Heroin Addiction and Related Clinical Problems

the official journal of
Europad
European Opiate Addiction Treatment Association
EUROPAD, formerly EUMA, was founded in Geneva (Switzerland) on September 26, 1994. It shall remain independent of political parties and of any government.

The vision

EUROPAD exists to improve the lives of opiate misusers and their families and to reduce the impact of illicit drug use on society as a whole. The Association works to develop opiate addiction treatment in Europe but also aims to make a major contribution to the knowledge of, and attitudes to, addiction treatment worldwide.

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Addiction: Challenging the dual diagnosis construct

Pier Paolo Pani

Social Health Service, Health District 8 (ASL 8), Cagliari, Italy, EU

The current ‘official’ nosology (e.g. DSM-IV) of addiction is largely limited to manifestations that can be objectively observed and suited to the maintenance of an ‘atheoretal’ perspective. However, addicted subjects display other psychic symptoms (in particular, those related to mood, anxiety, or impulse-control dimensions) that affect their well-being and social functioning. In practice, these symptoms are typically considered as being ‘comorbid’, thereby contributing to multiplying comorbid diagnoses in addiction. However, a close relationship can be detected between these symptoms and addiction, as underlined by the high frequency of association with that disorder, and by their strong neurobiological and neuropsychological links.

There are several reasons for taking these symptoms into account in clinical presentations of substance-use disorders.

First, the pre-existence of psychic precursors. Even if they are essentially viewed as the result of drug effects, affective, anxiety and antisocial-related symptoms may precede drug abuse and work as a specific risk factor in addiction. A psychiatric diagnosis may be absent, but specific psychological/psychiatric vulnerabilities such as dysmodulation in motivation and reward, stress resiliency, mood reactivity, impulsiveness -control imbalance, temperamental assets, and subthreshold mental disorders may constitute a background for the development of addictive disorders, by exerting an impact on willingness to try drugs and/or the progression to addiction [5, 6, 13].

Second, the short-term consequences of the interaction between psychopharmacologically active substances and their neurobiological substrates may have connections with vigilance, orientation, perception, cognitive functions, affects and mood, ways of thinking, and will. Psychiatric symptoms that accompany the use of specific substances, including irritability, sleep difficulties, anxiety, and attention/
concentration problems, are not necessarily so intense as to warrant a ‘disorder’ level; however, they may substantially contribute to compromising the individual well-being and social functioning of people with addictive disorders.

Third, more stable psychopathological manifestations depend on the prolonged interaction of substances with a predisposed neurobiological substrate and its active reaction. The resulting changes may not only justify the strictly behavioural presentation of addiction as a specific disorder – and psychological/psychiatric correlates such as craving and dyscontrol –, but also the onset/worsening of other psychiatric symptoms. Hypofunction of limbic dopamine circuits, hypoaactivity of prefrontal brain regions, changes in the reward and stress systems, and gene expression dysregulation, are all potential candidates underlying depression, dysphoria, anxiety and impulsiveness preceding addiction, featured moreover as an outcome of addictive processes [1, 2, 14].

Fourth, clinical manifestations produced as a consequence of addictive processes do not seem to merely add to those previous encounters with substances. Interactions between the above factors should be considered, particularly in view of the fact that while predisposing psychic conditions may facilitate substance use and activate addictive processes, these, in turn, by acting on the same neuronal background, induce a worsening of psychic conditions in the same domains [3, 4, 10-12].

DSM nosology does not seem to grasp the complexity of the interaction between the psychic structures involved, and neurobiological and physiopathological processes activated by encounters with substances of abuse. On these bases, an integrative unified perspective explaining the pathophysiology and phenomenology of addiction has been proposed [7-9].

The validation of an articulated clinical condition, encompassing part of the grey area of symptomatology that exists between addiction itself and other ‘independent’ psychopathologies would certainly imply the need to carry out specific research programmes. In the meantime, the possible benefit afforded by mention of the presence of symptoms pertaining to the domain of impulse-control, anxiety and mood spectrum in the DSM V description of substance-use disorders should be taken into consideration. Even in the absence of their specific inclusion among diagnostic criteria, the act of signalling their presence could induce clinicians to refrain from making possibly inappropriate dual or multiple diagnoses, encourage an integrated evaluation of symptoms consistent with psychic precursors, substance effects, addictive processes and psychic consequences, thus allowing a more comprehensive and appropriate treatment.

References


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**Conflict of Interest**

The author has no relevant conflict of interest to report in relation to the present editorial
Adherence and social antecedents in relation to outcome in Methadone Maintenance Treatment (MMT)

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Summary

Numerous reports of the effectiveness of methadone in reducing opiate use as well as mortality, criminality, prostitution and the risk for HIV-infection have been published during the last forty years. However, poor adherence to treatment, continuing drug use and increasing rate of premature termination may lead to less than optimal outcome results or in too many cases death. The aim of this paper is to investigate which of the background variables, collected at the admission procedure, that can be used to tell which type of patient will adhere to the treatment regime and succeed or who will fail and who either need special considerations or ought not to be accepted for a methadone treatment (MMT). As much as 86 percent of the compliers in this study did benefit from the treatment and were rated as medium to very much improved according to CGI-I. The group not improved or worse had significantly more background problems such as school problems, a history of non-opioid abuse, many non-MMT treatment episodes, low age at drug debut and opioid debut than the group much or very much improved. Those moderately improved is usually situated somewhere in between the others.

Key Words: MMT; social antecedents; adherence to treatment

1. Introduction

Methadone maintenance is the primary treatment modality for opiate addiction and has been used since the 1960s [8, 9, 26, 31]. Numerous reports of its effectiveness in reducing opiate use as well as mortality, criminality, prostitution and the risk for HIV have been published [10, 11, 38, 17, 14, 20, 4, 15, 1]. During recent decades methadone maintenance treatment has received wide acceptance in many countries with the new object in reducing HIV risk behaviour [1]. Adherence to methadone treatment is associated to low HIV risk behaviour [36].

Although methadone treatment has demonstrated clear effectiveness in treating heroin addicts, poor adherence to treatment [35], continuing drug use and increasing rate of premature termination [24] may lead to less than optimal outcome results or death [17]. Haskew and co-workers [23] found that 42 percent were partial or poor adherers to their prescribed methadone medication. Some studies report a yearly retention rate below 50 percent in methadone maintenance treatment for injecting heroin users [2]. Lehmann and co-workers [28] tried to predict retention and absence of opiates in the urine. Because they only found foster care before the age of 15 to be associated with success they concluded that until better predictors are available all applying for MMT should be admitted. Maremmani and colleagues [30] showed that there are statistically time effects in methadone treatment. Between three and twelve months of treatment they found that there were a decrease in opioids use and an improvement in clinical status.

The National Swedish Methadone programme in Uppsala had during 1967-1990 a yearly retention rate of 80-100% (mean 90%) and resulted in 70-80% patients with paid jobs on the Swedish labour market [20, 21, 15]. When heroin
addicts are accepted for methadone treatment it is of great interest to know if there are differences in outcome that are related to background history. Some patients will remain in treatment for years while others will drop out early or will be expelled due to program rule violations or imprisonment [21]. For clinical purpose, at admission, it is important when drawing up the individual treatment plan to know if there is a way to tell which type of background that is associated with treatment adherence and success and which is associated with partial or no recovery. The present paper tries to define the success and failures within our treatment system and to clarify to what extent outcome was associated with various background factors. Outcome was measured by global ratings of clinical success, using the CGI-I (Clinical Global Impression of Improvement) scale by Guy [22]. This rating instrument has been validated by Dhalke et al [7] and Benke & Rasmus [3] and is worldwide used [5].

The aim with this paper is to investigate which of the background variables, collected at the admission procedure, that can be used to tell which type of patient will adhere to the treatment regime and succeed and who will fail and who either needs special consideration or ought not to be accepted for a methadone treatment program. In this study treatment outcome is evaluated by clinicians using a global assessment scale of treated patients. Adherence is operationalized as following the treatment regime in taking the prescribed methadone at correct doses, be mainly free from other drugs and not to be involved in criminality to such level that the patient cannot remain in treatment. Non-adherence is operationalized as not taking the prescribed methadone dose and/or using other illegal drugs and/or involvement in criminality to such an extent that the patient is expelled from treatment.

Good adherence to treatment may increase the possibilities to succeed at lower doses of medication which may decrease the risk for side effects that are dose-dependent and may also decrease the risk of leakage of methadone to the illegal market.

2. Method

2.1 Subjects and procedure

This study includes 345 opiate addicts (102 female and 243 male addicts) admitted to a National methadone maintenance program at the University Hospital in Uppsala, Sweden. Detailed data of the sample are given elsewhere [20]. The set of background data combines variables obtained from medical and official records, criminal justice system and social agencies’ registers with self-reported data and filed according to a standardised model developed by Frykholm et al [13]. Subjects were admitted during 1966-1990 with all outcome data prospectively collected. There was a stand-still in intake of new patients during 1979-1984 due to political struggle around methadone treatment in Sweden [19]. Intake criteria have remained the same since the introduction of this program in 1966 with a minor change when HIV-infection showed up in 1984 [8, 18, 16, 4].

The reliability and validity of data have been examined for congruence by using an admission committee evaluating each admission procedure. All subjects were aware at the admission that the staff already knows their official history as they had given their written permission to collect all obtainable data. At the end of each intake interview a urine specimen was collected.

2.2 Treatment process

Participation in this methadone program was voluntary and the methadone induction phase was with a few exceptions conducted as inpatients at a special unlocked treatment ward with medical trained personnel and social workers. Subjects received a standard medical and psychiatric examination including blood sampling and if needed treatment for withdrawal distress. Mean methadone dose in milligrams was 80 mg followed-up by controlling plasma levels of methadone [24, 20]. In recent years the mean doses have increased to some degree and the present doses are around 100 mg in the program. During their stay at the treatment ward subjects left urine specimens under direct observation on a randomly assigned day and always after longer visits outside the ward. Subjects have weekly individual counselling sessions with paramedical and university trained counsellors who also served as counsellor during the outpatient phase of treatment.

Our program philosophy is non repressive and favours a rapid return to a working-life in a non-abusing society. Each patient is introduced to the program rules and together with the psychiatrist, and counsellors a complete rehabilitation plan with network system are set up. After the 6 week induction phase each patient are transferred to the outpatient team and now receives his/her daily methadone doses from the local pharmacy, sometimes adjusted according to treatment progress. Urine samples are delivered under observation at a frequency that corresponds to treatment progress. Thus, when the patients adhere to treatment rules and are improving, the frequency of mandatory urine samples will be lowered. Those who do not adhere to the main rules of treatment, such as remaining drug-free and free of criminal activity are running a risk to be expelled from the programme. However, we have earlier shown that those forced to stop taking methadone are at high risk for an early death [17].

