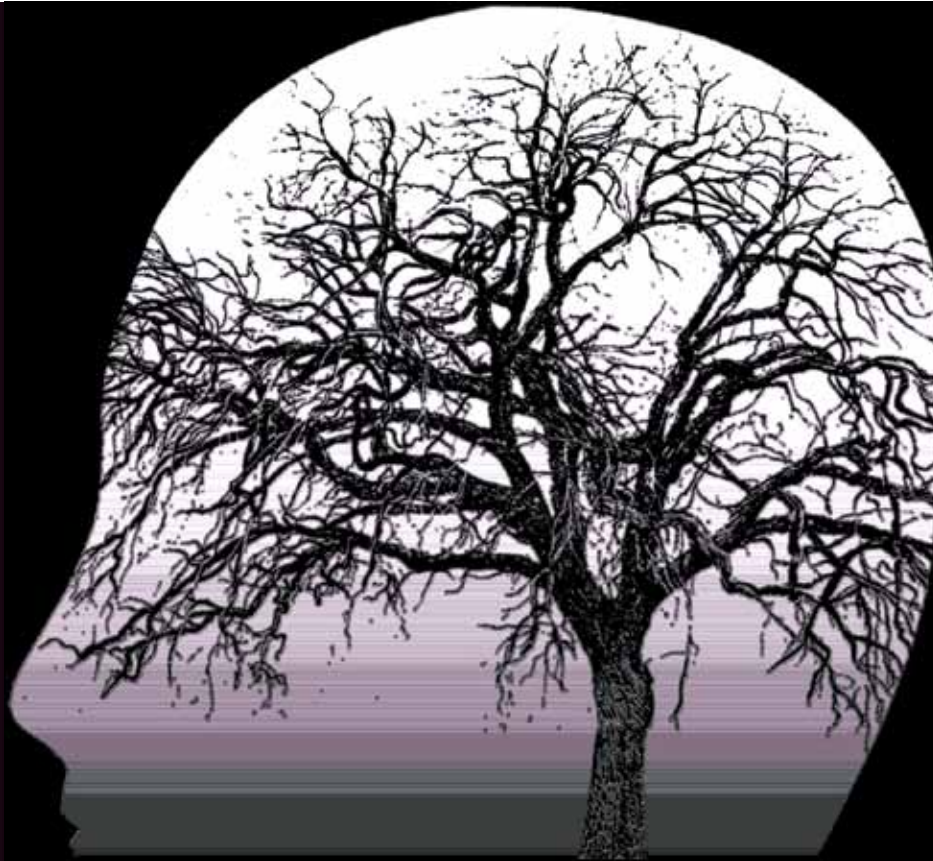


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# Heroin Addiction and Related Clinical Problems



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*Heroin Addict Relat Clin Probl* 2014; 16(1): 5-8

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# Addiction as an extended form of brain disease: heroin-free clinical pictures in the history of addiction. Towards the concept of masked heroin addiction

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Heroin addiction is a well-known condition that has been a major reason for concern about the state of public health and law enforcement over the last few decades. A major problem arises from the fact that its crucial clinical features and diagnostic elements are often mistaken for a veneer covering the illegal use of drugs as a social phenomenon. In fact, the stereotype of street drug use may be incorrectly perceived as the core of addiction, and other clinical pictures may be misinterpreted as remission, or a lower level of disease severity. To date, significant numbers of heroin addicts do not live the life of street junkies; these people keep a stable job and live with their families, although they experience considerable practical difficulties. In densely populated areas, addicts seldom need to travel, let alone change their

place of residence, to get a supply of their chosen substances. Since drug addiction does not originate in antisocial attitudes, but is itself the cause of antisocial behaviours as a consequence of craving and the illegal status of certain drugs, well-off addicts or socially integrated ones are likely to preserve their social adaptation and functional environment as long as it does not conflict with their access to drugs. It is also true that some addicts, after living for many years in drug-related environments, may reintegrate with their legal and social environment, while maintaining an addictive tie with their drugs of choice, or shifting it onto another substance. All in all, some clinical presentations of addiction may not be sufficiently well known, so that some individuals may not be recognized as true addicts, and some others may be clas-

sified as former addicts whose behaviour has spontaneously normalized. In other words, when diagnosis is focused on secondary criteria (linked to the social environment) rather than crucial ones (e.g. biological and psychopathological), many cases run the risk of being identified later than they should, and so remain untreated or be lost to addiction-focused follow-up.

To date, research has suggested that two conditions should essentially be viewed as part of the phenomenology of opiate addiction, although current perspectives do not even include heroin intoxication. The first of these refers to those addicts who are currently off heroin, but display a psychopathological profile that is a result of chronic heroin-mediated damage, and persists despite their detachment from heroin. Although there is a relationship between the persistence and intensity of what are usually termed 'long-term withdrawal' symptoms and the likelihood of relapse, some addicts may remain drug-free for long periods, by successfully adapting to their post-heroin functional status in order to avoid the emergence of discomfort and craving. If the core of addiction had a social and environmental origin, those patients would be correctly described as former addicts. By contrast, if addiction can be recognized as a psychopathological syndrome linked to acquired and enduring opiate dysfunctions, those cases should be assigned to the category of inactive opiate addicts.

The second condition to be reassessed is that of addicts who stop using heroin and switch to the use of another substance with opioidergic properties, or relapse into such use; they should continue to be assigned to their original category of opiate addicts, as that condition is still active behind the mask of another substance and the possible improvement of their social condition, which may be achieved by the transition from illegal to legal use. It is the case of former heroin users who remain opiate addicts but are later perceived as alcoholics, with little or no residual heroin use. These considerations may also apply to benzodiazepine abusers with a history of heroin addiction, who often go through anxious-depressive episodes complicated by benzodiazepine intoxication, despite their detachment from opiates.

The continuity between former heroin use and later 'heroin-free' pictures arises either from opiate-related dysfunctions, or the persistence of the uncontrolled use of opiate-related substances, such as alcohol, painkillers, and benzodiazepines.

The concern that should now be felt about such 'masked' pictures is justified by their frequency, impact and prognosis. For instance, in an endemic way,

former heroin addicts appear to make up a percentage as high as 15% of the alcohol abusers who apply for treatment at a day hospital facility in the urban area of Rome [9]. The heroin-using background of these patients accounts for the malignant course of their attachment to alcohol; they appear to become alcoholics as a result of their rapidly escalating use, with ever-higher peaks of consumption and ever-earlier patterns of heavy drinking. The incidence of former heroin addiction amongst benzodiazepine addicts is still unknown, but may be similar: it is reported that benzodiazepine addiction is strongly associated with current polyabuse, especially of opiates [1]. To date, the prognosis of those cases has been quite poor, in cases where their condition is approached with standard treatment procedures for alcohol abuse. On the other hand, the adoption of possibly on-going agonist opioid treatment may be effective in controlling alcohol abuse, thus closing the current gap between addictive alcohol use and the opiate system. In methadone treatment programmes, the reduction or extinction of heroin use is sometimes accompanied or soon followed by a rise in alcohol or benzodiazepine use. In fact, the effect of methadone treatment, especially at limited dosages, has the same impact on heroin use as that of surrogate alcohol use in untreated street addicts. The outcome is that residual craving guides the transition from heroin to alcohol use, with a temporarily favourable effect on rehabilitation, but a later evolution towards equally severe psychosocial impairment. Addicts in this category apparently stabilize at lower methadone dosages [6], while alcohol use increases. The empowerment of methadone treatment by dose increases has proved to be effective in counterbalancing this phenomenon, and so leading what had been an increasing use of alcohol to extinction [4, 7].

Another form of heroin-free picture of addiction can be observed in addicts who have been successfully rehabilitated while on agonist treatment, but seem to lose ground short after withdrawal from treatment, although the deteriorating picture may be due to the prescription of very low dosages. Emerging symptoms overlap with those originally described in abstinent heroin addicts who were out of treatment, or had had opiate antagonists administered to them [5, 8]. The prominent features reported were: chronic dysphoria, interpersonal sensitivity, reduced productivity, an alternation of emotional numbness and intense discomfort, enhanced sensitivity to pain, and impaired reward from once pleasant activities. Behind the mask of apparent dual diagnosis or gener-



ic poly-substance abuse, skilled clinicians should be able to recognize the indirect biological expression of the same opiate dysfunctions as those that supported the earlier relapse(s) into addictive heroin use.

There are two main cultural obstacles impeding the inclusion of masked heroin addiction within the spectrum of expected heroin-related clinical pictures. On one hand, there is the exclusion of addiction science from common psychiatric practice – a factor that favours the classification of addiction-related psychopathology as a ‘personality disorder’ or dual diagnosis rather than as being part of the expression of the core brain disease that is induced by heroin use. On the other hand, there is the unjustified separation between treatments for alcoholism and those for illegal drug addiction treatment; this division favours a substance-focused approach, rather than a new perception of accounting for opiate-related alcoholism as an opiate-centred disease still directly linked to its background of heroin use. The question whether such pictures are to be rated as subtypes of alcoholism or of heroin addiction is irrelevant, if the comprehensive perception is that opiate system dysfunctions are the source of apparently different phenomena. Lastly, former heroin abuse in alcohol or benzodiazepine abusers should not be explained by referring to generic poly-substance abuse, without giving a clear indication of the patient’s preference for specific types of substance.

In such cases, a post-hoc preference develops through the conditioning that depends on the first chronic intoxication (heroin), which is quite different from a non-oriented trend to self-stimulation, and is closely linked with the subsequently experienced kinds of chronic intoxication symptoms and the drug-free residual syndrome, possibly predicting relapses.

In our opinion, heroin addiction is best understood as the complex or spectrum of clinical expressions that link the addictive behaviours arising from direct (receptorial) or ‘indirect’ opiates with the acquired dysfunctions of the opiate system in the inner brain. A certain type of alcohol dependence, which had, at an earlier illness stage, turned into heroin-alcohol polyabuse, is an intrinsic part of this whole concept.

On this basis, agonist treatment should be considered as potentially useful in all the clinical pictures that belong to the spectrum, including heroin-free syndromes. Although this expanded view of opiate

addiction could be seen as a form of reductionism, it could equally well be considered as no more than an overdue updating of the metabolic disease theory originally described by Dole and Nyswander [2, 3].

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## Effects of Methadone Maintenance Therapy (MMT) on serum leptin, lipid profile and anthropometric parameters in opioid addicts

Farzaneh Montazerifar<sup>1a</sup>, Mansour Karajibani<sup>1b</sup>, Kobra Lashkaripour<sup>2</sup>, and Maryam Yousefi<sup>3</sup>

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### Summary

**Background and Aims:** In many drug abusers Methadone Maintenance Therapy (MMT) is accompanied by weight gain, changes in quality of diet, and improvement in hormonal disorders. The aim of this study was to evaluate serum leptin levels and their relationship with lipid profile and anthropometric parameters in addicts on MMT. **Methods:** Twenty-five drug addicts (mean age  $37.4 \pm 8.7$  years) who had been referred to the Addiction Treatment Clinic and twenty-two healthy controls (mean age  $35 \pm 9.5$  years) were included in the study. Anthropometric parameters (weight, height, waist circumference (WC) and waist-to-hip ratio (WHR), serum leptin and biochemical tests (serum albumin, total protein, glucose, cholesterol, triglycerides, LDL, HDL) were measured in the opioid-addicted group (before and after MMT) and in healthy controls one time only. **Results:** Serum leptin level was significantly lower than that of controls, at baseline ( $P < 0.001$ ). After 6 months of methadone maintenance treatment, the mean level of leptin had increased dramatically, along with body mass index, WC, WHR, and serum triglyceride levels ( $P < 0.01$ ). No changes were found in blood pressure or other biochemical parameters. **Conclusions:** Further studies are needed to evaluate serum leptin as a marker of atherogenic substances. In addition, the assessment of serum leptin concentration may contribute to identifying metabolic clinical problems.

**Key Words:** leptin; anthropometric; blood biochemical parameters; methadone maintenance treatment; opioid addicts

### 1. Introduction

Drug abuse has been recognized as a major health problem worldwide [14]. Opiate-dependent patients often show signs of malnutrition resulting from the loss of appetite and nutrient deficiencies that the drug induces [14, 27]. They have been shown to be at very high risk of infection with HIV as a result of secondary immune dysfunction [14]. Methadone, “a long-acting narcotic drug with effects similar to other opiates”, is used as an alternative treatment for those who are addicted to heroin and other opiates [14, 17]. Currently, methadone maintenance treatment (MMT) is performed in a wide range of cases in Iran [17]. Studies have shown that MMT is effective in the improvement of life style and nutritional habits

[17, 18]; it also improves many hormonal disorders that can be observed in drug abusers [14]. It has been reported that MMT changes the levels of adipose tissue-derived hormones in patients with a drug addiction [1, 12].

In response to specific extracellular stimuli or changes in metabolic status, adipose tissue releases some peptides, e.g., leptin, resistin and adiponectin. The release of these hormones can lead to changes in nutritional status and energy expenditure, as well as immune system and metabolic adjustments [1, 5, 22]. Leptin, the obese (ob) gene product, is a protein hormone produced by adipose tissue that plays the important role of regulating body weight through the regulatory control mechanism for food intake and energy expenditure, and it also provides information

about body fat content [10, 7, 12, 14, 22, 24, 26]. Serum leptin levels were found to be higher in dyslipidemia, insulin resistance and obesity [7, 14, 22]. These findings may be associated with leptin resistance – an inadequate peripheral or central response to increased leptin concentrations [22, 26]. It has also been suggested that leptin and its receptor in the artery wall during the calcification of vascular cells – which may be an important peripheral tissue target of leptin action – contribute to atherogenesis [7, 22, 26].

Due to the limited number of studies conducted on the leptin concentrations in drug abusers on methadone maintenance treatment, we have examined the relationship between serum leptin level and lipid profile and anthropometric parameters in drug addicts before and after methadone maintenance treatment and compared with healthy controls.

## 2. Methods

This clinical trial study was conducted in Baharan Psychiatric Hospital of the Zahedan, Sistan and Baluchistan Provinces. Twenty-five opioid addicts (20 males and 5 females) (mean addiction duration  $13.3 \pm 7.3$  years, mean age  $37.4 \pm 8.7$  years) and 22 healthy age-matched control subjects (12 males and 10 females, mean age  $31.5 \pm 9.5$  years) were enrolled in the study.

### 2.1. Anthropometric and blood pressure measurements

Weight and height were measured in subjects wearing light clothes and with bare feet, using a Detecto scale to the nearest 0.1 kg and 0.5 cm. Body mass index (BMI) was calculated as body weight in kilograms divided by height in meters squared. Waist circumference was measured at the high point of the iliac crest, and hip circumference at the maximum circumference of the buttocks, after which the waist to hip ratio (WHR) was calculated.

Resting blood pressure (BP) was measured using a mercury sphygmomanometer, Baumanometer (W.A. Baum Co. Inc., USA), after subjects had been in a sitting position for at least 20 min.

### 2.2. Biochemical and hormonal measurements

After an overnight fast, blood samples were obtained at 8:00 a.m. Serum leptin concentration was determined by using commercial ELISA kits (BioVendor [Cat. No: RD 191001100], USA). The lowest

limit of detection was 1 ng/ml. The coefficient of variation for intraassay was 3.3-5.4% and for interassay 6.7-8.4%. Samples were immediately frozen at  $-70^{\circ}\text{C}$  until needed for analysis.

Total cholesterol, LDL-C, HDL-C and TG were measured by applying a colorimetric method using Autoanalyser RA-1000. Albumin and total protein were measured using a photometric method (Pars Azmoon kits, Tehran, Iran).

Opioid-addicted subjects were treated with methadone (dose 40 to 120 mg per day) based on the protocol of MMT, severity of withdrawal symptoms and the cravings of patients. During the study period, an educational expert and a psychiatrist regularly followed up on these subjects for their health conditions; the morphine test was carried out monthly for all patients according to the protocol of the Ministry of Health, Treatment and Medical Education. After 6 months, anthropometric measurements and previous tests were repeated, whereas healthy controls were assessed only once.

The study protocol was approved by the local ethics committee. The participants were informed about the purpose of the study and provided informed consent.

### 2.3. Statistical analysis

Statistical analysis was performed using SPSS statistical software (version 15; SPSS, Chicago, Ill). All data were normally distributed and were expressed as means  $\pm$  S.D. One-way analysis of variance (ANOVA) followed by the Tukey test was used for comparison of the groups as appropriate. Student t-test was carried out for gender comparisons. The correlations between the variables were calculated by the Pearson correlation test. P values lower than .05 were considered significant.

## 3. Results

The levels of serum leptin, anthropometric and biochemical parameters were measured in a total of 25 drug addicts before and after 6 months of methadone maintenance treatment, and in 22 healthy subjects. The demographic data of these two groups are presented in Table 1.

At baseline, body weight, BMI, WHR and blood pressure of the opioid abusers did not differ from those of the healthy subjects, whereas waist circumference (WC) was significantly higher in the group of addicts ( $P < 0.01$ ) than in the control group.

**Table 1.** Demographic and clinical characteristics of controls and heroin addicts before and after methadone maintenance treatment

Parameters	Before MMT (n=25)	After MMT (n=25)	Control (n=22)
Gender (n (%))			
Male	20 (80.0)	20 (80.0)	12 (54.5)
Female	5 (20.0)	5 (20.0)	10 (45.5)
Age (y) (M±sd)	37.4±8.7	37.4±8.7	35 ± 9.5
Weight (kg) (M±sd)	62.6± 9.6	68±12.6 a	60.5± 4.9
BMI(kg/m <sup>2</sup> ) (M±sd)	23.2±7.6	28± 9.5 a	22± 1.9
WC (Cm) (M±sd)			
Male	87.40 ± 12.3b	93±10.8 a	82.2±8.3
Female	97.4± 10.8b	107± 9.6 a	77.2± 12.1
WHR (M±sd)			
Male	0.84 ± 0.1	0.87±0.1	0.85±0.1
Female	0.85±0.1	1.00± 0.1a	0.82± 0.1
Blood pressure (mmHg) (M±sd)			
Systolic	116 ± 11.0	113 ±6.6	115±9.6
Diastolic	76±5.0	73±4.8	73± 6.5

BMI: body mass index; WC: waist circumference; WHR: waist to hip ratio.  
 Data are presented as mean ±SD. One-way ANOVA, followed by the Tokey test, was used to analyse the data.  
 a < 0.01 vs. before MMT; b < 0.01 vs. control group.

As shown in Table 2, at baseline, the serum leptin level was markedly lower while the serum triglyceride level was higher than those of controls (P<0.01), whereas other biochemical parameters did not differ from those of the control group.

After six months of methadone maintenance treatment, the mean level of leptin increased significantly (P < 0.01), reaching that of the control group (P > 0.05). This increase paralleled that found in body mass index, WC and WHR, and the serum triglyceride level, which were markedly higher in the addicts than in the healthy controls (P<0.01). Methadone treatment did not significantly affect blood pressure

or other biochemical parameters. It should be noted that serum LDL level tended to increase, but the difference did not reach significance (Tables 1, 2).

