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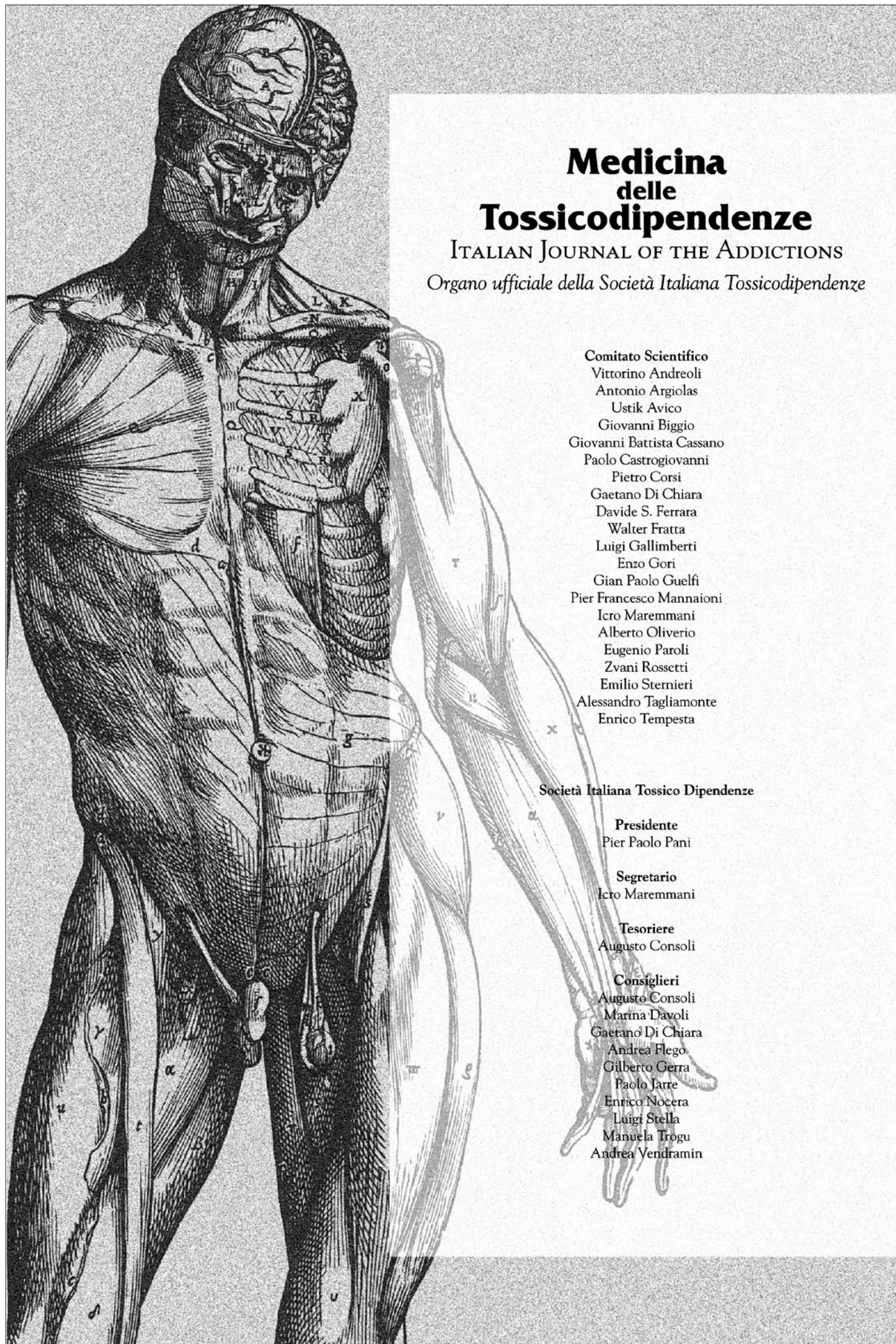
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Sexual Behaviour of Heroin Addicts In Treatment

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Summary

Addicts are a high risk group for diseases transmissible sexually or through the blood. Their pathological behaviour caused by addiction makes it a priority to collect information about the sexual conduct of addicts, especially those who are trying to cure themselves. It is important to get results about how they assess the risks related to certain kinds of behaviour and how they see the need to be educated about the issue. The aim of this study is to determine the sexual behaviour patterns of heroin addicts who have already begun treatment, while getting insights into how they assess the risks associated with being sexually active, and whether they need to be informed about the whole issue. According to the survey, heroin addicts displayed an uncritical attitude towards the risk assessment of their sexual behaviour and failed to understand that they need to be informed about protection.

Key Words: Sexual behaviour, Heroin addicts, Addiction, Drug abuse

1. Introduction

The World Health Organization defines addiction as a state of physiological or psychological dependence on any psychoactive substance [39]. This state is characterized by changes in behaviour and other psychological reactions, always including the compulsive need for occasional or regular substance use, guided by the pleasant psychological effects of the substance or, at least, of avoiding abstinence symptoms. Addictive behaviour is a major medical, psychological and societal problem, especially in view of the increasing incidence and availability of drugs. Although most epidemiological studies have depicted an increasing trend in drug abuse incidence among adolescents, only a small proportion have explored causation or tried to explain the nature of addictive behaviour or possible predictive factors [2,30,38,33]. By bringing together all the findings from the literature, we are able to conclude that the abuse of psychoactive substances is a

complex problem, and that both the inclination towards 'experimenting' with psychoactive substances and regular consumption itself result from the simultaneous impact of various interconnected factors. In other words, none of the aetiological factors appear to be decisive in a way capable of determining the individual's experiences with psychoactive substances independently of other factors [32, 5, 11].

The extent of drug abuse in Croatia has reached the levels of some West European countries. On the basis of epidemiological data and the data provided by the judiciary and by a repressive law enforcement system, the number of people addicted to illicit substances in Croatia has been estimated at 13,000 (a rate of 2.7 per 1,000 population). This figure is based on calculations which go to show that there is one non-treated for each treated heroin addict (around 6,000 in each category). This 1:1 ratio corresponds to the ratios calculated for other countries, where the heroin type of addiction prevails, but where methadone treatment has a broader

application [29]. Moreover, the Dutch experts think that, due to the administration of methadone in the programme (together with all other available forms of treatment), it is possible to attract and thereby register a proportion as high as 70% of opiate addicts [21].

As to the number of heroin addicts, the rate in Croatia is even higher than in some West European countries, since 80% of the addicts who are treated in Croatia suffer from heroin addiction. For all illegal substances, the rate of addicts per 1,000 population is 1.7 in the Netherlands, 4.0 in Switzerland, 4.7 in Italy, 2.7 in France, and 2.5 in Slovenia [21,22].

Abused drugs have several effects on sexual behaviour, which are related to the type, quantity, modality of assumption, and duration of abuse. Specifically, those under the influence of drugs may fail to practice safe sex, so increasing the risk of acquiring sexually transmitted diseases (STDs) and unplanned pregnancies. In recent years, many studies have been carried out to explore the association between drug use and the risk of contracting STDs, including HIV infection [27].

It is clear that a significant degree of sexual concern exists in male and female heroin addicts in the predrug, drug and postdrug periods. The Sexual Concerns and Substance Abuse Project recommends that each opiate abuser entering into treatment has a brief sex history taken and, if a primary or secondary sexual dysfunction is detected, then an additional evaluation should be formulated [31].

Much of what is known about the sexual partners of substance abusers comes from studies on alcoholics [35, 17]. Comparatively little research has been carried out on the sexual partners of heroin users [19, 28].

2. Methods

The aim of this study has been to collect information about the sexual behaviour of heroin addicts who have already been treated, and to recognize differences between the addicts who use condoms and those who don't.

The research project was performed for the Department for the Prevention of Addiction Diseases at the Public Health Institute of Split, in Dalmatia county, Croatia. It covered 100 examinees who are heroin addicts and who are in the outpatient care programme.

The majority of the examinees were on substitution therapy (methadone, buprenorphine).

The project was based on the use of a questionnaire which has three parts. Part One covers general and sociological information about the patient. Part Two deals with characteristics related to the misuse of drugs and possible complications. Part Three covers a set of questions related to the sexual habits and behaviour of heroin addicts who are in the treatment programme.

