mortality [10, 15, 25, 39].

A review of the prospective studies on mortality among heroin users supports the evidence that death rates seem to be 2.38 times higher for heroin users out of treatment than for those in opioid agonist treatment [14].

A comparison between the standardized mortality ratio (SMR) attributable to intoxication by illicit drugs in Slovenia and in the EU countries over a time period of 15 years (1990-2004) shows that young adults under 40 in Slovenia had a lower mortality than that found in the EU as a whole and in the old EU members, whereas the ratios were comparable with those nations that later joined the EU [12, 32].

In Slovenia, the mortality rate of illicit drug users caused by intoxication from illicit drugs has shown an increasing trend in both genders until 2007; in men the rate is higher and is increasing faster than in women; young people in urban areas are dying the most frequently; they usually die at home, and the most frequent illicit drug of intoxication is heroin [34, 45].

In Slovenia, overdoses account for most DRDs – more precisely, about 65% of all DRDs. The most frequent form of overdose is unintentional intoxication (covering about 30% of all direct deaths), followed by suicide (intentional intoxication, accounting for about 25% of all direct deaths), while in 40% of direct DRDs the intention is unknown. The most frequent indirect form of DRD is suicide (other than suicide due to an overdose); that is the cause of almost 50% of all indirect deaths [32, 34, 45].

In this study we assessed DRD in Slovenia, and compared mortality and causes of death among deceased subjects who had been treated for addiction in specialized centres in Slovenia with those who had not. The duration of this follow-up was 3 years. Our expectation had been differences would be found in the DRDs occurring in patients in Slovenia according to whether they had been treated for their addiction, or had been left untreated.

2. Methods

2.1. Data Collection

Data were obtained and extracted from two sources existing as routine statistical systems both run by NIPH: the GMR and the Drug Users’ Treatment Evidence (DUTE) data base. The third source was Special Mortality Register (SMR), which was collected too at NIPH from 2003 till 2007 and not only included data collected from GMR, but also centralized data from the Toxicology Department at the Institute for Forensic Medicine, Medical Faculty in Ljubljana and the General Police Administration on deaths connected with illicit drug use. The main purpose of SMR was the collection of data on indirect causes of death, whereas the data in GMR had been lost due to problems deriving from its methodology.

The NIPH has been the keeper and data manager of the GMR in electronic form since 1985. Data on deaths and their causes have been collected through the use of the “Medical Death Certificate and Civil Death Certificate” (the DEM-2 form). There may be one or more than one cause of death recorded in the Medical Death Certificate, and when there are various causes, only the underlying cause of death is selected and then stored in the GMR database. The underlying cause of death is encoded according to the WHO International Classification of Diseases, 10th edition (ICD-10).

The data on illicit drug addicts who spent time in treatment were collected by professional staff during a face-to-face DUTE questionnaire, at the moment of a patient’s entry into treatment within a given year.
The administration of DUTE coincides with the initiation of treatment for new patients; for those who are continuously in treatment there exists a shorter registration form and, for previously treated patients who had been out of treatment for over three months, there is the longer registration form that is the same as used for a first visit. For personal data protection, an identification code has been devised; this is based on the SOUNDEX coding of names, surnames, but patients’ dates of birth and gender were incorporated too as unique identifiers capable of eliminating duplicates (in other words, as a check against double counting).

The DUTE database includes 5845 cases registered between 2004 and 2006, and around 57,000 cases of deceased subjects were registered at GMR in the same period. As the first step in providing data linkage, a Soundex code was formed for approximately 57,000 cases of death in the 2004-2006 period. After obtaining a Soundex code for the deceased (which already existed for DUTE cases), a new identification number was formed from the existing Soundex code by adding the date of birth, gender and region of permanent residence for each DUTE and GMR case. After adding the new identification number (IDN) to the DUTE, there were 218 cases that turned out to have a double or triple IDN. The task of correctly attributing, wherever appropriate, cases that were shown in apparently identical form twice or even three times to just one person was performed by an expert who, incidentally, works in a CPTDA. For each case of apparent doubling or tripling, she decided upon the data that had been collected and sorted, and used her practical experience to decide whether the two or three identical IDNs actually belonged to just one person, or to two or three different subjects. After attaining the objective of having only one IDN for each single case in the DUTE and GMR, a specific linkage operation between the two databases was performed to yield a definitive set of data that, from that moment on, would constitute a unified database of the deceased who had been in treatment.

2.2 Sample

The retrospective cohort study included the records of 3950 illicit drug users (heroin addicts) who had entered opioid agonist therapy for the first time in 2004, 2005 or 2006, or had been in treatment before 2004 and then re-entered or were in continuous treatment during the follow-up period. Reports were collected from 17 out of the 18 outpatient Centres for the Prevention and Treatment of Drug Addiction (CPTDAs), covering 94.44% of the national network of all CPTDAs. The only centre in the CPTDA network that failed to send data did so for personal reasons. The records from hospital treatment were not included either, because treatment in hospital (drug-free) is not strictly comparable with outpatient treatment (agonist opioid treatment).

Of the 3950 subjects 3004 (76.1%) were males and 946 (23.9%) were females. Mean age at entering in a cohort was 27±7; females were younger (26±7) than males (27±6) (T=3.94 p<0.001).

The follow-up period lasted from 1st January 2004 (the beginning of the study) to 31st December 2006 (end of the follow-up); the vital status of all cohort members was checked at the GMR on the last day of follow-up, and a division was then made into two groups: of survivors and those among the deceased who had been treated for addiction.

We clustered 3881 surviving subjects as surviving treated illicit drug users (ST-IDUs). Of these, 2940 (75.8%) were males and 941 (24.2%) females. Mean age at entering in a cohort was 26±6 years. We clustered 69 deceased subjects as deceased treated illicit drug users (DT-IDUs). Of these, 64 (92.8%) were males and only 5 (7.2%) were females. Mean age at the moment of death was 31±8. The group of deceased subjects who had not been treated was formed by using data from the GMR and the Special Mortality Register (SMR), together with the retrospective cohort study for the 2004-2006 period. On the basis of unique identifiers, the data from GMR and SMR were linked to 69 DRDs which had been identified as belonging to a group of deceased treated illicit drug users from the cohort (DT-IDUs). The remaining 154 subjects from GMR and SMR, who had died due to, or in connection with, illicit drug use, were classified as deceased untreated illicit drug users (DNT-IDUs). Of these 123 (79.9%) were males and 31 (20.1%) were females. Mean age was, at the moment of death, 32±12 years.

Ethical approval for this procedure was obtained from the Medical Ethics Committee of the Ministry of Health of the Republic of Slovenia.

2.3 Statistical Analyses

We compared gender and age between the groups of ST-IDUs, DT-IDUs and DNT-IDUs. We then compared DRD between DNT-IDUs and DT-IDUs. Comparisons between groups were performed using ONEWAY analysis of variance (post hoc contrast
according to the Sheffe procedure) or t-test (between two groups) for numerical data and the chi-squared test for categorical data (post hoc contrast according to the Buonferroni methodology). For analyses, the SPSS statistical programme was used.

3. Results

We found 223 DRD causes among cohort members and DNT-IDUs. 134 (60.1%) of this number were Direct DRDs. Of this group of 134, as many as 115 (85.8%) were ‘narcotic poisoning’ DRDs (overdoses), while the remaining 19 (14.2%) were DRDs due to ‘non-narcotic poisoning’, 89 (39.9%) were indirect DRDs; of these, 60 (67.4%) were ‘injury’ DRDs, and 29 (32.6%) were due to a final event in a history of medical illness.

Regarding intentionality, 84 (37.7%) DRDs were accidental, 61 (27.4%) were intentional and 78 (35.0%) were with undetermined intent.

Of all indirect DRDs, transport accidents occurred in 18 (20.2%) DRD, other injuries in 6 (6.7%) DRD, homicide in 12 (13.5%) DRD, self-harm in 24 (27.0%), and medical and/or surgical illness in 29 (32.6%).

Comparing gender between ST-IDUs, DNT-IDUs and DT-IDUs the M:F ratio was 3.12:1 in ST-IDUs, 3.97:1 in DNT-IDUs and 12.8:1 in DT-IDUs. This difference is statistically significant (Chi-square 11.81 p=0.003). Females were strikingly less frequent in DT-IDUs.

Recorded age in years was (age at entering in a cohort) 27±6 in ST-IDUs (95%CI=26.60-27.01), (age at the moment of death) 32±12 (95%CI=30.59-33.75), in DNT-IDUs and (age at the moment of death) 31±8 (95%CI=29.54-33.75), in DT-IDUs. ST-IDUs proved to be the youngest compared with DNT-IDUs and DT-IDUs; DNT-IDUs was the group made up of the oldest subjects. These differences were statistically significant (F=67.61 p=0.000).

Table 1 reports differences in DRDs between DNT-IDUs and DT-IDUs. Direct DRDs - indirect DRDs ratio was 2.02:1 in DNT-IDUs and 0.82:1 in DT-IDUs (chi square 9.57 p=0.002). Direct DRDs were more frequent in deceased non-treated subjects than in deceased treated patients. Considering direct DRDs (poisoning by narcotics and poisoning by non-narcotics) this ratio was 8.36:1 in DNT-IDUs and 2.88:1 in DT-IDUs. We also found that indirect DRDs such as those due to medical illness were better represented in DT-IDUs.

Table 2 reports the intentionality of DRDs between DNT-IDUs and DT-IDUs. There were no statistically significant differences regarding the type of the intentionality of death (chi-square=0.97 p=0.613). Intentional poisoning by narcotics is less well represented in DT-IDUs.