Serum leptin levels were positively correlated with BMI, WC, WHR, triglyceride and LDL in drug addicts before and after MMT. There was a positive correlation between serum leptin levels and total cholesterol before MMT and a negative one with total protein after MMT only.

No significant correlation between the serum leptin levels with other parameters was seen in healthy subjects (Table 3).

**Table 2.** The levels of serum leptin and biochemical parameters of control and heroin addicts before and after methadone maintenance treatment.

Parameters	Before MMT (n=25)	After MMT (n=25)	Control (n=22)
Serum leptin (ng/mL)	8.30±6.8b (1.04-31.3)	12.50±10a (1.00-35.9)	12.00±9.8 (1.26-38.5)
Serum total protein (g/dL)	7.00±0.63	7.40±1.1	7.20±0.4
Serum albumin (g/dL)	4.20±0.2	4.40±0.4	4.40±0.3
Serum T-C (mg/dl)	177.70±38.8	177.30±36.5	170.00±39.2
Serum TG (mg/dL)	160.60±104.0b	171.00±116.0a	110.50±80.2
Serum LD L (mg/dL)	99.00±32.1	114.60±35.6	110.20±36.6
Serum HDL (mg/dL)	56.70±11.9	51.80±11.7	56.90±8.3

T-C: Total cholesterol; TG: Triglyceride; LDL: Low density cholesterol; HDL: High density cholesterol.  
 Data are presented as mean ±SD. One-way ANOVA, followed by the Tokey test, was used to analyse the data.  
 a < 0.01 vs. before MMT ; b<0.01 vs. control group.

**Table 3.** Correlation between leptin with other parameters in control and heroin addicts group before and after methadone maintenance treatment.

Parameters	Before MMT r (p)	After MMT r (p)	Control r (p)
Age (Y)	0.29 (ns)	0.09 (ns)	-0.12 (ns)
Weight (kg)	0.23 (0.03)	0.20 (0.04)	0.33 (0.02)
BMI (kg/m <sup>2</sup> )	0.45 (0.02)	0.28 (0.02)	0.42 (0.00)
WC (cm)	0.75 (0.00)	0.71 (0.00)	0.55 (0.02)
Systolic Blood pressure (mmHg)	0.32 (ns)	-0.03 (ns)	-0.17 (ns)
Diastolic Blood Pressure (mmHg)	0.10 (ns)	0.06 (ns)	-0.06 (ns)
Serum total protein (g/dL)	-0.03 (ns)	-0.45 (0.04)	0.12 (ns)
Serum albumin (g/dL)	-0.24 (ns)	-0.36 (ns)	0.14 (ns)
Serum T-C (mg/dl)	0.50 (0.01)	0.28 (ns)	0.40 (0.00)
Serum TG (mg/dL)	0.35 (0.04)	0.90 (0.00)	0.44 (0.00)
Serum LD L (mg/dL)	(0.04)	0.76 (0.04)	0.31 (0.04)
Serum HDL (mg/dL)	0.11 (ns)	0.26 (ns)	0.48 (0.00)

BMI : Body mass index ; WC: waist circumference; WHR: Waist to Hip ratio; T-C: Total Cholesterol; TG: Triglycerides; LDL: Low density cholesterol; HDL: High density cholesterol.

r: correlation coefficient, p: significance level (p<0.05), NS: non-significant (Pearson test)

#### 4. Discussion

We observed markedly lower leptin levels in the drug addicts than in the healthy subjects. Six months of methadone maintenance treatment dramatically increased leptin levels, so affecting all 4 anthropometric parameters (weight, BMI, WC and WHR) in both sexes, giving results similar to those of the study of Housova et al. [14]. A significant positive correlation was shown between serum leptin concentrations and the 4 anthropometric parameters in controls and addicts – both before and after methadone maintenance treatment. This finding may express a cooperative linkage between this hormone and the regulation of body weight and body fat content [9]. The correlation between leptin and BMI is in agreement with the results obtained by previous studies [4, 8, 1, 28, 29, 34]. By contrast, our results were not consistent with those of Velasque et al. [32] and Housova et al. [14]. Some studies have actually reported a negative correlation between leptin levels and total weight loss [33]. In addition, several studies have shown that leptin concentration is affected by methadone maintenance

treatment [14, 17, 18].

Leptin “secreted by adipose tissue” is a poly-functional hormone that has been shown to be an important marker in the regulation of food intake, weight gain, lipid metabolism, thermogenesis, and other physiological functions of the peripheral tissues [7, 14, 22, 26]. Leptin concentration is known to be correlated with central obesity [7] and varies with fat mass [4, 24, 25, 28, 34]. One study has reported that serum leptin levels increase with a high-fat diet [10]. Another study has demonstrated that high-fat/high-sugar diets lead to lower leptin production by increasing energy intake and weight gain [13].

The differences in serum leptin levels have been reported as probably being dependent on nutritional status [7, 2].

In the present study, we did not investigate food intake in the addicts and control subjects.

We measured the levels of serum albumin and total protein as valuable clinical markers of malnutrition-protein deficiency and malabsorption (insufficient intake and/or digestion of proteins). Serum proteins serve as a reserve source of energy for tissues

and muscle when an adequate amount is not ingested [2, 21].

As shown by our study, the levels of serum albumin and total protein after MMT did not differ from those of control subjects, in contrast with the results of the study of Housova et al. [14], which showed that one year of methadone maintenance treatment led to an increase in total protein in serum. A significant positive correlation was found after MMT between serum leptin and total protein levels, in agreement with the studies of Haluzik et al. [11] and Housova et al. [14]. Amirkalali et al. [2] did not find any significant correlations between serum leptin and albumin or total protein.

Age [15, 19, 20, 26] and sex [3] are known to independently affect serum leptin. Age was not significantly correlated with leptin in our study, but serum leptin levels in women were dramatically higher than those in men ( $P < 0.0001$ ) (data not shown). Sex differences have been reported to affect serum leptin, probably as a result of percentage differences in body fat mass [22, 23]. Similarly, Kheradmand et al. [17] reported that, after four years of MMT, women showed an increase in energy consumption, vitamins, minerals and main nutrition, whereas men showed a decrease in energy consumption, protein and carbohydrates.

Levels of the serum lipid profile were not pathologically higher in addicts than in the control group. The only exception was that serum triglyceride levels were found to be higher than before MMT and higher than those in the control group ( $P < 0.001$ ). Furthermore, serum LDL levels tended to increase, too, but the difference was not significant. Serum HDL levels fell after MMT compared with the earlier data and with the control group, but not significantly so.

A study carried out by Silver et al. [31] showed that leptin regulates the hepatic clearance of HDL cholesterol; HDL is an effective scavenger superoxide in vitro [16]. Previous studies have likewise revealed that leptin probably affects lipid-associated diseases such as atherosclerosis through oxidative stress in endothelial cells [5, 6, 26, 30].

The significant positive correlation found between serum leptin levels and total cholesterol, triglyceride and LDL levels before MMT, together with the significant positive correlation between serum leptin levels and triglyceride and LDL levels after MMT, that emerged in the present study, could mark important progress in understanding the pathogenesis of atherosclerotic complications. Haluzik et al. [11] did not find any significant relationship between

serum leptin levels and lipids (cholesterol and triglycerides). Several factors, including heredity, stress, and lifestyle (notably, physical activity), also affect the levels of serum leptin [7, 2, 17] and of certain lipids [26] that were not investigated in this study. The results showed that 6 months of methadone maintenance therapy significantly increased serum leptin levels, together with anthropometric parameters and serum triglyceride levels. Although leptin shows an angiogenic activity [26], our study showed no significant differences in the levels of the lipid profile after methadone maintenance treatment; this could, however, be due to the small number of participating subjects and the short duration of the study.

## 5. Conclusions

Further studies are needed to evaluate serum leptin as a marker of atherogenic effects. In any case, the assessment of serum leptin concentration may contribute to the identification of metabolic clinical problems.

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#### Contributors

Farzaneh Montazerifar designed the study, performed the statistical analysis, and drafted the manuscript. Mansour Karajibani and Kobra Lashkaripour contributed to the design of the study and carried out searches in the



literature. Maryam Yousefi performed the data collection. All the authors contributed to and have approved the final manuscript.

*Conflict of interest*

There is no conflict of interest.

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# Heroin Addiction and Clinical Problems Related



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## Heroin maintenance treatment and immunity: a 12 months follow-up study

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### Summary

**Background:** Comprehensive diacetylmorphine (heroin) prescription programmes for severely dependent opioid users having failed repeatedly in conventional treatment have been available in Switzerland since 1994. Several studies have shown the feasibility, safety and efficacy of such programmes for this specific group. In vitro studies have shown a negative influence on immunity of acute administration of heroin. **Methods:** We assessed, in a prospective observational study, the change in immunological parameters of 8 HIV-uninfected patients entering a heroin prescription programme in Geneva and followed up at 1, 6 and 12 months. **Results:** Immunity status at start of treatment and follow-up were within the normal range for most of the patients and there was a tendency towards improvement in immune status after 12 months. Clinical follow-up showed that patients globally improved; there were no hospitalization and few medical consultations for infectious problems in the first 12 months of treatment. **Conclusions:** There is no reason to suspect a negative impact of pure diacetylmorphine maintenance treatment on immunity status of chronic substance abusers.

**Key Words:** : substance abuse; drug treatment; diacetylmorphine; immunity; evaluation

### 1. Introduction

Comprehensive heroin substitution programmes for severely dependent opioid users having failed repeatedly in conventional treatment have been available in Switzerland since 1994. Global positive results of the heroin prescription programmes in terms of safety, feasibility and efficacy have been published recently [19, 21].

However, the issue of diacetylmorphine (heroin) prescription remains controversial, and often non- or pseudo-scientific arguments are used by opponents to criticise the use of heroin for maintenance treatment for substance abusers. One of these arguments is the negative influence that heroin might have on immunity functions.

The literature describing effects of morphine on cells of the immune system clearly shows that cells of the immune system have  $\mu$ -,  $\delta$ - and  $\kappa$ -opioid as well as non-classical opioid-like receptors, and that acute administration of morphine given to opiate-naïve cells or laboratory animals suppresses a variety of immune responses that involve the major cell types in the immune system, including natural killer (NK) cells, T cells, B cells, macrophages and polymorphonuclear leukocytes [7, 8, 10, 12, 23]. Acute withdrawal of opioids (in rats) also induced significant suppression of a subset of immune parameters [27].

Several studies have shown that intravenous heroin users have abnormal immunity functions, notably an increase in immunoglobulins and lymphocytes [9], a decreased mitogen response of the lymphocytes in

culture [3] and an abnormal rosette formation of the T- lymphocytes [13]. It is unclear whether these abnormalities are due to a direct effect of opioids, especially if taken in fluctuating quantities, to the diverse contaminants that are found in illegal street heroin or to other factors.

Different clinical and laboratory studies show conflicting results on a possible immuno-suppressive effect of morphine or other opiates on immunity. It should be kept in mind that doses used in experimental studies are often much higher than those used in humans, and the period of administration of treatment and the observation rather short, not allowing the evaluation of a possible tolerance to the immunosuppressive effect at long term [11].

Novick and Kreek [15] showed that former heroin addicts on methadone maintenance treatment (MMT) normalize their initially abnormal cellular immunological parameters several months after the start of the treatment. This is confirmed by *in vitro* studies on chronic morphine administration [10]. Chronic morphine treatment in monkeys was even found to be protective against HIV replication [6]. McLachlan [14] performed a literature review on methadone and immunity, and concluded that lasting methadone administration did not impair, rather improve, immunity functions among drug users.

Methadone is a long acting opioid, and we cannot extrapolate the findings relative to methadone to diacetylmorphine (heroin) maintenance treatment, since diacetylmorphine has a short duration of action.

The Swiss heroin prescription programmes provide a unique occasion to evaluate the influence of pure (non-contaminated) diacetylmorphine on the immune parameters of substance abusers.

Hereby we present the results of a prospective observational study of the change in immunological parameters and clinical observations of 8 new patients entering a heroin prescription programme in Geneva in 1998 and 1999 and followed up at 1, 6 and 12 months. The aim of the study is to exclude that the daily administration of diacetylmorphine in a maintenance programme will have a negative impact on immunological parameters of the patients. We hypothesised that the immunological status of substance abusers entering a heroin prescription programme, being in treatment failure and taking illegal heroin besides possibly prescribed opiates, would be abnormal at start of treatment, worse after 1 month, and normalise after several months of treatment.

## 2. Methods

### 2.1. Design and study setting

This is a prospective observational study of all HIV-uninfected patients entering the experimental heroin prescription programme in Geneva (Programme experimental de prescription de stupéfiants, PEPS) between May 1998 and May 1999 and followed for one year. Immunological parameters are measured at baseline, and after 1, 6 and 12 months (last follow-up May 2000).

The PEPS was, at the time of the study, part of the Substance Abuse Division (now Division for Addictology) of the Department of Psychiatry of the University Hospital, situated in an urban neighbourhood near Geneva centre. There is a multidisciplinary team of nurses, social worker, psychiatrist and general practitioner. The centre opened in 1995 with 40 treatment slots, it is open 3 times daily, 7 days a week. Treatment entry criteria are those defined by the Swiss Federal Office of Public Health (SFOPH): age over 18 years, having failed repeatedly in conventional substance abuse treatment, living in Geneva canton since > 18 months, willing to give up driver's license and willing to participate in the formal national evaluation of heroin prescription programmes (Addiction Research Institute, Zurich, see Rehm et al 2001). All baseline characteristics, additional treatment taken, dosage of diacetylmorphine, clinical and psychiatric evolution, are routinely taken within the framework of the national study and available for this study.

Doses of opiates were prescribed by the psychiatrist or GP, after an initial assessment, and were adapted regularly to patients' needs. The standard approach was to offer 3 injections of heroin per day, but the number of injections could be reduced and oral opiates could be added if requested by the patient. Methadone or slow-release morphine were used for oral substitution. No minimum or maximum dosage was enforced, for any of the drugs. All heroin injections were performed on the premises; there were no take-home privileges. In general, heroin was progressively introduced in the first weeks to reach a comfortable dose as soon as possible, average daily doses taken slowly decreased after 3 months [19]

### 2.2. Measurement

At baseline the usual blood check was performed: Human Immunodeficiency Virus (HIV), hep-

atitis A, B and C (HAV, HBV, HCV) sent to the viral serology lab, haematology (haematology lab), liver enzymes, creatinine (chemical analysis lab). For this study were added:

- Hormonal status: ACTH, cortisone (endocrinology lab)
- Nutritional status: albumin (chemical analysis lab).
- Immunological status, with the following parameters.
  1. Blood level of immunoglobulins
  2. Blood level of lymphocytes CD3, CD4, CD8, CD19
  3. Cellular immunity (in vitro response to mitogens et antigens)

These analyses were performed by the Clinical Laboratory of Immunology and Allergy. All laboratories belong to the Geneva University Hospital.

All tests (except viral serology) were repeated after 1, 6 and 12 months, viral serologies were repeated after 12 months.

Data on clinical (non-psychiatric) events (medical consultations, prescriptions for medical problems, hospitalization) were taken from the patient's files. Use of illegal heroin and cocaine was identified by self-declaration and urines (PROVE questionnaire), use of alcohol by regular alcohol breath test and self-declaration.

### 2.3. Description of the laboratory methods

Immunoglobulins : Dosages of immunoglobulin IgG, IgA and IgM were performed by nephelometry (IMMAGE, Beckmann), using standards calibrated according to international recommendations (IFCC).

Typisation of lymphocytes: Percentages of different lymphocyte populations were measured by flow cytometry (EPICS XL; Beckman-Coulter) using fluoro-chrome- conjugated monoclonal antibodies (FITC or RPE -conjugated monoclonal mouse anti-human T cell, Dako, Danmark) directed against CD3, CD4, CD8 and CD19 respectively.

Cellular immunity: Cellular immunity was measured by lymphocyte proliferation response to mitogens and antigens. Patient mononuclear cells isolated by Ficoll-Hypaque gradient (Pharmacia / Upjohn, Sweden) were cultured at 37°C in RPMI 1640 with L-glutamine (Gibco, Life Technologies), supplemented with 20% of human serum AB (Centre de transfusion Annemasse, France) and with 2% d'Hepes 1M (Gibco, Life Technologies), at a concentration of 1.10E6 cells/ml, in wells of 250 µl (96-wells cell cul-

ture plate, Costar) with various stimuli.

These stimuli included mitogens and antigens. Mitogens were: phytohemagglutinin A (PHA, Murex Diagnostic, Benelux) at a final concentration of 1 µg/ml; concanavalin A (ConA, Sigma) at a final concentration of 30 µg/ml; pokeweed mitogen (PWM, Seromed AG) a final concentration of 10 µg/ml. Antigens: tetanus toxoid antigen (concentrated antigen without glycerin, Pasteur Mérieux, France) at a final dilution of 1/1000; diphtheria antigen (concentrated antigen without glycerin, Pasteur Mérieux, France) at a final dilution of 1/10000; streptococci antigen (concentrated antigen without glycerin, Pasteur Mérieux, France) at a final dilution of 1/10000; candida albicans antigen (concentrated antigen without glycerin, Pasteur Mérieux, France) at a final dilution of 1/10000; proteus antigen (concentrated antigen without glycerin, Pasteur Mérieux, France) at a final dilution of 1/100; tuberculin antigen (PPD, Statens serum Institut, Danmark) at a concentration of 10 µg/ml

All incubation conditions were done in triplicates. After 3 days for the mitogens and 7 days for antigens, the cells were labeled by addition of 1 microCi of 3H-thymidine (Amersham Life Science) in each well. After 8 hours of incubation, cells were harvested into a filter (Cell-harvester, Wallac) and lymphocyte proliferation was evaluated by measurement of 3H-thymidine incorporation performed with liquid scintillation counter (beta -plate counter, Wallac).

For each condition, a proliferation index was calculated by the ratio between incorporation of 3H-thymidine in presence and in absence of the stimulus. The result is considered positive if this ratio is over 50 in presence of a mitogen, and over 5 in presence of an allergen.

Healthy subjects have positive results for the 3 mitogens and for at least 3 out of 6 of the tested antigens [2, 16].

### 2.4. Patients

All new HIV-uninfected patients entering at the PEPS between May 1998 and May 1999 were invited to participate in the study.