Of the 100 examinees in the study, 90 were males and 10 females.

All analyses were performed using the SPSS 10.0 programme including t-tests. Pearson's Chi square analyses were performed to determine significant statistical differences ($p < 0.05$).

3. Results

3.1. Sociological details

The examinees were mostly males (90%), while females were much less well represented (10%). The average age was 33.2 ± 5.8 (20-52) years; 57% of those in the group were unmarried, 29% were married and 14% had divorced. 40% of the examinees had children. Those chosen for the study had had 64 children altogether; 33% of these children were born while their parents were still married. Of the examinees who have had children, 25% of them had one child, 13% had two children, 3% had three children and 1% had seven. 23% of these children were living with both their parents, while 10% were living with their mother, and 1% was living with his/her father, while the rest of the children were living in one of various combinations of nuclear and extended families.

3.2. Drug abuse and their complications

The average age of first-time users is 19.8 ± 5.1 (13-42) years. On average, they had been using drugs for 13.4 ± 5.5 (2-30) years.

Abstinence from heroin use was found in 28% examinees, while 72% of them were unable to stop using heroin.

The methadone programme included 89% of the examinees, while the remaining 11% were taking buprenorphine.

All the examinees were heroin addicts. 29% of them were taking heroin intravenously, 7% by sniffing and 5% by smoking. 5% of these addicts take heroin by smoking and sniffing, while a total of 83% of these heroin users take heroin in a way that combined smoking, sniffing and intravenous injection.

Beside heroin, all the examinees were taking at least one other illicit psychoactive substance; most of them displayed polytoxicomania. Heroin was being used in combination with derivatives of cannabis, cocaine, amphetamines and ecstasy. As many as 21% were taking LSD, along with that same combination of drugs, while 19% added inhalation substances. 15% of the examinees were adding a combination of derivatives of cannabis and cocaine, while 9% were only adding derivatives of cannabis. Other types of polytoxicomania were found to be present in only a very small percent-

age of the group.

When taking heroin intravenously, 76.5% of these drug users shared their syringes with other users (2.35% once, 52.9% rarely, 21.1% often), while 23.5% of them had never shared their syringes.

During sexual intercourse, 16% of examinees used condoms as a form of protection against STDs, and 28% never used protection, while 56% claimed that they had sometimes used condoms as a means of protection against HIV and STDs. 99% of the examinees showed tattooing and piercing of the face and body; 38% of addicts participated in blood donation.

67% of heroin addicts have occasionally undergone testing for hepatitis and AIDS. 24% of addicts were tested only once, while 9% of them had not been through any testing at all. Their view was that it is unnecessary, or they were afraid of the result, or they simply did not care about it, or they found no good reason for being tested.

To the best of the knowledge of the examinees, 29% had tested positive to hepatitis B, and 61% tested negative, while 10% of them provided no information about their being positive or negative.

As many as 58% of the examinees tested positive to hepatitis C, and 34% tested negative, while 8% did not know whether they had contracted the disease or not.

Based on their knowledge, 90% of the group reported that they had no kind of sexually transmissible disease.

One drug addict was HIV-positive, while 88% of them claimed they were HIV-negative.

The other 11% of these drug users possessed no information about being HIV-positive or negative.

According to their personal evaluation, 65% of these drug users estimated that they were running a very low risk of contracting STDs and/or infectious diseases. 4% of those in the group thought that the risk of contracting transmissible diseases of this type was very high. The other examinees claimed that the risk could be evaluated as being somewhere between very high and low; the majority in this group gave an evaluation that was closer to a very low risk of contracting STDs or infectious diseases.

The largest subgroup of examinees (45%) thought that there was no need to obtain more information about the possible risks of contracting and transmitting STDs and/or infectious diseases, while 33% said they felt very little need to get more information about the whole issue, while 16% of them thought there is a need to be better educated about the problem.

3.3. Sexual behaviour

All of the examinees had been sexually active in an earlier period, 79% of them as teenagers, with an

average age at first sexual contacts of $16.24 \pm 2(12-21)$ years; 97% of these heroin addicts had had sexual contacts with partners of the opposite sex, 1% had had contacts with partners of the same sex, while 2% had had sexual contacts with partners of the same and the opposite sex.

99% of these drug addicts were heterosexually oriented, whereas 1% were homosexually oriented.

11% of the group showed no inclination to change partners, 37% favoured only rare changes in partner, 37% showed an inclination to change partners occasionally, and 18% showed a wish to change partners frequently.

90% of the group had had frequent sexual intercourse – 9% of them once a day, 42% once a week, 34% once a month and 5% once a year; 10% had not had sexual intercourse during the previous year.

24% of the group had received payment for their sexual services; all of these were males; 14% of them did this rarely and 10% frequently.

During sexual activities 91% of the group used psychoactive substances occasionally, 3% always used them, and 6% of them had never used them.

The majority of the males in the group (63%) assessed their potency as high.

70% of the females in the group had a regular menstrual cycle, 20% of them had had one or more spontaneous miscarriage (the overall figures for miscarriages and abortions were equal) (Table 1.)

In relation to the use of condoms as a form of protection against diseases transmissible sexually or through the blood, the examinees were classified in two subgroups according to the risks they had taken. One subgroup (16%) had always used condoms during sexual intercourse and therefore had run no risk of contracting diseases transmissible sexually or through the blood, whereas the other group (84%) had run a certain risk of contracting such diseases; of these, some (28%) had never, and others (56%) had sometimes, used condoms as a form of protection (Table 2).

We were unable to demonstrate any statistically important connection between the use of condoms and the time when those in the study had had their first sexual experience (as a minor, or as an adult) ($\chi^2=3.12$; $p=0.077$).

It is statistically important that the examinees that use condoms less frequently or sometimes changed their partners ($\chi^2=8.4$; $p=0.004$).

We have not yet been able to prove the significance of the relationship between the use of condoms and the frequency of sexual intercourse ($\chi^2=0.401$; $p=0.527$).

Parenthood is not statistically significant in relation to the use of condoms ($\chi^2=0.73$; $p=0.393$).

We have not yet been able to prove any statistically significant connection between the use of condoms and

Table 1. Sample characteristics

	N and %
1. Demographic data	
Gender	
Male	90
Marital status	
Married	29
Single	57
Divorced	14
Parenthood	
Yes	40
2. Drug abuse and complications	
Way of taking heroin	
Sniffing	7
Smoking	5
Sniffing and smoking	5
In combination with intravenous	83
Sharing of syringes	
Once	2
Rarely	53
Frequently	21
Never	24
Testing for hepatitis/AIDS	
More than once	67
Once	24
Never	9
Hepatitis B	
Positive	29
Negative	61
No knowledge	10
Hepatitis C	
Positive	58
Negative	34
No knowledge	8
AIDS	
Positive	1
Negative	88
No knowledge	11
STDs	
Yes	90
Subjective assessment of a presence of risks	
Yes	35
On need to be informed	
Yes	55
3. Sexual behaviour	
Use of condoms	
Yes	16
Never or sometimes	84

First sexual experience	
As a minor	79
As an adult	21
Multiple partners	
Never or rarely	48
Sometimes or often	52
Frequency of sexual intercourse	
Never, monthly or yearly	49
Daily or weekly	51
Payment for sexual services	
Yes	24
Whether a blood donor	
Yes	38
Substance abuse	
Occasionally, always	94
Never	6

blood donors ($\chi^2=0.330$; $p=0.565$). Nor have we been able to prove any statistically significant connection between the use of condoms and the frequency of testing ($\chi^2=0.570$; $p=0.449$).

So far we have been unable to prove any statistically significant connection between condom use and being paid for sexual activities ($\chi^2=1.4$; $p=0.241$). Nor have we been able to prove any statistically significant connection between condom use and subjective assessment of the risks involved ($\chi^2=0.118$; $p=0.732$).

We have not yet been able to prove any statistically significant connection between the use of condoms and being adequately informed ($\chi^2=1$; $p=0.315$). Nor have we been able to prove any statistically significant connection between the age of examinees and the use of condoms ($t=0.584$; $p=0.561$).