4. Discussion

The most important results of this study were that

- The patients who had survived in treatment were younger than the deceased patients (using this second category to refer both to treated and untreated illicit drug users);
- Females were strikingly less well represented in deceased treated patients with respect to deceased untreated illicit drug users;
- Direct DRDs were better represented in deceased non-treated illicit drug users, with special reference to poisoning by narcotics (heroin overdoses);
- In deceased treated patients, intentional poisoning by narcotics was a rare event.

The data for Slovenia revealed that the mean age of illicit drug users in opioid agonist treatment was always lower compared with those who died due to DRD [32, 45]. These data are closely comparable with those for the European Union (EU); in Europe a majority of victims of DRDs are aged between 20 and 40, and are mostly in their mid-thirties; in the pre-2004 EU member states, the percentage of victims of DRDs older than 40 is rising, and already accounts for over a third of overdose deaths [19]. Aging raises the mortality risk of DRD [46]. Other data drawn from the literature support the view that the rates of disease-caused death rise with age [14].

In our case the deceased patients were older to a statistically significant degree than those who survived (the oldest were in the DNT-IDU group) and had also been using drugs for a longer period (data for DT-IDUs); heroin was the main drug used, followed by cannabis and cocaine (data for surviving patients and DT-IDUs). This is consistent with the data for Europe, where, preceding agonist opioid treatment, heroin turns out to be the most frequently used substance, followed by cannabis and cocaine, while most patients are classified as polydrug users [19, 52]. Irrespective of this, among all the cohort subjects, 76.18% had already been treated and 91.30% of the deceased within the cohort had already been treated in the past, too [31, 33]. This finding runs parallel to the fact that heroin addicts frequently face the so-
Historically, males have been overrepresented among illicit drug users in cases centring on fatal overdoses and other DRDs, going to make up over 80% of some series [9]; most of the subjects from recent mortality cohorts among illicit drug users in Europe were males (around 8 in 10) [19]. Female illicit drug users have lower mortality rates than those of males, [1, 2, 19]. Opiate-using males had approximately twice the risk of death of females, because males run a higher risk of overdose than do women [8, 27]. Some other countries with higher rates of infection-related deaths have a similar crude mortality rate in the two genders among those using opiates and, therefore, a higher standardized mortality ratio called ‘revolving door phase’ during chronic illness (periods of heroin use and treatments, dropping out of treatment, prison, relocation, followed by repetition of the sequence) [26]. In addition, heroin addicts who seek treatment may continue to use heroin for decades [37] and, within this population, daily heroin use is punctuated by periods of abstinence, various drug treatments and imprisonment [48], as frequently happens with ‘old’ patients.

Opioid agonist treatment provides effective intervention with the aim of preventing DRDs, especially direct ones, but, to raise the probability of the desired outcome, treatment needs to be continuous and long-term [8], as reduced tolerance to opioids can increase the risk of overdose mortality (due to treatment drop-out and/or relapse) [3, 6, 9, 13, 19, 43].

<table>
<thead>
<tr>
<th>Variables</th>
<th>DNT-IDUs N=154</th>
<th>DT-IDUs N=69</th>
<th>Chi square</th>
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<td>Non-narcotic poisoning</td>
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<td>Total</td>
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<td>31 (44.9)</td>
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<th>DT-IDUs N=69</th>
<th>Chi square</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transport accident</td>
<td>10 (19.2)</td>
<td>7 (25.0)</td>
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<td></td>
</tr>
<tr>
<td>Injury</td>
<td>3 ( 5.8)</td>
<td>1 ( 3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-narcotic poisoning</td>
<td>3 ( 5.8)</td>
<td>0 ( 0.0)</td>
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<td></td>
</tr>
<tr>
<td>Narcotic poisoning</td>
<td>26 (50.0)</td>
<td>6 (21.4)</td>
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<tr>
<td>Medical or surgical illness</td>
<td>10 (19.2) a</td>
<td>14 (50.0) b</td>
<td>11.53</td>
<td>0.021</td>
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<tr>
<td>Total</td>
<td>52 (33.8)</td>
<td>28 (40.6)</td>
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<th>DT-IDUs N=69</th>
<th>Chi square</th>
<th>p</th>
</tr>
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<tbody>
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<td>Transport accident</td>
<td>1 ( 1.8)</td>
<td>1 ( 4.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injury</td>
<td>1 ( 1.8)</td>
<td>0 ( 0.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-narcotic poisoning</td>
<td>3 ( 5.4)</td>
<td>2 ( 9.1)</td>
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<tr>
<td>Narcotic poisoning</td>
<td>42 (75.40)</td>
<td>16 (72.7)</td>
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<tr>
<td>Homicide victims (Assault)</td>
<td>9 (16.1)</td>
<td>3 (13.6)</td>
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<tr>
<td>Total</td>
<td>56 (36.4)</td>
<td>22 (31.9)</td>
<td>1.27</td>
<td>0.865</td>
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</table>

Statistics: chi-square 16.66, p=0.011, *b* p<0.05

Historically, males have been overrepresented among illicit drug users in cases centring on fatal overdoses and other DRDs, going to make up over 80% of some series [9]; most of the subjects from recent mortality cohorts among illicit drug users in Europe were males (around 8 in 10) [19]. Female illicit drug users have lower mortality rates than those of males, [1, 2, 19]. Opiate-using males had approximately twice the risk of death of females, because males run a higher risk of overdose than do women [8, 27]. Some other countries with higher rates of infection-related deaths have a similar crude mortality rate in the two genders among those using opiates and, therefore, a higher standardized mortality ratio.
in females [13]. The data for opioid agonist treatment, overdoses, violent deaths, and the low prevalence of HIV infection recorded for women could have helped to determine the low percentage of DRDs among deceased treated females in our case.

Populations of illicit drug users are characterized by high rates of illness and death [5, 26]. Poisonings by narcotics (in most cases, heroin overdoses) are a major cause of death among heroin users and account for between one-third to half of the DRDs [8, 19, 23, 27, 29, 41, 50]. The vast majority of cohort studies on mortality among drug users have included people seeking treatment for their drug use. A small number of studies have compared the mortality of drug users while in and out of treatment [3, 4, 22, 44, 53]; these studies have found that the relative risk of death while in treatment varied from less than 0.2 to 0.8 compared with those out of treatment, with a mean of approximately 0.4. Heroin addicts were one-quarter as likely with those out of treatment, with a mean of approximately 0.4. Heroin addicts were one-quarter as likely to die while receiving methadone maintenance as addicts not in treatment, because they were significantly less likely to die as a result of heroin overdose or suicide while in maintenance [4]. Death rates, especially overdose, are high among patients who are unfavourably discharged or drop out of methadone treatment [53]. Heroin addicts who receive methadone maintenance treatment appear to have a lower risk of dying than drug users who have never been treated with methadone and drug users who have left methadone treatment [4, 13, 22]. Most cohort studies focus on treatment populations, and it is difficult to directly transfer results to untreated ones.

The lower figures recorded for mortality due to poisonings by narcotics among cohort subjects seems to be a consequence of agonist opioid treatment; taking part in methadone programmes could reduce injection drug use, stabilize opiate tolerance levels, regulate the concurrent use of alcohol and other drugs, and improve the general health status of drug users [52]. A direct effect of the narcotic blockade provided by tolerance to methadone is plausible as the basis for the lower narcotic-related mortality found in those who would otherwise have overdosed. It should be remembered that being out of treatment does not necessarily mean being tolerant to narcotics, but may correspond to a post-detoxification state of no narcotic tolerance that amplified raises the risk of lethal relapse-related overdosing or suicide by narcotics [47].

Also, voluntary poisoning by narcotics is quite rare, thus indicating ongoing agonist treatment as specific prevention means against suicidality by overdose in heroin addicts. On the other hand, overdosing with non-narcotics is concentrated among deceased treated addicts. So that such suicide prevention potential may be partly neutralized by resorting to the visible ways of committing suicide means that are open to subjects under narcotic blockade, i.e. by resorting to non-narcotics.

A link has been found between suicide attempts by poisoning and female gender [36, 49]. A further link is known to exist between bipolar disorder and suicidality in heroin addicts [35], which may indicate that the preventive effect is mediated by a positive impact on the core of mood instability and impulsive behaviour.

In summary, data from the literature show that stable retention (continuity) in opioid agonist treatment is a protective factor against DRD [3, 6, 13, 19]. In addition, long-term opioid agonist treatment has been shown to reduce rates of illicit drug use, drug injection and overdose risks [6, 11, 19]. In particular, if the average duration of opioid agonist treatment approaches or exceeds 12 months, it has a greater than 85% chance of reducing overall mortality among opioid users [8].

4.1 Limitations

Of course, this study presents some limitations. The data filed in the systems we have used (GMR, SMR, DUTE) could be underreported for various reasons (incomplete data in death certificates, lack of resources, administrative limitations, medical staff facing a work overload, and so on), but this shortcoming is limited by their national coverage, continuity and mandatory formal foundation (GMR, DUTE).

The number of deceased subjects is relatively small, and the time of observation is short; a study involving a higher number of deceased subjects over a longer observation time would offer more reliable results. The length of follow-up for this cohort could be problematic, because illicit drug use can change over any given time-period (the follow-up on drug use or injecting status), and this parameter can affect death rates. It should, however, be borne in mind that the average follow-up in this study lasted as long as 3 years, so any such bias is bound to be small.

We have assumed that all the subjects included in the cohort stayed in maintenance therapy over the whole period of observation; we had no opportunity to record dropouts, nor were we able to calculate the exact period of treatment for each patient included in the study. Also, the follow-up period was relatively
opioid treatment that calls for more thorough investi-
gation points to a gender-related aspect of agonist
treatment in preventing deaths related to the use of narcotics. One key result is that the profile of
the cause of death in deceased addicts in treatment
is much closer to that of the general population than
that of deceased non-treated addicts. Of particular in-
terest is the fact that female addicts in treatment prove
to be particularly well protected against DRDs; this
finding points to a gender-related aspect of agonist
opioid treatment that calls for more thorough inves-
tigation.