Inclusion criteria were the following: new admissions to the heroin prescription programme, prescription of intravenous heroin, agreement to participate and to sign the informed consent. Exclusion criteria: HIV infection, cortisone treatment, hepatic cirrhosis, diagnosis of cocaine dependence known before the start of treatment, psychiatric decompensation at the moment of signing the informed consent

**Table 1: Patient characteristics.**

	Patient 1	2	3	4	5	6	7	8
Gender/age (years)	M/37	M/34	F/40	M/38	M/39	M/39	M/40	F/31
Hepatitis C	+	+	-	-	+	+	+	-
Methadone dose before treatment entry (mg)	60	120	100	95	50	100	-	95
Diacetylmorphine dose after stabilisation (mg)	340	460	740	620	300	510	680	480
Alcohol abuse/dependence	+	+	-	-	-	+	+	-
Cocaine abuse	+	+	+	-	-	-	-	-
Medical consultations	8	8	13	9	2	2	0	4
Number reasons of visits for infectious problems	2 mycosis, gingivitis	0	4 conjunctivitis, bronchitis (2), dental abscess	2 bronchitis, sinusitis	0	1 bronchitis	0	0
Laboratory tests	ACTH↑ cortisone↑	ACTH↓ T1	IgG↑ T6-12	ACTH↑ cortisone↑ T12	IgG upper limit T6		ACTH↑ T0-1 Cortisone↓ CD4↓	ACTH↓ T0 cortisone↑ T12 IgG↑
Cellular immunity	normal	normal	limit T6	normal	normal	low T0,T6 normal T12	low T0, T1 normal T12	normal

↓= decreased; ↑=increased; +=positive/present; -= negative/absent

### 2.5. Practical aspects

Blood (30 ml) was taken (needle type « gauge 19 with butterfly ») by the nurses or GP at the PEPS or at the specialised laboratory of the Psychiatry Department for patients whose venous status was extremely bad. Blood tubes for the research contained an anonymous identification code. All blood was taken at 8 am and immediately transported to the different labs.

Patients were informed about the results by the GP if they wished so. Patient's health insurance paid for the analysis of the usual blood screen, additional analyses were paid for by the study grant. Patients received no payment for their participation in the study.

## 3. Results

Between May 1998 and July 1999, 15 patients entered the programme. Only 8 patients were eligible for the study, nobody refused to participate. Reasons

for exclusion were HIV infection (n=3) and cocaine dependence (n=4).

From a practical point of view, this study was time-consuming. It needs a lot of preparation and co-ordination between different actors (GP, patient, nurse, lab, preparation of tubes and ice, transport), especially since the PEPS is not situated close to the laboratory. Also, the difficulty to take at least 5 different tubes with blood from patients with bad venous status should no be underestimated.

For T1 (1 month after start of treatment) results of 2 patients are missing, for practical reasons (for 1 patient the laboratory was closed, 1 patient just started a new job and could not come at 8 am). For 1 patient T12 is not available since he detoxified between T 6 and T12.

### 3.1. Patient characteristics at baseline and follow up (table 1)

Of the 8 study subjects 6 were male, median age was 38 years (range 31-40 years). Five were infected

with HCV. Seven of them were in methadone maintenance treatment before treatment entry (average dose 88.6 mg, range 50-120 mg) and used illegal heroin intravenously besides prescribed opiates. One patient was using illegal heroin only (estimated quantity 400 mg per day)

Average dose of diacetylmorphine prescribed after stabilisation (1 to 2 months) was 516.3 mg daily (range 230 to 740 mg).

During the 12 months follow-up, patients globally improved. Most of them gained or normalised their weight, stopped illegal heroin use, improved in mental health and did not present major medical complications that might suspect decreased immunity. None of the patients was hospitalised in a medical ward during the one-year follow-up. Median total number of non-psychiatric consultations was 6 (average 6, range 0-13), 18.8% were for infectious problems; others were mainly for constipation, vaccinations, allergic reactions, contraception and menstruation problems. With regard to infectious problems, the average number of consultations was 1.2 in 12 months (range 0-4), most of them for bronchitis. There were no seroconversions for HIV, hepatitis B or C during the 12 months follow-up.

Several patients decreased the number of cigarettes daily smoked, but nobody stopped tobacco use. Three patients used cocaine occasionally or regularly, 4 patients had excessive alcohol use.

### 3.2. Immunological parameters

Results of immunity parameters are summarised in Table 2.

Overall there were few abnormalities in immunoglobulins, cellular immunity and lymphocyte count at start of treatment, and few changes afterwards in

the different parameters.

ACTH and cortisone abnormalities were rather frequent, at baseline and follow-up. In most cases they were patients abusing alcohol.

No participants had a low albumin levels at baseline suggesting the absence of severe malnutrition, although one patient suffered from anorexia. Values stayed within normal to upper limit (in 2 cases) at follow-up.

## 4. Discussion

Results of this 12 months prospective study of severely dependent opioid addicts starting heroin maintenance treatment show that immunity status at start of treatment and follow-up were within the normal range for most of our patients, and that there is no reason to suspect a negative impact of pure diacetylmorphine maintenance treatment on immunity status of substance abusers. There was a tendency towards improvement in immune status after 12 months. Clinical follow-up showed that there were no hospitalization and few medical consultations for infectious problems in the first 12 months of treatment. The study was in a small number of HIV-uninfected subjects, but results were consistent and follow-up excellent.

We found that immunity status is more or less normal at baseline in our study population. This is in contradiction with Kreek's findings [9] that immune status of active street heroin users starting methadone treatment was disturbed. However, there are several hypotheses to explain this discrepancy. We suggest that our patients were in a more "steady state" of opioids level compared to Kreek's study subjects. All but one of our patients were in methadone maintenance treatment at the moment they en-

**Table 2:** Immunological parameters.

	T0 (n=8)	T1 (n=6)	T6 (n=8)	T12 (n=7)
ACTH	6 N, 2↑	2 N, 3↑, 1↓	6 N, 1↑, 1 missing	6 N, 1↑
Cortisone	6N, 1↑, 1↓	4 N, 2↑	5 N, 2↑, 1↓	2 N, 2↑
Albumin	7 N, 1↑	not done	8 N	6 N, 2↑
Immuno- globulines	7N, 1 IgM↑	5N, 1 IgG↑	6 N, 2 IgG↑	2 N, 1 IgG↓ 1 IgG↑
Cellular immunity	6 N, 1↓ 1 limit	5 N, 1 limit	6N, 1↓, 1 limit	7 N
Lymphocyte count	7N 1 CD4↓	5 N 1 CD4↓	7 N 1 CD4↓	6 N 1 CD4↓

N= normal, ↓= decreased, ↑increased

tered the heroin prescription programme. Of course they were in treatment failure (since this is an entry criteria for heroin prescription programmes), using regularly street heroin besides their methadone, but they are not comparable to New York junkies having had no access to treatment before entering the MMT and thus probably using street heroin only. So, our patients are at start of treatment in a relatively « steady » state with a base level of opiates (methadone) inducing fewer fluctuations in total level of opiates when street heroin is taken on top of methadone. Also their general health was, probably, better than New York addicts in the seventies or eighties, and we excluded HIV-infected individuals.

Other hypotheses to explain the fact that we found almost normal immunity status at treatment entry in contrast to Kreek: difference in quality of street heroin (purity and type of substances used to mix with heroin), difference in frequency of parallel cocaine consumption or difference in regular, but not excessive, stimulation by different antigens gives high antibody response (false-normal immunity)

It is interesting to note that the only participant having a slightly decreased cellular immunity at baseline and after 1 month was also the only person using street heroin only, not being in a methadone maintenance programme any more at the time he entered the heroin prescription programme.

The fact that there are relatively few changes in immunity parameters over time is re-assuring and not surprising. It underlines previous hypotheses that immune function is impaired when opioids states of tolerance and dependence are disrupted [12]. After a possible initial phase of decrease in immunity after the first contact with opioids in naive subjects (as seen in vivo experiments; [11]), the body, with chronic administration of opioids, comes in a homeostasis with normalisation of immune parameters. It should be kept in mind that patients entering heroin prescription programmes are not opiates naïve and are probably in some form of homeostasis due to prior methadone and/or heroin use. Also, doses of prescribed heroin are high (around half a gram a day).

Although cocaine addiction was an exclusion criterion for taking part in this study, at least 3 of our 8 patients abused cocaine occasionally after entrance in the programme, making results on immunity more difficult to interpret, since cocaine has a negative impact on immunity [18]. Alcohol was a substance abused by half of the patients. Alcohol might negatively influence immune status [17, 25, 26] as it might influence ACTH and corticosteroid levels [22]. All

patients presented nicotine dependence. Also nicotine seems to alter immune response by direct interaction with the T cells [24].

Clinical research on opiates and immunity is complicated by the fact that chronic opioid users are in fact multi-substance abusers, this might induce confounding bias. However, we think that our results are not exaggerated; rather that improvement in immune status over time might have been underestimated due to the fact that some patients took cocaine, alcohol or nicotine. Secondly it means that ACTH and cortisone data are difficult to interpret in case of problematic alcohol use.

We limited our study to HIV uninfected individuals, to avoid too many confounding variables on immunity (effect of HIV, antiviral treatment, opportunistic infections). Almost one fifth of participants in Swiss heroin prescription programmes are HIV infected [21]. To our knowledge, to date there has been no clinical study on immunity of HIV infected individuals in such programmes. What we know is that, overall, the physical health of participants is improving over time and mortality low [19, 21, 1]. In the Geneva heroin prescription programme (26% of participants HIV infected), no patients had a new diagnosis of AIDS nor died from AIDS between 1995 and 2002. Acceptation of and compliance with antiviral and prophylactic treatment increased from 20 to over 70% of those who were in need of treatment. Our clinical impression is that, as has been suggested for methadone and buprenorphine maintenance treatment [14, 4], there is no negative impact of diacetylmorphine maintenance treatment on HIV-infection.

## 5. Conclusion and recommendations

This is the first clinical study on diacetylmorphine maintenance treatment and immunity, with a follow-up of one year and combining laboratory with clinical data. Results show that there is no reason to suspect that heroin maintenance treatment might have a negative impact on immunity status. There was a tendency towards improvement in immune status after 12 months of treatment. Possible confounders (nicotine, cocaine and alcohol use) might have underestimated this improvement. We expect that heroin maintenance treatment will not do “worse” than methadone maintenance treatment with respect to influence on immunity. It is thus important not to consider immunity but other aspects of safety and efficacy of both treatments to conclude which is the most adequate treatment option for severely addicted



heroin addicts who failed repeatedly in conventional treatment.

To support this conclusion more formally this study could be repeated in a greater number of patients, if possible in a multi-centre design. Alcohol dependence should be an exclusion criterion. From a practical point of view we recommend studies should be performed in large centres close to a laboratory. However, we could wonder if such costly studies are really needed. The different evaluations of heroin prescription programmes and clinical observations rather suggest an improvement in physical health, of both HIV-infected and –uninfected participants.

Furthermore, there are many other basic and clinical questions in the field of addiction and immunity to be elucidated, for example the influence of other drugs of abuse [5, 17].

Also, the influence of opiates detoxification on immunity, especially comparing ultra rapid versus rapid versus slow detoxification, is an interesting and open field of clinical research.

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## Illicit use and diversion of buprenorphine/naloxone among patients in buprenorphine/naloxone maintenance treatment in Istanbul, Turkey

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### Summary

**Background and aims.** Besides noting the measures taken in Turkey against the buprenorphine/naloxone (BNX) combination to suppress the misuse of therapeutic opiates, a detailed study on the illicit use of BNX has become a compelling priority. The aim of this study is, in fact, to evaluate the extent of the illicit use and diversion of buprenorphine/naloxone (BNX) by patients in BNX maintenance treatment (BMT). **Methods.** 281 heroin-dependent patients were included in the study. These patients had consecutively attended the Alcohol and Drug Research Treatment and Training Center (AMATEM) polyclinic as BMT outpatients, and had reached the end of the stabilization phase at least 2 weeks after induction. **Results.** Of these 281 heroin-dependent subjects in BMT, 110 (39.1%) were considered as belonging to the group that had used illicit (i.e. unprescribed) BNX. This group presented higher current doses, a higher use of BNX before treatment, a shorter period of BNX treatment and a lower frequency of remission of drug use. There was no difference between the two groups in estimates of dose adequacy, receiving education for BNX use, having a legal problem and/or probation, using different routes for BNX other than the sublingual route of administration, or giving away BNX doses. Those in the group that did use illicit BNX showed higher percentages both for the more frequent use of BNX or higher doses of it, and its less frequent use or for lower doses, besides the more frequent use of other substances during BMT, compared with the group unaffected by illicit BNX. **Conclusions.** Most of the patients that used illicit BNX had done this before their monitored use of BNX and had used it to relieve withdrawal symptoms, which suggests that the main difficulty for those seeking illicit BNX in Istanbul is how to access treatment.

**Key Words:** buprenorphine/naloxone; illicit use; diversion; heroin dependence; maintenance treatment

### 1. Introduction

Opioid maintenance treatment (OMT) for opioid dependence is effective in reducing mortality, HIV transmission, crime, and the use of other drugs [24]. Buprenorphine (BUP) maintenance is effective in treating opioid dependence, but problems with the misuse and diversion of BUP may limit its acceptability and dissemination [5]. Thus, the buprenorphine/naloxone combination tablet (BNX) was developed to reduce potential problems with misuse and diversion [7, 9, 23, 26]. Two qualitative, ethnographic studies based on interviews with people who abused opioids in Baltimore and throughout New England suggest that the avoidance of withdrawal symptoms is the pri-

mary motive for the use of diverted BUP [16, 27]. Previous studies exploring factors related to BUP injection have shown that the perception of inadequate BUP dosage prescription can influence BUP injection [8, 37], as well as the severity of drug dependence and suicide ideation or attempts, even in HIV-infected injection drug users (IDUs) receiving BUP treatment [8]. The prevalence of recent diversion was over 10 times higher among those receiving supervised BUP compared with methadone (MET), with 23.8% of BUP-maintained participants reporting that they had diverted their dose in the preceding 12 months in Australia [38]. In France, individuals perceiving their prescribed dosage as inadequate and feeling dissatisfaction with BUP treatment ran a higher risk of

sniffing [31] and injection [30]. The previous studies demonstrated that the illicit use of BUP is associated with attempted self-treatment rather than being an attempt to “misuse” it [30, 33]. Consistently with these data, in a previous study the percentage of BUP diversion was reported as 46.5% (9.6% daily and 50.6% sporadically) within 6-month follow-up, and the inability to access BUP treatment was reported as the main predictor (AOR: 7.31); as a result, the authors suggested that improving – rather than limiting – access to good quality, affordable BUP treatment may be an effective public health strategy to mitigate the illicit use of BUP [21]. Seven published studies have documented the diversion and/or injection of BNX [1, 6, 11, 19, 27, 29, 36]. Three of these studies found BNX to have a lower street value than BPN in the period immediately following the medication’s introduction [1, 11, 29], although it is not clear whether this has been sustained over time. Other studies found that the street price of BNX increased over time to a price that was equivalent to that for BUP [6, 19]. Although 80% of drug users who tried injecting BNX had a bad experience in Finland [1], a number of studies suggest that, while BNX may have lower abuse liability than BUP, the inclusion of naloxone may not completely eliminate its potential misuse [17, 26, 29]. A Malaysian study found that the introduction of BNX did not reduce injection-related risk behaviours among participants who had previously injected BUP, and even if withdrawal symptoms were reported, they did not result in a decrease in the self-administered BNX dose [6]. A two-wave survey of BUP among IDUs was conducted shortly before BUP withdrawal from the Malaysian market (n=276) and then again six months after BNX was introduced (n=204). The results suggest that the introduction of BNX and withdrawal of BUP may have helped to reduce, but did not eliminate, the problems experienced with diversion and abuse in Kuala Lumpur, Malaysia [36]. In 2009, while BNX was less commonly and less frequently injected than BUP, both sublingual medications were diverted more than liquid MET [19].

Abstinence-oriented symptomatic treatment was the most commonly offered treatment option in Turkey until the end of 2009. Agonist treatments, including methadone, a single form of buprenorphine or a combined form of BNX were not available. Starting in April 2010, BNX was approved for opioid dependence treatment as a detoxification or maintenance treatment by the Turkish Ministry of Health [35]. The prescription of BNX was, however, restricted to hospitals that included a state-approved special-

ized clinic for the treatment of substance dependency. In Istanbul, with a population exceeding 13 million inhabitants, only 2 centres provide a BNX maintenance treatment (BMT) programme. At the start of 2010 the Alcohol and Drug Research Treatment and Training Centre (AMATEM) in Istanbul started providing BMT, but only to patients who were hospitalized. At the beginning of 2011 AMATEM published a guideline [12] and extended the implementation of BMT to make it available on an outpatient basis. A previous survey conducted in Istanbul among 35 opioid-dependent outpatients in BMT suggested that these patients may use BNX illegally as a form of self-treatment before they enter treatment [39]. This is the first report of characteristics associated with BNX diversion in a large sample of Turkish heroin addicts in BMT.

The aim of this study is to evaluate the extent of the illicit use and diversion of BNX among patients in BMT and related variables. Specifically, this study seeks to answer the following questions: (1) What is the percentage use of illicit BNX and its street price?; (2) What knowledge do patients have about the illicit use of BNX?; (3) What are the sources of illicit medication and the reasons for using illicit BNX?; (4) What are the related variables associated with illicit BNX use?; (5) What is the percentage of illicit use of BNX before beginning BMT?; (6) What is the percentage of abuse of other substances during BMT, and the reasons for abusing other substances?; (7) What is the percentage of BNX use by routes other than sublingual administration?

## 2. Methods

### 2.1. Settings (use of buprenorphine/naloxone [BNX] combination treatment in Turkey, especially in Istanbul)

There are few specialists working in the field of addiction in Turkey, and there are even fewer in the clinics that have a license to prescribe BNX. A further consideration is that even among these few, most refuse to use BNX because of the fear that money could be made by diverting medication. The Alcohol and Drug Research, Treatment and Training Centre (AMATEM) in Istanbul and Adana prescribes 80% of the BNX administered in Turkey, among 18 clinics located in 8 cities. In addition, there are 7 other clinics that have a license to prescribe BNX but do not do so because of the fear of diversion, particularly the potential for selling it on the black market. 80%

of the population has government-based health insurance in Turkey and the government provides BNX to the opioid-dependent patients who have health insurance, although they still have to pay 20% of the BNX cost (5 U.S. dollars/box for 2 mg and 16 U.S. dollars/box for 8 mg) and an additional 2.50 U.S. dollars to include a psychiatric examination. Still, the total cost of the BNX treatment is much higher for patients without any form of health insurance – a category that comprises about 30% of heroin-dependent patients, because they have to pay not only for the BNX (5 times the cost to be met by those with insurance cover) but also for a psychiatric examination (7 U.S. dollars) and urinalysis (50 U.S. dollars). In this situation, those without any health insurance are encouraged to get “mandatory universal health insurance” before starting treatment. The final outcome is that about 5% of the patients in BNX maintenance treatment (BMT) have to manage without health insurance of any kind. Considering daily polyclinic admissions to AMATEM in Istanbul, about half of the patients are heroin addicts, and the number of the patients treated ranges between 60 and 80 a day. Although a medical examination and the prescription of a symptomatic treatment regime is possible on the day of admission to the polyclinic, the definitive situation is that patients have to wait 6 months for inpatient treatment, whereas 1 month is needed to obtain outpatient BMT in AMATEM, Istanbul. In Turkey the maximum dosage approved for BNX is 24 mg/day, whereas BNX doses range between 2 to 16, with a mean dosage of 8.6 mg/day ( $SD=2.5$ ) in AMATEM, Istanbul. The upshot is that doses in Turkey are lower than those generally used in Australia, Europe and North America. The main reason for this is the belief among Turkish specialists that the higher the dose, the greater the risk of diversion. Supervised administration is not used in outpatient treatment, and patients collect a prescription monthly as a take-home medication and get their supply from a pharmacy. Doses are stabilized in 1 to 2 weeks. Lastly, the street price of heroin ranges between 50 and 100 TL (25-50 U.S. dollars) in Istanbul, depending on the quality of the drug.