The subgroup of examinees who never or sometimes used condoms were younger than those who used condoms ($t=2.012$; $p=0.048$). A group of examinees who never or sometimes used condoms turned to be younger at the time of their first sexual experience than the subgroup who always used condoms ($t=1.86$; $p=0.066$).

4. Discussion

4.1. Sociological details

Within the group there were many more males than females. This finding is in accordance with the overall proportions of genders among addicts in treatment in the same institution.

Many studies have shown specific differences in

Table 2. Numbers of examinees and average values of variables, as assessed according to the use of condoms

		Use of condoms		p
		Always (N=16)	Never or sometimes (N=84)	
First sexual experience	as a minor	10	69	0.077
	as an adult	6	15	
Multiple partners	never or rarely	13	35	0.004
	occasionally or frequently	3	49	
Frequency of sexual intercourse	never, monthly or yearly	9	40	0.527
	daily or weekly	7	44	
Parenthood	yes	8	32	0.393
	no	8	51	
Whether a blood donor	yes	7	30	0.565
	no	9	53	
Whether tested for hepatitis/ AIDS	yes	9	58	0.449
	no	6	25	
Payment for sexual services	yes	2	22	0.24
	no	14	62	
Subjective evaluation of a presence of risks	yes	5	30	0.73
	no	11	54	
On need to be informed	yes	6	43	0.315
	no	10	41	
Age at first sexual intercourse (year)	mean $\pm$ SD	17 $\pm$ 1.8	16 $\pm$ 2	0.048
Length of drug use (years)		11.1 $\pm$ 4.6	13.9 $\pm$ 5.7	0.066
Age (years)		32.4 $\pm$ 7.7	33.4 $\pm$ 5.4	0.561

substance use and sexual behaviour between genders [4,3]. The average age of the examinees in outpatient treatment is high (33.2 ± 5.8).

In other outpatient centres there is a significant older population [10].

Even though most of the examinees were married, only about one third of them were still living with their spouse. Considering all the examinees, we found they had had 64 children altogether. One third of these children came from a marriage. These findings are the outcome of relatively well-preserved traditional and family values, which do not take dependency problems into account.

Most research findings support the view that heroin addiction is a major public health problem affecting both the addicted individuals themselves and their children, who have been shown to have a poor social, educational and health status, and to run a higher risk of abuse than their peers [20].

4.2. Drug misuse and complications

The period of earliest heroin use covers a wide

range, but the average age at which drugs were first consumed by this group of addicts almost goes further back than adolescence. This is because of the long experimental phase with other psychoactive drugs. This finding is supported by the research done on the consumption of drugs by young people, which shows that the mean age of first consumption comes in early adolescence [12].

At the same time the average duration of drug use is very high, as can be shown in various ways. Firstly, drug dependency is a chronic illness with remissions and recurrences. Secondly, dependency itself means that patients have to stay in treatment programmes over a long period. During the study, one third of the examinees reached the stage of abstinence, and most of these were in the methadone programme. They were older patients with many years of drug-taking, and their mental and physical state made the treatment less effective. Thirdly, methadone has been prescribed in this region of Croatia for the last fifteen years as a way of maintaining abstinence, while the prescription of buprenorphine only began three years ago [16, 36].

One of our concerns about the results of this study

is that they reveal that many of the examinees suffer from polytoxicomania, which makes the treatment process more difficult, so raising the risk of overdoses. Polytoxicomania has been found in all groups of drug users [23, 24].

A high percentage of intravenous drug users, a high percentage of sharing of drug use requisites during heroin consumption, the practice of tattooing and piercing, and a low percentage of drug users who practice safe sex, all increase the risk of acquiring sexually transmitted diseases (STDs) [24].

Research has shown that participation in a programme does not necessarily mean that examinees will take special precautions to prevent sexually transmissible diseases. Most studies show a very low percentage of drug addicts who use any form of protection during sexual intercourse [8].

Most studies show a very small percentage of drug addicts who use protection during sexual intercourse [13].

In contrast to this, there is a surprisingly high percentage of examinees who donate blood and a high percentage who have undergone testing for hepatitis or AIDS. It may be questioned whether these results are due to the initiative of patients or to the efficiency of the health service. Research shows that test-taking was more highly correlated with high-risk injection behaviour than with sexual behaviour [15].

There is a significantly high percentage of correlation linking hepatitis C and sexually transmissible diseases with hepatitis B and AIDS.

The epidemiological situation is different, because a certain number of examinees have no knowledge about the disease or have only been tested once.

Most studies reveal the high incidence of hepatitis C among drug addicts, and the prevalence of hepatitis among those suffering from sexually transmissible diseases [7, 1, 25].

At the same time the assessment of most examinees is that they only run a small risk of contracting diseases that are transmissible sexually or through the blood. As a result, they feel no need to be informed about the issue.

Education about the effects of drugs on sexuality and the risks of contracting sexually transmissible diseases [9], together with learning new ways of behaviour, lay a foundation for preventive action and harm reduction in dealing with this problem [14].

4.3. Sexual behaviour

Most examinees had their first sexual relations when they were still minors, they are mainly heterosexual, and half of them often change partners. This is in accordance with the behaviour of addicts in other studies [23].

As adolescents attempt to develop intimate sexual relationships, they may be at high risk of health consequences associated with sexual activity, such as pregnancy and sexually transmitted diseases (STDs) [6, 34].

Many studies have been carried out on forms of social and sexual sharing among addicts [19].

The degree of satisfaction with sex life was similar in patients and the rest of the population [36, 26]. Half of the examinees state that they have frequent sexual relations. At the same time, one quarter of them are paid for their sexual services.

Among the addicts there are two types of transaction: sexual services for money and sexual services to acquire drugs [13]. Most addicts use drugs during their sexual activities [24, 27, 9].

Under the influence of drugs they may fail to practice safe sex, so increasing the risk of acquiring sexually transmitted diseases (STDs) [27].

Among addicts, many hold the opinion that certain drugs increase their sexual performance, libido and pleasure, but are responsible for their partners' abusive and coercive behaviour [9].

More than half of the examinees reported improvement in sexual behaviour while using drugs. Almost all these patients remained sexually active and took no special precautions to prevent sexually transmitted diseases. Almost all patients remained sexually active and took no special precautions to prevent the contraction of sexually transmitted diseases [19, 24].

Comparing two groups of examinees, where the first always uses condoms, while the other group rarely or never uses them, there is statistically significant difference in the variables: change of partner, age of first sexual relations, duration of drug use.

The addicts who never or rarely use condoms and often change partners are younger at the moment of their first sexual experience, and they have been addicted for a longer time.

Conversely, the group of addicts who always use condoms and never change partners are much older at the moment of their first sexual experience, and they have been addicted for a shorter period of time.

It must, however, be pointed out that both groups are completely uncritical towards their sexual behaviour, because no significant differences emerge in important variables such as: parenthood, being a blood donor, testing for hepatitis and AIDS, being paid for sexual services and subjective assessment of the risk of contracting STDs.

5. Conclusion

Addicts have a dynamic sexual life, and they mostly fail to use any form of protection against STDs or blood-

born illnesses. Even addicts who do use protection are uncritical towards other risks to health, and towards other, more social forms of risk-taking.

As addicts assess the risks as being very small, and they feel little need for information, there is a real need to educate them in order to increase their knowledge and skills in dealing with the risks of addiction and drug-conditioned sexual behaviour.

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Contributors

All the authors contributed equally to this work.

Conflict of Interest

The authors have no relevant conflict of interest to report in relation to the present study.

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First Experience of Opioid Therapy with Buprenorphine in Ukraine

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Summary

Ukraine is the country that has the highest rate of HIV/AIDS among IDUs in Europe. The development of opioid maintenance treatment for opioid users is an important public health issue. The earliest utilization of buprenorphine for OMT was made in 2004-5, within the framework of the UNDP Applied Human Rights Project. It was accompanied by research which was a part of the WHO Collaborative Study on Opioid Treatment of Opioid Dependence and HIV/AIDS. There were 67 opioid drug users under observation. This was a prospective observational study with assessments at baseline, and at 3- and 6-month follow-ups. All assessments refer to the period of one month prior to interview. The main aims of outcome evaluation were to explore changes in the following domains: health status and well-being of individuals in opioid treatment; community/social benefits and also programme performance. Improvements in the main indicators were documented after 6 months of treatment. The retention level was 66% and the mean buprenorphine dose was about 8 mg/day. The main conclusion is that buprenorphine treatment is effective in the context of Ukrainian social conditions.

