

## Addiction today: A short Evaluation in Substitute Treatment of Heroin Users

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### **Abstract**

*Opiate addiction is a chronic disorder, accompanied by remissions and relapses. Treatment of drug addiction is a long-term process, involving multiple interventions to achieve withdrawal. The aim of the study was the evaluation of heroin addicted patients during treatment with methadone and Suboxone.*

*Our results showed significant differences among patients receiving both types of treatment, in terms of age, duration of heroin use and history of first treatment, which were higher in methadone receiving patients. Also there are no significant differences that have been observed among patients with regard to retention over the treatment monitoring period (1 year) and relapse to heroin use.*

*Methadone remains the most widely used substance in the treatment of opioid dependence, owing to its good acceptability by patients; at the same time, it reduces both illicit drug use and criminal activity associated with drug procurement. The treatment of a drug addict does not consist of administration of medicines alone: it requires psychological, social and medical interventions as well.*

**Keywords:** *addiction, heroin, methadone, Suboxone, related psychiatric co-morbidity.*

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## I. INTRODUCTION

Treatment of addiction, including diagnosis, medical care and social reintegration of drug addicts, is intended to improve health and the quality of life, which can be achieved by reduction of drug use as well as dependence-related morbidity and mortality and facilitation of access to public services and full social reintegration (Baconi et al., 2007, Dinis-Oliveira et al., 2012).

In 2005, the World Health Organisation supplemented the Model List of Essential Medicines with methadone and buprenorphine for treatment of opioid addiction (WHO, Essential Medicines, 2005).

The opiate addiction is defined as a chronic disorder, accompanied by remissions and relapses. Therefore the complex interventions for long-term detoxification are based on an accurate patient assessment and monitoring process (Ciobanu et al., 2009).

According to the American Society of Psychiatry, the goal of detoxification is safe reduction of acute withdrawal symptoms and facilitation of patient inclusion in a long-term treatment programmes (rehabilitation and insertion). Accomplishment of this “cleansing” programme requires use of cross-tolerance among various opioids, thus replacing heroin with other longer acting morphinomimetics, which are clinically easier to handle. To be feasible, the substitution in question demands consideration of equivalent doses of the two substances, as follows: for heroin purity between 10% and 30%, 1 mg of heroin equals 2.5 mg of methadone, 3 mg of morphine, 24 mg of codeine, 50 mg of propoxyphene (de Bakker et al., 2012; Degenhardt et al., 2011; Degenhardt et al., 2013).

Methadone is the most frequently used substance in the treatment of opiate addiction, which proves a real benefit due to the numerous studies conducted in that respect, some of which even provided comparative perspectives with other relatively more recent substances brought into therapy. For use in detoxification therapies, patient stability must first be achieved on a comfortable dose. During this time the dose progressively increasing until heroin withdrawal symptoms are no longer a danger (Fatseas et al., 2007; Feelemyer et al., 2013; Ferrant et al., 2011).

Treatment is initiated on occurrence of the first clinical signs of withdrawal, whereas induction consists of a 10-30 mg dose, going as far as 25-40 in serious cases of addiction. For unidentifiable or lower degrees of dependence, treatment is initiated with lower, 10-20 mg doses. Patient monitoring over the first hours of inception is performed irrespectively, giving small additional doses should signs be noted indicative of the withdrawal syndrome. To establish the dose of methadone, the likelihood of lethal overdose should be considered as well as the inefficacy of too low a dose.

For substitution treatment of opioid addiction in clinical settings, buprenorphine is used in 4:1 fixed combination with naloxone (an opiate antagonist). In that respect, the most frequently

prescribed is Suboxone (e-CPS, 2013; Orman, et al., 2009) sublingual tablets. Due to minimal absorption of naloxone when administered sublingually, addition of naloxone predicts low buprenorphine intravenous abuse, whereas intravenous administration may precipitate withdrawal symptoms. However, recent literature data point to 50% of clinicians considering that misuse of buprenorphine/naloxone combination-containing products may pose a serious safety problem (Schuman-Olivier et al., 2013).

Epidemiological reports on lethal cases determined by buprenorphine – sedative association as well as the high risk of accidental buprenorphine/naloxone combination ingestion by children have contributed to increased concern for regulation against misuse of such combinations (Maryland et al., 2011; Ferrant et al., 2011; Pelissier-Alicot et al., 2010; Reynaud et al., 1998).