2.3 Factors

The study design was based on two factors, Clinical Global Impression Scale (CGI-I) and gender. One special type of global rating scales refers to the change or improvement of patients during treatment after entry of a treatment modality [22].
Clinical Global Impression Scale (CGI-I) is a universally used rating scale for global clinical assessments for disease severity and change of a disease under influence of a treatment [22, 7, 3]. The CGI-I-scale is subdivided into seven grades from marked worsened through no change to marked improvement of a treatment variable. The rating scale has proved to have a high relevance to the individual patient in the evaluation of the efficacy of a treatment program. In a review of 24 different clinical trials the therapeutic impact was measured by global ratings in 14 out of 17 studies [27].

Five counsellors working in the methadone program in Uppsala were asked to rate all patients in the study sample of methadone patients with the CGI-I-scale. Their average clinical experience with methadone treatment was 7.4 years (range 2-17 years). In the preparation before the rating took place each counsellor rated ten other patients in order to become familiar with the scale. During the rating process of the 345 patients each counsellor had beyond their personal experience with the patient’s access to all case histories through patient records and other written documents. The instruction to the raters was to take the whole treatment period into consideration with emphasis on the last five years. The interrater reliability was calculated with the average value of the Spearman rank correlation coefficient between the 5 counsellor’s CGI ratings to be r=0.82 showing good correspondence between the raters, [12].

2.4 Variables

The variables can be grouped into six areas, (1) Heredity with two variables, (2) Childhood and adolescence with five variables, (3) Adult age with three variables, (4) Drug abuse with eight variables, (5) Treatment with six variables and (6) Criminality with four variables.

Heredity comprised two variables; fathers or mother’s psychiatric disorder and/or drug abuse. The measure was based on the individuals’ self-report and confirmed by means of medical and social agency records, police files and through contact with relatives.

The childhood and adolescence period generated five variables and they were based on the individuals self-report and confirmed by means of medical and social agency records, police files and through contact with relatives. Abnormal childhood experience was a global index and based upon the other four measures in such a way that if the individual had one of the other problems he or she was considered having an abnormal childhood experience. Foster-home was measured as a child below the age of seventeenth living in a home with none of its parents or other close relative. Broken home was measured as coming from a home where the parents were divorced. The variable school problem was measured as being bullied, truancy or having writing and reading problems. Completeld compulsory school was defined as the completion of secondary school to eighth or ninth grade depending on how old the individual was and what the requirement was when he/she was in school.

Adult age generated three variables and they were based on the individuals self-report and confirmed by means of medical and social agency records, police files and through contact with relatives. Own residence was measured as renting or owning the living space. Work experience was measured as having had a paid work of part-time or more. Partner, active addict was measured as having or not having a partner who used illegal drugs.

Drug abuse was described in eight variables and was based on the individuals self-report and confirmed by urinalysis, medical and social agency records, police files and through contact with relatives. If opioid was the first drug was measured as, either the first illegal drug was any opioid or the first drug was another illegal drug (alcohol was not counted). Frequent heroin ODs (overdoses) was measured as having a history of more than yearly heroin OD:s. The presence or absence of a history of non-opioid abuse was measured as use on a more regular basis of illegal drugs other than opioids (alcohol was not counted) and divided into three categories: No additional drug, one additional drug and more than one additional drug.

Age at first drug use was measured as a discreet variable based on the individuals self-reported age and confirmed by means of medical and social agency records, police files and through contact with relatives. Age at first use was defined as the age at first use, whether oral or intravenous, of cannabis, amphetamine, opioids, barbiturates, cocaine or the illegal use of benzodiazepines. Alcohol use was excluded as first use of drugs. Age at first use of opioid was measured as a discreet variable based on the individuals self-reported age and confirmed by means of medical and social agency records, police files and through contact with relatives. Years between drug debut (Yrs. btw. Drug) and opioid debut was measured as the time in years with one decimal between age at first drug and age at opioid use. Years of abuse was measured as the time in years between age at first drug and age at start of methadone maintenance treatment. Years of opioid abuse was measured as the time in years between age at opioid use and age at start of their first methadone maintenance treatment.

There were six treatment variables and they were based on the individuals self-report and confirmed by means of medical and social agency records, police files and through contact with relatives. Short-term hospital treatment episodes was defined as a non-MMT in treatment period of one week or less and long-term hospital treatment episodes was defined as a non-MMT in treatment period of more than one week. Months in treatment community was measured as the time in voluntary or involuntary in drug-free treatment community of various kinds. Age at entering MMT was measured as the age with one decimal when first entering MMT. Age at first treatment was measured as the age with one decimal...
Table 1. Presence of background variables of potential importance for the prognosis (heredity, childhood and adolescence, work, earlier treatment, court sentence and drug abuse pattern) in the case histories of 345 MT patients subdivided according to CGI-I rating of improvement

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<th>Variable</th>
<th>Total sample N=345</th>
<th>Much or very much improved N=130</th>
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<td>Heredity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorder and/or drug abuse, father§</td>
<td>85 (27)</td>
<td>25 (21)</td>
<td>35 (29)</td>
<td>25 (34)</td>
<td>3.9 (2)</td>
</tr>
<tr>
<td>Psychiatric disorder and/or drug abuse, mother §§</td>
<td>58 (17)</td>
<td>18 (14)</td>
<td>23 (18)</td>
<td>17 (22)</td>
<td>2.1 (2)</td>
</tr>
<tr>
<td>Childhood and adolescence</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal childhood experiences</td>
<td>239 (69)</td>
<td>77 (59)</td>
<td>97 (73)</td>
<td>65 (78)</td>
<td>10.4 (2)**</td>
</tr>
<tr>
<td>Foster-home</td>
<td>94 (27)</td>
<td>32 (25)</td>
<td>33 (25)</td>
<td>29 (35)</td>
<td>3.3 (2)</td>
</tr>
<tr>
<td>Broken home</td>
<td>182 (53)</td>
<td>57 (44)</td>
<td>76 (58)</td>
<td>49 (59)</td>
<td>6.7 (2)*</td>
</tr>
<tr>
<td>School problems</td>
<td>222 (64)</td>
<td>67 (52)</td>
<td>89 (67)</td>
<td>66 (80)</td>
<td>18.2 (2)**</td>
</tr>
<tr>
<td>Completed compulsory school</td>
<td>254 (74)</td>
<td>110 (85)</td>
<td>93 (70)</td>
<td>51 (61)</td>
<td>15.1 (2)**</td>
</tr>
<tr>
<td>Adult age, treatment and criminality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Own residence</td>
<td>183 (53)</td>
<td>85 (65)</td>
<td>67 (51)</td>
<td>31 (37)</td>
<td>16.4 (2)**</td>
</tr>
<tr>
<td>Work experience</td>
<td>232 (67)</td>
<td>97 (75)</td>
<td>88 (67)</td>
<td>47 (57)</td>
<td>7.5 (2)*</td>
</tr>
<tr>
<td>Partner, active addict</td>
<td>108 (31)</td>
<td>40 (31)</td>
<td>44 (33)</td>
<td>24 (29)</td>
<td>0.5 (2)</td>
</tr>
<tr>
<td>Compulsory treatment</td>
<td>135 (39)</td>
<td>38 (29)</td>
<td>52 (39)</td>
<td>45 (54)</td>
<td>13.3 (2)**</td>
</tr>
<tr>
<td>Court sentences</td>
<td>275 (80)</td>
<td>88 (68)</td>
<td>111 (84)</td>
<td>76 (92)</td>
<td>20.4 (2)**</td>
</tr>
<tr>
<td>Drug abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid as first drug</td>
<td>79 (23)</td>
<td>37 (28)</td>
<td>24 (18)</td>
<td>18 (22)</td>
<td>4.0 (2)</td>
</tr>
<tr>
<td>Frequent ODs</td>
<td>118 (34)</td>
<td>20 (15)</td>
<td>50 (38)</td>
<td>48 (58)</td>
<td>41.8 (2)**</td>
</tr>
<tr>
<td>History of non-opioid abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No additional drug</td>
<td>175 (51)</td>
<td>89 (68)</td>
<td>52 (39)</td>
<td>34 (41)</td>
<td></td>
</tr>
<tr>
<td>One additional drug</td>
<td>97 (28)</td>
<td>31 (24)</td>
<td>47 (36)</td>
<td>19 (23)</td>
<td></td>
</tr>
<tr>
<td>More than one additional drug</td>
<td>73 (21)</td>
<td>10 (8)</td>
<td>33 (25)</td>
<td>30 (36)</td>
<td>38.1 (4)**</td>
</tr>
</tbody>
</table>

*p<0.05 **p<0.01
Figures in parenthesis are percent. § n=314, §§ n=337

when the person was first in treated in hospital or community treatment. Compulsory treatment was measured as a history of being compulsory in treatment.

Criminality was described in four variables and were based on the individuals self-report and confirmed by means of medical and social agency records, criminal agencies, police files and through contact with relatives. Court sentence was defined as found guilty and sentenced due to criminal activity. Number of probation’s was measured as the number of sentence where the punishment was probation. Months of imprisonment was measured as the total number of month received in court sentence. Periods of imprisonment was measured as the number of separated times the individual were sentenced to imprisonment.

2.5 Statistics

Statistical analyses were performed using the SAS program [34]. Two way analysis of variance were conducted for continuous variables and chi-square tests for categorical variables. The mean rating from the five counsellors’ on each patient was used in the calculations. Interrater reliability was calculated with the Spearman rank correlation.

3. Results

3.1 Treatment outcome

Table 1,2a and 2b shows background variables of importance for the prognosis according to the CGI-I rating of improvement. The CGI-I rating gave rise to three groups of improvement from methadone treatment, much or very much improved (N=130, 38%), moderately improved (N=132, 38%) and not improved or worse (N=83, 24%).