5. Conclusions

On the whole, our data confirm the importance of agonist treatment in preventing deaths related to the
use of narcotics. One key result is that the profile for the cause of death in deceased addicts in treatment
is much closer to that of the general population than that of deceased non-treated addicts. Of particular in-
terest is the fact that female addicts in treatment prove to be particularly well protected against DRDs; this
finding points to a gender-related aspect of agonist
opioid treatment that calls for more thorough inves-
tigation.

References


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Financial support for the implementation of the study was provided by internal funds.

Contributors

BL, JS, ML, RT and JS designed the study and wrote the protocol. MP, LR, AGIM managed the literature searches and analyses. IM and JS undertook the statistical analysis, and all the authors discussed the results. BL, ML, IM 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 report no conflict of interest. IM served as consultant for Reckitt Benckiser Pharmaceuticals.
Changes in sleep quality and alertness in opiate-dependent subjects after stable methadone and buprenorphine maintenance treatment. A pilot exploratory report

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Summary

We evaluated changes in subjective sleep quality in 40 opiate-dependent patients in stable methadone and buprenorphine maintenance treatment. Scores that measured sleep were compared with available normative data. An overall improvement in sleep problems has been reported since the onset of treatment 23 months (SD 19) ago. Two-thirds of the subjects reported an increase in their quality of sleep and daytime alertness as compared with the period before treatment. Compared with normative data, however, quality of sleep remained highly impaired in all participants with low sleep efficiency. Patients with comorbid depression and anxiety were the most impaired.

Key Words: Opioid-Related Disorders; Buprenorphine; Methadone; Sleep Disorders; Self-Assessment

1. Introduction

Sleep complaints are highly prevalent among opiate-dependent patients in methadone maintenance treatment [8, 16, 20]. Previous studies on sleep difficulties and methadone treatment collected complaints such as impaired quantity and quality of sleep, insomnia, and excessive daytime sleepiness [8, 14, 16]. Other data assessing both subjective and objective sleep patterns in methadone patients confirm a high level of sleep pathology in this population, with a common finding of low sleep efficiency and short total sleep duration [14, 22]. The severity of sleep problems has been correlated with psychiatric symptoms, concomitant substance and benzodiazepine use, and pain [8, 10, 16], but also with methadone dosage [8, 19, 21].

The specific effects of treatments such as methadone and buprenorphine on sleep quality are not easy to highlight, because of other possible contributing factors such as substance disorders, co-occurring psychiatric disorders and patient characteristics which might modulate or hide some of these effects.

Acute exposure to opiates has been shown to induce insomnia, with a decrease in total sleep, sleep efficiency, REM and slow wave sleep, and an increase in wakefulness and muscle tension [5, 12]. Chronic exposure to opiates may also induce tolerance to some of these effects, such as waking REM sleep and delta sleep, while some authors have reported persistent significant sleep architecture abnormalities among patients in long-term methadone treatment [15, 17]. In some studies that addressed the issue of subjects
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treated with methadone and their sleep patterns, sleep disturbance has been associated with high methadone dosage [8, 19, 21], but other data have been inconclusive about this association [9, 10, 13]. It is difficult to determine whether subjective sleep complaints may be related to methadone treatment or may be better explained by pre-existing poor sleep patterns. In particular, the changes that occur during methadone treatment among opiate-dependent patients remain poorly documented. Recent findings based on a polysomnographic prospective exploration of 23 methadone patients [10] suggested that methadone did not negatively affect sleep patterns. It should be noted that no study has yet reported on the quality of sleep of buprenorphine-maintained patients. Our aim was to evaluate the subjective quality of sleep in opiate-dependent patients in stabilized long-term methadone or buprenorphine maintenance treatment, and to compare current sleep quality with sleep quality before addiction treatment.

2. Methods

2.1. Participants and study design

We recruited 40 patients from two Addiction Treatment centres in Aquitaine (Bordeaux and Bayonne, France, Europe) over a period of 4 months. Inclusion criteria were: being aged over 18, meeting DSM-IV criteria for opiate dependence, currently taking a stable buprenorphine or methadone dose (i.e. no change in dose and no withdrawal or underdose symptom in the past 30 days), and having documented continuously drug-free urinalyses for opiates, cocaine and amphetamines in the past 30 days. The University Ethics Committee approved the study, and all participants gave their written informed consent.

Methadone or buprenorphine treatments were prescribed by psychiatrists with experience of addicted patients, and the dosage of each individual was initially titrated on the basis of each patient’s clinical response (craving for heroin) and tolerance to the daytime sedative effects noted during dose escalation. Buprenorphine (sublingual tablets) was started at a dose of 8 mg/day, adjusted according to response by steps of 2-4 mg. Methadone was administered in an oral solution at a starting dose of 20–40 mg daily, which was increased by up to 10 mg daily to a maintenance dosage that in most cases reached an upper limit of 60 mg/day. Stable maintenance dosage was obtained when craving was alleviated with a good tolerance to daytime sedative effects. All patients received their dosage daily at the centre, weekends included. Pharmacotherapy was combined with individual behavioural treatment focused on relapse prevention and increasing social support. Drug testing was performed on a routine basis to monitor substance use outcomes.

The 40 participants had a mean age of 33 years (SD 5.8; range 21-53) and included 25 men (62.5 %) with an average of 10.1 years of education (SD 2.6). Twenty-eight patients were in methadone (mean dosage 93mg; SD 42) and 12 in buprenorphine treatment (mean dosage 11mg; SD 7.5). Median methadone or buprenorphine treatment duration was 23 months (SD 19) with a stable dose maintained for 11 months on average (SD 8.9). Twelve subjects had received a prescription for an antidepressant and 14 for a sedative or hypnotic. Fourteen subjects had at least one somatic disorder (mostly HIV-related) and 11 of them were undergoing a related treatment.

2.2. Assessment

Patients were first assessed through an interview to collect general characteristics (demographic data) and information on their use of prescribed and non-prescribed substances (including methadone/buprenorphine dose and use of benzodiazepines, neuroleptics, and minor stimulants such as tea or coffee), urinalysis results over the past 30 days, psychiatric and physical problems for the past 6 months, and complaints about sleep. For the subjective evaluation of sleep quality, participants were asked to respond to a set of standardized, validated instruments. The Pittsburgh Sleep Quality Questionnaire (PSQI) [3] evaluates the quality and pattern of perceived sleep and differentiates “poor” from “good” sleep by measuring 7 areas: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbance, use of sleeping medication and daytime dysfunction over the preceding month. The PSQI scores range from 0 to 21, with a global score of > 5 indicating poor sleep quality. The Epworth Sleepiness Scale (ESS) [4] is a self-administered 8-item questionnaire that assesses daytime sleepiness in adults. The scores range from 0 (not sleepy) to 24 (extremely sleepy). The Pichot-Brun Asthenia Scale [11] is a short self-rating inventory of 8 items that assess asthenia and daytime sleepiness, with a score ranging from 0 (no asthenia) to 40 (high level of asthenia). The Leeds Sleep Evaluation Questionnaire [7] was designed to assess the subjectively perceived changes in 7 sleep quality areas after an intervention, by comparing
the situation with what it was before the intervention ("worsened", "no change", "improved"). For the present study it was decided to compare the sleep quality changes recorded since methadone or buprenorphine treatment was first introduced, with the previous situation.

2.3. Statistical analysis

Data were analysed using SAS® (SAS Institute Inc., North Carolina) and EpiInfo software (the Atlanta Center for Disease Control and Prevention). Counts, means, standard deviations, and percentages have been reported to summarize the data. One-sample t tests evaluated mean differences between sleep measure scores (PSQI and ESS) in this study and available normative data drawn from general population samples (normative data were not available for the Pichot-Brun Asthenia Scale). The influence of major comorbidities (psychiatric and somatic disorders, and other non-opiate substance use) was assessed too, by comparing mean values.

3. Results

The PSQI global score and other component scores were significantly higher in the current sample compared with the normative data reported in the study of Buysse et al. [3] (Table 1). Results from the PSQI demonstrated poor quality of sleep in our sample, particularly for the item “usual sleep efficacy” (mean score 2.6 SD 0.7). Mean time of actual sleep (7.3h) was considerably shorter than time spent in bed (bedtime 12pm/getting up time 9am). Conversely, mean time spent asleep remained in a normal range, and 45% of the patients reported a sleep onset latency of ≤15 minutes (with a mean score of 1 = 16 to 30min). The mean ESS score for our sample did not show excessive current daytime sleepiness compared with controls [4], and 58% of participants had a score of 8 or less. Furthermore, patients did not report significant asthenia symptoms as measured on the Asthenia-fatigue Pichot-Brun Scale.

Based on the Leeds questionnaire, most of the patients retrospectively reported having experienced an improvement in quality of sleep since the inception of buprenorphine or methadone treatment (Table 2). The improvements most often reported were those for sleep onset (67.6% of patients), sleep onset latency (62.2%), and “Clumsiness in the morning” (64.9%). “Periods of wakefulness at night” and “Fatigue at waking” were the most severely impaired factors compared with the situation before treatment for opiate dependence began (both were reported by 37.8% of patients).