Key Words: Opioid Maintenance Therapy; Treatment; Opioid Dependence; Buprenorphine

1. Introduction

During the last decade Ukraine has experienced a remarkable increase in opioid addiction. Most addicts are young people still living with their parents; their addiction problem has lasted a few years. According to the Ministry of Health data, about 96% of those suffering from addictive disorders are intravenous opioid users. At the end of 2004 there were close to 88,000 registered drug addicts in the country. But this figure reflects only those who went to narcology institutions to ask for medical help. The estimated number of the whole IDU population in Ukraine is about 450,000 (937.5 on 100,000 of population). Most of these people live in big cities and are aged between 20 and 29. IDUs still

constitute a major part of PLHA. IDUs who are living with HIV/AIDS have no access to effective treatment for their addiction or somatic disease because of the lack of funds, the poor education of staff and double stigmatization. Besides, a drug treatment is an effective way of preventing HIV, as has been shown by many researchers all over the world.

IDUs accounted for 70% of HIV cases in the Ukraine between 1987 and 2004. In 2005, Ukraine was home to the fastest growing HIV epidemic in Europe, and one of the fastest growing epidemics in the world (Report of the Global HIV/AIDS Epidemic, 2002; UNAIDS/WHO 2005). With a growing HIV epidemic among opioid-dependent injectors, the need for both prevention

and treatment of opioid dependence, as well as HIV, became apparent. Drug treatment using opioid therapy (OT) was recognized to be indispensable in bringing opioid-dependent substance users into treatment, and so reducing the overall frequency of injection-related risk-taking behaviour. In addition, it was believed that OT would allow for those already infected with HIV to access life-saving anti-retroviral therapy (ARVs), which had previously been denied to them.

At the beginning of 2004 there were still no OT programmes in Ukraine. In the process of implementing the Applied Human Rights project, the UNDP was faced with the need to provide OT pilots to allow IDUs the highest possible level of physical, mental and social well-being.

UNDP-Ukraine decided to carry out two pilot projects in Kherson and Kiev with the aim of launching a model of opioid therapy for IDUs in the country in 2004. Buprenorphine was chosen as a replacement drug, as methadone was not yet available, and serious political and public resistance was directed against it. According to Ukrainian legislation, buprenorphine could only be used in a medical setting under the direct observation of medical staff. That meant that there was no opportunity to use take-home doses. Clients received buprenorphine every day; on Sunday only, they were given a double dose. Special premises were organized where clients took medication under medical control, and there were other rooms where they could spend their time and receive counselling.

2. Methodology

As for buprenorphine opioid therapy, we used the recommendations of R. Johnson (2001), E. Strain (2001) and Clinical Guidelines for the Use of Buprenorphine in the Treatment of Opioid Addiction (2004).

Pilot projects in Kherson and Kiev were accompanied by thorough observation according to the WHO standards. It was organized within the framework of the WHO Collaborative Multisided Study "Opioid Treatment of Drug Dependence and HIV/AIDS". The methodology of the study was worked out by WHO experts R. Ali (Adelaide University, Australia) and A. Uchtenhagen (Zurich University, Switzerland). All the clients were tested by diagnostic instruments at the beginning of treatment and after 3 and 6 months. The following research tools were used: for the evaluation of Individual Health Status and Well-being – Addiction Severity Index (ASI), Opioid Treatment Index (OTI), Zung Depression Scale, WHO Questionnaire of Quality of Life (WHOQOL), blood-borne virus risk-taking behaviour indicator (BBV-track); for the evaluation of Community/Social benefits – criminal involvement indicator (OTI, section 2).

3. Sample demographics

3.1 Sample description.

The total number of individuals participating in the study was 76 – 26 in Kherson and 50 in Kiev.

The mean age of participants at entry was 30.6 (range 47-21) – 33.5 for Kherson and 29.1 for Kiev. Participants were mostly males (90%) – 96% in Kherson and 86% in Kiev. The total number of females recruited for the programme was only 8.

Most of the participants had never been married (42%). 17% are currently married and 20% are cohabiting. 16% are divorced and 5% are widowed or married, but now live without a partner.

The median number of sexual partners at entry to treatment was 1; this figure stayed unchanged throughout the duration of the study (range 3-0).

Mean years of completed education is 12.6 (range: 19-8). In Ukraine basic school education lasts 9 years.

75% of the study participants are living in their own homes (or the homes which belong to their family). 23.6% are renting either an apartment or a room, and 1.3% (1 person) has no fixed address.

3.2 Clinical parameters

Among others, two of the basic criteria for inclusion in the programme were: a minimum of 2 years of problematic opioid drug use and several periods of unsuccessful drug-free treatments received by an individual.

The most common type of opioid drug first used is poppy straw (or so-called 'home-made opium') – 60% (77% in Kherson and 52% in Kiev). 16% of participants used heroin as their first opioid drug (24% in Kiev and none in Kherson). 24% of all the participants used other types of opioids (tincture of opium, morphine, acetylated opium solution).

Mean age at first opioid usage was 18.5 (range 33-14). Thus the group of people in the study included both: more common cases of early drug use debut and less common cases of a late debut (up to 33 years). Figures for this variable show no differences between Kiev and Kherson.

Mean years of problematic drug use at entry turned out to be as follows for different substances (mean $\pm$ st. deviation; range):

- Alcohol: 13 ± 7 (range: 33-0);
- Other opiates/analgesics: 10.3 ± 6 (range: 33-0);
- Barbiturates: 0.7 ± 2.4 (range: 16-0);
- Other sedatives/hypnotics/tranquillizers: 1.05 ± 2.5 (range: 16-0);

- Amphetamines: 0.2 ± 0.75 (range: 5-0);
- Cannabis: 6.6 ± 6.9 (range: 27-0);
- Cocaine: 0.05 ± 0.28 (range: 2-0).

For these variables, the figures for Kiev and Kherson do not differ.

As the reported data show, the most common problematic drugs are opiates, cannabis and alcohol. The prevalence of opiates is logical, considering the type of treatment received by the patients. Cannabis and alcohol are very common substances in Ukraine, in general.

As a rule, people involved in the study have previously used various types of drug dependency treatment. The following figures show the percentage of individuals who used the indicated type of treatment at least once in their lifetime.

Each of the figure in brackets shows the maximum number of treatment episodes for a single individual (minimum is 0 in each case).

- Inpatient detoxification: 70% (Max # of treatment episodes: 20);
- Outpatient detoxification: 60% (Max # of treatment episodes: 20);
- Outpatient counselling: 48% (Max # of treatment episodes: 40);
- Residential rehabilitation: 34% (Max # of treatment episodes: 12);
- Methadone and other opioid pharmacotherapy: 3% (Max # of treatment episodes: 6).

For the baseline interview, the following data were reported about drug use during the previous 30 days (mean $\pm$ st. deviation; range):

- Alcohol: 7.53 ± 8.13 (range: 30-0);
- Heroin: 0.52 ± 1.5 (range: 8-0);
- Other opiates/analgesics: 11.47 ± 11.9 (range: 30-0);
- Other sedatives/hypnotics/tranquillizers: 1.4 ± 5.5 (range: 30-0);
- Amphetamines: 0.61 ± 3.7 (range: 30-0);
- Cannabis: 6.32 ± 8.2 (range: 30-0);

For other opiates and cannabis the differences between the two cities are quite substantial (opiates: 26 ± 7.5 for Kherson and 4.2 ± 4.7 for Kiev; cannabis: 4.3 ± 8.1 for Kherson and 7.3 ± 8 for Kiev).

The mean severity of dependence (SDS score) at entry into treatment was 10.97 ± 2.7 (range 15-5), where 8% of individuals reported a score of 0-5, 32% a 6-10 score, and 60% an 11-15 score. The data obtained show that the severity of dependence is, on average, rather high for each of the groups under study. The differences recorded between the two cities did not reach significance.

The mean number of physical symptoms (OTI section 3) at baseline was 18.8 ± 8.4 (range 39-2), (13 ± 7.1 for Kherson and 21.7 ± 7.5 for Kiev).