In earlier studies [21, 20, 17] the patients were grouped according to their status of attendance in MMT. In the present study the sample was grouped according to the CGI-I ratings. We then compared the two ways of group allocation. In the group much or very much improved 15 % (19 individuals) had been discharged due to rule violations or imprisonment and were regarded as non-compliers. In the group of moderately improved 21 % (28 individuals) had been discharged due to rule violations or imprisonment and were regarded as non-compliers. In the group of not improved or worse 59 % (49 individuals) had been discharged due to rule violations or imprisonment and were regarded as non-compliers (see figure 1). To put it in another way, the counsellor’s rated 14 % (34 individuals) of those not discharged due to rule...
Table 2a. Presence of background variables of potential importance for the prognosis (heredity, childhood and adolescence, work, earlier treatment, court sentence and drug abuse pattern) in the case histories of 243 males and CGI-I rating of improvement

<table>
<thead>
<tr>
<th>Variable</th>
<th>Much or very much improved</th>
<th>Moderately improved</th>
<th>Not improved or worse</th>
<th>Chi (df)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heredity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorder and/or drug abuse, father§</td>
<td>16 (18)</td>
<td>19 (25)</td>
<td>5 (27)</td>
<td>1.9 (2)</td>
</tr>
<tr>
<td>Psychiatric disorder and/or drug abuse, mother §§</td>
<td>11 (11)</td>
<td>16 (20)</td>
<td>14 (24)</td>
<td>4.6 (2)</td>
</tr>
<tr>
<td>Childhood and adolescence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnormal childhood experiences</td>
<td>52 (53)</td>
<td>58 (71)</td>
<td>47 (75)</td>
<td>9.8 (2)**</td>
</tr>
<tr>
<td>Foster-home</td>
<td>24 (24)</td>
<td>20 (24)</td>
<td>23 (37)</td>
<td>3.4 (2)</td>
</tr>
<tr>
<td>Broken home</td>
<td>41 (42)</td>
<td>44 (54)</td>
<td>34 (54)</td>
<td>3.3 (2)</td>
</tr>
<tr>
<td>School problems</td>
<td>53 (54)</td>
<td>53 (65)</td>
<td>50 (79)</td>
<td>10.7 (2)**</td>
</tr>
<tr>
<td>Completed compulsory school</td>
<td>80 (82)</td>
<td>63 (77)</td>
<td>38 (60)</td>
<td>9.5 (2)**</td>
</tr>
<tr>
<td>Adult age, treatment and criminality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Own residence</td>
<td>58 (59)</td>
<td>34 (41)</td>
<td>17 (27)</td>
<td>16.7 (2)**</td>
</tr>
<tr>
<td>Work experience</td>
<td>72 (73)</td>
<td>60 (73)</td>
<td>35 (56)</td>
<td>6.9 (2)*</td>
</tr>
<tr>
<td>Partner, active addict</td>
<td>19 (19)</td>
<td>23 (28)</td>
<td>14 (22)</td>
<td>1.9 (2)</td>
</tr>
<tr>
<td>Compulsory treatment</td>
<td>31 (32)</td>
<td>28 (34)</td>
<td>35 (56)</td>
<td>10.3 (2)**</td>
</tr>
<tr>
<td>Court sentences</td>
<td>70 (71)</td>
<td>69 (84)</td>
<td>59 (94)</td>
<td>13.1 (2)**</td>
</tr>
<tr>
<td>Drug abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid as first drug</td>
<td>28 (29)</td>
<td>15 (18)</td>
<td>14 (22)</td>
<td>2.7 (2)</td>
</tr>
<tr>
<td>Frequent ODs</td>
<td>12 (12)</td>
<td>26 (32)</td>
<td>34 (54)</td>
<td>32.3 (2)**</td>
</tr>
<tr>
<td>History of non-opioid abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No additional drug</td>
<td>67 (68)</td>
<td>32 (39)</td>
<td>28 (44)</td>
<td></td>
</tr>
<tr>
<td>One additional drug</td>
<td>22 (22)</td>
<td>33 (40)</td>
<td>14 (22)</td>
<td></td>
</tr>
<tr>
<td>More than one additional drug</td>
<td>9 (9)</td>
<td>17 (21)</td>
<td>21 (33)</td>
<td>26.2 (4)**</td>
</tr>
</tbody>
</table>

*p<0.05  **p<0.01
Figures in parenthesis are percent, § n=221, §§ n=236

violations or imprisonment to be not improved or worse. Thus, 86 percent (125 individuals) of the compliers have benefited from the treatment. More exactly 42% (104 individuals) of the compliers were moderately improved while 45% (111 individuals) were much or very much improved. The comparison between compliers and non-compliers with regard to the CGI-I improvement groups yielded a significant difference (chi-square= 20.2, df=2, p>0.001) with more non-compliers falling into the not improved or worse group and more compliers in the moderately and much and very much improved groups (see figure 1).

Of the 96 patients discharged due to rule violations or imprisonment 20% (19 individuals) were regarded as much or very much improved prior to the discharge and 29% (28 individuals) were regarded as moderately improved prior to the discharge. The remaining, 51% (49 individuals), were regarded prior to discharge as not improved or worse (see figure 1). According to a chi-square test this difference in proportion was significant (chi-square=54.4, df=2, p<0.001).

Heredity as a set of background data showed no significant difference between the three CGI-I improvement groups. Among background variables during childhood and adolescence only time spent in foster-home before methadone treatment showed no significant group difference between CGI-I rated groups. Abnormal childhood experiences were lowest in the much and very much improved groups and highest in the not improved or worst group. Broken homes were most common in the not improved or worst group and most rare in the much or very much improved group. The experiences of school problems were more usual in the least improved group and most rare in the most improved group. A higher proportion of those most improved had completed compulsory school and fewer in the least improved group.

![Figure 1. Comparison between Compliers (solid line and filled triangles) and Non-compliers (broken line and filled circles) with regard to improvement according to CGI-I ratings (p<0.001).](image-url)
had done so (See table 1, 2a and 2b).

During adult age fewer in the not improved or worse group had own residence and earlier work experience compared to the other two groups. The group much or very much improved had the highest proportions. The reverse was true for compulsory treatment and court sentences where the least improved group were in top and the most improved group at bottom. No significant difference was found with regard to if the partner was an active addict or not.

No differences in proportion between the three groups were found with regard to opioids as first drug. Frequent over-doses on the other hand were far more common among those not improved or worse than among those that were much or very much improved with those moderately improved in between. A history of non-opioid use was least common among those most improved and most common among those least improved with moderately somewhere in between.

In table 3 the continuous background data in this study is presented according to the CGI-I rating of outcome. The three groups did not differ according to years between drug and opioid debut, years of abuse before MMT, years of opioid abuse before MMT, months in treatment community before MMT nor age at entering MMT.

Six of the continuous background variables show significant difference between the outcome groups. Thus, those most improved have a higher age at drug debut, opioid debut and age at first treatment than the not improved or worse group, with the moderately improved group situated in between on the first two variables but have the lowest age at first treatment. Both short- and long-term treatment episodes are fewer for the most improved group and they have fewer number of probation’s than the least improved group, while the moderately improved group are situated in between.

When it comes to criminality only numbers of probations differ between the groups while neither periods of imprisonment nor months of imprisonment differ significantly between the groups.

The age at drug debut and opioid debut are not significantly different between men and women (see table 4), nor are the years of drug abuse or opioid abuse before methadone treatment. Despite the nearly same age at debut of drugs and opioids there is a slight, but significant, difference (8 months) in time between drug debut and opioid debut. Men move quicker from general drug use to the heavier opioid use than women do. Women have significant more short-term treatment episodes, long-term treatments episodes and months in treatment community than men. Men have a significantly higher number of probations, months in imprisonment and
Table 3. Mean±sd main effect of continuous background data for patients in methadone treatment, subdivided according to CGI-I ratings of improvement. Type III sum of squares are used.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total sample N=345</th>
<th>Much or very much improved N=130</th>
<th>Moderately improved N=132</th>
<th>Not improved or worse N=83</th>
<th>F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dug Abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at drug debut</td>
<td>15.7±4.5</td>
<td>16.8±4.5</td>
<td>15.2±3.1</td>
<td>14.8±3.1</td>
<td>8.76**</td>
</tr>
<tr>
<td>Age at opioid debut</td>
<td>19.1±4.5</td>
<td>20.1±4.5</td>
<td>19.0±3.3</td>
<td>17.8±3.3</td>
<td>8.90**</td>
</tr>
<tr>
<td>Yrs btw drug and opioid debut</td>
<td>3.4±3.4</td>
<td>3.3±3.4</td>
<td>3.8±3.3</td>
<td>3.0±2.9</td>
<td>0.47</td>
</tr>
<tr>
<td>Years of abuse</td>
<td>14.1±5.7</td>
<td>13.9±5.7</td>
<td>14.4±5.7</td>
<td>14.0±5.5</td>
<td>0.15</td>
</tr>
<tr>
<td>Years of opioid abuse</td>
<td>10.7±4.8</td>
<td>10.6±4.8</td>
<td>10.7±4.5</td>
<td>11.0±4.7</td>
<td>0.19</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term treatment episodes</td>
<td>7.7±6.5</td>
<td>6.0±6.5</td>
<td>8.0±8.2</td>
<td>10.1±10.3</td>
<td>7.14**</td>
</tr>
<tr>
<td>Long-term treatment episodes</td>
<td>4.4±2.8</td>
<td>3.8±2.8</td>
<td>4.3±3.9</td>
<td>5.3±4.7</td>
<td>3.96*</td>
</tr>
<tr>
<td>Months in treatment community</td>
<td>5.5±3.4</td>
<td>4.0±3.4</td>
<td>7.1±13.4</td>
<td>5.6±7.7</td>
<td>2.76</td>
</tr>
<tr>
<td>Age at MMT entering</td>
<td>29.8±5.9</td>
<td>30.6±5.9</td>
<td>29.7±5.1</td>
<td>28.9±5.5</td>
<td>2.87</td>
</tr>
<tr>
<td>Age at first treatment§</td>
<td>22.9±5.2</td>
<td>23.9±5.2</td>
<td>22.6±4.2</td>
<td>21.7±4.0</td>
<td>6.50**</td>
</tr>
<tr>
<td>Criminality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of probation's</td>
<td>2.5±2.6</td>
<td>2.1±2.6</td>
<td>2.7±2.6</td>
<td>3.0±2.5</td>
<td>3.13*</td>
</tr>
<tr>
<td>Months of imprisonment</td>
<td>16.9±7.3</td>
<td>15.2±7.3</td>
<td>14.5±7.3</td>
<td>23.5±29.8</td>
<td>0.98</td>
</tr>
<tr>
<td>Periods of imprisonment</td>
<td>1.9±3.2</td>
<td>1.6±3.2</td>
<td>1.6±2.9</td>
<td>3.0±4.1</td>
<td>1.68</td>
</tr>
</tbody>
</table>

*p<0.05  **p<0.01  § for this variable there are 242 men and 101 women  §§ data and statistics for men and women on these variables are adapted from Gunne et al, 2005