Patients with major depression reported more asthenia symptoms according to the Pichot-Brun scale (mean 11.16, SD 7.27, p<0.05) than the non-depressed patients (mean 6.04, SD 5.84). Patients with an anxiety disorder reported a more severely im-

| Table 1. Reported sleep problems in methadone and buprenorphine patients (n = 40) and general population scale norms |
|---------------------------------|-----------------|-----------------|-----------------|
| Study group                     | Normative sample |
|                                 | M±sd            | M±sd            | p (t test)      |
| PSQIa                           |                 |                 |                 |
| Total score                     | 16.0 ±3.4       | 2.67 ±1.7       | <0.001          |
| Subjective Sleep Quality        | 1.4 ±0.7        | 0.35 ±0.48      | <0.001          |
| Sleep Latency                   | 1.4 ±1.2        | 0.56 ±0.73      | <0.001          |
| Sleep duration (±hours)         | 1.0 ±0.9        | 0.29 ±0.50      | <0.001          |
| Usual sleep efficacy            | 2.6 ±0.7        | 0.10 ±0.30      | <0.001          |
| Sleep disturbances              | 1.5 ±0.6        | 1.00 ±0.40      | <0.001          |
| Use of hypnotics                | 0.8 ±1.2        | 0.04 ±0.28      | <0.001          |
| Daytime Dysfunction             | 1.0 ±0.9        | 0.35 ±0.46      | <0.001          |
| ESSb                            |                 |                 |                 |
| Total score                     | 7.0 ±4.7        | 5.9 ±2.2        | NS              |
| Asthenia Pichot-Brun            |                 |                 |                 |
| Total score                     | 7.7 ±6.7        |                 |                 |

PSQI: Pittsburgh Sleep Quality Index; ESS: Epworth Sleepiness Scale [NS: Non-significant; a: Normal sample from Buysse et al. ±6); b: Normal sample from Johns et al. ±7]
paired quality of sleep, based on PSQI scores (mean score 18.50, SD 2.07, p<0.05) than those without any anxiety disorders. Patients who had been using minor stimulants such as coffee and tea regularly reported higher ESS scores (mean 11, SD 5). No differences were found between subjects with and without somatic disorders.

4. Discussion

The aims of this pilot study were to assess subjective sleep quality among opiate-dependent patients in remission, or in stable methadone or buprenorphine treatment, and to compare it with the situation previous to treatment for opiate addiction. There is some evidence that many patients in methadone treatment report sleep difficulties, but few data have been used to compare subjective sleep quality before and after methadone treatment, and no previous study has investigated the sleep quality of buprenorphine-maintained patients. Our data show that all participants in stable methadone or buprenorphine treatment showed a severely impaired quality of sleep based on the PSQI total score. However, participants reported an overall improvement in sleep problems after the onset of treatment.

The current findings are in line with other studies on methadone patients who showed a high level of sleep complaints compared with controls, with low sleep efficiency, shorter total sleep time and frequent awakenings [8, 10, 16, 22]. In our sample, sleep efficiency was the most strongly impaired dimension, with similar sleep times but more time spent in bed compared with the reference group in the study by Buysse et al. [3]. In addition, differences in mean age between that group and our sample (59.9 years versus 33 years, respectively) might have led to an underestimation of sleep duration impairment, as older age is associated with shorter sleep duration and a lower quality of sleep [1, 6]. The higher value for “time spent in bed” could be attributable to social exclusion and a higher unemployment rate, regardless of true sleep disturbance, but it could also be explained by depressive comorbid symptoms [20]. Daytime sleepiness, as measured by ESS, did not appear to have risen significantly, as its mean value ranged within the clinical normal range (<10) [4]. These data are consistent with those of some studies that examined daytime sleepiness in methadone patients [2, 10, 17, 18, 20, 22]. Wang et al. [20] evaluated 50 patients in methadone treatment and 20 normal control subjects, and found an average ESS score of 7.10 (SD 5.00), compared with 2.05 (SD 1.76) in controls. Xiao et al. [22] studied 20 methadone patients and 20 controls, and reported an average ESS score of 11.4 (SD 2.9), compared with 4.7 in controls (SD 2). The higher mean score in this last study could be explained by the fact that the patient group was at an earlier stage of methadone treatment than our patients. The absence of significant differences in the current sample compared with normative data may be explained by the wide range of normality for ESS scores in the general population [4], but also by the fact that our patients were all in methadone or buprenorphine treatment at a stable dose, and had received maintenance treatment for an average of 23 months. The impact of agonist treatment on alertness may develop during acute administration and dose escalation, with further tolerance to daytime sedative effects [20]. Our data support this hypothesis, as the daytime fatigue reported mostly improved over the course of addiction treatment. This result strongly supports the notion that opiate agonist maintenance treatment is highly compatible with an active life, as well as with social

<table>
<thead>
<tr>
<th>Leeds questionnaire items</th>
<th>More impaired</th>
<th>No change</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep onset</td>
<td>21.6 (8)</td>
<td>10.8 (4)</td>
<td>67.6 (25)</td>
</tr>
<tr>
<td>Sleep onset latency</td>
<td>21.8 (8)</td>
<td>16.2 (6)</td>
<td>62.2 (23)</td>
</tr>
<tr>
<td>Bedtime sleepiness</td>
<td>29.7 (11)</td>
<td>27.0 (8)</td>
<td>48.6 (18)</td>
</tr>
<tr>
<td>Agitated sleep</td>
<td>16.2 (6)</td>
<td>27.0 (10)</td>
<td>56.8 (21)</td>
</tr>
<tr>
<td>Wakefulness periods at night</td>
<td>37.8 (14)</td>
<td>21.6 (8)</td>
<td>40.5 (15)</td>
</tr>
<tr>
<td>Morning awakening difficulties</td>
<td>24.3 (9)</td>
<td>16.2 (6)</td>
<td>59.5 (22)</td>
</tr>
<tr>
<td>Awakening duration</td>
<td>32.4 (12)</td>
<td>21.6 (8)</td>
<td>45.9 (17)</td>
</tr>
<tr>
<td>Fatigue at waking</td>
<td>37.8 (14)</td>
<td>16.2 (6)</td>
<td>45.9 (17)</td>
</tr>
<tr>
<td>Daytime fatigue</td>
<td>29.7 (11)</td>
<td>13.5 (5)</td>
<td>56.8 (21)</td>
</tr>
<tr>
<td>Clumsiness on waking up</td>
<td>5.4 (2)</td>
<td>29.7 (11)</td>
<td>64.9 (24)</td>
</tr>
</tbody>
</table>

Table 2. Retrospective sleep quality evaluation after at least 1 month stable methadone/buprenorphine treatment compared with situation before treatment for opiate dependence: Results from the Leeds questionnaire (n = 40).
integration and adjustment. It is worth stressing the manoeuvrability of methadone treatment, which, on one hand, allows an active life at stable doses, and, on the other, by means of acute dose increments, can be used by some clinicians for sedative purposes.

When asked to retrospectively assess their sleep quality since treatment initiation and after attaining stability, the participants reported a general improvement according to the Leeds Questionnaire, though sleep quality remained impaired compared with normative PSQI scores. These findings corroborate those of Peles et al. [10] showing polysomnographic sleep improvement after 6 and 12 months of methadone treatment. This suggests that neither methadone nor buprenorphine treatment had any negative effect on subjective sleep patterns over the course of treatment, and it raises the question of the effects of other possible contributing factors to sleep quality in this population. Furthermore, the overall reported sleep improvement found in our study could be explained by significant changes in lifestyle associated with addiction treatment programmes or by improvements in other associated factors, such as anxiety and mood disorders. However, although the sleep problems reported seemed to improve compared with the situation before treatment, we note that complaints related to states of wakefulness at night and fatigue on getting up in the morning remained particularly prevalent, and highlighted persistent numerous wakeful periods and agitated sleep.

Based on our current findings, we strongly recommend a systematic assessment of sleep quality in patients undergoing buprenorphine or methadone treatment both at treatment entry and during follow-up. It is important to note that the present study suggests that opiate agonist treatment by itself does not account for the sleep disturbances of patients in stabilized treatment. When persistent symptoms of poor sleep quality are reported after stable methadone or buprenorphine dosage, clinicians are encouraged to investigate other associated factors that are potentially implicated in sleep difficulties. Psychiatric symptoms or other substance uses should be evaluated with particular care in order to improve sleep problems by offering more carefully targeted interventions.

Some important limitations have to be acknowledged. First, the cross-sectional design and the retrospective method of sleep change assessment may be associated with memory bias. Secondly, sleep quality scores were compared with normative data from general population samples that were not matched with factors like age, gender or other characteristics that may affect sleep patterns. Despite this limitation, our patients exhibited much higher scores than those of the normative sample, which emphasizes the magnitude of sleep difficulties in our sample. Lastly, data on tobacco and cannabis use were not collected, and their possible effects on our measurements of sleep were not verified.

The present findings document the fact that long-term opiate agonist treatment may not worsen sleep quality over time, although patients still reported poor sleep in a context of stable treatment, especially their high level of sleep fragmentation and low sleep efficiency. Whether these persistent sleep problems were related to opiate exposure, or other factors, particularly depressive symptoms, remains in question and should be further assessed.

References


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Contributors
All the 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 editorial control and final responsibility for the decision to submit the paper for publication. All the authors contributed equally to this research.

Conflict of interest
The authors report no conflicts of interest.
The effects of a novel take-home treatment strategy in patients with opioid-dependence receiving long-term opioid replacement therapy with buprenorphine/naloxone in Italy: a cost analysis

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Addiction Treatment Centre, Local Health Unit, Soverato, Italy, EU

Summary

During opioid agonist maintenance treatment (OMT) in Italy, patients may experience problems accessing addiction assistance from the local drug addiction centers (SerTs [Servizi territoriali per le Tossicodipendenze]), resulting in reduced long-term adherence to treatment. To overcome this, the SerT in Soverato (CZ, Italy) has developed a pilot project called Distribuzione per Conto (DPC), which distributes OMT through local pharmacies and involves general practitioners in the management of patients instead of the traditional treatment of these patients which was run solely through SerTs. Results of this study show that the DPC treatment strategy is a viable strategy as it increased patient satisfaction compared with the traditional strategy with no negative effects on the adherence to OMT and patient relapse rates. DPC also reduced the number of visits and counseling sessions at SerT, with a positive impact on time management and associated costs both for patients and clinical practitioners.