Mean psychological morbidity indicator (Zung score) at baseline was 46.11 ± 11.3 (range 74-21), where 58% reported 49 or less (likely not depressed), 40% reported in the 50-69 range (likely to be mildly depressed), and 2% reported 70 or more (likely to be moderately to severely depressed). The differences between the two cities did not reach significance.

The average daily buprenorphine dose at entry into treatment was 13 ± 5.4 (range 30-2), (9.12 ± 5.1 for Kherson, and 14.4 ± 5.02 for Kiev).

4. Key Results

3- and 6-month follow-up interviews were conducted only for those individuals who were still in the programme, so the number of cases analyzed for the 3-month follow-up was 54, and for the 6-month follow-up was 50.

The average daily buprenorphine dose at the 3-month follow-up was 7 ± 4.4 (range 20-2), (without significant differences between Kherson and Kiev). At the 6-month follow-up, it was 5.5 ± 3.2 (range 18-2), (7.1 ± 4 for Kherson, and 4.6 ± 2.2 for Kyiv).

There were no significant differences in indicator variables between individuals who received prescriptions for relatively high and relatively low doses of buprenorphine (for more or less than 8 mg/day throughout the period of study).

Paired t-tests were used to verify the hypothesis of no difference in the values of variables from baseline to the 3-month follow-up and from the 3-month to the 6-month follow-up.

4.1 Outcome evaluation

4.1.1 Individual Health Status and Well-being

The substance use fell significantly ($P < .05$) after 3 and after 6 months compared to baseline. The average number of days out of the previous 30 when an individual had used a substance is the following:

- Alcohol: after 3 months 2.32 ± 4.7 (range: 30-0), after 6 months 1.4 ± 2.15 (range 7-0);
- Heroin: 0 both for 3- and 6-month follow-ups;
- Other opiates/analgesics: after 3 months 0.02 ± 0.132 (range: 1-0), after 6 months: 0;
- Other sedatives/hypnotics/tranquillizers: after 3 months 0.18 ± 1.3 (range: 10-0), after 6 months: 0;
- Amphetamines: 0 both for 3- and 6-month follow-ups;
- Cannabis: after 3 months 1.77 ± 6.9 (range: 30-0), after 6 months 0.66 ± 1.9 (range 10-0).

The differences between the two cities are only significant ($P < .05$) for alcohol usage (greater in Kher-

Table 1. Self-perceived quality of life indicator (WHOQOL) for baseline, 3-month follow-up and 6-month follow-up.

	Baseline	3-month follow-up	6-month follow-up
Domain 1	44.8 ± 17 (range 81-6)	60.8 ± 17.6 (range 100-19)	73 ± 11.7 (range 88-25)
Domain 2	44.08 ± 18.2 (range 75-6)	62.6 ± 13.17 (range 94-19)	69.7 ± 9.2 (range 81-25)
Domain 3	45.4 ± 20 (range 100-0)	55.25 ± 15.3 (range 94-25)	52.4 ± 11.5 (range 81-0)
Domain 4	50.3 ± 15.36 (range 94-25)	60 ± 13.7 (range 88-25)	67.6 ± 11.12 (range 94-31)

son).

The mean number of physical symptoms (OTI section 3) at the 3-month follow-up was 4.35 ± 3.3 (range 18-0), (no significant differences between the two cities). At the 6-month follow-up: 2.63 ± 3.9 (range 24-0), (4.45 ± 5.8 for Kherson and 1.5 ± 1.14 for Kiev).

Both from baseline to after 3 months and from after 3 to after 6 months, the decrease was statistically significant ($P < .000$).

At the 3-month follow-up, the mean psychological morbidity indicator (Zung score) was 37.76 ± 11.78 (range 69-21), (the difference between cities was not significant). At the 6-month follow-up: 29.13 ± 7.2 (range 53-22), (31.75 ± 10 for Kherson, and 27.5 ± 4.7 for Kiev).

Both from baseline to after 3 months and from after 3 to after 6 months, the decrease was statistically significant ($P < .000$).

The following table represents the Mean $\pm$ StD (range) for self-perceived quality of life indicator (WHOQOL) for baseline, 3-month follow-up and 6-month follow-up. The indicator is divided into 4 domains.

Both from baseline to after 3 months and from after 3 to after 6 months, the increase is statistically significant ($P < .01$). The exception is the 3- 6-month decrease for Domain 3, which is not statistically significant.

Table 2 represents the Mean $\pm$ StD (range) for the blood-born virus risk-taking behaviour indicator (BBV-traq) for baseline, 3-month follow-up and 6-month follow-up. The indicator is divided into 3 sections: Injecting practices, Sexual practices, and Skin penetration.

The reported figures for the section "Sexual practices" were significantly higher in Kiev (compared to Kherson) for all 3 interviews. For the two other sections, the differences between the two cities did not reach significance.

From baseline to after 3 months, the decrease is statistically significant ($P < .05$).

From after 3 to after 6 months, the difference is not significant.

As no testing for blood-born infections was done during the study, it is impossible to report the prevalence of BBV.

4.1.2. Community / Social benefits

At baseline the percentage of employed individuals was 45%. At the 3-month and at the 6-month follow-ups, the figure was 14% and 54% respectively. However, only 20 (3-month) and 12 (6-month) individuals answered this question during follow-up interviews.

Mean value (range) of the criminal involvement indicator (OTI, section 2) was as follows (the differences

Table 2. Blood-born virus risk-taking behaviour indicator (BBV-traq).

	Baseline	3-months follow-up	6-months follow-up
Injecting practices	12.8 ± 14.15 (range 59-0)	1.04 ± 5.8 (range 42-0)	0.68 ± 4.9 (range 36-0)
Sexual practices	11.14 ± 9.5 (range 36-0)	7.6 ± 7.9 (range 27-0)	8.34 ± 7.4 (range 27-0)
Skin penetration	1.81 ± 2.5 (range 8-0)	0.15 ± 0.63 (range 3-0)	0.11 ± 0.47 (range 3-0)

between the two cities were not significant):

- Baseline: 1.6 ± 2 (range 7-0);
- 3-month follow-up: 0.02 ± 0.134 (range 1-0);
- 6-month follow-up: 0.

From baseline to 3 months the decrease is statistically significant ($P < .000$).

From 3 to 6 months the difference did not reach significance.

4.1.3. Programme performance

Of the initial total of 76 individuals involved in the programme, 54 (71%) were retained in treatment after 3 months and 50 (66%) after 6 months.

The respective rates for Kherson only were 77% / 73%; for Kiev only, they were: 68% / 62%.

Only those receiving opioid treatment (as a drug) were interviewed after 3 and 6 months.

5. Conclusion and recommendations

- Buprenorphine is effective for Opioid Maintenance Treatment (OMT) in terms of: reduction of opioids, other illicit substances and alcohol use; improvements in health status and quality of life; reduction of depression; reduction of risky behaviour; decrease in criminal involvement;
- The most dramatic changes were recorded in the three months following the initiation of treatment;
- In the stabilization phase, buprenorphine was effective at a dose of ~ 8 mg/day, and even less;
- The retention in treatment level was 66%; this must be considered a very good indicator for treatment programmes in Ukraine;
- OMT should be recommended in Ukraine and expanded rapidly.

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Contributors

The authors contributed equally to this work.

Conflict of Interest

The authors have no relevant conflict of interest to report in relation to the present study.

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Administration of Nalbuphine to Heroin Addicts. Feasibility and Short-Term Effects

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Summary

Kappa-opioid agonists attenuate some of the neurochemical and behavioural effects of opiates and are under consideration as potential treatments for opiate dependence. We have shown that mixed kappa-agonist mu-antagonist nalbuphine (0.25 mpk im b.i.d.) was effective in reducing opiate consumption in 29 patients with a broad range of ages (29.4 ± 6.4 years) and with a long history of substance abuse (9.3 ± 3.6 years). Administration of nalbuphine for at least 14 days, up to at most 6 months, on an outpatient basis, led to a dramatic fall in the consumption of heroin and other totally illicit substances, along with a decline in criminal behaviour, as well as a higher level of retention of patients in the study, but also to improvements in patients' quality of life. Nalbuphine was safe, effective and highly compatible with the traditional therapy used to combat opiate addiction in Russia. Nalbuphine can also be used to stabilize HIV-positive patients. The study showed that both the current Russian medical infrastructure and medical professionals themselves could successfully contribute to the long-term agonist-antagonist treatment of patients with opiate addiction. We believe that our study warrants the further investigation of nalbuphine in treating opiate addiction.