## 2.2. Design of the study

The study was carried out in the Bakirkoy Research and Training Hospital for Psychiatry, Neurology and Neurosurgery, AMATEM, Istanbul. The Ethical Committee of the hospital approved the study and the written consent of the patients was obtained after the study protocol had been thoroughly explained.

When individuals start BMT as outpatients, they are advised to participate in the Outpatient Therapy Programme (OTP) once a week for at least a year, whereas they were previously obliged to come to the AMATEM outpatient clinic every month to be able to continue receiving BNX prescriptions. The induction and stabilization phase of treatment ends after one to two weeks. Research forms are given to the patients to complete at the end of the stabilization phase, in other words at least two weeks after their induction into use of BNX. Patients have to receive their prescriptions each month, so the study was conducted between 15 July and 31 August 2013, and lasted 6 weeks to include all the patients that were compliant with the outpatient BMT during this period. There was no ceiling on how long patients could continue with their treatment. Duration of treatment was considered as the total duration of their current BMT episode, considering that various patients began treatment at different times, and the number of previous treatment episodes was evaluated, too.

## 2.3. Subjects

Three hundred and ten heroin-dependent outpatients who had consecutively attended for BMT were considered for participation in the study. All the participants fit the DSM-IV diagnostic criteria for heroin dependence. The criteria for exclusion were illiteracy, mental retardation or cognitive impairment, comorbid psychotic disorder and dependence on substances other than heroin. The result was that five patients were excluded for illiteracy, three patients because of cognitive deficits and three patients due to their being dependent on drugs other than heroin. Five of the patients refused to participate in the study and 15 patients were excluded because they had left some parts of the scale forms unfilled. The outcome was that a total of 281 heroin-dependent inpatients participated in the study. Opioids other than heroin, such as those used as pain medication, are hard to obtain for heroin dependents. Patients were asked if they had ever received illicit BNX from others or had ever bought it on the black market. According to the answer given to this question, patients were grouped either with those who used illicit BNX or with those who did not. We also evaluated whether individual patients had ever used illicit BNX before beginning their first BMT.

## 2.4. Instruments

Using a semi-structured sociodemographic

form, and a survey which included detailed questions about the illicit use and diversion of BNX, all patients were assessed. The survey was developed specifically for the present study after carrying out an overview of previous studies on this subject [19, 31, 36, 39]. The survey consisted of 26 questions about the duration of BNX use, daily dose, route of heroin administration, witnessing illegal BNX exchanges, using illegal BNX, diverting BNX, abusing heroin or other drugs during this treatment. Illicit BNX use is defined as purchasing it on the black market or receiving it from a friend, in other words accessing BNX illegally from sources other than legal prescriptions. The participants were asked to numerically define the duration and dose of treatment. Other questions were multiple choices, some of which included the choice of "other", so that patients can respond by giving detailed answer. Participants self-completed the survey anonymously, and put the surveys into an envelope provided by the researchers. Then participants dropped the envelope into a box in front of the polyclinic, as if they were casting a vote in a poll.

### 2.5. Data analysis

The statistical package SPSS 11.5 for Windows was used for all the analyses. Frequency and mean values were given. Categorical variables were compared by means of the chi-square statistics. We used the Student t-test to compare the groups on continuous variables, since these variables were normally distributed.

## 3. Results

### 3.1. Percentage of illicit BNX use and street price

Of 281 patients who were dependent on heroin and were using BMT, 171 (60.9%) were considered as belonging to the group that did not use illicit BNX, whereas the other 110 (39.1%) were considered as belonging to the group that had used illicit BNX (Table 1). The median street price of a 2 mg tablet of BNX was 15.00 Turkish Lira (TL, equivalent to about 7.50 U.S. Dollars: min: 5.0 - max: 40.0), whereas the median street price of an 8 mg tablet of BNX was 40.00 TL (about 20 U.S. Dollars; min: 10.0 - max: 80.0). None of these patients reported selling this medication to others.

### 3.2. Knowledge about illicit use of BNX

Of those who reported that they had not received BNX illegally (n=171, 60.9%), 124 (72.5%) had heard that people purchase illicit BNX, 15 (8.8%) had witnessed others receiving BNX illegally, 12 (7.0%) had witnessed a friend receiving BNX illegally, 13 (7.6%) had received an offer to purchase BNX on the black market, and 31 (18.1%) reported that they did not know BNX could be provided illegally.

### 3.3. Source of illicit medication and reasons for using illicit BNX

Of those who reported that they had used illicit BNX (n=110; 39.1), 93 (84.5%) obtained BNX from

**Table 1.** Comparing groups according to sociodemographic and clinical variables.

	No Illicit Use of BNX n=171		Illicit Use of BNX n=110		Chi <sup>2</sup> /df	p
	n	%	n	%		
Male gender	159	93.0	102	92.7	0.01/1	0.94
Marital status					6.35/2	0.04
Single	71	41.5	38	34.5		
Married	90	52.6	56	50.9		
Divorced/widow	10	5.8	16	14.5		
Employment status					1.56/2	0.46
Without employment	50	29.2	40	36.4		
Employed	33	19.3	19	17.3		
Employed part time	88	51.5	51	46.4		
Age (mean±sd, year)	33.02	11.34	31.43	9.19	t=1.30	0.20
Duration of education (mean±sd, year)	8.29	2.89	9.06	3.00	t=-2.17	0.03
Duration of heroin use (mean±sd, year)	8.43	8.14	8.64	8.04	t=-0.22	0.83
Heroin injection	51	29.4	40	36.4	1.31/1	0.25

BNX: Buprenorphine/naloxone

**Table 2.** Comparing groups according to variables related with abuse or diversion

	No Illicit Use of BNX n=171		Illicit Use of BNX n=110		Chi <sup>2</sup> /df	p
	n	%	n	%		
Illicit use of BNX before first BMT	2	1.2	95	86.4	214.94/1	<0.001
Duration of BNX treatment (mean±sd, month)	13.37	10.42	8.97	7.70	t=4.06	<0.001
Longest remission with BNX (mean±sd, month)	12.80	10.30	7.41	5.49	t=5.70	<0.001
Current BNX dose (mean±sd, month)	8.28	2.36	9.09	2.73	t=-2.56	0.011
Daily dose of 10 mg or higher	48	28.1	38	34.5	1.32	0.25
Number of BMT episodes					16.83/2	<0.001
This is the first	145	84.8	71	64.5		
This is the second	23	13.5	30	27.3		
This is the third or later one	3	1.8	9	8.2		
Considering the BNX dose as sufficient	152	88.9	101	91.8	0.64	0.42
Education for BNX use	114	66.7	75	68.2	0.07	0.79
Legal problems or probation	98	57.3	73	66.4	2.30	0.13
Giving away BNX	2	1.2	5	4.5	3.14	0.076
More frequent or higher doses	17	9.9	20	18.2	3.98	0.046
Less frequent or lower doses	15	8.8	24	21.8	9.53	0.002
Different route of BNX administration	1	0.6	4	3.6	3.57	0.079
Use of other substances	19	11.1	32	29.1	14.57	<0.001

BNX: Buprenorphine/naloxone

a drug dealer, 46 (40.8%) from a friend, and 6 (5.4%) from a doctor or a pharmacy. The reasons given for using illicit BNX were to get rid of withdrawal symptoms while quitting heroin for 86 (78.2%) of the participants, being unable to get heroin for 12 (10.9%) of the participants, and to relieve pain or psychological boredom for 15 (13.6%) of the participants (not shown).

### 3.4. Related variables with illicit BNX use

There were no statistical differences found for gender, employment status or age, whereas a longer duration of education and being divorced were ranked higher in the group that used illicit BNX. Duration of heroin use and the injection of heroin did not differ between the groups (Table 1). Illicit use of BNX before beginning the BMT, current BNX dose, and number of previous treatments were higher and the duration of BNX treatment and duration of remission with BNX treatment were placed lower in the group that used illicit BNX. Patients who considered their BNX dose sufficient, those receiving lower (8 mg or lower) or higher doses (10 mg or higher), those receiving education for BNX use, having a legal problem or probation, using other routes for BNX than the sublingual one, and giving away their BNX dose did not differ in frequency between the groups. The

group that used illicit BNX had a higher percentage for the use of a more frequent or a higher dose, but also for a less frequent or a lower dose (18.2% and 21.8%, respectively, as against 9.9% and 8.8% for the group that did not use illicit BNX) (Table 2). The reasons given for using more frequent or higher doses of BNX than those prescribed were: to decrease craving for 25 (67.6%) of the participants, to relieve withdrawal symptoms for 20 (54.1%) of the participants, and to 'get high' for 2 (5.4%) of the participants. The reasons given for using less frequent or lower doses of BNX than those prescribed were because the prescribed dose was high for 9 (23.1%) of the participants, to test craving and withdrawal for 9 (23.1%) of the participants, to use alcohol or benzodiazepine for 5 (12.8%) of the participants, and to keep it for later use for 3 (7.7%) of the participants, whereas four (10.5%) of the participants reported that they forgot to take their dose (not shown).

### 3.5. Illicit use of BNX before beginning BMT

Those who reported the illicit use of BNX before beginning BMT (n=97, 34.5%) had a lower duration of their current BMT (8.36±7.16) than the group that did not report the illicit use of BNX (n=184, 65.5%; 13.38±10.38; t=4.76, p<0.001). The percentage of patients who had started on BMT for the second time or

more was higher (33.0%, n=32) among those who reported illicitly using BNX before starting on BMT for the first time than those who did not (17.9%, n=33) ( $\chi^2=8.10$ , d.f. =1,  $p=0.004$ ).

### 3.6. *Abusing other substances during BMT and reasons for abusing other substances*

The percentage of those using other substances during BMT was higher in the group that had used illicit BNX (29.1%) than in the group that did not (11.1%) (Table 2). Of those who reported that they had abused other substances while they were using BNX (n=51, 18.2%), 28 (54.9%) reported that they abused heroin, 36 (70.6%) reported that they abused substances other than heroin, and 19 (37.3%) used multiple substances. The reasons given for using other substances while using BNX were to 'get high' for 21 (41.7%) of the participants, because of an insufficient BNX dose for 14 (27.5%) of the participants, to relieve withdrawal symptoms for 11 (21.6%) of the participants, and other reasons for 9 (17.6%) of the participants.

### 3.7. *Routes of BNX administration other than the sublingual one*

Only 2 of the patients reported injecting BNX and 3 reported smoking, inhaling or using BNX nasally instead of the sublingual route of administration (not shown).

## 4. Discussion

The main finding of this study is that, of the patients who reported that they had used illicit BNX at least once (39.1%), 86.4% had previously used this drug illegally before starting on their first BMT, mostly to relieve withdrawal symptoms. These results are consistent with previous studies [16, 27] and may suggest that in Istanbul the difficulty of supplying treatment for those who seek it is a more serious problem than misuse. The reason for BNX to be found on the black market may be that clinics prescribing BNX may not have been carefully choosing appropriate patients for BMT, who may be selling their treatment drug to dealers on the black market, because the demand for BNX on the black market may be related to attempted self-treatment [39]. In other words, this behaviour may be considered as a diversion rather than an abuse.

The duration of heroin use, injection as a route

of heroin administration, and having a legal problem or a probation were factors that did not differ between the two groups, which may suggest that illicit use and diversion are independent of the severity of dependence. In Australia, of all BMT clients, 13% reported recently injecting their medication and 22% reported the removal of supervised doses [19]. These percentages are much higher than those found in the present study. Nevertheless, since 81.9% of the patients who reported that they did not use illicit BNX stated that somehow they knew that BNX could be obtained illegally may suggest that diversion cannot be ignored in Istanbul. Consistently with previous studies [21, 32], dealers and friends were the most common source of illicit BNX, followed by a patient's doctor or pharmacy, the latter source accounting for 5.4%. In the study by Cicero and coll. [10] patients identified doctors as the most common source (57%), followed by drug dealers (35%) and friends (23%). Buying a supply from a doctor may be a practice reflecting inadequate dosage prescription, and the need for higher dosages for the majority of patients receiving BMT [14, 15]. In some cases, illicit use or the diversion of BNX might, to a certain extent, be an attempt at self-treatment, influenced by prescribers who are inattentive to individual variations in the severity of opioid dependence or are unaware of psychiatric and/or medical comorbidity. Lack of training and the lack of national guidelines for BNX prescription were found to be the major causes of insufficient dosage prescription by French general practitioners [14, 15]. Thus, it is possible that doctors are an indirect source of diverted BNX and could benefit from continuing educational activities [22]. In the present study, although there was no difference depending on the education given for BNX use between the groups, compulsory education was only given to 67.3% of the patients. This percentage might be even lower in the dropout patients, who were not included in the present study. It has already been shown that diversion occurs more frequently in patients who are given prescriptions in primary care than in those who are prescribed in a drug treatment centre [4], where social and psychiatric services are available. Nevertheless, these results may suggest that when prescribers are educated for the use of this drug and when they carefully evaluate their clients' needs, illicit use and diversion may lessen.

Previous meta-analyses suggested that slow BUP induction and/or using lower doses of BUP, even lower than recommended, may be associated with poorer retention in treatment [3, 25]. In an obser-



vational study on adults, initial induction doses of 16 mg were associated with better retention in treatment [34]. Consistently with these, a recent study conducted in AMATEM Istanbul suggested that the severity of craving and withdrawal symptoms were related to dropout in a 6-month follow-up, rather than the severity of opioid dependency or motivation for treatment [20]. In the case of inadequate dosage, patients may have to self-manage their opioid dependence. The increase in illicit use and diversion may be driven by the increase in abuse, but it may also be driven by therapeutic demand, suggesting treatment expansion may be necessary [2, 18, 39]. The physicians mostly attributed the diversion to “therapeutic” reasons [16]. Consistently with this, when opioid-dependent treatment seekers gained access to legal prescriptions, the illicit use of BNX decreased [33]. Although current BNX doses were higher in the group that used BNX illegally, and considering the BNX dose as sufficient did not differ between the groups, the duration of BMT and the duration of remission with BMT were lower in the group that used illicit BNX. A percentage of using a more frequent or a higher dose, a less frequent or a lower dose and other substances during BMT was higher in the group that used illicit BNX. The reasons most frequently given for using these were to relieve craving or withdrawal symptoms, and that the dose of BNX was insufficient. These results may suggest that the dose of BNX may be insufficient for some of the patients, even if they themselves consider the dose to be sufficient. Nevertheless, BNX may be insufficient for those with a severe opioid dependency, to whom methadone may be beneficial. Unfortunately, alternative treatments are not available in Turkey.

#### Limitations

Since survey participants were a non-random sample of heroin-dependent patients that were in BMT in AMATEM, Istanbul, one limitation of the study is that the study sample may not be representative of Turkey and the results may not be generalizable to all the patients in BMT in the country. Another limitation is that the collected data, including receiving illicit BNX, is based on self-report. Finally, since these patients included in the present study were compliant with the treatment and the study was a cross-sectional one, further follow-up studies that also include dropout patients are needed.

## 5. Conclusions

The findings of the present study suggest that the prescription of the BNX as a take-away medication for unsupervised administration, such as that applied in Turkey, needs to be based on a careful risk assessment of diversion. Although supervised dosing may minimize diversion, it can be a serious obstacle to people participating in treatment, and an obstacle to social reintegration, too. Our previous study showed that the patients who had been started on BMT during two weeks of hospitalization, stayed in outpatient BMT longer than those who had started on an outpatient BMT programme without any inpatient treatment [13]; as a result, supervised dosing at least during the initiation phase of the treatment, when dropping out of the treatment is most common [13, 34], may be helpful in AMATEM, Istanbul. During this period patients should be provided with clear guidance on how and why medication is given, and, when diversion happens, it may be useful to take the opportunity to discuss the reasons and thoughts behind the diversion with the patient. A reassessment of treatment efficacy through a possibly higher dosage increase could potentially reduce diversion and assure sustained compliance with BMT [30]. For example, clinicians in AMATEM, Istanbul should consider giving higher doses than they usually prescribe to patients with a higher severity of craving and withdrawal symptoms during the initiation phase of the treatment [13]. Also, clinicians working in AMATEM, Istanbul should improve their understanding of the comorbidity of other psychopathologies in these patients by giving structured interviews, which do not seem to be implemented. Prescription monitoring programmes [28] may also help to limit the illicit use and diversion of BNX in Turkey. Our findings are consistent with previous findings stating that BNX maintenance programmes should be made more easily available in Turkey, especially in Istanbul, to decrease the diversion of BNX [2, 39]. In any case, the continuing education of doctors [14, 15, 22] and a national guideline for BNX prescription [14] may be needed to improve the quality of these programmes.

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## Requests for quetiapine from jailed substance abusers: are they a form of abuse or self-medication in response to long-term opioid dysphoria?

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### Summary

**Background and aims:** Quetiapine is an available resource in the treatment of psychotic symptoms and agitation in schizophrenia and bipolar disorder. It has also proved effective in relieving withdrawal from opiates and other substances, with a favourable impact on anxiety, pain perception, insomnia, reduced appetite and negative craving. Cases of abuse have been documented in jails. So far no study has related illegal quetiapine use to one specific category of substance abuse. **Methods:** the anamnestic and clinical data of 17 substance abusers who had been asking for quetiapine, were gathered during a period of imprisonment. **Results:** Subjects were adult males, mostly of Arabian origin, who asked to be given quetiapine after imprisonment, showing stabilization at therapeutic dosages, especially in the lower dosage range. Their shared clinical features were dysphoria and aggressiveness, while they showed heterogeneous profiles for substance abuse patterns and pictures, psychiatric history and on-going treatments. **Conclusions:** All the cases described in this paper, indicate a phenomenon of quetiapine use, with no clear core features of abuse or addiction, but a usage pattern that is, certainly, specifically oriented towards quetiapine.

**Key Words:** quetiapine demand; jailed substance abusers; self-medication; opioid dysphoria.

### 1. Introduction

Quetiapine is officially marketed as an antipsychotic drug, and has shown its effectiveness both on pictures of schizophrenia and on the symptoms and course of bipolar disorder. Its pharmacological profile is characterized by an antagonist action on receptor subtypes alpha1 and 2 (noradrenergic), D1 and 2 (dopaminergic), 5HT1A and 2 (serotonergic), H1 (histaminergic). Its inclusion in the class of atypical antipsychotics accounts for a 5HT2/D2 affinity ratio greater than one, as well as a lower degree of binding strength to D2 receptors [17].