Key Words: Agonist maintenance treatment; take-home therapy; buprenorphine/naloxone; general practitioners.

1 Introduction

Opioids with long half-lives, such as methadone, buprenorphine and buprenorphine/naloxone, have been shown to be the most effective opioid agonist maintenance treatments (OMT) in opioid-dependent patients addicted to heroin [11]. The use of these drugs, in particular the combined use of buprenorphine and naloxone, improves quality of life by reducing the use of illegal drugs, criminal behavior and risk of infections and increasing the subjects ability to work [3, 6, 11], which is considered by WHO and NTA a key factor in treatment program together with the reduction of morbidity and mortality [7,12]. In fact, OMTs stabilize both the physical and mental health of heroin-addicted patients. However, while the efficacy of opioids with long half-lives is not in doubt, one of the challenges for the research in the field is to find strategies to more effectively help patients through this transition. As such, it is necessary to develop a more efficient long-term treatment strategy for opioid-dependent patients which focuses on intervention strategies that can guarantee the proper management of patients and their maintenance treatment [10]. In particular, treatment strategies that increase the length of time a patient continues to receive OMTs (i.e. patient retention) are increasingly important for patient recovery [5].

One treatment strategy that has been identified which may improve the retention of opioid-dependent patients on OMT is the use of take-home therapies [1, 4, 6]. It is well-known that take-home therapies
increase the attractiveness of OMT for opioid-dependent patients, and that they are associated with improved quality of life, two aspects that can allow the gradual social reintegration of the patient [8]. In Italy, the use of take-home OMTs is high, with approximately 60% of opioid-dependent patients receiving take-home opioids from SerTs [9].

However, few studies investigating the cost to implement, sustain and modify OMT treatment strategies, or whether such a program might yield a better return on invested resources have been conducted [8]. Thus, further research focusing not only in improving the use of take-home therapies but also evaluating the cost-effectiveness of these programs would be indispensable.

In the SerT of Soverato (CZ, Italy), which belongs to the Azienda Sanitaria Provinciale (ASP) of Catanzaro, the traditional take-home procedure for patients receiving long-term OMT requires the supply of drugs by the SerT. However, having OMT treatments only available from the SerT center creates problems related to both the accessibility of treatment, as patients may not have easy access to the center, and of adherence of certain patients to treatments. In particular, this can be the case in patients who experience difficulties related to employment, logistics, privacy and interpersonal relationships.

To overcome the issues that can negatively impact treatment retention, the Soverato SerT has conducted a pilot study which utilizes a new take-home treatment strategy (Distribuzione Per Conto [DPC]) in patients with opioid-dependence. This manuscript aims to evaluate the main achievements of this pilot strategy over the first 6 months of its implementation. Particular attention in the evaluation has been dedicated to the degree of satisfaction of the treatment by the patients, the control of their drug-free condition, as well as the optimization of professional resources and the advantages related to cost containment.

2 Materials and Methods

In this ‘cost-consequence analysis’ study, patients receiving long-term OMT with buprenorphine/naloxone were enrolled. To be eligible for this study, patients had to: i) be receiving OMT therapy, drug-free according to urine and trichological tests in the six months preceding the study; ii) have a stable social and family life; iii) have no known logistical problems, such as a distance between residence and SerT of more than 50 km; iv) be in stable employment; v) have motivation to achieve full rehabilitation.

Patients were randomized to two different treatment strategies. In group 1, patients received OMT using the experimental DPC treatment strategy, which distributes OMT through local pharmacies which have been agreed upon by the Italian National Healthcare System (Servizio Sanitario Nazionale [SNN]) and involves general practitioners (GPs) in the management of patients.

During the trial, patients in group 1 were provided with instructions for their individual therapeutic program (which were also communicated to both the GPs, the pharmacies involved in this pilot study and the ASP key account pharmacist) and were instructed to obtain their OMT drugs from the pharmacies involved in the study. At this time, concomitant administrative records of the operation were recorded. Patients also underwent fortnightly or monthly visits with their GP for their drug prescription and had a monthly checkup at the local SerT, which included a urine test and social-educational and psychological counseling. Trichological testing was undergone every third month.

In group 2 (control group), patients received OMT from the local SerT using a traditional treatment strategy. Patients were instructed to obtain their OMT drugs from the local SerT on a weekly basis and underwent weekly general visits and urine tests and fortnightly social-educational and individual-psychological counseling.

Patients were followed for 6 months, with data collected at time 0 (baseline), during the quarterly follow-up (time 3) and after six months (time 6). In particular, the following data was collected and monitored: i) the patient characteristics and; ii) patient satisfaction; iii) resource use and cost of treatment; iv) the effectiveness of each treatment strategy, assessed by clinical (adherence, efficacy, the number of misuse episodes, etc.) and social-economical parameters (monthly average costs, time employed by the patients in treatment and controls, etc.).

Patient satisfaction was assessed using a survey which included five main domains: i) independence from SerT; ii) usual activities; iii) ability to work; iv) interpersonal relationship; and v) privacy protection anxiety. These domains included various questions where patients rated their satisfaction on a 5-part scale from 1 (highest satisfaction) to 0 (no satisfaction). For example, for the “ability to work” domain of the survey the options included were the following: i) no difficulties in the execution of usual activities (score 1); slight difficulties (score 0.75); moderate difficul-
ties (score 0.5); serious difficulties (score 0.25) and inability to carry out usual activities (score 0). The efficacy of each treatment strategy was assessed using the treatment satisfaction scores, the number of patient drop-outs, the change from baseline in the results of urine and trichological tests and the number of negative behavior episodes (misuse) after three and six months of treatment.

Resource use was assessed using a survey that analyzed the different tests and activities utilized by the SerT during the study, their time taken to do these tasks, and an estimation of the unitary cost associated with each task, and these were used to estimate the average direct health-care costs for each treatment strategy. Indirect health-care costs included costs associated with the distance in kilometers between the patients residence and the SerT (travel costs), the average time spent travelling and the time that the patient spent undergoing control tests, visits and counseling at the SerT.

### 2.1 Cost Analysis

Analysis of the project’s cost had the aim of evaluating the feasibility of the project and in particular, to demonstrate the ability of the project to optimize and therefore minimize the structure cost (direct healthcare related) of SerT as well as to diminish the expenses (direct not-healthcare related) falling on patients due to travelling to SerT and working hours lost. The estimate of direct healthcare-related costs was required to detect the various type of services provided by the SerT and their run-times and finally to estimate the unitary cost of each of them.

The indirect costs have also been estimated. These are costs incurred by patients for travel from their homes to the SerT. This type of cost was calculated by multiplying the kilometers travelled by patients by an estimated unitary cost (€0.215739 per kilometer).

The monthly average direct costs were calculated by multiplying the frequency of use of various services by their related unit costs. Of interest, when assessing the monthly costs of the DPC group, the costs associated with the distribution of the OMTs to the pharmacies was included and estimated to be 6 euro per unit. However, this cost was not included in the monthly total cost of each patient as it was hypothesized that distribution of the OMTs to the pharmacies would be associated with zero additional costs. As such, the costs associated to the stowage and distribution of the replacement drugs for the control treatment strategy were also not taken into account.

### 2.2 Clinical-therapeutic indicators

The efficacy of each treatment strategy was assessed using three indicators, namely: 1) the adherence of each patient to the treatment strategy; 2) the maintenance of drug-free condition in each patient, assessed by urine and trichological tests; 3) the presence of negative behavioral episodes such drug misuse and OMT non-compliance.

### 3 Results

Nine GPs and two pharmacists who were owners of pharmacies agreed upon by the SSN actively participated to the pilot project. Twenty four patients were enrolled in this study and randomly assigned to DPC or control group. All patients show comparable baseline characteristics (Table 1). Most of the patients were male, with a mean age of 38 years. The patients’ usual residences were on average 52-47 km from the

<table>
<thead>
<tr>
<th>Table 1. Patient characteristics at baseline</th>
<th>DPC</th>
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<tr>
<td></td>
<td>mean/%</td>
<td>st.dev</td>
</tr>
<tr>
<td>Age (years)</td>
<td>37</td>
<td>8,2</td>
</tr>
<tr>
<td>Sex (M)</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Distance (km)</td>
<td>52,7</td>
<td>12,3</td>
</tr>
<tr>
<td>Mean buprenorphine/naloxone dose (mg)</td>
<td>11,3</td>
<td>4,1</td>
</tr>
<tr>
<td>Civil status (Married)</td>
<td>58%</td>
<td>49%</td>
</tr>
<tr>
<td>Work (stable occupation)</td>
<td>58%</td>
<td>49%</td>
</tr>
</tbody>
</table>
SerT and approximately half of the patients enrolled were married and/or had stable employment. All patients were receiving OMT with buprenorphine/naloxone with an average daily dose of 12 mg. There were no statistically significant differences between the two groups with regard to the mean age, patient sex, the distance travelled during the study and the dosage of buprenorphine/naloxone received. However, fewer patients in the control group were employed.

### 3.1 Cost Analysis

Table 2 presents the frequency, time and unitary costs of the healthcare services provided by the SerT in each treatment strategy group. It shows that the two treatment strategy groups utilized services differently (DPC vs controls).

The direct costs associated with each treatment strategy are reported in Table 3. The average direct health-care cost per patient, which was identical for
the two groups at baseline (€337.88), remained unchanged in the control group over the 6 months. In contrast, the direct costs associated with the DPC treatment strategy decreased significantly after 3 months (by 61% to €131.18) and remained stable throughout the rest of the study. This decrease was mainly due to a lower frequency of SerT visits and services in the DPC group.