Key Words: Nalbuphine, Heroin Addiction, Short-Term Treatment

1. Introduction

Although the current heroin addiction epidemic is becoming more and more daunting, together with the associated problem of HIV-infection, no adequate medical tools are available in Russia to face the worsening situation. In fact, methadone and buprenorphine maintenance treatment [1,2], which represent highly effective medical interventions against narcotic addiction and the spread of HIV infection among IDUs, are not allowed by Russian law.

As a result, only detoxification followed by naltrexone treatment is available for IDUs; this combined

therapy requires recourse to heavily sedating medication and hospitalization to ensure patients' compliance, even in the short-term. Hence, there is an increasingly urgent need to find safe alternatives for the treatment of opiate addiction and to combat the related spread of HIV infection in Russia, in the hope that effective agonist treatment will soon become legal and widely applied.

Nalbuphine, a mixed kappa-opioid agonist / mu-opioid antagonist, has been widely used as an analgesic drug in clinical populations [3]. On one hand, according to recent investigations, nalbuphine prevents morphine effects and attenuates the effects of morphine

withdrawal. [4,5,6]. On the other hand, it has been shown to have little or no abuse potential, and does not induce long-term tolerance [7], which makes it a good candidate substance for the treatment of opiate abuse. Furthermore, it is characterized by such a strong “ceiling effect” that dose increases above 30 mg do not produce any aggravation of respiratory depression or other side-effects. The safety window is wide: toxic effects only become significant at 160mg, which is roughly eight times higher than both the doses used in this study and generally recommended analgesic doses.

Aim: To determine the feasibility of nalbuphine among opiate-dependent injectors, and register the course of heroin use and related behaviours, in order to support the hypothesis of effectiveness against narcotic addiction. To our knowledge, this is the first reported study of nalbuphine administration to patients with opiate addiction.

2. Method.

2.1 Study Design

We performed an open-label, 2-week feasibility study including 29 participants recruited at two different sites. Study completers were included in a further 6-month observation period under nalbuphine treatment. Due to limited supplies of nalbuphine, only eight patients were allowed to proceed with nalbuphine maintenance, on a ‘first come, first served’ basis. After three months, all three HIV-positive patients included in the longer-term programme were excluded from follow-up, due to the potential risks of combining nalbuphine with antiretroviral drugs.

2.2 Sample

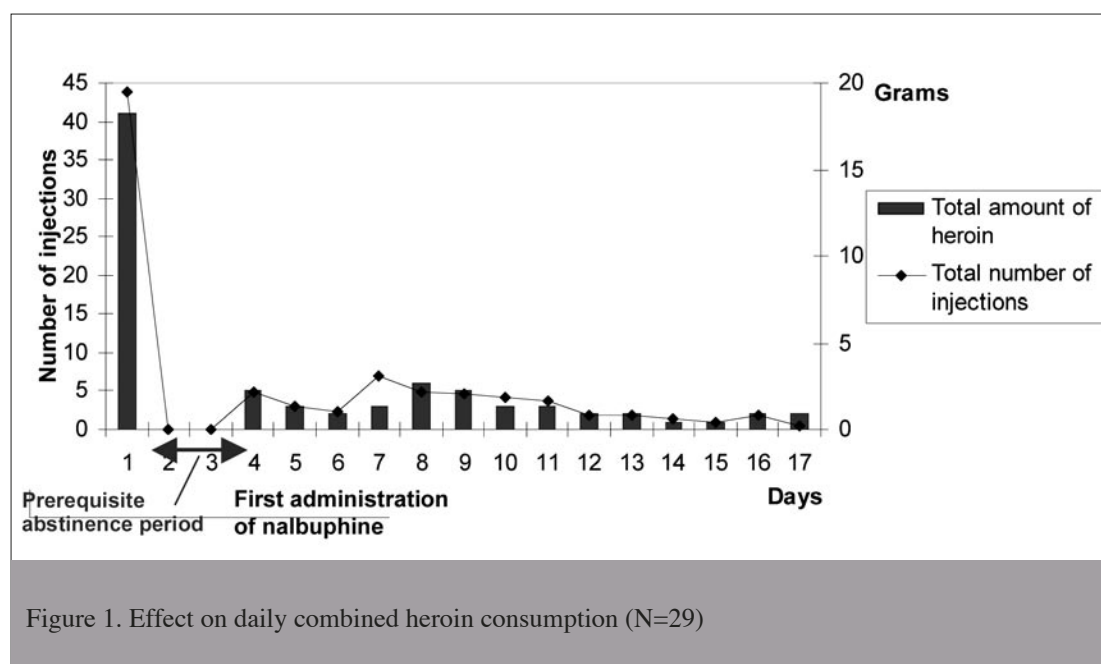
29 active injection heroin-addicted patients over a broad range of ages (29.4 ± 6.4 years, 22-46 years of age), 16 males and 13 females, with long histories of narcotic abuse (9.3 ± 3.6 years, from 5 to 16 years), and three or more unsuccessful treatment attempts (detox, outpatient detox, Christian rehab centres, etc.), were recruited from a community involved in case management project (primarily dealing with requests for HIV treatment, job placement, legal help, and other social services besides drug treatment). The average individual reported that his/her heroin dose before the study was 0.67 ± 0.35 g/day. The combined reported heroin consumption for the entire sample ($n=29$) before the study was 19.50 ± 2.24 g/day, while the frequency of injection was 1.41 ± 0.61 a day.

Five IDUs with HIV infection were included in the study. Changes in viral loading, immune status, and compliance with ARVT were also monitored for these patients.

2.3 Treatment Regimen

Subjects were required to abstain from opiates and alcohol for two days prior to nalbuphine administration, in order to avoid nalbuphine-induced acute withdrawal, and possible withdrawal was managed by standard symptomatic treatment. On this basis, nalbuphine treatment began on the third day after the previous heroin injection, along a 0.25 mg/Kg im b.i.d. schedule.

All these patients also received case-management and risk-reduction counselling. The counselling was delivered individually by staff who had undergone specific training for addictive diseases and HIV prevention; it was focused on achieving and maintaining



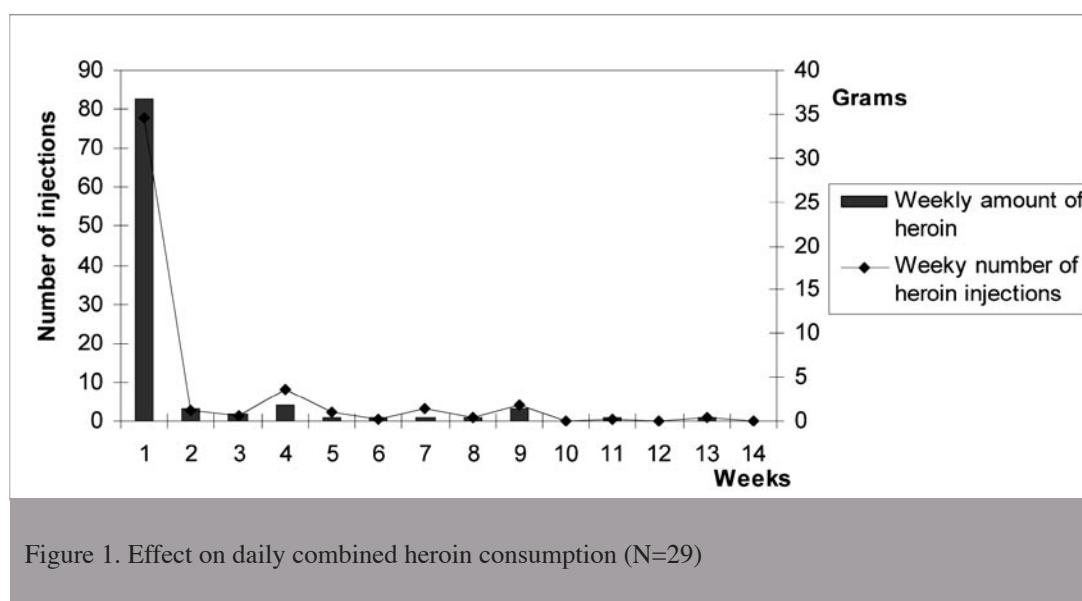


Figure 1. Effect on daily combined heroin consumption (N=29)

the goals of drug use reduction and avoidance of HIV infection.