More recently, the properties of a slow-release formula of quetiapine have been described reporting a variety of kinetics that results in a processing

of quetiapine by the liver that involves the accumulation of its metabolite nor-quetiapine. Since this latter has been shown to possess a significantly selective noradrenergic reuptake inhibition (NRI) activity, the slow-release formula appears to ensure significant action on depressive symptoms, by providing a higher, longer-lasting plasmatic concentration of nor-quetiapine. Some papers suggest the usefulness of quetiapine in the dimensional treatment of dysphoria and aggressiveness linked to suicidal risk, and in the anxiety outbursts displayed by drug abusers [17].

Small-size studies suggest quetiapine's potential effectiveness in treating cocaine addiction in subjects with bipolar disorder [1, 9], while a single uncontrolled study reports its positive effect in curtailing alcohol abuse in bipolar alcoholics, as an add-on to

lithium or valproate [20]. Lastly, quetiapine proved useful in relieving a variety of symptoms brought on by acute opiate withdrawal [16] (at doses ranging from 25 to 600 mg/day) or following detoxification from opiates and other substances [8, 19], in particular on anxiety symptoms, pain perception, insomnia, reduced appetite and craving rising in relation to discomfort.

On the other hand, cases of quetiapine abuse have been documented [14], at least among substance abusers, and especially in prisons [6], by an intranasal route, [13], intravenously [7] or orally [18]. Quetiapine can elicit rapid-onset reward (often called a 'rush') in subjects with a history of cannabis, alcohol and depressant use, and may become the object of chronic misuse in experimenters [2, 5, 23].

We report a series of consecutive cases of non-medical quetiapine use reported by detainees in an Italian prison, mostly resulting in a request for quetiapine during imprisonment. Our aim was to clarify whether this need for quetiapine, and its previous non-medical use are peculiar to certain specific substance abuse patterns (in particular, those centring on heroin) or else is related to other demographic and clinical features.

## 2. Methods

We gathered data about 17 consecutive cases that had come to the attention of the medical staff of a prison. Detainees were all held in custody in sections that had a high turnover, and were mainly assigned to convicts serving terms for minor offences. Definition criteria for inclusion in the analysis were:

An explicit request for quetiapine, in some cases due to its being needed as a replacement for other poorly tolerated and ineffective antipsychotics, and in other cases as the only acceptable treatment.

A self-reported history of non-medical use of quetiapine before imprisonment, in some cases taken for the first time according to medical prescription.

The singularity of such cases is also related to the prescription laws regulating the use of quetiapine in Italy. It is, in fact, quite expensive when bought directly from pharmacies with a normal medical prescription (with a legal price to the public of 1-3 Euros for a single 100 mg oral dose, and as much as 300 Euros for a high-dose package containing 60 pills); otherwise a special document must be issued by Local Health Districts (but only after diagnosis followed by treatment failure with typical antipsychotics) for an authorized prescription allowing the cost to be

charged to the public health system. Assuming it may be available through illegal channels, its cost should be considerable, whereas a constant source of supply on the black market through the diversion of prescriptions is unlikely too, since there is not known to be any major demand for quetiapine, and therapeutic supply requires an electronically codified prescription, due to the rules for public reimbursement. Diversion of large quantities would therefore have to take place in an organized way, at least involving a prescribing doctor working in the public system, in a way that would be traceable, so creating the risk that he/she would have to reimburse all costs personally, as the penalty for signing improper prescriptions.

## 3. Results

### 3.1. Demographic data

Subjects were male, with an average age of  $27.18 \pm 4.6$  (median 26, range 18-37), 13 coming from Tunisia, 1 from Algeria, 2 from Italy, 1 from Palestine, all with a recent and/or past history of substance abuse.

### 3.2. Lifetime substance use

Ten (58%) were abusers or addicts of opiates, 14 (82%) of cocaine, 3 (18%) of amphetamines; 10 (58%) had a history of continuous cannabis use, 11 (64%) had abused or were addicted to alcohol, 2 (18%) had abused hallucinogenic drugs, 3 (18%) had a history of clonazepam use and 4 (24%) of anticholinergic drugs (orphenadrine, biperidene). Polydrug abuse was the prevalent condition (14 subjects, 82%).

### 3.3. Division into groups according to the first substance of abuse

First involvement with regular psychoactive substance use concerned alcohol and/or cannabis (9, 53%), cocaine (3, 18%), heroin (3, 18%). Age at first continuous substance use was  $18.00 \pm 3.8$ , more precisely  $20.11 \pm 6.0$  for heroin,  $20.70 \pm 4.8$  for cocaine,  $18.50 \pm 4.2$  for cannabis,  $19.33 \pm 3.1$  for alcohol. Student's T-test for matched samples failed to reveal any constant sequence in the chronology of substance abuse.

### 3.4. Urinalyses

Subjects were tested for recent substance use by

urinalyses, which turned out to be positive in 47% of these cases for morphine, 58% for cocaine, 5% for amphetamines, 58% for cannabinoids, 5% for alcohol, and 37% for benzodiazepines.

### 3.5. Psychiatric History

Although language problems, and the high incidence of acute psychomotor excitement at the time of admission into a prison, made it quite awkward to gather full anamnestic information, it was possible to assess the presence of some psychiatric history in 65% of these subjects (hospitalization or outpatient treatment); as many as 16% reported a clear first-degree family history for major psychiatric events (acts of or attempts at suicide, hospitalizations). Past aggressive behaviours were reported by 4 (23%), self-injuring behaviour and attempted suicide by 8 (47%).

### 3.6. Therapeutic aspects

Various therapies were administered in different detention periods. Nevertheless, some clinical aspects were recurrent: psychomotor excitement (dysphoric mania, mixed mania or agitated depression) was displayed by 13 (76%), self-injuring behaviour by 2 (12%), insomnia by 3 (18%). Only one subject (6%) expressed delusional ideas. All subjects explicitly requested quetiapine: two of them (12%) reported taking it at the time of entry into prison. Three subjects refused to take any antipsychotic drug other than quetiapine (18%). Five subjects (29%) explicitly requested the immediate-release formula or asked for their slow-release dose to be replaced by an equivalent immediate-release dose, and three (18%) did not express any preference. The majority were in polydrug treatment, and the average benzodiazepine dose administered after the stabilization of acute symptoms was equal to  $7.88 \pm 7.7$  mg/day (2-12). In all subjects, the maintenance or introduction of quetiapine did not lead to health problems, and, including those who had had another antipsychotic treatment that had been replaced, resulted in the improvement of psychiatric conditions, with special regard to excitement and aggressiveness. Patients were stabilized on quetiapine at dosages of  $263.33 \pm 120.2$  mg (150-600 mg/day).

## 4. Discussion

Reports in the literature indicate the possibility of quetiapine abuse [2, 7, 12, 13, 15, 18, 23]. However, self-directed administration, illegal means of

supply, withdrawal symptoms and consumption by the same routes as other substances of abuse are not enough to define a clinical picture of abuse or addiction in psychiatric terms. Indeed, the subjects included in our sample, though appearing to be quetiapine-seekers outside a therapeutic context, actually showed stabilization after quetiapine administration, consistently with their claim of self-medication. In this light, quetiapine use does not seem to be related to specific withdrawal symptoms: it may take place during withdrawal from different substances, but the demand for quetiapine after imprisonment does not run parallel to acute withdrawal. Subjects who asked to have their quetiapine maintained did not show a trend towards dose increases, and stabilized at therapeutic dosages, located in the lower range.

Subjects who were not in methadone treatment did not request greater dosages; their requests were, in fact, for 600 mg in one case, and 200 mg in the other two. Moreover, requests for quetiapine may persist over the course of acute withdrawal, and do not rise in coincidence with the onset of acute withdrawal, so that there is no evidence of causal correlation with withdrawal symptoms. Generic dysphoria, including self-injuring behaviour, suicidal ideation or aggressiveness, was displayed by all these subjects except for one, who was already in mood-stabilizing treatment (sodium valproate) and reported resorting to quetiapine to limit cocaine craving. That kind of use is also indicated by other reports in the literature [1, 9, 19]. The shared syndrome looms as being characterized by dysphoria, agitation and aggressiveness, with a variety of accessory features and roots, which could not be further defined in terms of categorical diagnosis or toxicological status.

The hypothesis of quetiapine abuse may be supported by its sedative properties, which are also found in other substances with hallucinogenic and rewarding properties, as well as medical drugs which may be an object of abuse, like amitriptyline [3]. Four subjects in the sample had a history of anticholinergic drug use in a therapeutic context, although they had first tried those results as a result of a medical prescription against the side-effects of antipsychotic treatment. The anticholinergic effect is, however, negligible for quetiapine, which is sedative rather than acting through an adrenolytic, antistaminic effect. Having said that, it must be stated that some facts fail to confirm the hypothesis of quetiapine abuse: not all subjects requested immediate-release quetiapine, and some explicitly asked for slow-release quetiapine. Dosages were low-to-average within the thera-

peutic range, which suggests self-medication use against non-psychotic symptoms rather than uncontrolled use. Although non-oral use is reported in the literature, all the subjects in our sample had used oral quetiapine and then requested quetiapine in that form. An alternative hypothesis is that subjects choose to self-medicate themselves by using quetiapine as a remedy for dysphoria, in a way similar to what can be done by experimenting with some benzodiazepines. The channel of supply is likely to be based on the diversion of quetiapine by subjects who get it by medical prescription, or through black market operators buying quetiapine directly from stores or pharmacies. This latter form of illegal supply should be quite expensive for illegal users, and is unlikely to be acceptable for clandestine foreign, jobless individuals, while diversion from factitious patients may provide a source of quetiapine that is available at low prices. Since quetiapine is not widely available on the black market, and quetiapine abuse is not featured as a reason for treatment demand in public centres, a sharply oriented illegal supply channel for quetiapine does not appear to be so lucrative, looming instead as an extra source of income for some substance abusers, favoured by small-scale diversion in local environments. Some subjects may try to control spontaneous dysphoria, others substance-induced dysphoria or withdrawal-related dysphoria, and others again may add it on to their ongoing psychiatric treatment to control peaks of dysphoria. In other words, illegal quetiapine may follow the same routes as illegal methadone [11]. Self-selection of quetiapine may take place through alignment with a genetic feature, as suggested by the clear majority of Arab subjects in the sample.

The association of quetiapine with methadone has proved to increase methadone blood levels up to 150% of the expected levels [21]. Also, some neurochemical properties may be common to both compounds, since they cross-react at toxicological tests [4, 10, 22].

## 5. Conclusions

All the cases described here indicate a phenomenon of quetiapine use, with no clear core features of abuse or addiction, but a usage pattern that is, certainly, specifically oriented towards quetiapine.

The subjects whose case histories have been reviewed here resemble those who are eligible for quetiapine treatment, on the basis of displayed symptoms and psychiatric histories, whereas they differ in

their substance use history and current toxicological status. The sedative and anti-dysphoric properties of quetiapine, especially in combination with ongoing treatments, and taking genetic factors into account, may be crucial in orienting individuals towards self-directed illegal quetiapine use, after initial exposure in a medical context. Such use is better described as self-medication rather than abuse.

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#### *Contributors*

Authors contributed equally to this article.

#### *Conflict of interest*

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## Prevalence of HCV infection and adherence to DOT therapy in Italian and non-Italian iv drug users in Rome, Italy

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### Summary

**Background:** The prevalence of HCV-related liver disease among Italian drug addicts is high. Although screening for HCV infection should be offered to all injection drug users (IDUs), only a few of them have been tested for the virus in recent years, and even fewer have been treated. **Aims:** To assess the prevalence of HCV infection in an IDU sample in Rome and to compare adherence to treatment in Italian vs non-Italian patients. **Methods:** 261 IDUs underwent screening for HCV, HBV and HIV infection. Patients eligible for treatment were treated with Directly Observed Therapy (DOT). **Results:** The prevalence of HCV infection among IDUs screened in our Unit was 47.1% (123/261). 96 patients were males, 37 females; average age was 46.2±11.2 years. The most frequent genotype was 1 (45.4%) followed by genotype 3 (36.1%), genotype 4 (11.6%) and genotype 2 (6.9%). Among HCV-positive drug addicts, the prevalence of HBsAg and HIV positivity was 7.2% and 1.5%, respectively. Only 23.1% of subjects had been vaccinated, whereas 48.2% were negative for any HBV marker. The HCV-RNA qualitative test was performed on 53.5% (66/123) of patients; of these, 84.3% (56/66) were HCV-RNA positive. A higher percentage of foreign patients started treatment than Italian ones (69.5% versus 48.3%), but a higher percentage of dropouts was reported among immigrants than among Italian drug users (56.2% versus 23.3%) ( $p < 0.05$ ). **Conclusions:** The present study confirms the importance of DOT therapy (showing a considerably lower percentage of dropouts) and of the multidisciplinary approach, together with the inclusion of cultural mediators in the management of foreign IDUs in overcoming linguistic and cultural barriers, and in raising awareness of the disease.

**Key Words:** HCV infection; injecting drug users; DOT therapy

### 1. Introduction

The prevalence of HCV-related liver disease among drug addicts is very high worldwide and, in particular, in Italy [4-6,8-12,14]. Although screening for HCV infection should be offered to all IDUs, few patients have been tested for the virus in Italian Drug Addiction Units in recent years; even fewer have received antiviral treatment [14], despite the high efficacy of the current therapy for HCV [2,7,13,15].

Aim of the study is to assess the prevalence and characteristics of HCV infection in a sample of drug addicts in Rome, Italy; and to compare adherence to treatment in Italian with non-Italian patients managed with Directly Observed Therapy (DOT).

### 2. Methods

From September 2011 to September 2012, 261 IDUs were observed in the Drug Addiction Unit of the local ASLC health service in Rome; all of them underwent screening for HCV, HBV and HIV infection. The initial screening test was a third-generation enzyme immunoassay (EIA) for HCV antibodies. If the EIA anti-HCV test gave a positive result, infection was confirmed by a highly sensitive PCR-based qualitative HCV-RNA assay. The HCV-RNA quantitative assay and HCV genotype were performed before starting antiviral therapy.

Enrolled Italian drug addicts (21 patients) were treated with directly observed therapy (DOT), which means a direct observation by a healthcare worker of

each patient swallowing pills and of each weekly injection of pegylated interferon.

Adherence was defined as the intake of >80% of scheduled PEG-IFN doses for >80% of the scheduled treatment period.

Counselling, psychiatric and toxicological pre-treatment evaluation were provided, too.

### 3. Results

The prevalence of HCV infection among IDUs screened in our Unit was 47.1% (123/261). 96 patients were males, 37 females; average age was  $46.2 \pm 11.2$  years. The most frequent genotype was 1 (45.4%) followed by genotype 3 (36.1%), genotype 4 (11.6%) and genotype 2 (6.9%). Among HCV-positive drug addicts, the prevalence of HBsAg and HIV positivity was 7.2% and 1.5%, respectively. Only 23.1% of subjects had been vaccinated, whereas 48.2% were negative for any HBV marker. The HCV-RNA qualitative test was performed on 53.5% (66/123) of patients; of these, 84.3% (56/66) were HCV-RNA positive.

The 56 HCV-RNA positive subjects were evaluated for therapy; 10 patients were not eligible for treatment because of contraindications such as alcohol abuse (n=5), psychiatric problems (n=4), thrombocytopenia (n=1), while another 9 patients refused treatment. As a result, out of a total of 56 candidates for therapy, 37 (66%) actually started treatment.

Until August 2012, of 37 patients under treatment, 19 (51.3%) were taking methadone, 3 (8.2%) buprenorphine and 15 (40.6%) were not receiving agonist therapy (4 of them were active opiate users, 6 occasional users, 5 ex-drug users). Of 66 patients, 43 were Italian (65.2%) and 23 (34.8%) were immigrants from Eastern Europe (14/23, of which 11/14 from the former Soviet Union, 9 from Georgia, 1 from Ukraine, 1 from Kazakhstan), Africa (8/23) and Asia (1/23)). The average age of Italians was  $44.3 \pm 8.6$ , whereas that of foreigners was  $36.7 \pm 8.7$ , ( $p < 0.002$ ); 81.4% of the Italians were males and 8.6% females, while 91.3% of the immigrants were males and 8.7% were females.

No statistically significant differences were recorded as regards the educational level of Italians and immigrants; 56.5% of immigrants and 37.2% of Italians were unemployed ( $p = 0.05$ )

Enrolled Italian drug addicts (21 patients) were treated with directly observed therapy (DOT), whereas immigrant patients (16 patients) did not receive DOT. Compliance (80-80) with treatment was good in 72.7% of patients, poor in 27.3%; therapy was dis-

continued in 14 cases out of 37 (3 due to thrombocytopenia, 2 due to psychiatric problems, 9 for non-compliance) and 14 subjects completed treatment and follow-up.

Of 43 Italians, 21 (48.3%) started antiviral therapy, whereas 22 (51.7%) did not. Of the 21 patients undergoing therapy, SVR was obtained in 6 cases, 4 cases were non-responders and 5 discontinued therapy (3 due to thrombocytopenia and 2 for non-compliance). Therefore, the total dropout rate from therapy amounted to 23.3% (5/21). The 22 drug addicts did not start treatment due to negative HCV-RNA (9 cases), psychiatric problems (3 cases), alcohol abuse (3 cases) and thrombocytopenia (1 case), whereas 6 patients refused therapy.

Of 23 immigrant patients, 16 (69.5%) started antiviral therapy and 7 (30.5%) did not. Among the 16 patients who underwent therapy, 4 obtained SVR, 3 are still undergoing treatment and 9 discontinued therapy (2 due to psychic disorders and 7 due to poor compliance). Total dropout rate amounted to 56.2% (9/16). Seven immigrant patients did not start treatment due to: negative HCV-RNA (1 patient), alcohol abuse (2 patients), psychiatric disorders (1 patient), therapy refusal (3 patients).

A higher percentage of foreign patients started treatment than Italian ones (69.5% versus 48.3%), but a greater percentage of dropouts was reported among immigrants than in Italian drug users (56.2% versus 23.3%) ( $p < 0.05$ ).

### 4. Discussion

HCV infection prevalence in the cohort under review was high (47.1%), in conformity with the national and international literature [4,5,6,8,9,10,11,12,14]. In accordance with the results recently published in the DAVIS study [14], one prominent result was the high prevalence of genotype 4 HCV; this is increasing in Italy, partly due to migration inflows from areas where this genotype is highly endemic, such as Africa. In agreement with the study just mentioned, we found a low percentage of HCV-positive drug users vaccinated against HBV (23.1%), a high percentage of subjects who were negative for all HBV markers (48.2% in the present study, 42.3% in the DAVIS study). These results should lead to an increase in vaccinations against HBV among drug addicts with HCV-related liver diseases attending Drug Addiction Units in Italy. Study results also confirmed the feasibility of administering antiviral therapy to drug addicts undergoing maintenance treatment with methadone or

buprenorphine, to occasional drug users or to active drug addicts (in the latter group compliance is lower), as suggested by Belfiori et al. [2]. The prevalence of HIV/HCV co-infection was low in our study (1.5%) as also in the DAVIS data (3.1%) [14], but differed from the data reported by Curcio et al. [3] where the prevalence was higher (8.9%). Furthermore, our data confirm that a multidisciplinary approach involving hepatologists, psychiatrists, clinical psychologists, toxicologists and nurses should be adopted in order to improve HCV infection management in IDUs, who are otherwise difficult to reach and treat. This approach includes counselling that aims to increase patient motivation, DOT strategy and periodic psychological, psychiatric and toxicological assessments (before, during and after antiviral treatment). Even though the multidisciplinary approach proved to be effective with all patients, some differences emerged between Italians and immigrants.