Suboxone is indicated for use in treatment of opioid dependence in patients with methadone contraindication such as high-risk patients or patients with prolonged QT interval or hypersensitivity to methadone (Soykut et al., 2013; Stover et al., 2014; CADTH, 2008).

Administration of medicinal products in drug treatment aims at removal of heroin addiction withdrawal symptoms, reduction of heroin craving during withdrawal and decrease of tolerance to heroin as well as choice of the best therapeutic options consecutive to treatment of withdrawal (Orman et al., 2009; Drugs, Orman et al., 2009; Soyka et al., 2012).

Despite obvious benefits derived from the ceiling effect, buprenorphine is still less prescribed than methadone in many European states, suggesting the greater weight of other aspects. There is significant proof showing better treatment results in case of stronger activity at the level of  $\mu$  opioid receptors, so that “drug blockage” may be achieved with higher doses of methadone (Ganguly et al., 2008).

Therefore, lower activity at the level of  $\mu$  opioid receptors characteristic to buprenorphine seems to correlate with poorer performance found in certain clinical trials (Whelan et al., 2012). Literature data show efficacy of buprenorphine intervention for use in maintenance treatment of heroin addiction, inferior however to methadone in appropriate doses. Buprenorphine acts as both partial opioid agonist and opioid antagonist, displaying lower sedative and euphoric effect as compared with full opioid agonists such as heroine or methadone - whose effects are inferior for methadone itself in comparison to heroin (Mattick et al., 2004, 2008; SAMHSA, 2004; Royal College of General Practitioners, UK, 2004).

The objective of this study was to determine an evaluation of heroin addicted patients during the treatment with methadone and Suboxone as it was received in a treatment centre.

## **II. METHOD**

### **1. Participants**

The study group consisted of 30 drug addicted patients (mainly to heroin, hereinafter also called beneficiaries), receiving methadone substitution treatment (Metadon Bioeel, 5 mg and 20 mg, tablets) and 10 beneficiaries receiving Suboxone substitution treatment (2 mg/0.5 mg and 8 mg/2 mg, sublingual tablets, containing buprenorphine combined with naloxone).

## **2. Procedure**

The participants were recruited from a treatment centre of Bucharest between 2013 and 2014. Patient evaluation was conducted for a one-year period, aiming at a comparison between patients newly entered into the program and those already under treatment.

Treatment centers act as direct reception center, open to all drug addicts residing in a centre assigned area, providing outpatient care and reference to care services according to the individualized care plan established with the patient's informed consent.

Demographic Questionnaires were administrated individual and before that an informed consent for participation in the study has been obtained from each patient. Participation was voluntary and patients did not receive any financial reward.

## **III. RESULTS AND DISCUSSION**

In this study were observed and measured the following indicators: socio-demographic status, drug use history, somatic co-morbidities and psychiatric co-morbidities (Table 1). For the indicator concerning co-morbidities the results showed that psychiatric co-morbidity associated with heroin addiction has low prevalence among patients in the study group. Therefore 5 beneficiaries (12.5%) are diagnosed with psychiatric disorders (one patient with panic attack, two patients with depression and two patients with generalized anxiety disorder) requiring mandatory care for successful therapy of opioid dependence.

Regarding indicator heroin manner of administration, the majority (38/40) of patients monitored were observed to inject their heroin, only two patients in the group using other methods [(i.e. inhalation (snorting/sniffing)]. In terms of the overlap between the date of first use of heroin and the year of the first injection, the respective dates have been found to coincide. Therefore, for 70% of patients, first heroin use occurred directly by intravenous administration. Twelve of the patients (30%) have administered their first heroin injection after already having become acquainted with addictive substances i.e. that have started use by other means (snorting or smoking). They may have switched to parenteral administration in an attempt to experience faster and stronger effects.

Concerning the indicator: Type of drug addiction 34 of the patients in the study group (85%, 34/40 patients) display multiple drug use. The drug most frequently associated to heroin addiction belongs to the benzodiazepine class, although, in their therapy, addicts also use other drugs with hypnotic, anxiolytic and muscle relaxant effects, in an attempt to relieve certain symptoms of withdrawal or to potentiate the effect of the substance used as main drug. Thus, the most frequently associated are benzodiazepines (62.5%), followed by tricyclic antidepressants (57.5%). In addition to the main drug (heroin), a significant percentage of patients (50%) have used a hallucinogen less reported on the Romanian drug market, i.e. phencyclidine, a hallucinogen with dissociative properties and low safety profile.