The indirect healthcare costs associated with each treatment strategy were also significantly reduced from baseline in the DPC group (-75%); this was mainly due to a lower frequency of travel from the patients’ home to the SerT (Table 3). From a monthly cost per patient of €45.45, the cost of travel decreased to €11.2 in the DPC group. Overall, the total cost (direct + indirect) of treating opioid-dependent patients using the DPC treatment strategy was reduced to €142.48 at the end of study, with a decrease of €240.85 (-63%) compared with the initial cost of treating these patients (€383.33).

3.2 Benefit Analysis

3.2.1. Patient Satisfaction

The change from baseline in patient satisfaction is presented in Table 4. At baseline, patient satisfaction was generally low in both the DPC and control groups (0.42 vs 0.43). In particular, the scores for the domains “independence from SerT” (0.27 vs 0.29), “ability to work” (0.33 vs 0.31) and “privacy protection anxiety” (0.35 vs 0.31) were notably low in both treatment strategy groups. This indicator confirms the initial hypothesis of a clear logistic and working discomfort most likely due to the necessary weekly attendance to SerT with a subsequent strong concern for privacy. After the 3 months, DPC treatment strategy increased the satisfaction of patients by 64%, whereas it remained stable in the control group (0.69 vs. 0.45). Patient satisfaction was further improved in the following 3 months in the DPC treatment strategy group (+ 19%). At 6 months, the DPC treatment strategy improved for the patient satisfaction domains “independence from SerT” (0.75 vs. 0.31), “usual activities” (0.83 vs. 0.46), “ability to work” (0.81 vs. 0.33) and “privacy protection anxiety” (0.81 vs. 0.31) compared with the control strategy (Table 4). Only the scores for “interpersonal relations” were similar between treatment strategies. Overall, with regard to personal satisfaction, the project has achieved the goal of enabling patients to perform their work more easily and to improve their autonomy as well as preserving their privacy.

3.2.2 Clinical-therapeutic indicators

At 3 and 6 months, the adherence of patients to each treatment strategy was high in both treatment strategy groups. At 3 months, more patients in the DPC treatment strategy dropped-out (75% adherence: 9 out of 12 patients remained) compared with the control strategy group (92% adherence: 11 of 12 patients remained). However, by 6 months, the drop-out rate was similar between the treatment strategy groups, with a study adherence of 75% in both treatment strategy groups observed. Of the patients in the DPC treatment strategy group who dropped-out of the study, one patient withdrew due to relapse and the other two (although initially negative at baseline) were removed from the study as they failed to comply with the agreed procedural rules. In contrast, in the control group, the three patients who dropped-out relapsed, which was confirmed by positive urine tests and trichological exam. Finally, there were no signifi-

<table>
<thead>
<tr>
<th>Table 4. Average individual degree of satisfaction (1)</th>
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<tbody>
<tr>
<td></td>
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<tr>
<td></td>
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<tr>
<td>Functional domains</td>
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<tr>
<td>Independence from SerT</td>
</tr>
<tr>
<td>Usual activities</td>
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<tr>
<td>Ability to work</td>
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<tr>
<td>Interpersonal relationship</td>
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<td>Privacy protection anxiety</td>
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<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>N.I. (T0 = 100)</td>
</tr>
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</table>

(1)This marker has value from 0 (no satisfaction) to 1 (highest satisfaction)
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This study showed that the implementation of the DPC treatment strategy, which distributes OMT through local pharmacies and involves GPs in the management of patients, greatly improved the satisfaction of patients compared with the traditional treatment strategy, which utilizes SerTs only. This improvement was mainly due to increased patient independence from the SerT. It has been shown that an increased patient satisfaction improves a treatment potential acceptance and can greatly improve patient’s quality of life thus increasing the chance of complete recovery.

Both treatment strategies were associated with similar clinical parameters. After 6 months, there were no significant differences between the two treatment strategies (DPC vs. controls) in terms of maintaining opioid-independence, with few patients relapsing during the study period. In addition, while there was a slight difference in the adherence of patients to the treatment strategies at 3 months by the end of the study this was normalized, with a study adherence of 75% in both treatment strategy groups observed. Furthermore, there were no significant differences between the two treatment strategies with regard to the incidence of negative behaviors (misuse, OMT non-compliance, illegal behavior) and discipline.

The use of a DPC treatment strategy appears to be less costly than a traditional treatment strategy in opioid-dependent patients. Over 6 months, the total costs (direct + indirect) of treating opioid-dependent patients using the DPC treatment strategy were lower for the DPC treatment strategy compared with the control group. This result shows the economic sustainability of the experimental procedure by the SerT. Furthermore patients required a minor amount of time to access the SerT, thereby improving the time dedicated to work.

This study has some limitations, particularly the

cant differences between the two groups regarding behavior and discipline, with a single doubt episode recorded in the DPC group.

3.2.3 Time analysis

The time associated with the management of patients for each treatment strategy are presented in Table 5. In the DPC treatment strategy group a significant reduction in time that patients devoted to attending the SerT was observed, with a reduction from a baseline value of 511.3 minutes per month (about nine hours) to 188.3 minutes (approximately 3 hours) at 3 and 6 months. The 63% decrease in time was mainly due to the reduced number of visits to the SerT.

4 Discussion

This pilot study, undertaken by the Soverato SerT of ASP-CZ, investigated the feasibility and sustainability of a novel treatment strategy for opioid-addicted patients receiving OMT with buprenorphine/naloxone. This new treatment strategy differs from the traditional one as it provides an alternate distribution of the drug, and reduces the patients’ attendance to the SerT based on the assumption that a lower attendance to SerT may be beneficial in patients with employment, logistics and privacy problems.

Table 5. Average monthly time for patients (minutes)

<table>
<thead>
<tr>
<th></th>
<th>DPC</th>
<th>Controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>T0</td>
<td>T3</td>
</tr>
<tr>
<td>Urine collection</td>
<td>40</td>
<td>10</td>
</tr>
<tr>
<td>Urine sample shipping</td>
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<td>15</td>
</tr>
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<td>Trichological collection</td>
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</tr>
<tr>
<td>Trichological sample shipping</td>
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<td>Control visit</td>
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<td>Medical examination</td>
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<tr>
<td>Psychological counseling</td>
<td>120</td>
<td>60</td>
</tr>
<tr>
<td>Drug administration</td>
<td>28</td>
<td>0</td>
</tr>
<tr>
<td>Delivery/custody of drug</td>
<td>40</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>511.3</td>
<td>188.3</td>
</tr>
<tr>
<td>For travel</td>
<td>277</td>
<td>69.0</td>
</tr>
<tr>
<td>Overall Total</td>
<td>788.3</td>
<td>257.3</td>
</tr>
</tbody>
</table>
small sample size of patients. While the sample size is small, this study was a pilot study which aimed to determine if changing the way patients with opioid-dependency receiving OMT were monitored and received treatment would have any effect on clinical outcomes and costs. Further studies, conducted in more Italian regional centers and with larger sample sizes are required to draw any firm conclusions about the benefit of the DPC treatment strategy. Another limitation of this study is that costs related to drug purchase or those for distribution through local pharmacies or for storage and management of the drug by SerT were not considered.

Despite these limitations, this study shows that the novel proposed treatment strategy (DPC) is a feasible and economically sound treatment strategy for the management of opioid-addicted patients receiving OMT with buprenorphine/naloxone. DPC can be proposed as a tool to improve the efficiency of the public health system in the field of pathological addictions.

References


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INFORMATION FOR CONTRIBUTORS

To submit an article, please, go to www.heroinaddictionrelatedclinicalproblems.org

Instructions for Authors

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The treatment goal in maintenance treatment of heroin addiction ought to be more than retention

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TO THE EDITOR:

1. High goal – low dose

Any leader of a methadone/buprenorphine programme for the maintenance treatment of heroin addiction will be studied by its prospective patients, and there will be a discussion going on between them about the best strategy for participants. When one of the authors (LG) returned to Sweden in 1966, after a year’s stay at the Rockefeller University, working in Dr. Dole’s laboratory, one of the first European methadone maintenance treatment (MMT) programmes was started. The treatment goal was focused on enabling patients to return to a productive life as self-supporting, vocationally rehabilitated citizens. All opioid addicts started therapy as inpatients in a treatment unit belonging to the Psychiatric Research Centre at Uppsala; they were initially detoxified, before the field in which the patient should work had been decided. If they were unable to decide what profession to choose, they had to visit a job counsellor and undergo testing to identify their personal talents. After a while, the situation was that newly arriving patients took their own decision before they met us, and would present themselves, saying: “Hello, I am Calle Karlsson and I am going to be a plumber [or: electrician, or nurse’s assistant, etc.]”. After this kind of presentation the dose-finding of methadone could begin right away. The patients knew in advance that our methadone treatment was long-term and that their craving for heroin would be kept under control as long as needed. Since they were not helped by the social services (which were against MMT), we had to train them how to behave when applying for a job, which some of them had never tried to do before. Our work-directed treatment made it necessary to find a minimal effective dose of methadone, and our results for 23 years were an outstanding yearly vocational rehabilitation rate between 70 and 80% (on the average 76% ceased to abuse opioids, managed to find and retain a paid job on the open market and became respectable taxpaying citizens). They all regularly sent us monthly written documents from their employers to prove that they still had their the job, and urinary test results for drug excretion were monitored.