2.4 Measures

Patients were asked to estimate their daily dose of illicit drugs before and during the study. Assessments took place at baseline and twice a week during the observation period: self-reporting on daily use, number of injections, heroin dosages and polyabuse were all recorded. Claims about not using heroin were verified by urinalyses.

3. Results

The effect of 2-week administration of nalbuphine on heroin consumption ($n=29$) is shown on Figure 1. The average level of consumption was reduced to under one thirteenth of the previous level, to 0.05 ± 0.02 g/day, while overall consumption by the entire sample fell to 1.35 ± 0.69 g/day, with nine patients abstaining completely. The number of heroin injections during the observation period fell to just one fifteenth of the previous figures, to 0.09 ± 0.05 injections a day. As was to be expected, a majority of patients (20/29) did use heroin during the study on at least one occasion, while 7 patients used it more than once. Heroin use peaked on day 4 (the second day on nalbuphine) with 17% of use episodes, and on day 7 (the fourth day on nalbuphine), with 21% of use episodes.

All the patients successfully completed the two-week study and expressed interest in receiving further treatment. Two chose to switch to naltrexone maintenance, while 8 patients were allowed to proceed with nalbuphine. Of these, five remained in treatment for six months, and the other three for three months.

Figure 2 shows data for eight patients receiving

nalbuphine for at least 3 months. An average individual heroin dose for these patients fell from 0.62 ± 0.17 g/day to 0.02 ± 0.02 g/day, and the overall heroin consumption for the entire sample fell from 4.94 ± 1.17 g/day to 0.13 ± 0.10 g/day. The individual number of heroin injections fell from an average of 1.48 ± 0.53 to 0.19 ± 0.17 injections a day. Six out of eight patients actually became abstinent during the last five weeks, and two patients had a stably sporadic pattern of consumption (1-2 times a month) with no dose or frequency peaks.

Patients with higher baseline levels of heroin use (> 0.8 g/day) were not more likely to consume heroin during the study than those with lower levels (< 0.8 g/day). Overall, we found a statistically significant (Fisher coefficient (F) = 7.02. $p < 0.001$) fall in heroin consumption after two weeks of nalbuphine therapy.

None of the patients reported concurrent consumption of other illicit substances or any increased in alcohol consumption. Even if, significantly, the reported fall in opiate abuse was confirmed by urine analysis, the actual consumption of alcohol or other stimulants was not biochemically monitored. No patient experienced an overdose during the study. A mild abstinent syndrome was observed in cases of patient non-compliance. In approximately one quarter of patients, very mild sedation was noted initially, while other side-effects typical of higher doses of nalbuphine (e.g. dysphoria, vertigo, dry mouth) were not observed.

Among HIV-positive patients, 4/5 displayed better immune status (CD4 counts) and one was unchanged. Patients gained weight (nearly 1 kg on average) and had no increases in viral loading. Three patients received ARVT, with compliance levels of 97% and 100% (Compliance with a treatment regimen, in particular with an ARV regimen, is determined using an 'average adherence' value calculated using the formula: $(A-B) / A \cdot 100\%$, where A is the number of tablets or gel

capsules scheduled by the protocol for administration to a patient over four weeks; and B is the number of tablets or gel capsules which were not actually taken by a patient over the same period of time). One of the patients started ARVT during the study. All these patients expressed interest in harm-reduction training and ARVT, and they regularly visited their doctor's office. The small size of the sample meant that the statistical values of drug consumption for this subgroup were not meaningful, but the actual drug use outcomes appeared to present a coherent picture.

4. Discussion

We found that the recommended analgesic dose of nalbuphine [9] for opiate-naïve patients (0.25mg/Kg i.m. b.i.d.) was effective in reducing heroin consumption among IDUs.

The course of heroin use during treatment was characterized by two peaks. While the first wave of use coincided with discharge from hospitals, the second wave might be explained as the attempt to overcome opiate antagonism. Nevertheless, it was remarkable that no challenge exceeded one's habitual dose, involved multiple injections or was accompanied by consumption of other types of drugs, or alcohol, as typically happens in naltrexone-treated populations [10, 11]. Furthermore, many patients reported that they felt calm while they watched their mates dispensing, preparing the liquid or injecting. As one patient with a eight-year history of heroin abuse put it: "I came to my friend's place [this friend supplied him with heroin] and he was weighing out and packaging heroin right in front of me. It was right in front of me but I felt no excitement. My heart didn't skip a bit. Nothing. It shocked me so much that I just left". In other words, all this evidence points to a successful containment of cravings for opiates.

Similarly, the administration of nalbuphine lead to what could be called a pattern of controlled heroin consumption, in so far as it coincided with some positive event (such as a payday at work, birthday parties, or New Year's Eve). Patients referred to those events as moments "when it was time to relax" or said "there must be something to enjoy in life" or even "that was just for fun because it was under control".

Furthermore, two of the patients with a higher than average heroin dose have had previous experience with MMT outside of Russia. This too may have had an impact on the collected data.

As a mu-opiate receptor antagonist, nalbuphine does not produce euphoric effects; in this study it did not lead to requests from patients to increase their dose or the frequency of administration.

It is worth noting that the medical personnel of both clinics, who conducted the study despite having adopted

initially negative attitudes towards substitution therapy, very quickly 'bought into' the idea of long-term maintenance with agonist-antagonists, even though it put them at odds with some Russian medical officials.

5. Conclusions

Nalbuphine can be used safely in the management of opiate addiction, and can be safely administered to IDUs. Although controlled studies on larger samples are needed now to allow comparison with naltrexone, some self-reported aspects, and its proven effectiveness in successfully treating different levels of heroin consumption, suggest it may turned out to be a viable alternative to full antagonist maintenance treatment.

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Contributors

The authors contributed equally to this work.

Conflict of Interest

The Authors have no conflicts of interest.

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Evidence of Reliability and Validity of the Opiate Dosage Adequacy Scale (ODAS) in a Sample of Methadone Maintenance Patients

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Summary

Introduction: The testing and adjusting of methadone dosing is a clinical procedure that must be individualized to meet the needs of each patient. So far no evidence has been published of a tool capable of providing a global measurement of dose adequacy. For this reason, we have devised the Opiate Dosage Adequacy Scale (ODAS), which is intended as a means of implementing a theoretical construct called 'dose adequacy'. **Aim:** To provide evidence of the reliability and validity of the ODAS. **Methods:** The study was carried out on a total of 300 patients on MMT, randomly selected from 10 public out-patient drug abuse treatment centres. We used ODAS, Addiction Severity Index (ASI), Outcomes Clinical Impression Form (OCIF) and laboratory tests (serum methadone levels, serum EDDP levels, serum a-1 acid glycoproteins levels [AAG] and urinalysis). **Results:** Internal consistency for the ODAS was acceptable (alpha Cronbach = 0.70). Very high inter-rater reliability was found across items (kappa values between 0.95 and 1). The factor analysis yielded a four factor structure exactly coinciding with the dimensions of the 'dose adequacy' construct proposed a priori ('opiate withdrawal syndrome', 'craving', 'overmedication' and 'drug use'). As far as construct validity is concerned, methadone dose adequacy as measured by the ODAS was correlated with clinical stabilization variables (heroin use, OCIF, ASI), while neither the methadone dose nor SML values correlated significantly with these variables. **Conclusions:** This study provides sufficient evidence for the reliability and validity of the ODAS as a tool for measuring methadone dose adequacy. The results of the construct validity test support the hypothesis put forward by several authors that an individualized clinical assessment of methadone dose adequacy is better able to account for a patient's condition than either the methadone dose or the patient's serum level.