Certain patients (25%, 10/40 patients) have associated methadone even before admission to the treatment program, the reason being not their desire to lower the dose of heroin for progressive withdrawal, but lack of money or sources of heroin. At the same time, 15% of patients simultaneously use stimulants such cocaine, whereas 15% smoked marijuana. Barbiturates were less reported among substances of choice, and occasionally hallucinogen use was reported such as LSD-type drugs and dissociative anaesthetics such as ketamine.

Table 1. Demographics, addiction and co-morbidity related data of patients.

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N	40
Gender	33 men, 7 women
Male : Female ratio	4.71
Education (years)	12.8 ( $\pm$ 2.7)
Age (years) (Mean $\pm$ SD)	30.48 ( $\pm$ 5,15) (range 21 – 48)
Mean age on first use (years) (M $\pm$ SD)	19.25 ( $\pm$ 3.67) (range 12 – 30)
Age groups	20 – 25 years (12,5%, 5/40); 26 – 30 years (37,5%, 15/40); 31 – 35 years (35%, 14/40); > 35 years (15%, 6/40)
Age on first use	< 15 years (5%; 2/40); 15 – 20 years (62,5%; 25/40); 21 – 25 years (25,5%, 11/40); 26 – 30 years (5%; 2/40)
Heroin use history (years) (M $\pm$ SD)	11.25 ( $\pm$ 4.06) (range 1 –23)
Previous therapies	85% (34/40 patients with previous therapy)
Time since previous therapy (years) (M $\pm$ SD)	7.40 ( $\pm$ 4.13) (range 1 –15)
Other drugs experienced	benzodiazepines 47,5% (19/40); tricyclic anti-depressants 42,5% (17/40); phencyclidine 37,5% (15/40); novel

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	psychoactive substances, “ethnobotanical substances” (New Psychoactive Substances) 10% (4/40); methadone 17,5% (7/40); marijuana 12,5%; (5/40); cocaine 10% (4/40); barbiturates 5% (2/40); LSD 2,5% (1/40); ketamine 2,5% (1/40)
Somatic co-morbidities – HVC positive	37,5% (15/40)
Psychiatric co-morbidities	12,5 % (5/40) Panic attack, depression, generalized anxiety disorder

We have assessed possible correlation among indicators/parameters examined utilizing specific statistical methods (Pearson correlations, Spearman). Thus, positive and statistically significant correlations have been obtained among the following parameters (Table 2):

Table 2. The parameters age and duration of use, age (entry into the study) and age at first use, duration of use and previous substitution treatments, substitute dose and other drugs used - correlation coefficients *r*

Parameter	Parameter	<i>r</i>
Age	Duration of use	$r = 0.705^{**}$ ; $p < 0.001$
Age (entry into the study)	Age on first use	$r = 0.623^{**}$ ; $p < 0.001$
Previous treatments	Duration of use	$r = 0.410^{**}$ ; $p = 0.009$
Substitute dose	Other drugs used	$r = 0.405^*$ ; $p = 0.026$

N=40; \*  $p < .05$ ; \*\*  $p < .01$ ;

### *Substitution Therapy*

For patients considered, the program for heroin substitute maintenance is not a novelty, and 85% of them had received prior treatment for opioid dependence. In terms of the number of patients given prior treatment for heroin addiction, 84% of them had undergone previous attempts resulting in treatment failure. Relapse can have many causes, but one thing to be appreciated is their perseverance and determination prompting them to return to the day care centre and apply for admission into the maintenance substitution programs.

As regards the substitute dose, it is evident that most treated patients receive doses of agonists between 50-100 mg of methadone (average dose= 92.83 mg, range 30-140 mg) and Suboxone 10 to 20 mg (average dose= 15.40 mg, range 6-24 mg), which shows good compliance and adherence to therapy in patients from the treatment centre. Note can be made of the fact that substitute doses used comply with doses recommended for use in the literature. Thus, for methadone, the highest proportion (53.33%) involves patients receiving between 51 and 100 mg; in the case of buprenorphine, the most commonly prescribed doses range between 11 and 20 mg.