It cannot be excluded that our patients may have represented a selection, because they were people who found our treatment goals attractive, but we considered such a selection as acceptable. We were looking for heroin addicts who wished to find an exit
strategy from their heroin abuse and illegal way of life. After heroin craving had been reduced or eliminated, the main obstacle to success was found to be benzodiazepine misuse. If patients took repeated overdoses, and had to be taken more than once in an unconscious state to an intensive care unit, the combination of methadone and benzodiazepines meant a higher risk of a lethal outcome. In this situation MMT sometimes had to be abandoned. We thus had a very stable and successful treatment programme, (figures 1 and 2) until LG had to retire for age reasons. We made an evaluation of treatment efficacy [7], the results of which elicited protests from the Board of Health & Welfare, where it was proclaimed that drug addicts should not be given drugs. In the end, however, our results received the approval of a new Director General, Barbro Westerholm, and the hostile group within this authority had to give up. After five years of standstill in our patient-intake 1979-84 [8], we were back in business.

2. Looking for the minimal effective dose level

Heroin addicts who are receiving methadone or buprenorphine/naloxone treatment often show cognitive deficits in attention, working and verbal memory. A couple of studies have compared patients on methadone or buprenorphine/naloxone maintenance with untreated controls. In their early phase of treatment, MMT patients tended to make more ‘risky’ choices on a decision-making task than an untreated control group [5]. Methadone-treated patients as a group had a significantly slower simple reaction time (RT) than either heroin addicts or untreated controls [16]. It is thus difficult to avoid a lowering of attention even at low daily doses of the maintenance opioid drug. When the treatment goal is for the patient to return to an ordinary, vocationally rehabilitated, non-drug-abusing, well-adjusted life, treatment-induced deficiencies are only acceptable to a limited extent. There are, however, other reasons for remaining in the lower dose area, even if close attention must be dedicated to the patient’s ability to stay free of drug abuse. In this context it is important to never allow the patient to negotiate for a dose increase. During LG’s 23 years as leader of the Uppsala programme, staff members were instructed to only discuss symptoms with patients, and never to inform them whether a complaint would give rise to an alteration of the methadone dose (a policy identical with that applied at the Rockefeller University during the first few years, when there was a high percentage rate for the retention of patients [3]). Once patients had accepted that they were not going to be told about dose or plasma levels of methadone, they often expressed the conviction that changes had meant dose increases, even when the opposite was true. Our patients displayed their inability to discern even considerable dose reductions, when they had been hoping for a rise in dose. After a couple of years it was found that the mean daily methadone dose, 80 mg (range 30-130), had been the same in New York and Sweden [7]. The total number of Swedish patients had reached levels 345 accepted as long as this treatment system was in use.

3. Methadone doses above 150 mg/day

In 1989, after LG’s retirement, the centralized
national approach was abandoned, new physicians took over and the MMT programme was more intensely controlled by the National Board of Health. The newly installed Dependence Centres (currently there are 77 of these) were instructed to tell patients that they would soon have to leave this programme and manage without long-term maintenance medication. Patients felt that it would not be possible to apply for a new job and, at the same time, let the prospective employer know that work may have to end later, after an unknown period of time, due to treatment restrictions. Thus the return from a criminal to an orderly way of life came to a sudden halt in 1989. The Uppsala model that allowed 76% of patients to achieve vocational rehabilitation suddenly turned into 0%, and all patients had to be supported by a social allowance or an early retirement pension. In a long-term follow-up of 261 patients in methadone treatment held in 1989-1998 and organized by the Board of Health, no comparison was made with our earlier results for 23 consecutive years [18]. The study responded to concerns focused on the low retention rate; the evaluators seem to have forgotten that an early treatment interruption had been recommended by the Board of Health! The follow-up showed that only 8 out of the 261 long-term patients investigated had not had new legal procedures taken against them during the follow-up period, meaning that criminal activity had continued in at least 97% of these cases. A third of the population died, a majority of them after they were excluded from treatment for various disciplinary reasons.

During the 1990s there were increasing numbers of MMT reports in which high methadone doses had been applied, bringing reported improvements in the initial results [2, 4, 11,12,13], although there were often worse side-effects [2,10,13]. In the high-dose programmes, greater emphasis was laid on patients’ continuing heroin abuse, their retention in treatment and their reports of continuing subjective symptoms of withdrawal and signals of craving for opioids. Whenever something was wrong with any of these measurements, the dose was raised. During the present century high doses are often recommended, and the misuse of heroin has become just another reason for giving more methadone. A few studies did, however, report that individual therapists were getting better results irrespective of dose [1], or that a voucher reward was as effective in reducing heroin abuse as raising the methadone dose level [15]. Robles et al. [17] found that dose reductions down to 80% of the previous dose, or increases up to 120% were not possible to discern for MMT patients, and they concluded that this observation argues against a patient-regulated dosing of methadone.

Payte [14] suggested that a suitable individual dose level could always be found between 10 and 500 mg/day, or even more, and Gonzales-Saiz [6] provided an Opiate Dosage Adequacy Scale (ODAS) based essentially on the patients’ self-reported feelings of craving and withdrawal symptoms, and MMT reduces their illicit drug use. In addition, patients were asked to express their opinions about the methadone dose being used, and if they had any suggestions for a change of dose. All the arguments in favour of dose increases are taken into consideration, whereas the dose restrictions of the early Rockefeller University policy and the early National Swedish MMT programme were disregarded. Patients with the methadone doses indicated in table 1 are likely to be chronically euphoric and they are hard to rehabilitate vocationally, even if their quality of life is claimed to be good.

### Table 1: Maximal methadone doses reported.

<table>
<thead>
<tr>
<th>Author</th>
<th>Publication</th>
<th>Methadone dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Shinderman MS:</td>
<td>AATOD 2008</td>
<td>1400 mg/day</td>
</tr>
<tr>
<td>Cruciani RA et al.:</td>
<td>J. Pain 2005;29:385-201</td>
<td>1200 mg/day</td>
</tr>
<tr>
<td>Hobbins DF:</td>
<td>J. Addictions Nursing 2010;21:22-26</td>
<td>1200 mg/day</td>
</tr>
</tbody>
</table>

By the Swedish Medical Product Agency, and Professor Kreek at the Rockefeller University have defined a recommended highest methadone dose level of 150 mg/d. If doctors wish to provide a higher dose in an individual case, they should be able to explain what precautions were taken, particularly if the patient died or had high dose-related side-effects [2,10]. Prescribing methadone for MMT at doses above 150
mg/d should also require taking a position on the issue whether the patient can keep his or her driver’s license. If possible, the high-dose and low-dose policies should be compared at intervals, but it is difficult for any supervisory public authority to regulate them in a sensible way, as illustrated by events in Sweden and other countries. On the other hand, the prescription of euphoria-delivering amounts of opioids or, as sometimes recommended, the distribution of heroin maintenance for intravenous self-administration may ruin an ongoing high-goal treatment programme.

Patients who could have been resocialized may contribute to high retention figures by their regular visits to obtain free heroin or euphoria-inducing amounts of maintenance drugs at the dependence clinics. If such programmes become dominant in the future, then we may lose the advantages provided by the Dole-Nyswander treatment altogether. This would lead to a situation where the acquisition and retention of patients has become more important than offering those subjects a chance to return to a normal society from a life dominated by drugs and criminal acts.

References


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Is opioid agonist treatment the only way to treat the psychopathology of heroin addicts?

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TO THE EDITOR: The impact of long-acting opioid treatment on the psychopathological profile of heroin addicts has not yet been fully investigated, despite the likelihood that opioid agents have a specific therapeutic action on psychopathological symptoms. In the literature, opioid agents have, in fact, been reported to have a therapeutic effect on a wide range of psychopathological conditions [9].

Opiates were used to treat major depression until the 1950s. The high concentration of opioid receptors and endorphins in the limbic and hypothalamic regions, and their interaction with noradrenergic and dopaminergic systems, have suggested the involvement of endorphin systems in depression, as is also suggested by certain clinical observations. These observations, as well as the euphoric, analgesic and calming effect of opiates, suggested that decreased functional activity in endorphin systems may be involved in the pathophysiology of depression. As soon as the early 80’s, consistently with the endorphinergic hypothesis for the dysthymic disorder [8], opioid peptides have been considered potential candidates for the development of novel antidepressant treatment [6]. Thirty years ago, Gold suggested the potential antipsychotic, antidepressant, and antianxiety-antipanic effects of the endogenous opioids, endorphins, and exogenous opioids [9]. As soon as it first appeared, buprenorphine, thanks to its partial agonist activity, bringing with it a reduced risk of dependence and abuse, turned out to offer an effective therapeutic strategy for depressed patients who are unresponsive to, or intolerant of, conventional antidepressant agents [2, 3, 7]. Although opiates are known to produce euphoric states, and spontaneous states of elation are associated with high central nervous system levels of endorphins, a low incidence of manic states has been reported among heroin addicts. Methadone maintenance has been observed to achieve major
mood stabilization in bipolar 1 patients. In particular, in a sample consisting of opioid-dependent subjects without psychiatric comorbidity and opioid-dependent subjects with one or more additional axis 1 diagnoses, significant differences were found between these two groups with respect to the methadone dose required for clinical stabilization, but not in the rate of retention in treatment. Among Dual Diagnosis patients, those with psychiatric comorbidity required a higher stabilization dose of methadone [21]. This is in line with clinical observations on a subject who spent a total of seven years in methadone maintenance and only one year out of it; in that case both the polarities of the mood disorder became concentrated and were rapidly resolved on re-entry into methadone maintenance opioid treatment. That favourable outcome suggests that methadone most probably played a role in preventing mood disorder relapses [23].