Table 4. Mean±sd main effect of continuous background data for patients in methadone treatment, subdivided according to gender and the interaction between CGI-I ratings of improvement. Type III sum of squares are used.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Men  N=243</th>
<th>Women N=102</th>
<th>Gender F</th>
<th>Interaction CGI-Gender F</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dug Abuse</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at drug debut§§</td>
<td>15.8±4.0</td>
<td>15.2±3.6</td>
<td>2.39</td>
<td>1.15</td>
</tr>
<tr>
<td>Age at opioid debut§§</td>
<td>19.1±3.8</td>
<td>19.1±4.1</td>
<td>0.02</td>
<td>2.35</td>
</tr>
<tr>
<td>Yrs btw drug and opioid debut</td>
<td>3.2±3.1</td>
<td>3.9±3.4</td>
<td>3.88*</td>
<td>0.55</td>
</tr>
<tr>
<td>Years of abuse</td>
<td>14.0±5.8</td>
<td>14.4±5.3</td>
<td>0.34</td>
<td>0.09</td>
</tr>
<tr>
<td>Years of opioid abuse</td>
<td>10.8±4.8</td>
<td>10.5±4.3</td>
<td>0.42</td>
<td>0.02</td>
</tr>
<tr>
<td>Treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-term treatment episodes§§</td>
<td>6.5±7.1</td>
<td>10.8±10.1</td>
<td>19.18**</td>
<td>1.43</td>
</tr>
<tr>
<td>Long-term treatment episodes§§</td>
<td>4.0±3.4</td>
<td>5.3±4.4</td>
<td>8.64**</td>
<td>0.94</td>
</tr>
<tr>
<td>Months in treatment community§§</td>
<td>4.5±8.7</td>
<td>8.1±14.4</td>
<td>5.62*</td>
<td>0.90</td>
</tr>
<tr>
<td>Age at MMT entering§§</td>
<td>30.0±5.6</td>
<td>29.5±5.4</td>
<td>0.19</td>
<td>0.87</td>
</tr>
<tr>
<td>Age at first treatment§</td>
<td>23.2±4.6</td>
<td>22.6±4.6</td>
<td>2.18</td>
<td>1.17</td>
</tr>
<tr>
<td>Criminality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of probation's</td>
<td>2.7±2.8</td>
<td>2.2±2.1</td>
<td>5.47*</td>
<td>2.16</td>
</tr>
<tr>
<td>Months of imprisonment§§</td>
<td>21.1±31.2</td>
<td>6.9±14.4</td>
<td>17.75**</td>
<td>1.81</td>
</tr>
<tr>
<td>Periods of imprisonment</td>
<td>2.5±3.8</td>
<td>0.7±1.3</td>
<td>21.17**</td>
<td>1.40</td>
</tr>
</tbody>
</table>

*p<0.05  **p<0.01  § for this variable there are 242 men and 101 women  §§ data and statistics for men and women on these variables are adapted from Gunne et al, 2005
periods of imprisonment than women.

Age at first treatment and age at entering MMT are not significant different between men and women. There are no significant interactions between CGI-I and Gender (see table 4).

4. Discussion

Our result that non-compliance to treatment is associated with poor outcome is congruent with earlier research [35]. In the present study 28% (96 patients) were discharged due to non-compliance to the program instructions for reason such as criminal activity/imprisonment or other rule violations (cheating with urine tests or drug use, usually poly drug use). Before discharge 51% of them were regarded as not improved or worse. In the group with adherence to the treatment regime only 14% were rated according to CGI-I criteria by the counsellor’s to be not improved or worse. Thus, 86 percent of the compliers have benefited from the treatment and were rated as medium to very much improved. The difference in improvement between compliers and non-compliers were highly significant. If the results are looked at from another angle significantly higher proportions of the CGI-I group not improved or worse were discharged at follow-up compared with the improved groups. Earlier studies [for instance 17, 37] have shown that the death rates are very high among those involuntarily discharged and drop-outs of methadone treatment. Our result that compliers had better improvement than non-compliers is consistent with the work by Maremmani and colleagues [30] who showed that there are statistically time effects in methadone treatment. Between three and twelve months of treatment they found that there are statistically time effects in methadone treatment. Before discharge 51% of them were regarded as not improved or worse. In the group with adherence to the treatment regime only 14% were rated according to CGI-I criteria by the counsellor’s to be not improved or worse. Thus, 86 percent of the compliers have benefited from the treatment and were rated as medium to very much improved. The difference in improvement between compliers and non-compliers were highly significant. If the results are looked at from another angle significantly higher proportions of the CGI-I group not improved or worse were discharged at follow-up compared with the improved groups. Earlier studies [for instance 17, 37] have shown that the death rates are very high among those involuntarily discharged and drop-outs of methadone treatment. Our result that compliers had better improvement than non-compliers is consistent with the work by Maremmani and colleagues [30] who showed that there are statistically time effects in methadone treatment. Between three and twelve months of treatment they found that there are a decrease in opioids use and an improvement in clinical status.

The group not improved or worse has significantly more background problems in childhood and adolescence than the group much or very much improved. Those moderately improved are usually situated somewhere between the others. For both men and women school problems and an uncompleted compulsory school history were associated with a low grade of improvement. For men abnormal childhood experience was also more common among those with lower grades of improvement. Although, broken-home was not significantly related to improvement neither among men nor women, there was a significant association in the combined group. In this sample there were no significant association between improvement and foster-home. When Lehmann and co-workers [28] defined positive outcome in MMT as one year retention in the program and urine samples negative for opiates they found that foster care before the age of 15 were the only variable of a large number that were associated with success. The differences between there sample and ours may have its origin in the difference between our Swedish social service and their Canadian counterpart. Although, Lehmann and co-workers did not define less benzodiazepine use as a measure of success they found that working/studying, low criminal activity and being man were associated with low use of benzodiazepine.

In the present study work experience and to have had own residence was important for men’s improvement, but not for women. For neither men nor women there was no association between improvements and if the partner was an active drug addict.

For both men and women to have a history of compulsory treatment was associated with low levels of improvement. To be young at first non-MMT treatment was associated with low level of improvement, while age at entering MMT was not significantly related to grade of improvement. There was no significant difference between men and women in age neither at first non-MMT treatment nor age at entering MMT.

To have a criminal record before MMT was associated with low level of improvement. To have a court sentence was negative for both men and women. Those less improved also had a higher number of probations, but not significantly higher numbers of months in prison or periods in prison. To have many short- or long-term treatments and need of treatment at an early age was associated with poor improvement, but number of months in a drug-free treatment community did not appear to be associated with improvement.

The drug-related variables had an impact on both men and women. Frequent overdoses (OD:s) and a history of non-opioid abuse were related to poor improvement. Low age at drug debut and debut of opiates appears to indicate a severe form of addiction that is hard to treat. For women an early initiation of drugs are also associated with selling sex at an earlier age [32]. Compared to the moderately improved the not improved or worse are one year ahead initiating drug and opiate use and need of treatment compared with the much and very much improved group. However, there was no association between initiating drug abuse with opioids or other drugs. Years of general abuse or opioid abuse did not appear to be associated with rate of improvement and neither did the time between drug and opioid debut. However, women’s time between the initiation of drug use and the switch to opioid use were roughly 20 percent longer than the men’s time.

There were no significant interactions on the continuous variables between improvement measured according to CGI-I and gender which can be interpreted to indicate that the association, if any, is in the same direction for men and women. However, there were an interesting difference between men and women regarding treatment and criminality. Women had a higher number of short- and long-term treatment episodes and months in treatment community while men had a significantly higher number of probations, months of imprisonment and periods of imprisonment. Thus women are to a higher extent treated and men are punished.

Poirier, et al [33] found the response to be better to buprenorphine in opiate addicts with no family history of
addiction or mood disorder while we found no difference in improvement with regard to the combined index of psychiatric disorder and/or drug abuse neither on the father’s side or the mothers. The difference in results between the studies can be due to the sample, the way family history was measured and the substitute (buprenorphine versus methadone). According to a review by Maremmani, Pacini and Pani [29] buprenorphine may have good effects in addicts with low severity and low psychiatric problems. Davstad and co-workers [6] found that those with a psychiatric diagnosis had an higher retention rate in MMT than those without such a diagnosis.

5. Clinical implications

The finding in the present study that non-improvement or worsening of addictive behaviour is associated with non-compliance and higher discharge rates provide a strong urge to find background variables that can be used to identify these individuals in advance so that they can receive special considerations. Consistent findings of risk factors in the whole group and in men and women are (1) the pattern of drug use with frequent heroin overdose (ODs), additional drug abuse beside opioid use, an early drug and opioid debut, (2) a treatment pattern with low age at first treatment, many non-MMT treatments and being convicted and (3) school problems. Thus, drug use pattern and treatment history together with school history can be used to identify risk groups that need extra consideration and treatment efforts. The results of the present study suggest that extra effort should be put in to enhance adherence to the treatment regime and thereby increase improvement, avoid involuntary discharge and prevent death.

References


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We thank Professor emeritus Lars Gunne for valuable comments on an earlier draft of this paper and for valuable discussions.  

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Contributors  
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Conflict of Interest  
None of the authors have any relevant conflict of interest to report in relation to the present study.  

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Additional take-home dosages

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Summary

Objectives: The objective of the study was to analyse the practice of giving take-home dosages of opioid medications to patients with reference to the reasons for and the quantity of the medications given as additional or extra take-home dosages. Methods: All the patients were checked regarding the kind of medication, urine samples, reasons for extra take-home dosages and their quantity. Results: Of the 150 patients selected for the group in the programme, 27 needed one or more extra take-home dosages in 2007. 10 (11*) of those patients had negative urine samples for all illicit drugs and never used alcohol at any stage of the year of the study. 7 patients used marijuana, benzodiazepines or alcohol only once or just occasionally in that year. 10 patients used other illicit drugs or used alcohol and benzodiazepines more often. Among the reasons for extra take-home dosages, hard physical work was listed 7 times, vomiting because of the bad taste of the medication 3 times, difficulties in initiating medical therapy after entering the programme 3 times, vomiting as a part of illness twice and lowering the dosage too quickly twice. Other reasons were listed once each. Altogether, the percentage of the overall quantity of medications received by patients during the year as extra take-home dosages was: 0.47% for methadone, 0.75% for buprenorphine and 0.10% for SR morphine. Conclusions: Reviewing the fairly good results of treatment at the centre, therapeutic decisions to give additional take-home dosages to the patients have proved to be reasonable and usually correct. Throughout this study a continual therapeutic wish to achieve a better understanding of opioid addiction as just one among other chronic diseases has been made evident.

Key Words: Opioid treatment; Extra take-home dosages.

1. Introduction

Take-home dosages of opioid medications are a matter of delicate balance in the therapist-client relationship. There are various important reasons for the therapist to worry about the destiny of the medication that has been handed over to the patient. Some medications (methadone, SR morphine) can ‘kill’ the person who has not adapted to the medication or the dosage.

Treatment education for patients, medical training for prescribers and the right choice of pharmaceutical forms appear to be means that need to be developed simultaneously to optimize treatment [1].

Opioid medications are also present on the Slovenian black market. In 2005, 6 of 45 drug-related death cases involved methadone, usually combined with other drugs and alcohol [8].

The decision whether to hand the medication over to an opioid-dependent patient is a difficult one, as it involves a risk of misuse. In 2004 there were 2,944 arrests/reports for drug offences (use and/or possession) in Slovenia; 42 of these involved methadone. There was a total of 545 cases of drug-related dealing/trafficking and 20 of those referred to methadone; the numbers recorded for drug-related use and trafficking was 94 in all and 2 of those referred to methadone [9].