A datum in apparent disagreement with the observation just made, but which is not significant due to low sample power, is that the percentage of foreign patients who started treatment was higher than in the case of Italian ones. The higher percentage of drop-outs among immigrant IDUs could be explained by the fact that they did not undergo DOT for practical reasons (work, difficulty in reaching Drug Addiction Units, and so on); it was also due to linguistic and cultural barriers (cultural mediators were not always available). Other factors could be the lower average age and the higher percentage of unemployed people in this group. As regards the higher percentage of immigrant patients who started therapy (even though the datum is not statistically significant), this could be explained by underestimation or lower comprehension of the possible side-effects of therapy in this group.

## 5. Conclusions

The present study confirms the importance of DOT therapy (which shows a considerably lower percentage of dropouts) and of the multidisciplinary approach, together with the inclusion of cultural mediators in the management of foreign IDUs to overcome linguistic and cultural barriers, and raise awareness of the disease.

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## How to treat the treatment system

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### *Summary*

The ancient Greek maxim "Know thyself" also applies to health care systems, which cannot adequately cure the patients if they cannot cure themselves. They should be able to identify and repair their own shortcomings. Treatment should be available for all patients who need it and there should be no waiting-lists. To reach this availability primary care physicians should provide these treatments. Regulations should be eased, because excessive regulations and controls are counter-productive. They are a barrier to treatment and they increase the risk of death for patients.

*Key Words:* treatment system; treatment issues; critics

The ancient Greek maxim "Know thyself" also applies to health care systems, which cannot adequately cure the patients if they cannot cure themselves. They should be able to identify and resolve their own shortcomings.

Let us imagine a medical fiction: drugs against hypertension would be insufficiently available, patients could only have limited take-home doses, and failure to respect their diet would be sanctioned by the discontinuation of treatment. This would lead to the emergence of a black market. Some patients would be tempted to sell their drugs to make easy money they would spend in excessive food and drinks, which would increase their morbidity and mortality. People excluded from the treatment system would try to treat themselves with drugs bought on the black market.

Reduced to self-medication, without supervision, they would also suffer from higher morbidity and mortality.

### **1. A chronic relapsing disease**

This absurd system is however considered normal in the treatment of opiate dependence. In most of the world, the availability of opiate agonist treatment is significantly below requirements. Hence, the black market for medicine, the use of illicit substances, overdoses, injections in dire conditions and infections proliferate. This creates a vicious circle where the lack of treatment makes the treatment more difficult.

The general medical ethics is to move as soon as possible from diagnosis to treatment, in order to

reduce human suffering. There is no reason to do otherwise with illicit drugs' users. Fifty years of research have shown that opiate addiction is a long-term problem marked by relapses, that is to say a chronic relapsing condition. As with any condition of this type (diabetes, hypertension, etc.), opiate dependence requires most of the time a long-term treatment with adequate dosage of opiate agonist treatment like buprenorphine (Subutex, Suboxone ) or methadone.

**2. Effectiveness of treatment**

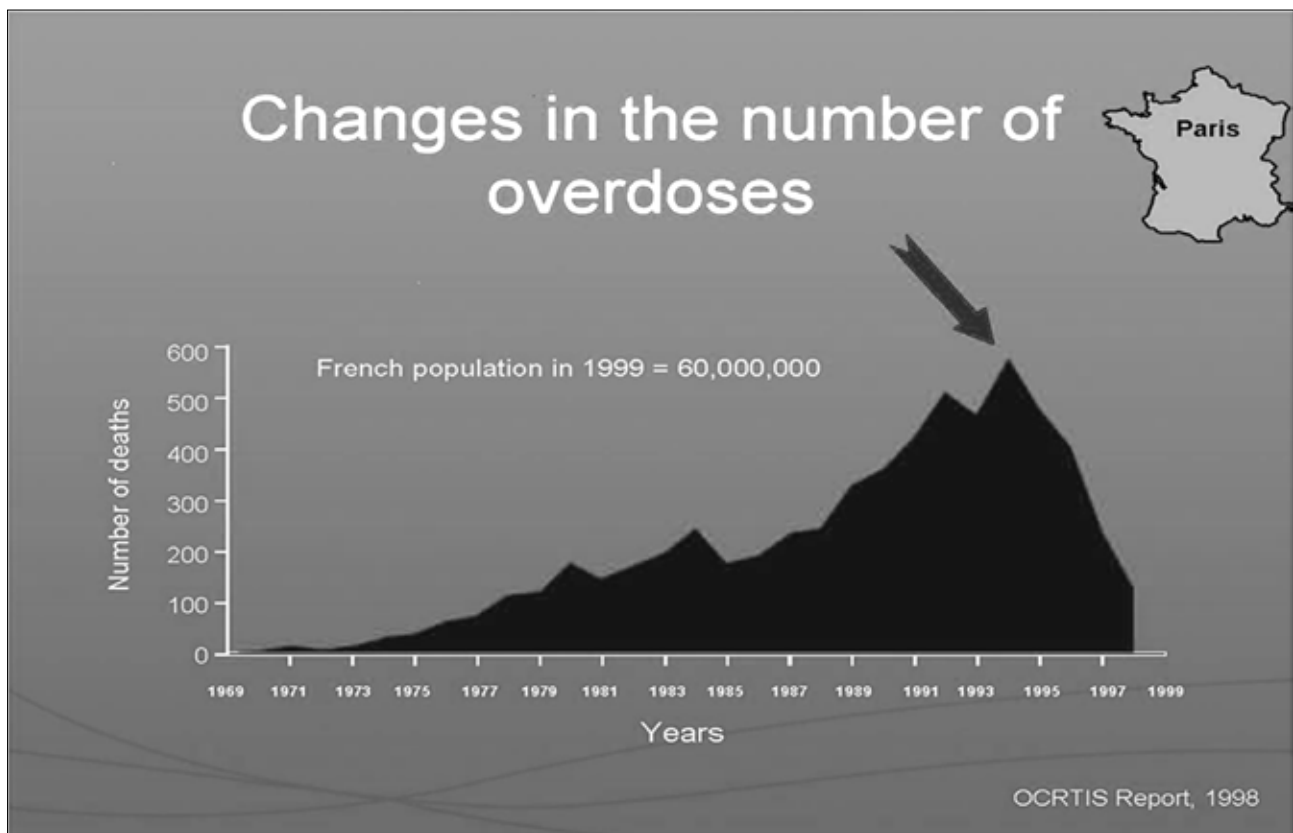
Yet this process is far from being considered as normal everywhere. What is the problem? It is not a problem of diagnosis of opiate addiction, which is quite simple. It is not either a therapeutic challenge because appropriate treatment is easy to carry on. The problem is in the transition from diagnosis to treatment, and more specifically in the barriers that society opposes to opiate agonist treatment.

To better understand this phenomenon, consider the natural history of a heroin addict. The first stage is a period of occasional use without dependence, which can be shorter or longer, depending on the personal history and the environment. Dependence appears

there, that is to say the need to use heroin every day. The dependence can last one to five years before a heroin addict makes an initial request for care. The treatment itself will take between three to twenty years (or more), depending on the personality and the environment.

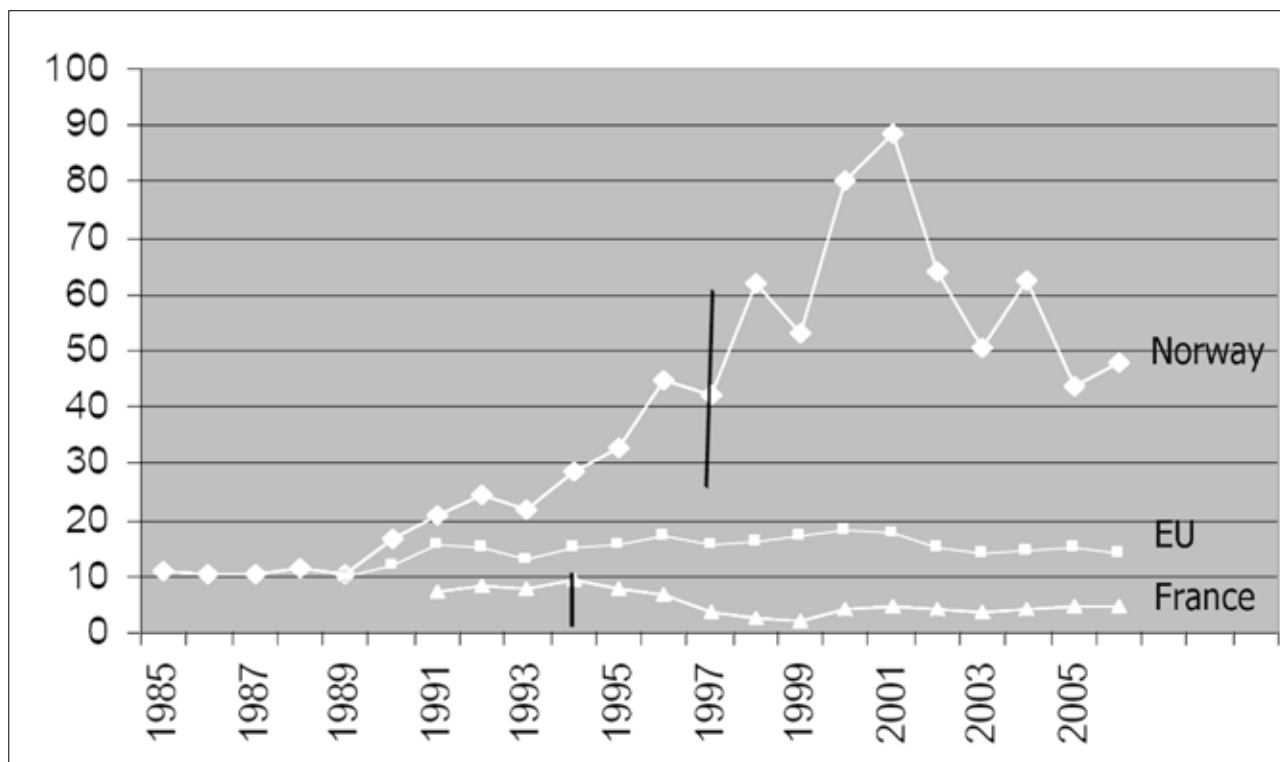
Heroin addiction is a double dependence: dependence to a substance and to a lifestyle, to an environment. This is why there are two strategies for therapeutic approach. One is to give medication withdrawal for a few weeks, then followed by "substitution environment", (i.e. residential post-cure) of six months to a year at least. Observation shows that at a given moment not more than 5 % of active addicts are willing to follow this pathway. Another therapeutic approach leads to a higher recruitment rate: the treatment with " substitution drugs " which are delivered on an outpatient basis and do not require removal from the environment. When this treatment is sufficiently available, about 70% of active heroin users are willing to enter.

The retention rate in residential treatment (" substitution environment ") is at best 30 %, while it reaches easily 70% with substitution drugs. The efficiency rate of the first processing system is around 5% x 30%



**Figure 1:** Mortality from overdose in France





**Figure 2:** Drug-related mortality in Norway, France and the European Union. Vertical lines: rapid increase of opiate agonist treatment in France (1995). Beginning of the “medically assisted rehabilitation treatment” in Norway (1998) [3].

= 1.5% of all heroin users, while the second system reaches 70% x 70% = 49%. Both systems have their necessity and their indications, but their social impact is obviously quantitatively different.

### 3. Realistic and utopic approaches

In a realistic perspective there should be no gap between treatment supply and demand, in order to avoid waiting lists. Access to treatment should be limited only by the cost/effectiveness ratio. In this perspective, in Belgium and France, for example, 85% to 90% of treated opiate addicts are in office-based treatment and 5% to 10% in outpatient clinics. 90 to 95% of patients are treated with opiate agonist treatment, buprenorphine (Subutex®, Suboxone) or methadone. A small number of patients are staying in residential aftercare centers.

On the contrary, some countries have chosen an utopic perspective. They pursue a dream of perfection regardless of the accessibility of care. For example, the Norwegian Health Department considers that Norway has the “most expensive treatment system” and “also one of the best system of the world” [4]. But if one compares the realistic and the utopic approaches based on a key criterion, namely the number of lives saved, we see that the number of deaths re-

lated to drug use is much higher in the utopic system.

In France, the dramatic increase in access to opiate agonist medical treatments (primarily Subutex) has led since 1995 to a sharp drop in the number of drug-related deaths.

On the contrary, the Norwegian system causes a drug-related death rate 10 times higher than the European Union average.

The difference is related to the fact that in the Norwegian “medically assisted rehabilitation” system, the provision of care is grossly inadequate compared to the demand. This induces the death of patients waiting for treatment. Norwegian studies have yet demonstrated that patients receiving buprenorphine, while they wait for a more comprehensive treatment, die less than those receiving a placebo (how surprising!) [6]. Despite these observations the Norwegian system continued to prescribe “time-limited buprenorphine replacement therapy” with a high mortality rate: in a study 5 out of 75 patients (6.6%) died in 24 months [5]. Another study has shown that the mortality rate was 1.9% per year while waiting for treatment and 0.4% during treatment [1].

Other countries offer insufficient access to opiate agonist treatment, despite its effectiveness. This can be explained by the fact that the treatment of drug users is just an option, that some countries did not

take yet or do not completely assume. The opposite option is expressed in the words of a responsible of public health in Russia, where opiate agonist treatment is totally banned: "You call addicts 'patients', we call them lost citizens..."

In countries who prefer to hide drug addiction problems, drug deaths contribute to this goal. However, addicts who disappear from society reappear in the statistics. This is why the Norwegian researchers have to recognize that "Norway shows a high mortality in drug statistics of the European Monitoring Centre for Drugs" [2] .

#### 4. How to cure the system

Such awareness could help to improve health care systems. In order to do this, one must first establish a diagnosis. It could be based on three main symptoms:

1. Availability of opiate agonist treatment
  - a. Proportion of patients in treatment
  - b. Treatment options
  - c. Flexibility or rigidity of supply
  - d. Stigmatization
2. Waiting-time before treatment
3. Existence of "open drug scenes".

Treatment should be available for all patients who need it and there should be no waiting-lists. To reach this availability primary care physicians should provide these treatments. Regulations should be eased, because excessive regulations and controls are counter-productive. They are a barrier to treatment and they increase the risk of death for patients.

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## Case report

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# Does a buprenorphine augmentation control manic symptoms in bipolar disorder with a past history of heroin addiction? A case report.

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### Summary

**Background and aim.** Bipolar disorder (BD) is often associated with substance use disorders with resulting negative outcomes, including increased severity of symptoms, more hospitalizations and poor treatment response. The aim of this case study presentation is to support the hypothesis that augmentation treatment with an opiate agonist may be indicated in psychotic patients with a history of heroin addiction during an acute psychotic episode. **Case Presentation.** A 40-year-old female with BD and a previous history of opiate addiction was treated with a combination of an antipsychotic, mood stabilizers and benzodiazepine for an acute dysphoric manic episode. She did not show any significant clinical improvement until the introduction of an opiate agonist medication. Although the patient did not present with a relapse into heroin use, it was considered that the severity of her symptoms and the low level of her response to therapy could be related to a hypophoric/dysphoric syndrome induced by previous long-term opiate abuse. We decided to start with a very low dose, considering that our patient had no opiate tolerance. Buprenorphine treatment was initiated at a dose of 1 mg on day 14 and was increased to a maintenance dose of 2 mg on day 15. There was a consequent rapid reduction in levels of agitation and dysphoria. **Conclusions:** The good clinical outcome in this case suggests that augmentation with an opiate agonist may be indicated in patients with BD and a history of opiate addiction, even in those who have not had a recent opiate relapse.

**Key Words:** buprenorphine; psychosis; pharmacological combination; hypophoria, dysphoria; dual diagnosis; bipolar disorder; heroin addiction

## 1. Introduction

Patients with bipolar disorder (BD) have a higher prevalence of substance use disorder (SUD) than those who have other psychiatric disorders [6, 8, 11, 12, 15, 23]. Lifetime prevalence of SUD in patients with BD ranges between 20% to 60% [1, 5, 19, 29, 31, 32, 35]. Several studies have documented the fact that comorbidity between BD and SUD is associated with a higher probability of hospitalization(s), a higher incidence of dysphoric mania, earlier onset of mood symptoms, more comorbid axis I disorders, and

a risk of suicide [3, 7, 16, 24]. It has also been shown to be associated with poor treatment response and increasing suffering, disability and health costs [13, 26, 28, 30, 33].

“Hypophoric syndrome” has been described by Martin and Ingles [18] in subjects with heroin addiction in remission. It is thought to be caused by residual damage to the opioid system, with consequently lower dopaminergic transmission, and is characterized by somatic, vegetative and mental symptoms, including susceptible or irritable mood, amplified pain perception, inability to perform simple tasks and inability to

experience reward without substance use [25].

In patients with opiate addiction, “hypophoric/dysphoric syndrome” related to the chronic use of heroin is often induced by the discontinuation of maintenance opiate agonist treatment and can lead to a relapse into substance use [34].

Moreover, in patients with comorbid BD and opiate addiction, drop-out from long term opiate agonist treatment can be associated with the worsening of psychopathological symptoms and reduced treatment response.

In this case report, we describe the effects on psychopathology symptoms of a treatment that combined an antipsychotic, a mood stabilizer and an opiate agonist (buprenorphine); the patient had comorbid BD and opiate addiction in remission.

## 2. Case presentation

### 2.1. Personal data

The patient was a single, unemployed 40-year-old female with a low-middle socioeconomic status currently receiving welfare benefits. She had completed primary school. She was right-handed. Between the ages of 16 and 20, she frequently changed jobs (in tourism and the agricultural sector). At the age of 22, she started abusing drugs and came into contact with the criminal justice system for the first time. Between 23 and 30 she spent around 6 years in prison for crimes related to her drug addiction pathology. The patient has a 5-year-old daughter who lives with one of the patient’s sisters.

### 2.2. Family history

The patient’s father died at the age of 61 from a myocardial infarct and had a history of alcohol abuse. The patient’s mother has no substance or alcohol or other psychiatric disorders. The patient has two sisters and one brother. One sister has a history of alcohol and sedative abuse.

### 2.3. Recent anamnestic data

In October 2012, the patient was involuntarily hospitalized for 3 weeks for an acute manic episode; it was the sixth episode in 9 months. In the previous 18 months she had failed to achieve a period of full remission of symptoms, and was poorly compliant with psychotropic medication. In that manic episode she displayed agitation, assaultive behaviour towards

family members and neighbours, incessant and boastful talk, and a decreased need for sleep. She had previously been abstinent from heroin for over 2 years.

### 2.4. Physical Examination

Physical examination showed a body weight of 72 kg and BMI of 31.8. Findings on physical examination were unremarkable. She had no history of significant medical illness (not even of hypertension or other kinds of cardiovascular disease) or neurological disorders.