To motivate and reward program beneficiaries, the treatment centre may allow them not to report to the centre on a daily basis; instead, they are provided with a legally required certificate or prescription, which accomplished the treatment for the privilege days earned. This may be gained by outstanding behavior in the day centre and, as may be seen, it applies to most patients, so that more than half of them only report to the clinic once a week or even every two weeks. Adherence and compliance to therapy is encouraging, as shown in the chart displaying the time interval for patient reporting to the clinic.

Thus, 35% of the patients are provided with a medical certificate for medication needed for two weeks' time, 27.5% report for treatment once a week and only 12.5% had a daily dosing regimen. The latter are either newcomer to the program, not prepared for this test yet or have violated rules of procedure of the treatment centre. For nine users, the privilege is weekend +1, +2, +3, +4 days, which means receipt of treatment for the two days off when the treatment centre is not open plus the days that they have gained themselves due to faultless behavior.

No differences have been observed between patients in terms of privilege, depending on the type of treatment, indicating good adhesion to the program. As regards results of rapid identification tests applied for urinary screening for drug use detection, the two groups were found to be similar; thus, approx. 47% of patients under methadone treatment and 50% of those treated with Suboxone have been tested positive for opiates.

Results are consistent with those in literature, indicating that buprenorphine given in flexible doses is no different from methadone in terms of suppression of opiate use.

Study results outline the generic profile of a patient enrolled in methadone/Suboxone substitution therapy: male aged 26-35 years, with a long history of heroin use (approximately 11 years) and intravenous administration of the drug on the very first administration. Multiple drug use, associated to heroin as the primary drug is the predominant pattern of use for the patients in question, most of whom have a history of prior treatment for opioid dependence.

#### **IV. CONCLUSIONS**

Our results showed the highest percentage regards patients with an average history of heroin use for 11 years, who have used injection since their first administration, most commonly using benzodiazepines for multiple drug use. More than half of individuals monitored during research had previous treatment for opioid dependence.

Over 50% of patients receiving substitute doses also recommended in the literature, and most have substitute administration privileges allowing reporting to the clinic once every two weeks, thus reflecting proper adhesion to and compliance with therapy.

No statistically significant differences could be observed in terms of age on first use, previous treatments for addiction, and other drug use, psychiatric and somatic co-morbidities, depending on the type of substitution treatment (methadone or Suboxone). Statistically significant differences have been outlined among patients receiving both types of treatment, in terms of age, duration of heroin use and history of first treatment, which were higher in methadone receiving patients.

No differences have been observed among patients with regard to retention over the treatment monitoring period (1 year) and relapse to heroin use. This suggests similar clinical efficacy of the two types of treatment, in line with results of most studies published in the literature (Baconi et al., 2008; Fisher et al., 2012; Mattick et al., 2012).

However, the study reveals that the ratio of Suboxone treatment is considerably lower compared to methadone. The most important arguments for more limited buprenorphine use (as fixed buprenorphine: naloxone combination, 1: 4, Suboxone) in substitution treatment for opioid dependence are related to higher treatment cost as well as the finding across clinical trials that low-doses of methadone cause greater patient retention in treatment programs than low-dose buprenorphine.

Despite its imperfections, methadone remains the most widely used substance in the treatment of opioid dependence, owing to its good acceptability by patients; at the same time, it reduces both illicit drug use and criminal activity associated with drug procurement. In addition, it substantially influences morbidity and mortality (including by decrease of HIV infection rate). Pharmaco-therapeutic alternatives to methadone have been increasingly developed because its lack of universal effectiveness and availability and not properly indicated. The purpose of these alternatives is to allow treatment individualization in response to heterogeneity of patients' and communities' characteristics and goals.

The study indicates superior effectiveness of drug use prevention programs, as easier to set up and requiring fewer financial means than necessary for treating addiction. One should bear in mind that the treatment of a drug addict does not consist of administration of medicines alone: it requires psychological, social and medical interventions as well. To conclude, results revealed by the study may contribute to implementation of programs for prevention and treatment that are more effective by the very approach of the issue in its most affected and the most sensitive points. Prevention should be thoroughly established, so as to avoid the stage where treatment of addiction is the only solution.

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