In 2005, out of a total of 45 cases of victims of a drug-related death in Slovenia, methadone was involved in 6; in a majority of these cases, methadone overdose was diagnosed as accidental, not as suicide [8]. According to the Slovenian Therapeutic Agreement, in centres for the prevention and treatment of drug addiction (CPTDA) only “trustworthy” patients can get the medication into their own hands. Take-
home dosages are generally a bonus that patients can get by showing good and stable behaviour [10]. In the international inquiry into the quality of work in Slovenian CPTDAs in the year 2007, it was stressed that “leakage is difficult to control, and it is hard to prevent someone from selling his/her medication” [10]. Patients can get their first take-home dosages after 3 to 6 months of negativization of urine samples for illicit drugs – with the debatable exception of marijuana. After 6 to 12 months of negative samples, they can get take-home dosages for the whole week or, in case of holidays, for 10 days. However, the “actual rules” for giving take-home dosages differ from one centre to another, as the inquiry showed [10]. The numbers and the motivation of staff play a role in these decisions [10].

In Slovenia the percentage of the medications used in CPTDAs in 2007 was 81% for methadone, 13% for buprenorphine and 6% for SR morphine [4]. Compared with medications for other chronic diseases, opioid-dependent patients sometimes need additional (extra) dosages of medications even when they are clinically perceived as being stable. According to the National Therapeutic Agreement, they have no right to get extra dosages. This decision was made by the Coordination Committee of CPTDA therapists to prevent misuse of the medication. On the other hand, clinical work showed the need for a better understanding of patients’ problems, and, therefore, the appropriateness of giving extra take-home dosages for a variety of therapeutically sound reasons.

In France, because of positive outcomes maintenance treatments were not officially questioned [2]. A national evaluation of maintenance treatment in France showed that the decrease of 80% in fatal overdoses and of 67% in arrests for heroin use (1994–1999) were directly related to treatment accessibility [2]. Once the authorities decided to implement control measures over patients, the innovations approved might make access to treatment more difficult. The effectiveness of substitution treatment could be affected as a result [2].

One general objective of this study was to provide an important practical tool for improving the quality of the work carried out by the CPTDA in Logatec. The therapists give extra take-home dosages to implement a motivational approach as a powerful resource in enhancing staff-client interactions, quality of services and programme functioning as a whole [7].

The specific aims of this study were:

a) to check the topic of so-called «therapeutic reasons» for giving extra take-home dosages;
b) to check the therapeutic status of patients at the moment when they receive extra take-home dosage;
c) to find out the amount of extra take-home dosages for each medication with reference to the quantity taken over one whole year and the percentage of total medication distributed in this way.

2. Methods

At the centre the data were collected from the protocols on giving medications to patients. The research involved included the collection of the following data:

a) dosages given to patients at the centre to be used under close observation by the nurse
b) dosages given to patients as their take-home dosages
c) dosages given to patients as their extra take-home dosages

The number and proportion of all dosages for each of these three types of medication were calculated from the written dispensary protocols (i.e. the nurse’s book and the computer programme setting out the regime for giving medications).

The reasons for extra take-home dosages were taken from the therapist’s protocol for each patient. For all extra take-home dosages there were two descriptions, of the psychosocial and somatic status of the patient and the «reasons» for prescribing extra take-home dosages. The first was selected by the therapist herself in writing the protocol, and the second was chosen by the patient at home and added to that protocol, together with the patient’s application for extra take-home dosage or dosages.

As one of the measures for discovering the therapeutic stability of the patients, their urine samples were used. The results were taken from the documentation on each patient. In descriptions of the frequency of drug use, the word «occasionally» meant the use of a substance more than once but less than four times during the year.

2.2 Description of the patients

On the question of extra take-home dosages, the population of all 150 opioid-substituted patients attending the centre (29 females and 121 males) in 2007 was checked. 101 patients (19 females and 82 males) were receiving methadone; 32 (7 females and 25 males) were being treated with buprenorphine, and 17 patients (3 females and 14 males) with SR morphine.

At the centre, mean daily dosages were 101.9 mg for methadone, 14.2 mg for buprenorphine and 672.3 mg for SR morphine.

Mean age of patients who got extra take-home dosages was 28.6 years (min. 20 years, max. 39 years) for methadone (3 F and 18 M); the ages of the buprenorphine patients (all men) who got extra take-home dosages were 25, 27 and 31. The one patient (a man) who was given extra take-home dosages of SR morphine was 25.

Mean duration of the opioid treatment of the patients with extra take-home dosages was 5.43 years (min. duration was 1 year and max. was 11 years).

Most of the patients that needed extra take-home dosages were working (17/25): 12 of them had a regular job with a working contract, 3 were working regularly but without a contract, 2 were working without a contract and at the same time going to school, and 4 patients were working occasion-
ally to earn some money. Only 4 patients out of 25 (16%) had no organized work or school.

At the time when they needed extra take-home dosages the patients were coming to the centre at varying frequencies, depending on the therapeutic agreement, the duration of treatment and their therapeutic stability: 2 came once every 2 weeks, 14 once a week, 2 twice a week and 2 three times per week. Two thirds (2/3) of them were travelling to the centre, 20 to 40 km one way. Others were living nearer.

3. Results

In 2007 at least one or sometimes more extra take-home dosages of the medication were given to 27 patients out of 150 (15.3%). Extra methadone was given to 20.7% of the methadone patients, to 12% of buprenorphine patients and to 5.08% of SR morphine-substituted patients.

Regarding urine samples in the year of the research, 10 of the patients (10/27) who got extra take-home dosages (10/27) were negative for all illicit drugs and with complete abstinence from alcohol throughout the year. For 1 patient who needed extra take-home SR morphine, abstinence was very likely but impossible to confirm – because of the cross-reactivity of the tests. 4 patients had once or only occasionally positive THC in urine, 1 had THC and BZO in urine occasionally. 1 had THC occasionally in the urine samples and was drinking alcohol occasionally. Altogether, 17 patients used no other illicit substances or used marijuana, benzodiazepines or alcohol once or only occasionally (table 1).

The most frequent reason for extra take-home dosages was a heavier physical or sometimes psychological burden at the workplace. The following reasons were cited regarding a) physical status of the patient, b) characteristics of the medication and c) the patient’s social environment. (Table 2).

The total quantity of all medications given to the patients attending the centre in 2007 as extra take-home dosages was calculated. The percentages of the medications given to all patients as extra take-home dosages were as follows: 0.49% of the total quantity of methadone taken; 0.75% of the total quantity of buprenorphine; 0.1% of the total quantity of SR morphine. (Table 3)

4. Discussion

Most patients responded well to methadone maintenance, whereas about one in four tends not to respond well to treatment [6].

From the very start of the programme in the CPTDA in Logatec, in 1995, the therapists at the centre have been trying to get the most complete picture possible of the centre’s therapeutic situation. In 2005, when the centre celebrated its 10th anniversary together with its history of using methadone as the only medication for opioid addiction, an overview of the treatment in the centre was published in the Journal of Slovenian Medical Association: “Before starting methadone treatment the detoxification without medical help was accomplished by 37% of the patients, 15% were hospitalized in psychiatric clinics for the purpose of detoxification, 6% were treated in the therapeutic communities, 3.9% in the therapeutic community Project “Človek” (man). 11% of the
patients spent a part of their youth in juvenile correctional facilities. 13% experienced imprisonment. At the time of their therapy in the centre 79% were working or/and attending school. 30.8% of them had children and they had a partner included in methadone treatment in 23%" [8].

In 2005 a study on one-year abstinence was published: “In the group of 61 patients treated in CPTDA with methadone for at least one year, in the last year of treatment in the centre 67.2% didn’t use heroin, 34.4% didn’t smoke marijuana, 72.1% didn’t use cocaine, 85.2% didn’t use ecstasy and 65.6% didn’t use any medications of benzodiazepines type. Alcohol was not used at all in the last year by 21.3% of patients. Only 3% of them didn’t smoke tobacco. Chronic infection with hepatitis C viruses was present in 16.4% of patients. None was infected by HIV”[4].

These results give a fairly good overview of the patient population of the centre and the level of treatment success. Intractable problems in substitution therapy include the distance to be travelled in reaching the centres (18 centres cover an area of 20,256 km2) and their working hours. The CPTDA in Logatec must meet the needs of a region of 13,000 people. Its premises are shared with the primary health centre, and it has the same opening hours as other medical departments, while operating under the same regime; that means

Table 2. Reasons for extra take-home

<table>
<thead>
<tr>
<th></th>
<th>N patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patient related</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Working hard (employment-related)</td>
<td>7</td>
<td>25.9</td>
</tr>
<tr>
<td>Entering program</td>
<td>3</td>
<td>11.1</td>
</tr>
<tr>
<td>Lowering dosage too quickly</td>
<td>2</td>
<td>7.4</td>
</tr>
<tr>
<td>Physical comorbidities</td>
<td>2</td>
<td>7.4</td>
</tr>
<tr>
<td><strong>Medication related</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bad tests</td>
<td>3</td>
<td>11.1</td>
</tr>
<tr>
<td>Spoiled solution</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>Theft of the medication</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td><strong>Social environment related</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aggression by father</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>Conflict with partner</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>Small baby</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>Divorce</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>Sick mother</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>Birthday</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>Laps with cocaine</td>
<td>1</td>
<td>3.7</td>
</tr>
<tr>
<td>Laps with cocaine ?</td>
<td>1</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Table 3. Quantity and percentage of medication for extra take-home

<table>
<thead>
<tr>
<th>Medication</th>
<th>All in 2007 (mg)</th>
<th>Extra dosage (mg)</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>3.085.050</td>
<td>14.418</td>
<td>0.47</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>84.938</td>
<td>640</td>
<td>0.75</td>
</tr>
<tr>
<td>SR morphine</td>
<td>2.528.530</td>
<td>2720</td>
<td>0.10</td>
</tr>
</tbody>
</table>
it is open every weekday for half the day: Mon Wed Fri 6.30 a.m.-1.30 p.m. and Tue Thu 1 p.m.-8 p.m. The centre can count on contributions from 5 family doctors, 1 paediatrician, 1 school doctor, 5 stomatologists, 1 part-time gynecologist and 1 part-time specialist for occupational medicine. The centre sometimes uses the help of its GPs for exceptional distribution of take-home dosages to patients outside the working hours of the centre (during other weekday hours, plus Saturdays, Sundays and holidays). For patients who are obliged to take their medication daily – including Saturdays and Sundays – and for stabilized patients in situations that prevent their coming to the centre during opening hours, their dosages are left in the refrigerator of the emergency department by the nurse at the centre. She arranges this in agreement with the doctor at the centre, the patient and the staff of the emergency department.