Regarding antagonist opiates, naloxone has likewise shown antimanic properties probably attributable to its hypothesized negative influence on basal mood, formulated on the basis of observations on addicted or non-addicted patients [25]. Endorphin excess may underlie euphoria and mania, as demonstrated by the antimanic effect shown by naloxone in a sample of manic patients. Thus, considering that opioid agonists can have a positive impact on psychopathological symptoms, it is not surprising that an opioid antagonist can worsen these same symptoms. In non-addicted subjects it might induce a state of anxiety, with the onset of panic attacks. This mechanism is related to opioid agonists’ action on the hyperactivation of noradrenergic cells that is at the basis of the worsening of anxiety [16]. In evaluating a treatment with naltrexone maintenance, it has been seen that the presence of psychosis, aggressiveness and depression increased the percentage of dropouts at one-year follow-up, so highlighting the worsening of psychopathological symptoms treated with antagonists by showing the subsequent negative outcome for patients [17].

Some authors have hypothesized a direct involvement of opioid neuropeptides in the pathophysiology of psychotic disorders. In the 1980s, beta-endorphin administration was associated with a statistically significant, but clinically imperceptible improvement in schizophrenic symptoms [1]. The antipsychotic effectiveness of opiate agonists is supported by the fact that methadone maintenance is responsible for the prevention of psychotic relapses in individuals with a history of psychotic episodes. In those subjects, the gradual elimination of methadone was followed by psychotic relapses [11]. This therapeutic pattern is in line with the antidopaminergic activity of methadone, as documented by the increase in serum prolactin after methadone administration. On the basis that potential antipsychotic medications block dopamine receptors while stimulating prolactin secretion, a dose of morphine produces a significant increase in basal serum prolactin, which again suggests the probable antipsychotic role of opiates [10]. From this standpoint, it has been pointed out that psychotic heroin-dependent patients who presented for agonist opioid treatment had more severe psychopathological aspects combined with a shorter, less severe addiction history (except for polyabuse) than their non-psychotic peers. The fact that they requested agonist opioid treatment earlier, despite their less severe addiction history, supports the view that patients like these may mainly benefit from an opioid medication through the improvement of their psychopathology, rather than through the alleviation of their heroin dependence [12]. It is not surprising that, at least in Italy, heroin addicts who resort to street methadone do not seem to indicate a form of behaviour that points to a surrogate form of heroin addiction, but rather at a way of achieving harm reduction, with treatment-seeking occurring shortly after the initiation of that behaviour [18]. Moreover, the fact that opioids can be useful in psychosis is further strengthened by the temporal relationship that is observed at the onset of diseases in dual diagnosis heroin addicts, according to which psychosis usually precedes the onset of heroin dependence [13].

Moving on now, when they are combined with methadone, low dosages of antipsychotics are needed to control psychotic symptoms – a finding supported by the biological evidence that neuroleptics and exogenous opioids act as the same neuronal site, the DA synapse, in both cases suppressing neurotransmission through the synapse, even if the mechanisms activated differ [4]. Focusing on the need for antipsychotic and antimanic agents in heroin addicts who have been hospitalized for manic and/or acute psychotic episodes, independently of the reasons for their hospitalization, subjects who had received increasing dosages of methadone were judged to be less in need of antimanic and antipsychotic drugs at discharge [22]. Similarly, previously resistant bipolar 1 heroin addicts, when treated with above-standard doses of methadone combined with mood stabilizers, showed the same level of retention in treatment as heroin addicts without psychiatric comorbidity [15].

After looking at the efficacy of opioids on psy-
chopathology, as reported in the literature, we wondered whether therapeutic opiates (more specifically, methadone and buprenorphine) showed the same impact on psychopathological symptoms. Symptom checklist-90 (SCL-90) [5] has been used to evaluate the efficacy of buprenorphine and methadone on psychopathological symptoms. Considering heroin-dependent patients in treatment with methadone or buprenorphine, a favourable effect has been observed on the clinical course, psychiatric well-being, and social adjustment of opioid-addicted patients. The improvements in drug use, problematic symptoms and general quality of life were significant and comparable for methadone and buprenorphine. Considering all the SCL-90 items that have been grouped into nine factors, the main finding was the strong efficacy of buprenorphine-related to different psychopathological dimensions, SCL-90 items that have been grouped into nine factors in treating psychiatric comorbidity.

In conclusion, after reviewing the addiction history of our patients, we can state that the high rate of psychiatric symptoms among heroin addicts should never be overlooked or undervalued. These symptoms, which have an impact on treatment outcome, are likely to show a good response to therapeutic opioids. It is therefore likely that psychiatric conditions should be viewed as predictors of outcome in methadone- or buprenorphine-treated patients, and it is probable that, by treating heroin addiction with therapeutic opioids, we will also obtain better results in treating psychiatric comorbidity.

References

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Comparing medications used in opioid addiction treatment in Greece

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TO THE EDITOR: clarification is needed regarding the recent article by Geitona and colleagues comparing methadone, Subutex and Suboxone in the treatment of addiction in Greece (1). For starters, the data that were analyzed are said to have been derived from the experience in 2008, but it is noted that Suboxone was not introduced in Greece until the end of that year. Also, total costs do not seem to reflect the sum of the components: the average daily cost of Suboxone is more than 14 times (!) that of methadone (€ 3.12 v. € 0.25), and the “mean daily managerial cost per participant was lower for methadone” as well. And yet, the authors conclude that the use of Suboxone “reduced the mean cost [of treatment] by 49%.”

It is noted that “an ever greater number of participants ask to be switched from methadone to buprenorphine.” Whether this trend refers to Subutex, Suboxone or both, it certainly is no surprise given the demand for daily clinic attendance imposed on methadone recipients, while others need attend only weekly. Furthermore, this is an unnecessary discrepancy. In the US, for example, weekly (and even monthly) attendance is permitted longer-term patients who are responding well to treatment. If the more flexible attendance schedule is believed by the authors to be associated with greater cost-effectiveness, the same benefit could be achieved with methadone.

The article states that less than 17% of the estimated 24,097 opioid-dependent people in Greece were receiving any form of medication-based treatment. Of those not in treatment, over a quarter were on waiting lists, “with a mean waiting-list time of 6 years”! Frankly, these figures seem to demand an urgent change in public policy more than a change in medications!

Finally, the authors state they have “no relevant conflict of interest to report …” This seems disingen-
uous given that the entire funding for the project was derived from the firms that make and sell buprenorphine products. Surely the companies did not agree to assume full financial responsibility without knowing (and approving) in advance the key aspects of the study for which they were asked to pay.

References


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Can outcomes monitoring of opioid maintenance treatment be improved in Europe? A statement by some European experts with interests in opioid maintenance treatment and its safety

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5 Klinik für abhängiges Verhalten und Suchtmedizin, LVR-Klinikum Essen, Kliniken der Universität Duisburg-Essen, Germany, EU
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TO THE EDITOR: Despite the long tradition of treatment in Europe, wide variation exists in opioid maintenance practice both in regard to the settings for treatment and in regard to the treatments and methods used; such variation can even be seen within a given country. Although a wide set of guidelines for the management of opioid dependency exist, these are often literature review evidence-based and are not always practical in terms of managing adverse events or making clinical decisions. Safety and mortality rates differ between countries in Europe and beyond, a phenomenon that is not fully explained or understood. As there is currently no standard approach to data collection across borders in Europe beyond statutory pharmacovigilance, it is difficult to obtain a real world evidence-based picture of the safety of treatment and outcomes for patients in routine care. Each country has its own systems for monitoring and there is a great range of outcomes data available. In many EU countries, adverse drug reactions are reported voluntarily by physicians (and from June 2012 also by users) to the local agencies, and prescriptions (but not medications distributed directly from treatment centres) are reported to the prescription database maintained by local authorities. Data collection based on country reporting may only have data from public institutions, whereas a significant amount of evidence will come from patients treated in community settings or private practice that are not surveyed, with no information forwarded to EMCCDA.

Although there is no central registry in Europe for drug related deaths, the departments of forensic
Heroin Addiction and Related Clinical Problems 15(1): 63-64

medicine for several European countries report annually on all drug findings in the medico legal cause of death, which can provide some information on drug-related mortality.

The EMEA recently implemented new regulations with regard to safety monitoring, which came into force in July 2012. This change in legislation provides an opportunity to consider whether new standards and approaches for safety and outcomes data collection can be implemented for opioid maintenance treatment. Standardisation of key data for collection would provide the opportunity for integration of data across Europe, with the potential to increase our knowledge in this field and thereby improve safety and treatment outcomes for patients.

Measures of rates of abuse, misuse and diversion of prescription drugs throughout the United States are available through several sources but the most comprehensive is The Researched Abuse, Diversion and Addiction-Related Surveillance (RADARS®) System, a non-profit operation that collects timely product-and geographically-specific data. The data from the RADARS System contribute to the understanding of trends and aiding the development of effective interventions. These data also assist pharmaceutical companies in fulfilment of their regulatory obligations such as risk evaluation and mitigation. This system has been established over 10 years and can provide us with valuable direction. Rather than attempt to start a similar, huge project in Europe it is probably more realistic to take a more simple step-by-step approach, starting small and building. Initially, we should ascertain what are the key data we require in Europe and focus on standardising a system for collection and collation of that data.

The available data are currently collected and reported by EMCDDA but variable data collection methods and irregular reporting by local authorities create challenges and uncertainty on reports. For example, widely differing retention and mortality rates exist according to EMCDDA data. If these differences are genuine, then it would be of scientific interest to compare standard practices between countries.

The data collection and reporting that the EMCDDA does is a valid achievement, and acts as a useful repository for the guidelines. However, funding is needed both to widen the remit of the EMCDDA and to ensure that countries give meaningful data. We believe that a pan-European approach to linking existing databases of outcomes, including mortality, related to medical assisted treatment for opioid dependence management should be set up. In addition existing databases containing evidence of harm associated with medical assisted therapy for opioid dependence, such as misuse and diversion should be commenced at the European level.

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