### 2.5. Mental Status Examination

At medical examination, the patient was extremely dysphoric, agitated, and disinhibited. She was verbally expletive and went so far as to spit at staff. She was extremely demanding, making continuous requests to staff for coffee and cigarettes, and to be allowed to leave the ward. She had to be physically restrained to her bed to manage the risk of her becoming aggressive to others. She had mood-congruent delusions of a grandiose type. She believed that she was in touch with God, but displayed no auditory or visual hallucinations. She showed no evidence of cognitive impairment. On the other hand, she had no insight into her illness. It was difficult to establish any therapeutic rapport with the patient. She refused psychotropic medication.

### 2.6. Psychiatric History

History of bipolar disorder stretching over twenty years, characterized by recurrent manic episodes, interrupted by only a few brief periods of complete remission when a return to her premorbid level of functioning was recorded. Prior to 2002, there was a history of only sporadic contact with the Psychiatric Services due to her poor compliance with treatment and frequent incarcerations.

Between 2005 and 2010, the patient achieved a prolonged period of stability for her bipolar and substance use disorder and had a job at a psychiatric rehabilitation centre. During this period she was given prescriptions for Zuclopenthixol and Valproate – medications that had been effective during the past treatments for her bipolar disorder – and buprenorphine for her heroin addiction. In July 2011, the patient discontinued buprenorphine treatment.

## 2.7. Substance use disorder history

We investigated the use of the following substances of abuse:

- Heroin: onset of abuse at the age of 20 and dependency established by the age of 22 with occasional intravenous use.
- Cocaine and cannabis: occasional intermittent abuse of cocaine and cannabis since the age of 20. Abuse by patients of both these substances has been associated with a rise in aggressiveness and paranoid ideas.
- Alcohol: occasional abuse since the age of 20
- Nicotine: she smokes 20-30 cigarettes/day.
- Caffeine: she drinks 4-5 cups of coffee/day.
- No use of unprescribed benzodiazepine use was found.

Patient started opioid maintenance treatment (OMT) at the age of 24 at the Drug Addiction Unit (SerT) of Bolzano, Italy, but before 2002 she had engaged poorly with the service.

In contrast, between 2002 and July 2011 she engaged well in treatment with only short interruptions. In the last 2 years, she has remained completely abstinent from illegal drugs.

## 2.8. Laboratory and clinical exams

Routine investigations, including haematological and renal functions, blood sugars, triglyceride and cholesterol levels, liver and thyroid functions, urine analysis, electro-cardiogram and brain Computed Tomography did not reveal any abnormalities. Hepatitis (B and C) and HIV screening were negative. Drug urine test was negative for opiate and other illegal drugs. Zuclopenthixol blood level on day 14 was at 48.0 ng/ml (range 4.0-50.00 ng/ml), Valproate on day 14 was at 81.6 mg/ml (range 40-100 mg/ml).

## 2.9. Diagnosis

The patient was diagnosed as suffering from bipolar disorder type 1, the most recent event being a severe manic episode associated with psychotic features and a comorbid substance dependency, currently in remission. In addition, she was diagnosed as having a mild learning disability, as confirmed by Raven's Progressive Matrices. Antisocial personality disorder, and attention deficit hyperactivity disorder (ADHD) were evaluated with MINI-PLUS, but were not confirmed.

## 2.10. Assessments

We used:

- International Neuropsychiatric Interview-Plus (M.I.N.I.-PLUS): a short structured diagnostic interview for DSM-IV and ICD-10 psychiatric disorders [27].
- Young Mania Rating Scale (MRS): this is an 11-item, clinician-administered scale to measure the severity of mania. Scores in the 21-60 range indicate the presence of Manic symptoms (with increasing severity as scores rise) [36].
- Raven's Progressive Matrices: this is a non-verbal group test consisting of 60 multiple choice questions designed to measure reasoning ability, and generally referred to as testing general intelligence [22].

## 2.11. History of the patient's hospitalization

At hospital entry the patient was dysphoric and agitated. The MRS score was 46 (middling-severe mania). Before hospitalization, she was treated with Zuclopenthixol decanoate, 300 mg every 14 days. This therapy had been discontinued for a week. She was started on Zuclopenthixol oral drops, 40 mg/day, and Delorazepam oral drops, 4 mg/day. On day 2, she continued to be extremely agitated, and Zuclopenthixol (Acuphase) 100 mg i/m was administered. By day 3, there was minimal clinical response other than an improvement in sleep. On day 4, Zuclopenthixol decanoate, 300 mg i/m, was administered. Her psychomotor agitation had improved, but she remained dysphoric and developed extrapyramidal neuroleptic side-effects. Over the next five days, her clinical presentation failed to stabilize. By day 9, we started with Valproate, intravenous 1600 mg/day. By day 14, the patient had become more agitated and dysphoric. Even though dysphoria may have been partly related to the neuroleptic's dopamine antagonist action, given her past history of opiate dependency we considered the possibility of a persistent hypophoric/dysphoric syndrome. We therefore decided to restart her opiate agonist treatment. Buprenorphine 1 mg. was administered; after one hour, the patient no longer presented as dysphoric and became more cooperative. By day 15, buprenorphine 2 mg/day was administered. The MRS score fell to 24. The patient remained calm and cooperative: over a period of one week, Zuclopenthixol oral drops were gradually discontinued and Delorazepam was reduced to 2 mg/day. On day 22, the patient's symptoms continued to

improve and the MRS score had fallen to 17 (manic symptoms were no longer present). It was possible to administer Raven's Progressive Matrices: the raw score was 26, below the third percentile (medium-low intellectual level).

#### 4. Discussion

In this clinical case of comorbid bipolar disorder and opiate addiction in remission, we found that a combined treatment with neuroleptic medication, a mood stabilizer and an opiate agonist improved agitation and dysphoria. This observation is in line with the results of a study conducted by Pacini and Maremmani among patients with bipolar disorder and/or an acute psychotic episode who were treated with methadone [20]. In our case, another opiate agonist, buprenorphine, contributed to the resolution of manic symptoms and the reduction of hypophoria and/or dysphoria related to a long-term opiate withdrawal syndrome. Similar findings were reported in various studies by Maremmani and colleagues [10, 17, 21]. These studies did not demonstrate evidence of a significant difference between methadone and buprenorphine in reducing psychopathological symptoms in patients with heroin addiction.

In patients with current heroin addiction, various different guidelines recommend a rapid dose titration regime when starting treatment with buprenorphine [2, 4, 9], reaching a therapeutic dose (12-24 mg/day) within 2-3 days, which is in conflict with the approach recommended for methadone ("start low, go slow") [14]. In light of the fact that our patient was in remission from heroin addiction, and did not have a high opiate tolerance, we started with a very low dose of buprenorphine, which we titrated to a maintenance dose of only 2 mg/day. This dose is below the therapeutic range recommended for heroin addiction treatment, but it was effective in reducing the hypophoric/dysphoric syndrome, which was related to a lifetime opiate addiction.

On the basis of the good clinical response observed in this case, we conclude that in patients with BD and a history of opiate addiction, there may be a clinical indication for the introduction of an opiate agonist, even in the absence of a recent opiate relapse.

#### 5. Conclusions

The good clinical outcome achieved in this case suggests that augmentation with an opiate agonist may be indicated in psychotic patients with BD and a

history of opiate addiction, even in those without any recent opiate relapse.

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## Case Report

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# Case note review - Transfer of patient to buprenorphine from daily doses of methadone greater than 30mg

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### Summary

**Background:** Commencing a patient on buprenorphine is relatively easy and common practice if the patient is using opiates with a short duration of action because the time the patient needs to be free from opiate medication (prescribed or illicit) and experiencing withdrawal is short. The process is more complex and challenging if commencing treatment with buprenorphine from long acting opiate agonists. As a result, the process of transferring from daily doses of methadone under 30mg is accepted as a routine and common practice, with patients experiencing less severe withdrawal symptoms and, thus, proving more acceptable. At daily doses of methadone greater than 30mg, reported a greater potential for patients to experience a more severe induced withdrawal and greater risk of a full precipitated withdrawal. **Aims:** To demonstrate that transferring to buprenorphine from methadone doses higher than 30 mg/daily is possible and safe. **Methods:** This paper examines 5 cases studies of patients transferring from greater than 30mg daily of methadone to buprenorphine using the agreed protocol in NHS Lanarkshire. **Results:** The history and circumstances of the patients all vary as does their previous daily dose of methadone; this is demonstrated in the demographics of the group selected. The article reflects on the personal experiences the patients had during the process and also records and examines some of the biophysical measurements taken. **Conclusions:** This article demonstrates that the patient experiences are unique and beneficial whilst the overall transfer is safe and effective.

**Key Words:** Methadone; buprenorphine; transfer >30mg; case studies

## 1. Introduction

Methadone has been the opiate substitution therapy of choice for people with addiction since the 1960s [1], both for maintenance and detoxification. Methadone has been the subject of many reviews and been proven to be effective as a maintenance therapy, help retain patients in treatment and improve a range of other patient outcome measures including criminality and illicit consumption [11].

As with all treatments, methadone will not necessarily be the most effective or appropriate treatment option for all patients, and therefore there is a need for effective alternatives. The most commonly used alternative to methadone currently is buprenorphine.

Buprenorphine was introduced as a treatment

option in the 1990s for both maintenance and detoxification from opiates. Buprenorphine offers some additional benefits to full opiate agonists such as methadone as it is only a partial agonist. The most significant benefit is the greater safety profile that it offers, which is due to partial agonist activity at the mu opiate receptor and action as a kappa receptor antagonist. The partial agonistic activity of buprenorphine provides a "ceiling" effect on some outcomes associated with full agonists, particularly respiratory depression. Buprenorphine has the additional property of a very high affinity for the opiate receptors which, coupled with a low dissociation rate, blocks them from further occupation [3]. Buprenorphine has a reported benefit from patients of leaving them feeling less cognitively impaired and more "clear headed" than methadone,

this is an important factor in the selection of patients who are suitable for buprenorphine treatment and advance notification of this potential effect should be discussed with the patient [8].

Commencing a patient on buprenorphine is relatively easy and common practice if the patient is using opiates with a short duration of action because the time the patient needs to be free from opiate medication (prescribed or illicit) and experiencing withdrawal is short. The process is more complex and challenging if commencing treatment with buprenorphine from long acting opiate agonists [3]. As a result, the process of transferring from daily doses of methadone under 30mg is accepted as a routine and common practice [3], with patients experiencing less severe withdrawal symptoms and, thus, proving more acceptable. At daily doses of methadone greater than 30mg [10], there is a greater potential for patients to experience a more severe induced withdrawal and greater risk of a full precipitated withdrawal. The rationale for this is the higher affinity of buprenorphine for opiate receptors, and the resultant displacement of the opiates already in situ, coupled with the low intrinsic activity at the mu receptor sites. The paper [10] formed the basis of the current recommendations of reducing the daily dose of methadone to a maximum 30mg daily before commencing the transfer.

There are few research papers on the topic of transferring methadone maintained patients to buprenorphine at daily doses greater than 30mg and, of those papers which have been published, all have been on work conducted in clinical in-patient units [2]. These papers have demonstrated that this practice is possible and safe for patients although some studies have also used some symptomatic relief during the process e.g. Lofexidine. The recent paper published from Australian research [9], although stating the process can be conducted as either in-patient or outpatient, recommends in-patient transfer followed by dosing at the service for the following 7 days, before returning the patient to their usual pharmacy for dosing.

Scottish drug misuse strategies and reports, such as the "Road to Recovery"[7] and The Scottish National Forum on Drug Related Deaths reports [4, 5], have had a gradually strengthening recommendation to "use alternatives to methadone".

The aim of the "Road to Recovery" is to encourage patients with opiate misuse problems to recover and return to a more socially inclusive position. Many patients prescribed methadone are on daily doses greater than 30mg, which would possibly impact on

the choices of treatments available.

In NHS Lanarkshire there has been a growing number of transfers to buprenorphine from methadone at doses greater than 30mg daily. The number of transfers has been as a response to increased patient requests, as they continue on their recovery journey; some people are unable to reduce to the recommended 30mg daily to allow transfer.

The current local product of choice is Suboxone (buprenorphine/naloxone). The prescribed methadone doses, prior to transfer, range from 35mg to 120mg daily. The patients have been treated at a clinic setting, with no residential/hospital treatment or prescribed symptomatic relief. These patients are supervised during the transfer process to monitor any adverse effects.

This paper will demonstrate, through a small number of retrospective case studies, the transfer process and the patient experiences.

Very little evidence of this treatment transfer has been documented or published. This paper aims to;

- Present 5 case studies retrospectively where High Dose Transfer (HDT) have been completed and demonstrate the safety of the process, the patients only attending the service for the period of the transfer.
- Provide a review of the process with some basic bio-physical measurements assessing withdrawal scales, blood pressure and pulse observations to show the effects of the transfer and demonstrate any links between methadone dose and adverse effects.

## 2. Methods

The transfers have all taken place using the Transfer Protocol (Appendix 1), as agreed by Alcohol and Drug Services in NHS Lanarkshire.

The 5 case study patients have been stabilised on a daily methadone dose greater than 30mg for differing lengths of time. They are engaged in treatment services and have been offered or wished to transfer to buprenorphine/naloxone for a variety of reasons, documented in the case discussions. Patients attend a clinic for the transfer.

They are requested to attend at 9.30am on the day of the transfer, following a methadone free period of at least 36 hours. They are reviewed and have some basic biophysical readings taken (pulse and blood pressure) and an assessment of their withdrawal, using the standardised Subjective Opiate Withdrawal Scale (SOWS) [6].

Appendix 1



**Protocol for Transfer from Methadone to Suboxone at daily doses of Methadone greater than 30mg**

**The transfers should only be carried out by Dr Conroy, but the process and protocol is to be circulated to staff with in NHS Lanarkshire to ensure correct procedure is followed.**

High dose transfer is the term used to describe any transfer of a patient’s medication from more than 30ml methadone to treatment with Suboxone (at an appropriate level the patient is titrated to)

The patient requires having their liver function checked before the process can occur and a sample should be taken and sent to the lab to ensure recent LFT has been conducted. A copy of the LFT results should be put in the patient’s notes.

Worker fully discusses transfer with patient, if agreeing to the transfer, the worker contacts [redacted] to arrange the date for the transfer by Dr S Conroy.

The patient will be urine screened at the appointment with the worker prior to transfer and the worker should ensure Dr Conroy has the patient’s medical notes prior to the transfer.

The patient’s last dose of methadone should be more than 36 hours before transfer. i.e. if transfer is arranged for the Monday, the last dose of methadone should be consumed on the Saturday to reduce the possibility of precipitated withdrawal, and ensure the patient attends Dr Conroy in a withdrawal state on the day of transfer. The patient should be reminded they are not to use any other opiates before the appointment for transfer, and that they will need to attend in a state of withdrawal.

The patient should attend Dr Conroy at 9.30am on the day of transfer.

On attending the patient will be examined and assessed using the SOWS withdrawal scale and will sign to agree the score of withdrawal and the information they have given is correct. I.e. consent to the transfer.

The transfer process with then begin.

The initial dose of Suboxone will be 2mg. The patient will be titrated to an appropriate level of suboxone in the clinic. The approximate time scale for the transfer is below.

**Suboxone initiation chart**

9.30	Initial dose	2mg Suboxone	Requires supervision and observation for first 30 minutes then check every 15 minutes
10.30		2mg Suboxone	Continue checks 15 min intervals
11.30		2 x 2mg Suboxone	Continue checks at 20-30 min intervals
12.30		8mg Suboxone	Continue checks at 20-30 min intervals If patient doing well, can leave for lunch
13.30	if required	8mg Suboxone	Continue to check at 30 min intervals

The observation checks should be used to identify the patient’s progress and lack of precipitated withdrawal or withdrawal symptoms.

Patient can be discharged once the appropriate dose of suboxone is reached and there are no further withdrawal symptoms or side effects.

Patient should be provided with a prescription at the appropriate Suboxone dose until the date of their next appointment with the addictions team.

Patient notes should be returned to the addiction team before the next appointment is due with the worker.

Protocol for Transfer from Methadone to Suboxone at daily doses of Methadone greater than 30mg

Authors: Dr S Conroy and D Hill

Written: August 2012

Approved by Clinical Governance: August 2012

Review: August 2013

**Table 1.** Dosing schedule for transfer

Time	Process	Dose to administer	Total Buprenorphine dose given
9.30	Assessment and commence	1 x 2mg / 0.5mg Buprenorphine/naloxone	2mg
10.30	Assessment	1 x 2mg / 0.5mg Buprenorphine/naloxone	4mg
11.30	Assessment	2 x 2mg / 0.5mg Buprenorphine/naloxone	8mg
12.30	Assessment	1 x 8mg/2mg tablet Buprenorphine/naloxone	16mg
13.30	Assessment	1 x 8mg/2mg tablet if required	24mg

The potential for using the clinical opiate withdrawal scale (COWS) for the initial assessment [6,9] was considered, however, as withdrawal symptoms rely on subjective information from patients, it was felt that use of COWS would not be beneficial as patients would have given information of the same nature and content.

The patient's medical history is taken and the details of their recent opioid consumption recorded. Once the patient is assessed and confirmed as being in a state of withdrawal, they are asked to consent to the transfer and follow up. This is also a declaration that the information they have provided is correct.

The transfer process is:

Table 1 Dosing schedule for transfer

Also see Appendix 1

The assessment allows the dose to be titrated to the patient's requirements. A dose of 24mg of buprenorphine/naloxone within the first day is not included in the product licence but patients are informed of, and consent to, this off licence use prior to commencing transfer.

From the 39 completed transfers from methadone to buprenorphine/naloxone, 5 case studies were selected to demonstrate the process used and the experiences of the patients. The patients selected ensured there was a representative sample, including a mixture of gender, age, methadone dose and time in treatment. They also highlight the differences as well as the similarities in experiences.

The case studies have been reviewed retrospectively and consent to the process has been received from the patients involved in the transfers.

Following advice from the West of Scotland Ethics Committee and MHRA, no formal ethical approval was required, as the retrospective review does not involve contact with any patients and is a case note review subsequent to the process.

### 3. Case discussions

#### 3.1. Patient A

Demographics – 42 year old male in treatment for about 10 years, always been prescribed methadone.

Other health issues / treatments -prescribed Mirzapamine by GP (is non compliant), and Diazepam, 5 mg 4 times daily (total 20mg daily); denies illicit use of diazepam on top.

Criminal history- extensive criminal history. Court appearance in 2 weeks.

Current methadone prescription is for 90mg, daily dispensed under supervision (DDUS). Dose has been much higher previously, but he has never been able to stop illicit use of heroin.

Employment - never worked, due to his addictions and his methadone treatment.

Reason for transfer- wants a chance of a “normal” life. His partner has recently also transferred to buprenorphine/naloxone and is amazed at her improvement.

Medication free period- Did well to manage the medication free period before transfer; he didn't think he would.