All medications that are given under control at the centre are prepared and delivered by the nurse or by the doctor at the centre. Take-home dosages of buprenorphine and SR morphine are prepared by the nurse for each patient separately at the time of the patient’s visit to the centre. Take-home dosages of methadone are prepared by the pharmacy on the basis of a doctor’s prescription for all take-home dosages at the centre on Thursday afternoons, applying the Soundex code for each patient. This allows the patient to get his/her own exact take-home dosages for some days or for the whole week ahead. The nurse brings all the take-home dosages of methadone solution mixed with orange juice in 100ml plastic bottles from the pharmacy to the refrigerator at the centre. She gives them to each patient in the centre according to his/her take-home regime as ordered by the doctor.

In the year of the study, a majority of patients who got extra take-home dosages needed only one or few extra dosages. There was an exception: a 26-year-old girl in the year of the study started to encounter difficult family problems caused by her extremely aggressive father. She lived near her primary home with her old and sick grandparents and with her mother, who was seeking this girl patient’s help. Before these family troubles reached a climax, this girl was abstinent from all illicit drugs and had drunk no alcohol for three years in our programme. She was working morning, afternoon and night shifts and was living more than 20 km from the centre. Her grandparents and her parents visited the centre at the very beginning of the treatment, but stopped doing so afterwards. During that whole period, she refused to tell them about her taking methadone. She was receiving take-home dosages of methadone to last one week at a time. Apart from the distress experienced at home, she also split with her boyfriend. In those days she started to use cocaine for the first time in her life. Because she was taking extra dosages of methadone and due to her stressful personal situation, her tolerance grew. The therapists slowly raised the daily dosage to 230 mg. She became stable again and stopped using cocaine. She has managed to keep her job, which is very demanding. Her employer is satisfied with her work. This year she was promoted to a more demanding position. Unfortunately, she got infected by hepatitis C at the time when she was using cocaine. A month ago she started treatment with interferon and ribavirin.

The National Therapeutic Agreement in Slovenia is very demanding. To ensure successful therapy, some therapists decide to provide take-away dosages even before some patients have actually qualified to receive their bonus. Such a decision is always a question of “sailing between Scylla and Charybdis”, besides raising the eternal questions of right and wrong.

Doctors have to help people live, and primum nil nocere has to be the rule. But there is always the question of how each doctor applies these solutions in treating individual patients. Less frequent visits to the centre may create an opportunity to work better with those who come. In some ways it also prevents patients from grouping around the centre. Unduly strict regulations can be harmful in another way. We can learn this from the German experience, where the official reaction to the troubles emerging in an organization providing ongoing opioid treatment was to tighten the regulations; most of the primary care physicians responded by giving up their work. “When therapy was predominantly offered by special maintenance centres, strong concentration of these specific patients took place.”[11]

Having discussed the results of urine testing compared with the patient’s real abstinence, we are aware of well-known difficulties. The frequency of urine testing in the centre varies from 2 or 3 times per week for some patients to once in 3 or even 6 months for the few of them who are stable and abstinent in the opinion of the therapist. Besides testing devices for drugs in urine, saliva test devices are sometimes used. For the assessment of drinking habits, a saliva test and quite often the AUDIT and CAGE questionnaires are used. Each year the therapists at the centre carry out some research. Patients are asked to fill in a patient satisfaction questionnaire yearly. The philosophy of the centre aims for an attitude of “listening, understanding and acceptance” towards patients or, as the expression goes, of “dancing with clients”.[1] This attitude of therapists provides an explanation for giving extra take-home dosages, as most patients mostly do not misuse the therapist’s trust. Each difficult situation is used as a convenient moment to discuss with a patient his/her decisions in life, his/her feelings and troubles, worries or anger. After such discussions the patients usually feel better.

At the beginning of the study, the therapists were afraid of taking on the task of calculating what had previously been an unknown (potentially large?) quantity of extra take-home medications that had been supplied to their patients. But the top priority of the therapists in carrying out this inquiry was an honest check on the work they were doing. At the end of the study therapists have reached a strong conviction that this has been a positive experience in improving the medical and
social status of their patients, partly through the distribution of additional take-home dosages; this outcome makes it is worth discussing the risks involved in not always obeying the rules set by the National Therapeutic Agreement. Not giving extra take-home dosages would mean putting the patient in the position of lacking a required medication. He or she would have to search for the medication on the black market or have to buy a certain amount of heroin. A relapse would be the inevitable result.

The explanations for such therapeutic decisions are easy to understand in diabetes patients, when dietary mistakes have been made or when these patients have an acute illness, or in allergic asthma patients who need more inhaled corticosteroids when an attack of asthma has been exacerbated by visiting an old friend who owns a cat or a rabbit.

5. Conclusion

In reviewing the fairly good results for abstinence and employment in all the years during which the CPTDA in Logatec has provided treatment, and its continual objective of achieving a better understanding of opioid addiction as just one of many chronic diseases, the therapists at the centre view their decisions to give extra take-home dosages to their patients as having been mostly correct.

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From methadone to buprenorphine or back to methadone. The Croatian experience

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Centre for Addiction Treatment, Porec, Croatia

Summary

In Croatia maintenance treatment is made widely available through a network of GP offices that covers the whole of the country. More than 50% of all GPs in Croatia have at least one patient in MT. Methadone was the only opioid agonist used for over a decade, but this changed when buprenorphine was introduced 4 years ago.

There is little difference in the regimen for the prescription and provision of the two medications: both are free of charge and are prescribed by GPs; in addition, there are no restrictions on the dose to be used or on 'take home' policy. The decision on which medication will be used is based exclusively on the clinical assessment and patient-doctor agreement.

The example of Croatia gives an opportunity to compare the acceptance of this medication by patients and doctors in situations of equal availability.

Key Words: Methadone-Buprenorphine Transfer, GPs

1. Introduction

Methadone and buprenorphine are the most widely used opiate agonists in the treatment of heroin addiction worldwide. Numerous studies indicate that the clinical characteristics and effects of both medications are similar and comparable [1, 3-5], but for different reasons the model for their provision is substantially different in many countries. Thus, the real 'public health value' of both medications remains strongly biased.

In Croatia maintenance treatment has been made widely available through a network of GP offices covering the whole of the country. More than 50% of all GPs in Croatia have at least one patient in MT. The model used for patient care is shared between Centres for Outpatient Treatment and General Practitioners.

The role of the Centres comprises: clinical assessment, the recommendation of Meth. or Bup. treatment, periodic evaluation, urine testing and psychosocial counselling.

The role of General Practitioners (GPs) in an Opioid Treatment Programme (OTP) is to prescribe methadone-buprenorphine, provide methadone dispensing, supervise consumption, and prepare ‘take home’ doses.

Methadone was the only opioid agonist used for over a decade, but this changed when buprenorphine was introduced 4 years ago.

There is little difference in the regimens for the prescription and the provision of the two medications.

The prescription and dispensation regimen for methadone is characterized by: a recommendation issued by a Centre, prescription by a GP, supervised consumption in a GP's of-
Heroin Addiction and Related Clinical Problems 12 (2): 25-28

Table 1. Baseline sample characteristics (N=71)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>M (min-max)</th>
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<tbody>
<tr>
<td>Age (yrs)</td>
<td>24 (17-34)</td>
</tr>
<tr>
<td>Heroin Use (yrs)</td>
<td>4.7</td>
</tr>
<tr>
<td>Gender (males)</td>
<td>62 (87.3)</td>
</tr>
<tr>
<td>i.v. use</td>
<td>35 (49.3)</td>
</tr>
<tr>
<td>HIV positive</td>
<td>0 (0.0)</td>
</tr>
</tbody>
</table>

It is important to stress that both methadone and buprenorphine are free of charge for virtually all patients. Since its introduction in 2004 the use of buprenorphine has been rising steadily, while the use of methadone has remained stable (Figure 1).

The aim of this survey is to compare acceptance of these two medications in the 'real life environment' imposed by the model that requires this kind of availability.

Specific aims include evaluation of the: drug of choice, retention in treatment, and definition of which drug 'works better' on the basis of the number of switches.

In the city of Porec (30,000 inhabitants) there is a Centre for Outpatient Treatment that supports the network of 13 GPs who have heroin addicts in maintenance treatment. Porec is an example of the good level of cooperation established between Centre and GPs that can be quoted as an example of how the Croatian model for treating of heroin addicts works.

2. Patients and methods

Heroin addicts who asked for and met the clinical criteria for Opioid Agonist (OA) treatment in the Centre for Addiction Treatment in Porec from 2005 to 2007. The only exclusion criterion was that of having been in Opioid Maintenance treatment recently (less than 3 months), prior to induction. The total number of patients was 71. Baseline characteristics are reported in table 1. The medicines used were methadone, in 5 mg. tablets, and buprenorphine, in 2 mg. s.l. tablets, which in that period were the only forms of these medications available in Croatia.

Patients got information on both drugs (intrinsic activity, side-effects, overdose potential, dispensing regimen, and its implications on working schedules and travel costs. Unless there were compelling reasons to the contrary, the patient's preference for one or other drug was respected. Most of the patients had had previous experiences with one or both medications, mostly illegally (table 2). From the start all the patients were informed that the drug could be switched at any time in response to a revaluation of needs and results.

Table 2. Patient's previous experience with methadone-buprenorphine (N=71)

<table>
<thead>
<tr>
<th>Medication</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone or buprenorphine</td>
<td>74.4</td>
</tr>
<tr>
<td>Methadone</td>
<td>64.4</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>53.2</td>
</tr>
<tr>
<td>Both</td>
<td>43.2</td>
</tr>
</tbody>
</table>

3. Results

After an interview, the initial assessment and the doctor-patient agreement, the two medications were chosen in almost equal numbers of cases. Dose at the end of induction was 43.2 mg for methadone and 4.5 mg. for buprenorphine (table 3).

About 20% of the patients in both groups changed their medicine of first choice, with no significant difference between groups. There was a significant difference in the moment of the switch. This happened at 3.2 weeks after induction with buprenorphine and 15.3 months with methadone (table 4).

There were no significant differences in retention in treatment in the two groups (table 5).
Table 3. Drug of choice and doses

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
<th>Final dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>34</td>
<td>47.8</td>
<td>43.2</td>
</tr>
<tr>
<td>Buprenorhine</td>
<td>37</td>
<td>52.2</td>
<td>4.5</td>
</tr>
</tbody>
</table>

Table 4. Nr of switched to and the time after induction

<table>
<thead>
<tr>
<th>Switched to</th>
<th>Nr</th>
<th>%</th>
<th>Time after induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methadone</td>
<td>Bup</td>
<td>7</td>
<td>20.6</td>
</tr>
<tr>
<td>Buprenorhine</td>
<td>Meth</td>
<td>8</td>
<td>22.0</td>
</tr>
</tbody>
</table>

Table 5. Retention in treatment

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>%</th>
<th>Dropouts</th>
<th>Retention %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>71</td>
<td>100</td>
<td>15</td>
<td>78.9</td>
</tr>
<tr>
<td>Buprenorhine</td>
<td>37</td>
<td>52.1</td>
<td>7</td>
<td>81.1</td>
</tr>
<tr>
<td>Methadone</td>
<td>34</td>
<td>47.8</td>
<td>8</td>
<td>76.5</td>
</tr>
</tbody>
</table>

4. Discussion

This small-scale survey from one of the centres in Croatia demonstrates what really happens with the patients and their treatment in the course of time.

The main outcome feature – retention in treatment – was virtually identical in the two groups, but, as must be stressed, was generally very high. The final doses chosen were low when compared with the recommended ones, but it was adjusted according to assessment and patients preferences. What is typical is the phenomenon of patients who request and sometimes insist on receiving lower doses, driven by the idea of ‘gradual detoxification’.

There were low, virtually identical percentages of switches in the two groups. This was probably due to good assessments and respect for the patients preferences.

Lastly, it is important to stress that in the model where the two opiate agonists have similar prescription and dispensation procedures (with slightly more comfort on the buprenorphine side) and where the patients’ preferences are respected, the level of acceptance and the main indicators for the two medications were virtually identical. This is consistent with the interesting and controversial Swedish 3 G study, where the authors conclude that “close to half of patients do well on bup/nlx” [2]; in this case, however, there was no “stepped care strategy”:

5. Conclusions

Opioid agonist treatment in Croatia is provided exclusively in Primary Health Care settings. Methadone and buprenorphine are provided under similar conditions that enable comparison of their effectiveness and acceptance in ‘a real situation’.

In Porec, with 30,000 inhabitants, 13 GPs provide maintenance treatment for their heroin-addicted patients in collaboration with the local Centre for Addiction Treatment. The results of follow-ups with patients new to treatment demonstrate that methadone and buprenorphine receive a virtually identical degree of acceptance by patients and providers. It confirms the importance of both medications for the maintenance treatment of heroin addicts.

Monitoring and respecting patients’ preferences seem to be crucial in obtaining good outcomes, especially in terms of retention in treatment.

References

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Conflict of Interest

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Methadone treatment for pregnant heroin addicted women

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Summary

A review of methadone-related issues and the approach to heroin addicted patients is presented with the aim to clarify what is practiced by the establishment of anti-craving treatment and what is expected within a history of addiction. A series of clinical situations occurring throughout pregnancy to early child development are described, and the etiological hypothesis discussed. Moreover, some methodological considerations are described in order to better understand some ambiguity about the effectiveness and harmlessness of methadone treatment, particularly with regard to neonatal opiate withdrawal. Limitations to the outcome of pregnancies in heroin addicted women seems to be due to misconceptions about methadone toxicity and neonatal damage, which may lead to the mishandling of methadone as a therapeutic modality, especially with regard to maintenance at effective dosages.

Key Words: Pregnancy; Heroin Addiction; Methadone Treatment; Neonatal Withdrawal Syndrome

1. Methodological and conceptual issues

In some cases, treatment of pregnant addicted women is flawed by major omissions and misconceptions. For example, methadone treatment is often regarded as substitution, pointing at its withdrawal-preventing usefulness, which has little to do with its actual employment in an anti-craving and behaviour-modifying view. The main goal of treating women with methadone should be that of minimizing illicit opiate use throughout pregnancy, and to permit them to normalize their health and psychosocial issues. Effective dosages are associated with better outcome. Opiate abusing pregnant women, who are currently receiving methadone treatment, should have their dose increased to control craving. The use of ineffective dosages will produce an incomplete opiate blockade and can be harmful to the pregnancy, causing an unstable intrauterine environment and potentially foetal withdrawal. Apart from a minority of addicted patients who are able to stop using heroin at low doses, the majority receiving less than 80 mg/day will continue abusing practices combining substances in a struggle against the blockade. In such settings, these low dose treated patients may have a worse outcome than untreated addicts. Since most authors agree on the global benefit of effective methadone doses on the course of pregnancy in opiate-addicted mothers, when evaluating treatment effectiveness, in addition to receiving adequate doses, they should be provided with comprehensive services within structured programs especially designed to meet their needs.

2. Premises

Heroin addiction during pregnancy is associated with increased rates of perinatal morbidity, including spontaneous abortion, premature delivery, meconium stained liquor, neonatal infection and withdrawal syndromes varying according to which substance has been abused [18, 53]. Recurrent exposure to fast-acting, short-lasting opiates produces...
a condition of continuous swinging from states of opiate intoxication and withdrawal due to a heightened tolerance level to their narcotic action. Fluctuations of opioid concentrations result in an irregular blood supply to the utero-placental unit and the foetus suffers from recurrent hypoxia. Such a mechanism is responsible for delayed foetal development, foetal death and morbidity [18]. Providing opiates equivalent in potency, but characterized by long-lasting, slow-acting kinetics and administered in a maintenance schedule, will normalize opioid metabolism of tolerant individuals and prevent foetal damage.

As for addiction-related issues, a series of addictive behaviours may imperil pregnancy: lack of use of sterile equipment, sexual promiscuity, the involvement in violent acts, decreased hygiene, environmental influences, poverty, and refusal to comply with the health supporting guidelines of treatment facilities. The main goal of effective addiction treatment is that of leading addictive behaviour to extinction and normalizing opioid metabolism. Beyond tolerance/withdrawal related issues, the clinical correlates of opioid metabolism are of a behavioural nature, so that increasing dosages of therapeutic opiates can override the compulsion to seek illicit opiates.

Some opiates, such as methadone, display pharmacological characteristics which allow a health-promoting interaction with the brain due to the possibility of behavioural control and long-term damage reversal, at least in less severe cases. Methadone maintenance has been the standard treatment, and the only treatment approved for pregnant heroin addicts [12, 34]. As for non-pregnant addicted individuals, adequate methadone dosing is crucial to enhance compliance to treatment guidelines and achieve health objectives [13]. Even at no blocking dosages, pregnant heroin addicts’ behaviour is modified enough to allow attendance at healthcare facilities and to obtain abstinence from cocaine by voucher incentives [19, 32-34, 67]. Methadone treatment may render women capable of attending services without any short-term or monetary advantage [67]. Given the combined benefit for both the mother and the foetus, and the potential double damage caused by treatment omission or delay, pregnant addicts, who apply for treatment, should be given priority for enrolment in methadone maintenance programs.

3. Teratogenicity and pregnancy abnormalities

No congenital abnormalities have been related to methadone. The widespread exposure of opioid abusing mothers to methadone in therapeutic settings provides an opportunity to normalize the pregnancy and prevent untoward damage to the foetus. When evaluations of drug-induced abnormalities are performed on neonates of women undergoing treatment, the role of poly-drug abuse and alcohol abuse should be considered [1]. Methadone exposed newborns have been reported to have higher birth weights and less morbidity than heroin exposed babies. A trend towards increased birth weight has been reported by Hagopian et al., 1996 [24]. No delivery abnormalities have been noted in women who have followed successful methadone maintenance during their pregnancy.

4. Methadone management during pregnancy

Methadone metabolism in pregnancy is different than that of the non-pregnant patient and is influenced by the increased body fluid of pregnant women, especially during the 3rd trimester [68]. Methadone elimination is more rapid in pregnant women, so that the half-life is significantly shorter and methadone absorption may be also reduced [13, 30]. In blood sampled from the same subjects, peak methadone levels after equal oral dose loads are lower in the pre- than in the post-partum phase [43]. When withdrawal symptoms are monitored in a population of heroin abusing pregnant women entering methadone treatment at variable stages of their pregnancy, symptomatic women display methadone serum levels below the 0.211 mg/l [27], while administered dosages are similar. [Also a discrepancy seems to occur between higher methadone dosages and foetal serum levels of the drug: this latter tend to be similar regardless of increases of oral maternal dosages [14]. It should be remembered that different oral dosages may actually correspond to similar blood levels: therefore, such discrepancy may have no actual implication as long as the administration of methadone to pregnant women is rather based on clinical needs than on a scale of absolute oral dosage value [15]. As a consequence, some pregnant heroin addicts are provided ineffective medication due to unjustified cautions by the clinician [20].

5. Neonatal abstinence syndrome in methadone-exposed newborns

Since opiates traverse the placental barrier and foetal tissues become tolerant to their presence, the sudden deprivation of an opioid source at delivery may result in a withdrawal state, called the neonatal abstinence syndrome (NAS). More than one substance may be involved, and one should be aware of the possibility of a combined tolerance to opiates and gabaergic neurodepressants (benzodiazepines). NAS occurrence is variable and is generally seen in 60 to 90% of exposed neonates [6, 16, 26, 54, 59]. NAS intensity is widely variable. Onset of abstinence seems to depend on the interaction between the newborn’s slow metabolism and the agents’ own slow dissociation from binding sites. Long acting morphine substitution is not preferable to methadone in preventing the occurrence or severity of neonatal withdrawal [21]. When buprenorphine was evaluated, withdrawal was rated as milder and hospitalization time was consistently shorter [56]. Symptoms generally occur within 72 hours. The course
of withdrawal traverses a period of a week to several weeks with a gradual decrease in intensity within an undulating pattern. During this period the infant can gradually be stabilized [70]. Duration of hospitalization is generally longer for methadone than for heroin withdrawal. Polydrug abuse further contributes to the duration of withdrawal symptoms (Johnson et al., 2003). When morphine is used (as a tincture of opioid solution), lower dosages administered more frequently are associated with fewer days of hospitalization in comparison with higher dosages at longer dosing intervals [31]. An earlier (within the first three weeks), transient hyperphagic picture has been described which does not correspond to an increase in weight and appears to be unrelated to other withdrawal symptoms and maternal methadone dosage [49].

The relationship between NAS and maternal methadone dosage is controversial. Some authors have found no association with dose [4, 5, 24, 35, 37, 38, 42, 46, 51, 58, 64, 69], while other authors have ascertained a dose-dependent relationship with regard to incidence and severity of abstinence in their samples [14, 26, 41, 47, 48, 50, 52, 53, 62, 63, 66]. Some of the studies evaluating this relationship used very low doses, far below average effective dosages. Such a methodological choice is likely to correspond to patients being treated at ineffective dosages and not representing the level of health and behavioural stability achievable by methadone maintenance. Anti-withdrawal and partially blocking dosages, such as those between 20 and 60 mg, do not suppress craving and favour the combination with other opiate-boosting or replacing drugs, such as benzodiazepines, leading to the misinterpretation of clinical findings. Patients, for whom a 20-30 mg dose is enough are likely to be low-severity individuals and will not abuse opiates during pregnancy; on the other hand, average-to-high-severity patients not provided with effective doses will continue abusing drugs when provided a 40-60 mg dose. In some studies, [10, 50], NAS severity is predicted by benzodiazepine and cocaine abuse, respectively, while no other opiate-related predictive factors are identified. The possibility of a combined withdrawal, (opiate and alcohol-benzodiazepines) may also be considered [57].