Problems during transfer - experienced a spike in withdrawal symptoms, but felt able to cope due to prior warning.

Comment at end of transfer- wishes he had tried this earlier.

#### 3.2. Patient B

Demographics – 38 year old female in treatment for over 10 years. Methadone prescribed most of this time.

Other health issues / treatments -none.

Criminal history - none.

Current methadone prescription is for 120mg, DDUS.

Employment – unemployed, last worked in September, 2011 as a barmaid.

Reason for transfer- determined to transfer to buprenorphine/naloxone and, eventually, to abstinence. Methadone is holding her back; “I’ve got a brain that wants to work and a body that wants to sit on the couch”. She is fed up with life on methadone and wants to stop heroin having any influence on her children’s lives.

Medication free period- last used heroin 2 weeks ago, but was using on a daily basis prior to this.

Problems during transfer - Initially she felt terrible because of her missed methadone. However, she successfully transferred to 24 mg of buprenorphine/naloxone. She felt gradually better throughout, but did feel worse after her second dose, demonstrating the spike in the SOWS assessment.

Comment at end of transfer- describes the process as “brilliant” and wouldn’t change any of it.

### 3.3. Patient C

Demographics – 32 year old female in treatment for 12 years. Only had methadone prescribed.

Other health issues / treatments - prescribed fluoxetine and amitriptyline.

Criminal history - none.

Current methadone prescription is for 35mg daily, dispensed weekly, no supervision.

Employment – unemployed.

Reason for transfer- states “methadone suited her and she liked it”; however, her family felt she was “out of it”. She knows that buprenorphine/naloxone leaves people clearer headed and she feels able to cope with clarity, she decided to “give it a go”. Her immediate aim is to eliminate illicit use; and her ultimate aim is abstinence. She has not used heroin for 3 weeks now. The transfer will help her get her children back, currently being looked after by her mother.

Medication free period- experienced quite severe withdrawals from a low dose of methadone; worse than expected, but completed the transfer.

Problems during transfer - last hour of the transfer was fine, but had felt awful before that; “never rattled that bad before”. She said that the advice given to sometimes expect an initial deterioration did help.

Comments at end of transfer- she would do it again and has said she wished she had done this years

before, but was unable/unwilling to reduce to the necessary 30ml for the transfer and feared the withdrawals.

### 3.4. Patient D

Demographics – 28 year old female in treatment for 18 months. She tried buprenorphine/naloxone at the beginning of this treatment episode but experienced precipitated withdrawal as she took opiates immediately prior to treatment, so transferred to methadone.

Other health issues / treatments - none.

Criminal history - none.

Current methadone prescription is for 55mg, DDUS.

Employment – unemployed, possibility of work in near future.

Reason for transfer- Previous positive treatment episode with buprenorphine. She stopped her treatment because she was not using any illicit drugs and was ready to move on, relapsed due to family problems.

Medication free period- no comment.

Problems during transfer - After each dose she felt immediate relief, but this was quickly followed by deterioration; she described feeling progressively worse with each incremental dose. Timings of her previous methadone dose and any opiate use was confirmed and agreed. Although feeling bad, she continued and managed to complete the transfer.

Comments at end of transfer- despite feeling so bad, she had nothing but praise.

### 3.5. Patient E

Demographics – 43 year old male in treatment for 10 years, predominantly in prison.

Other health issues / treatments - not used heroin for over 2 years. Describes methadone as his drug of addiction. Despite previously severe problems, denies problem drinking. Claims to consume, up to 200 mg daily of illicit diazepam.

Criminal history - released from prison within the last month. He has no further charges pending, but has an extensive history.

Current methadone prescription is for 100mg daily, DDUS.

Employment – unemployed.

Reason for transfer- wants to try buprenorphine/naloxone to initially become stabilised then abstinent. He wants his life back, including his relationship with

an estranged daughter.

Medication free period - No comment.

Problems during transfer - withdrawal pattern showed the frequently encountered “spike” but, once explained, he decided to continue.

Having received his buprenorphine dose, taking his cumulative dose to 16 mg, he reported that his withdrawals “hit (me) like a ton of bricks”. He was unable to stand and had severe abdominal pain- admitted to consuming 200 mg extra methadone daily. He was not able to continue with transfer at this point.

Returned the next morning feeling much better, although still experiencing withdrawal symptoms. He was given 24 mg at that point and observed. No further problems encountered.

Comments at end of transfer- quite emotional and already remarked on how clear headed he felt.

### 3.6 Overall results

By gathering the information recorded and placing into tabular and graphic forms, the biophysical parameters can be analysed.

### 3.7 Basic demographics

Table 2 demonstrates the range of gender, age and current methadone dose of the patients included.

Patient	Sex	Age	Methadone Dose
A	Male	42	90
B	Female	38	120
C	Female	32	35
D	Female	28	55
E	Male	44	100

### 3.8 SOWS scores

From the collected and analysed data of the SOWS scores (table 3 and figure 1), only one person reported and recorded an overall worsening of the SOWS score through the process. Patient D did persevere and complete the transfer as she was determined to proceed and although feeling uncomfortable, did not feel the discomfort was sufficient to withdraw from the process; this patient is the only person from all 39 transferred that reported this occurrence of worsening symptoms. A possible ration-

**Table 3 – SOWS scores**

Patient	2mg	4mg	8mg	16mg	24mg
A	15	11	12	10	11
B	24	10	10	8	6
C	13	15	15	4	2
D	7	21	29	30	30
E	4	7	4	8	1

ale for the worsening of symptoms experienced by patient D, which were alleviated between doses, may be the psychological expectation of increased severity of symptoms as experienced in the previous precipitated withdrawal they had experienced. The remainder of the patients used here had a reduction in the SOWS score at the end of the process, compared with the beginning.

It is noticed there is a small “spike” in the SOWS score at some point in the transfer for most patients. The cause of this is unknown currently and merits further investigation.

### 3.9 Blood pressure

There is no identifiable pattern to the fluctuations nor do they seem to relate to the SOWS scores experienced.

### 3.10 Pulse rates

On examination, there appears to be no significant changes as a result of the transfer. The initial reading tends to be slightly higher, this may be due to more withdraw symptoms experienced or the patient’s anxiety with regards to starting the transfer and the initial dose consumption.

## 4. Discussion

All the above cases, and a further 34 completed transfers, have been made safely and effectively. The range of prescribed daily doses of methadone has been from 35 to 120ml, with the same protocol used for all transfers. Patients responses vary slightly as does the dose the patient are stabilised on, generally between 16mg and 24mg daily of buprenorphine/naloxone; the vast majority of patients finish on 24mg.

Most patients remain at this dose for a short period and then commence reductions. Many patients report benefits very quickly following the transfer,

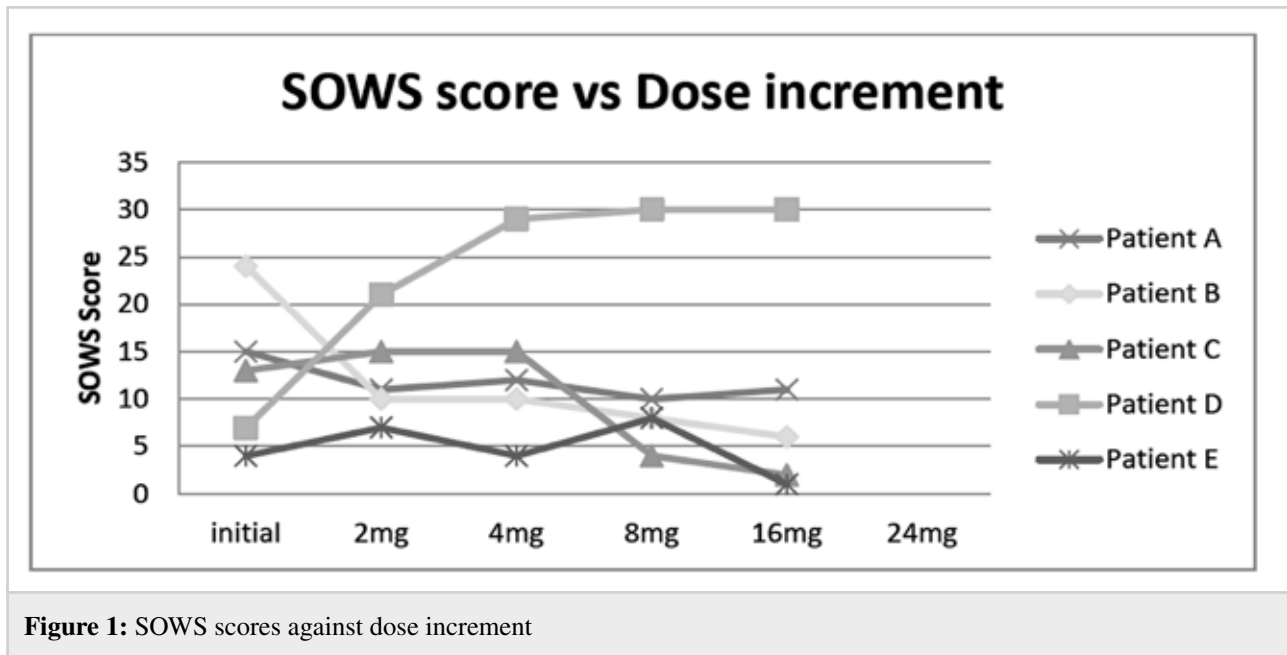


Figure 1: SOWS scores against dose increment

with the remainder feeling the benefits after 1 – 2 days. The predominant view of patients is that the process is much easier than they anticipated; although some experienced withdrawal effects they continued and completed the transfer. Many felt it could be done quicker, and they regretted not transferring to buprenorphine/naloxone before.

Many patients appear to have a spike in the SOWS score after 2-4 doses of buprenorphine. Most patients are able to cope with this increase in withdrawal symptoms experienced. It is not possible to relate the spike to the initial assessment SOWS score, nor the dose of methadone; it tends to be very individually specific and unpredictable, although patients do tend to persevere and feel much better with fewer withdrawal experiences by the end. It is now practice to explain this potential effect to patients undergoing the transfer. The exact cause of this spike is not clear.

Rarely severe withdrawals are experienced as with patient E - where there is a need to halt the process and continue the next day. Patient E had not admitted to consuming a significant quantity of illicit methadone as well as his prescribed dose when starting of the process. The transfer was still completed on the second day.

From these case studies, the reasons for transfer differ between patients, as does the length of time in methadone treatment; however the outcomes are the same with a successful transfer to buprenorphine, with many patients reporting positive benefits soon after the process including a “clearer head” [8].

These patients tend to be older and many have

had opioid substance misuse issues or been in treatment for a period of time before transferring to buprenorphine/naloxone. Being able to change to buprenorphine/naloxone can be seen as an enabling step, allowing patients progression on their recovery journey.

This paper has reviewed 5 case studies. The authors have prepared an article reviewing all of the transfers, demonstrating the benefits and disadvantages that patients have experienced as a result of a change in opioid substitute treatment. The authors plan a further study article to discuss the continued outcomes of the group undergoing the transfer to buprenorphine and the differences this has made to the patients and their recovery journey.

## 5. Conclusions

This article demonstrates that the patient experiences are unique and benefit the patients whilst the overall transfer is safe and effective.

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#### *Contributors*

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## Letter to the Editor

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# Can the buprenorphine-naloxone association outperform buprenorphine alone?

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**TO THE EDITOR:** Sir, eleven years after the decision taken by the FDA, and seven years after the European Medicines Agency authorized an association of buprenorphine plus naloxone in a 4:1 mass ratio for the treatment of opioid dependence, the time may have come for a critical reappraisal of its claimed ability to deter misuse through other routes of administration than sublingual.

At present, and after all these years, we still lack any randomized controlled trial that specifies an estimate of the misuse ratio of the buprenorphine-naloxone association among primary outcomes, by comparison with buprenorphine alone.

By contrast, intravenous use of the association has been repeatedly reported in clinical studies worldwide [1, 2, 3, 4, 7, 10]. Accounts of other unintended self-administration techniques like snorting and smoking are available too [6, 8]. Retrospectively, after the forced substitution of pure buprenorphine with the association, an increase was noted in the number of injectors [2, 10], and unsafe injection practices [2]. Forced substitution also led to a 50% inci-

dence of adverse events, and a 59% dropout rate, with 12% of patients lost to treatment [10], which should be considered a serious adverse event considering the high morbidity and mortality known for opioid addicts out of treatment.

It has also been reported that parenteral use of the association caused fatal poisoning in a proportion higher than that for parenteral buprenorphine alone [4].

Awareness of the actual misuse of the association has reached the general population through mainstream journalism, from the early years of its adoption [9] till now [11].

The pharmacological rationale of the clear incongruity with the manufacturer's claims has been attributed to the ability of buprenorphine, after the first intravenous shots, to occupy mu opiate receptors, so preventing naloxone from exerting a significant aversive effect [5, 12].

In addition, naloxone cannot induce withdrawal in subjects without tolerance of opiates, including drug experimenters devoid of opiate dependence, and

newly detoxified former opiate addicts [5, 12].

In view of the above, while awaiting future developments in agonist medications, clinicians and policy makers should carefully reconsider whether the buprenorphine plus naloxone association meets their demands in terms of the benefits to costs ratio, or whether for the time being the use of pure buprenorphine at a reduced price tag might be wiser.

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**Letter to the Editor**

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**HEROIN ADDICTION &  
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## **The probable impact of the global financial and economic crisis on medical addiction treatment**

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**TO THE EDITOR:** The effect of the current global financial and economic crisis on health is a topic of great importance to policy-makers, as cuts in public and private spending on health are bound to have a strong impact. In these circumstances it is hard to predict the future quality of health services, and still harder to know how the general level of public health will be affected. In Slovenia, as in many other countries across the globe, we are being confronted by conditions of financial restraint that are likely to endanger the efficiency of the medical treatments for addiction that are currently available.

In Slovenia treatment with opioid agonist methadone became possible early in the 1990s, and at present it is implemented by the network of Centres for the Prevention and Treatment of Drug Addiction;

it is organized at the primary level as part of the public health service network, carried out by professionals on the basis of public health institutions and performed on a carefully regulated basis [4, 5]. Social health insurance systems are an important source of funding, and with regular personal basic health insurance patients are provided with drug treatment free of charge. In addition, the availability of prescribed opioid pharmacotherapies for heroin addiction treatment has increased over the last 15 years; at present, various opioid (full or partial) agonists are available (methadone, slow release morphine, buprenorphine and buprenorphine–naloxone). The starting points just described could be defined as optimal for the implementation of effective evidence-based drug treatments.

The present world economic crisis has triggered an ill-considered wish to reduce financial budgets that are dedicated to addiction treatment, often in order to obtain the lowest possible cost as top priority, while considering the highest treatment quality and the best treatment outcome only as secondary priorities. This kind of situation could induce policy-makers to fall into the trap of actually creating “higher costs”, especially for patients, as the end-result. The need for policy-makers to work on the basis of past evidence should be the chief guideline in implementing opioid pharmacotherapies, and the diversity of opioid agonists should function as an added value, not as a hindrance to ensuring the best treatment outcome, as happens all too often. To allow a deeper understanding of this question we will now present a group report that is founded on our own past experience.

Heroin addicts who seek help from substitution programmes can generally be divided into two subgroups: patients at their first treatment (new patient=NP) and patients who have returned after previous treatment (old patient=OP); the data show that ‘old patients’ have always been predominant, and that, over time, the proportion of these patients has continued to increase [1].

As part of a larger study, we surveyed 40 patients (30 males, 10 females; 26 OP and 14 NP) at their (re)entry into a specific low-threshold methadone treatment, at a time when this opioid agonist was the only one available in Slovenia. During face-to-face interviews patients were asked to provide their demographic and clinical data. There were significant statistical differences between NP and OP patients in gender (NPs: males 7/14, 50% (the 50% proportion of females seems to be a peculiarity of this study); OPs: males 23/26; 88.46%;  $\chi^2=7.18$ ;  $p=0.007$ ), mean age (years) at the moment of the treatment (OPs: mean=24.96, SD= 4.47; NPs: mean= 20.71; SD=3.66;  $t=26.95$ ;  $p=0.042$ ) and mean duration of drug dependence in months (OPs: mean=46.86; SD=30.81; NPs: mean=10.14; SD=10.02;  $t=28.75$ ,  $p=0.007$ ), but not in mean age (years) at: first heroin use, onset of continued heroin use, first therapeutic contact. There were no statistically significant differences between OPs and NPs in somatic and mental problems in general, but the difference was almost significant in mood symptoms (NPs: 7/14; 50%; OPs: 4/21; 19.05%;  $\chi^2=3.73$ ;  $p=0.053$ ) and was significant in self-aggressiveness (NPs: 8/14, 57.14%, OPs: 4/21; 19.05%;  $\chi^2=5.41$ ;  $p= 0.020$ ). There were no statistically significant differences between OPs and NPs in drugs used, and most of the patients consumed heroin daily.

All OPs had been previously treated with methadone, whereas only 42.86% of NPs had already received medical treatment (none of them had received opioid substitution treatment) (6/14; 42.86%,  $\chi^2=15.55$   $p<0.001$ ). There was a statistically significant difference in actual medical treatment, too: the NPs were more frequently given psychopharmacological treatment (in NPs benzodiazepines and analgesics were used to cope with withdrawal, but there was no opioid substitution, whereas in OPs antidepressants and benzodiazepines were used) (NPs: 12/14; 85.71%, OPs: 9/21; 42.86%;  $\chi^2=6.42$ ;  $p<.011$ ) and psychotherapy (NPs: 12/14; 85.71%; OPs: 5/21, 23.81%;  $\chi^2=12.88$ ;  $p<0.001$ ); short-term detoxification with an agonist (NPs: 0; OPs: 10/21; 47.62%,  $\chi^2=9.33$ ;  $p=.002$ ) was not used in NPs, in line with the rules valid in Slovenia at that time, because the initial treatment with methadone could not be started until two previous treatments had been tried but had proved to be “ineffective”.

Because of the small sample we cannot draw any further conclusions. What counted most at the time was the need to find a way of gaining mastery over the withdrawal situation; in these cases the use of benzodiazepines, antidepressants, analgesics and other drugs was not a new practice [2] and it was probably rooted in the past (considering the recommendations that used to be made about keeping the use of methadone to a minimum: the other advice given then was to use it only in extreme cases), while the other major problems were the use of maximum dosages of 60 mg of methadone (in combination with benzodiazepines if necessary), stigma and ignorance of topic. Although these preliminary findings should be interpreted with caution, they suggest that the need to make decisions based on evidence was not always the major priority in the implementation of medical addiction treatment. Nowadays the situation seems better, but the economic crisis has acted as an important challenge which might lead to good practices being gradually discarded, especially considering the cost of managing various different opioid (partial) agonists (e.g. long-acting morphine versus buprenorphine or methadone).

A fundamental, reliable guideline for the decisions to be taken by policy-makers on bringing changes to current health policies, independently of costs, should always be to work on a scientific basis, while bearing in mind that remarkable progress has been made in this field in the last few decades, while the literature is being made richer all the time by professional publications and even by implementing the

'know how approach' [3].

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