Therefore, NAS will tend to be more severe for higher dose patients, whose dosage is still not enough. However, no difference is reported by Berghella and colleagues, who studied NAS in infants exposed to less than 80 mg/day to those exposed to more than 80 mg/day [3]. Sinha et al [63] report NAS being more often in need of morphine treatment in women taking higher methadone doses, but methadone-only exposed children are at lower risk of NAS than heroin-exposed ones. Overall, most results indicate NAS is less frequent in infants of methadone treated mothers than heroin using peers. Although there is a risk of NAS in methadone exposed infants, the syndrome is treatable and not lethal if it is assessed and managed appropriately. The NAS is overshadowed by the acquired gain in pregnancy and delivery outcomes and the mother and child’s health status as well as many psychosocial aspects that can be ameliorated [29].

Many clinicians still practice medically supervised withdrawal from opioids during pregnancy [45]. Along the stated reasons for withdrawing pregnant women is to prevent NAS, prejudice or lack of knowledge about addiction and its clinical features [55]. Medical withdrawal is not indicated during pregnancy except in a few instances where logistics hamper the delivery of methadone maintenance.

Some clinicians have tried a fast detoxification procedure with the claimed aim of NAS prevention. At twelve-day schedule of methadone withdrawal shortly before birth resulted in 29% of relapses just after the schedule completion, and a global short-term abstinence rate of 59%, while 15% of newborns required treatment for a clinically relevant NAS [11].

Safe management of pregnant opioid addicted women should start by methadone maintenance at effective dosages. NAS resulting from methadone exposure should be evaluated by clinical surveillance and treatment when needed with an opiate at tapering doses [60]. Moreover, the administration of higher methadone dosages should never be offset by the priority to avoid neonatal withdrawal since NAS is manageable through adequate care and treatment, whereas damage resulting from untreated addictive behaviours can be permanent.

Opiate withdrawal can be effectively treated by following a tapering schedule [2, 56]. Shorter dosing intervals of opiate-containing solutions have been found to reduce the duration of withdrawal [9]. Morphine solution is preferred for the treatment of NAS.

Breast feeding of mothers on methadone may be helpful in flattening the withdrawal slope to a drug-free state [21, 28, 44]. Breast-feeding alone is not likely to provide the infant with enough methadone supply, and is not always viable due to concomitant conditions, such as HIV infection. Barbiturate treatment may be indicated in addition to morphine when benzodiazepine withdrawal coexists.

6. Neonatal thrombocytosis

Increased platelet count and aggregating function have been reported in newborns of methadone treated mothers [6-8, 25], with an estimated prevalence of 3.65% [22]. A similar finding has been described in the offspring of opiate-tolerant female mice [7]. Platelet overcrowding may occur regardless of which opiate has been administered, that is both for heroin addicted mothers and opiate treated subjects. Its timing seems to follow that of neonatal opiate withdrawal, with a delayed onset one week after discharge and a protracted course lasting several weeks [22]. The causes and mechanisms of such a phenomenon have not been reported, however, the parallel evolution concomitant with the abstinence syndrome suggests it may be reversed by cross-tolerant opiate drug treatment.
7. **Strabismus.**

Surveillance for the development of strabismus is needed in children of opiate-dependent mothers. Available data do not indicate any correlation with either methadone dosage or altered opiate tolerance (NAS-related features) [23].

8. **Methadone for pain in pregnant women**

Chronic pain control may benefit from increased long-acting opiate coverage without employing further analgesic agents. Breakthrough pain control needs fast-acting agents. Morphine is suitable to relieve acute pain in methadone maintained patients with its dosage to be established on a subjective basis. As a rule, methadone tapering during pregnancy is not recommended. Pain can be one possible consequence of lowered opiate coverage. Other combinations with non opiate analgesics may be considered [61].

Women receiving methadone for pain control during pregnancy deliver earlier, differently from methadone maintained pregnant heroin addicts [23]. Methadone for pain is administered for shorter periods and generally at lower doses than that used for the addicted individual. NAS has been observed in 11% of the neonates. Wholly, neonatal outcomes of methadone treated pregnant women differ along the reason for methadone administration (pain vs. addiction).

9. **Early child development**

Developmental delays have been reported in methadone-exposed babies [55, 72]. Growth is slower during the first trimester, but no difference in achieved dimensions is noted at six months: a compensatory acceleration of growth takes place farther from discharge. Head circumference is normal within one year of age [40] while no cognitive delay is documented during infancy [36, 39, 40, 65]. However, when methadone is provided to pregnant women at effective dosages within structured programs, newborns tend to weigh more and have a larger head circumference; the latter in proportion with the average dose administered during the third trimester [24]. Examining the possible factors which may contribute to developmental abnormalities in a group of children of addicted mothers treated with methadone, no relationship was documented with opiate-related characteristics, such as methadone dose and duration of exposure to methadone [17].

10. **Breast-feeding**

Breast-feeding is possible for methadone maintained women. The milk contains approximately 2% of daily dose and concentration [71]. Values range from 0.05 to 0.57 mg/ml for dosages varying from 10 to 80 mg/day [71]. Daily methadone exposure is approximately 0.02-0.09 mg/die, far below the theoretical lethal dose in non tolerant babies. On the other hand, such a dose is not enough to prevent NAS in opiate-tolerant newborns. However, methadone maintained mothers who breastfeed their babies should not stop abruptly if dosages are average-to-high [48]. A study linking prenatal methadone exposure to delayed development examined a group of women treated with an average dose around 40 mg, which does not shield against poly-drug abuse and addictive behaviours [70].

11. **Psychological aspects**

‘Pregnancy’, as a life event, is often experienced by patients, or suggested from others, as somehow psychologically linked with the natural history of addiction. Redemption themes should never be supported or induced, and pregnancy should never be considered as a healing opportunity through a withdrawal from therapy. In fact, expectations and motivational drives have nothing to share with the destiny of a metabolic disease. On the contrary, patients will have to be provided with adequate information on treatment opportunities and feasibility in order to complete pregnancy in the best way. A good counsellor could motivate, through the experience of treatment during pregnancy, a stronger relationship with the therapeutic program. In this case, pregnancy can really become a motivation to treatment and can be so turned into an “opportunity of treatment”.

12. **Parental role**

Heroin dependence can compromise one’s capacity to provide parental functions. The loss of maternal priorities in a heroin addicted woman with children allows us to understand its severity as a disease and its power to deviate behavior from instinctive and fixed patterns, such as that of maternal attachment to her infant. Feelings and emotions linked with the contact with and the responsibility for their children are often present in heroin addicted women. The incoherence between the importance that mothers claim to attribute to their children and their behavior, which is contrary to the maintenance of a parental role, is therefore an evident sign of addiction. Motherhood can represent in a woman who is a drug abuser but not drug addicted, an opportunity to stop her abuse, however, this is not the case in the presence of drug addiction. The awareness of their one parental responsibility and the presence of maternal feelings can cause in drug addicted mothers demoralization, guilt and feelings of inadequacy and suicidal thoughts. Maternal psychotoxic effects of abused substances expose children to the risk of a chronic lack of emotional interaction, neglect and abuse and experiences of violence in their environments. Drug addicted women are conscious of what could improve their parental function (i.e. a behavioral control recovery), but are not able to plan a coherent, adequate line of conduct. Drug addicted women, as with most drug addicted individuals
whose addiction is not very severe, aim to recover control of the substance of abuse, in order to continue its use freely, and resort to a treatment able to solve the critical situation of the moment. Questions such as home care or resorting to a family collaboration are considered secondary with respect to the solution of those linked with substance use. An anti-addiction therapy has to restore the mother so that she can maintain a parental role. Parental dysfunction is an expression of the disease of addiction and so its recovery has to pass necessarily through the treatment of the addictive disorder. As for every category of drug addicted individual, a therapeutic approach must have the aim of allowing patients to recover through a continuum between intention, planning and behavioral drives.

References


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Contributors

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Conflict of Interest

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What is the right dosage for our patients?

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TO THE EDITOR: To prepare a discussion about the right dosage, I took our own documentation, using the charts for all patients treated during the last 20 years, with entries for the dosage used (n = 184) and made an evaluation: What was our average dosage after 2 months, 1 year, 2 years, and so on, up to 10 years. I also evaluated the changes in average dosage in a particular treatment-phase as that progressed. Our hypothesis was that of an average reduction in dosage. We were permanently aiming for abstinence and, in most cases, trying carefully to reduce the dosage after initial stabilization.

For the evaluation, the Dihydrocodeine dosage was divided 1:10 (1000 mg DHC corresponding to 100 mg Methadone), whereas the Buprenorphine dosage was multiplied by 3.3.

The average dosage after 2 months corresponded to 81.5 ± 7.3 mg Methadone, that of the year 10 to 73.5 ± 8.9 mg. Hence the average dosage is nearly constant over the whole time considered (Figure 1). During the last 20 years, there has been a trend to higher dosages. Our mean dosage at

Figure 1. Average prescribed Methadone dosage for 10 years
month 2 was 66 mg in 1989 and 108 mg in 2008 (Figure 2), with a similar development for all later dosages (year 1, 2, 3 etc.). For many years we excluded very high dosages (> 200mg). Only in the last few years did we prescribe much higher dosages (up to 450 mg) for a few patients – and we were able to record very good results and had a very good general impression in some of these patients. The 10-year-dosage information was only available from 26 patients. Of 12 patients, we know that they have died, and our latest information from 12 other patients was a successful completion of the maintenance treatment, reaching stable abstinence. The other patients are either lost to follow up or have not completed 10 years yet.

The almost constant average dosage over a period of 10 years was a surprise, because we had expected that our ongoing attempt to reduce dosages would lead to lower average dosages after a number of years. The constant average dosage is a consequence of the fact that some patients need a repeated increase in their dosage, and, with a few patients, we did not find out for several years that it is much better to treat them with much higher dosages (as found out especially by M. Shinderman, but also following other published data). The results make it clear that some of the patients are not on the way to abstinence. These patients are not being treated optimally if we continue to prescribe the lowest possible dosage, always aiming for abstinence in some distant future. The consequence to be drawn from the de facto constant average dosage over such a long period must be that we should always prescribe the clinically optimal dosage.

References


Leavitt SB, Shinderman M, Maxwell S, Eap CB, Paris P:


Maxwell S, Shinderman M: Optimizing long-term response

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INFORMATION FOR CONTRIBUTORS

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