Key Words: Plasma Level, Methadone, Opiates, Assessment, Opiate Dosage Adequacy Scale

1. Introduction

The efficiency and effectiveness of methadone maintenance programmes have been amply documented [24, 64]. The identification of individual prognostic factors

and a knowledge of the programme variables that modulate the therapeutic response are of undoubted practical interest, as these inputs help to improve outcomes [7, 13, 15, 45, 10, 5, 8, 9, 26, 48, 42, 17, 60, 32].

Of the single factors involved, the one that gives

the best results in predicting treatment outcomes is the daily methadone dose taken by the patient [1]. In this connection, it has been demonstrated that subjects receiving the lowest dose have the strongest craving for heroin, and are the most persistent in consuming it, whereas methadone programmes with higher doses have better outcome indicators (e.g., reduction in heroin use, reduction in severity of use-related problems and higher retention rates) [4,1,5,57,58,41,43].

Data drawn from these epidemiological studies cannot, however, be directly extrapolated for application to a specific patient as a basis for methadone dose adjustment. As warned by Maremmani et al. (43), if a study concludes, for example, that doses over 100 mg/day are more effective than doses of 50 mg/day, this should not be interpreted as implying that all patients should receive the highest dose possible. In this sample there would be patients taking 50 or 60 mg/day and responding sufficiently well to treatment, but among the subjects who are receiving the highest doses, the probability of finding good therapeutic outcomes will be higher. The most direct clinical result of these data is that adjustment of the methadone dose must be individualized for each patient. We should therefore not speak of 'high' or 'low' doses as defined in epidemiological studies, but of an 'adequate dose' from an individual clinical perspective [36, 37, 43, 28].

How can it be that patients taking such different methadone doses should display similar clinical efficacy? On the other hand, how is it possible that patients receiving the same methadone dose should show such sharply different responses to it? The reasons must be sought in the clinical pharmacology of methadone. There are pharmacokinetic factors (that mediate the relationship between the dose and plasma levels) and pharmacodynamic factors (that mediate the relationship between plasma levels and effect) which explain the wide variability that has been found in therapeutic responses [65, 22].

Some authors have proposed the routine determination of serum methadone levels (SML) as an instrument able to contribute to the adjustment of the dose in a context of therapeutic drug monitoring, such as the monitoring that is employed with lithium [33, 34, 68]. This type of analysis is based on the existence of a therapeutic SML range between a peak, above which the patient feels overmedication symptoms, and a trough, below which the patient begins to show opiate withdrawal symptoms and signs [50, 36, 51]. With this approach, the purpose of monitoring is to determine the SML of each patient and, if the SML falls outside the therapeutic range, be able to modify his/her methadone dose accordingly. It is true that a great deal of research work has already been done in an attempt to establish this range, but the desired degree of precision has not

been achieved so far [22]. Some studies have proposed a minimum SML threshold needed to eliminate opiate withdrawal symptoms, reduce craving or achieve narcotic blockade, but the figures quoted are very disparate (from 50 to 600 ng/ml), so this information cannot be used to accurately determine the methadone dose that a specific patient needs [2, 34, 39, 67, 68]. Most importantly, there should be no 'high' or 'low' SML, but only an 'adequate SML' for each individual patient, which would be the level at which he/she becomes clinically stable.

It is worth bearing in mind that SML determination only monitors some of the sources of variability in the relationship between methadone dose and its clinical effect (only one aspect of pharmacokinetic variability) [3]. In fact, there are clinical and pharmacodynamic factors, such as the prior tolerance level to other opiates taken previously and genetic polymorphisms associated with the mu-opioid receptor; neither of these can be controlled by SML monitoring, but they certainly influence the clinical response to methadone [63, 30, 35, 40]. In coming years, advances in pharmacogenetics may help to improve the effectiveness of methadone treatment.

Torrens et al. [61] suggest that therapeutic drug monitoring may be useful in assessing compliance with treatment, but not for predicting withdrawal symptoms or heroin use. In this sense, Leavitt et al. [36] believe that SMLs are more appropriate for confirming the inadequacy of a dose than for optimizing one. Okruhlica et al. [49] see SML determination as providing useful orientation when a patient is taking a relatively 'high' dose, his SML is low and he feels craving and/or withdrawal symptoms, which could be pointers to the fast metabolism of methadone. The identification of patients who are fast metabolizers is probably one of the main practical applications of discovering the SML. In this connection, the suggestion of Payte, Zweben and Martín [51] is that an SML peak at 3 or 4 hours after taking the methadone dose should not be more than twice the SML trough (by contrast, a peak/trough ratio over 2 would identify a fast metabolizer).

Assessing and adjusting methadone dosage for each individual patient should remain a basically clinical process [43, 28, 52]. We are in complete agreement with the following statement by Okruhlica et al. [49], "Our findings suggest that neither the daily methadone dose alone, nor methadone concentrations in plasma alone, can be interpreted as a univocal indicator of a patient's stabilization. It is, rather, the criteria derived from assessment of a patient's clinical condition that should set the ultimate guidelines for a doctor's decision as to whether daily doses of methadone in a methadone maintenance programme should be increased or decreased".

To test this hypothesis, a standardized instrument for measuring the clinical stabilization of a patient on a given methadone dose is required. An appropriate dose is usually considered to be one that: a) suppresses the opiate withdrawal symptoms, b) reduces opioid-drug craving, and c) reduces the reward effects of illicit opioids ('blockade') [20, 50, 36, 37, 43]. In research, several different scales have been used to examine items such as withdrawal [25], craving [16], checklists with reported symptoms [21] or analogical-visual scales [59]. Each of these scales, however, measures only one of the items that should be borne in mind when adjusting methadone dosage to optimum levels. For example, doses considered adequate only in terms of withdrawal symptoms will lead to an underestimation of the doses required.

This is why we have designed the Opiate Dosage Adequacy Scale (ODAS) [28], which is intended to provide a means of achieving a theoretical construct called 'adequacy of dosage'. The ODAS attempts to provide clinical measurements of the degree to which a given methadone dose is 'adequate' for an individual patient. The purpose of this paper is to provide evidence of the reliability and validity of the ODAS construct in a sample of patients in a methadone maintenance programme.

2. Methods

2.1 Subjects

The study was performed on a total sample of 300 opiate-dependent patients in treatment in a methadone maintenance programme (MMP) in 10 outpatient centres belonging to the public Provincial Drug Addiction Service of Cadiz. The study design is observational, transversal, and multi-centric. Sampling was random, and was based on quotas, so that each centre participated with a subsample proportional to the total number of patients in the MMP. To be eligible for the study, each patient had to meet the DSM-IV criteria for Opiate Dependence and be an adult under treatment in an MMP for over four weeks. Subjects who, at the time of recruitment or once data collection was already under way, had taken additional unprescribed methadone doses, or had not taken the prescribed dose, were excluded.

2.2 Instruments

2.2.1 Opiate Dosage Adequacy Scale (ODAS)

The Opiate Dosage Adequacy Scale (ODAS) has been designed by F. González-Saiz [28]; it is a brief semi-structured clinical interview whose purpose is

to clinically assess how adequate the methadone dose prescribed in the context of the patient's methadone maintenance programme is to his or her individual needs. This instrument attempts to approximate the construct that we have called "methadone dose adequacy". Operationally, we interpret a methadone dose as being 'adequate' when the patient: a) uses no heroin or uses it only occasionally; b) does not experience continuous opiate withdrawal symptoms (OWS) or, if any, only very mild ones; c) does not experience frequent episodes of craving for heroin, or, if there is any craving, it is very mild; d) in the event of heroin use, the patient does not experience any subjective effects, or any such effects are very mild (narcotic blockade or crossed tolerance); and e) he/she does not experience continuous symptoms of overmedication, or, if any, they are very mild. The ODAS is designed to assess the degree of adequacy of the dose taken by the patient during the previous seven days or so. As a minimum, therefore, the patient has to continue on that same dose during this period to ensure that he has reached the steady state for that dose.

The ODAS clinical interview comprises 10 items that evaluate the six specific attributes or components of the 'dose adequacy' construct: Continuous use of heroin (Item 1); Narcotic blockade or crossed tolerance (Item 2); Objective OWS (Items 3a and 3b); Subjective OWS (Items 4a and 4b); Craving for heroin (Items 5a and 5b); and Overmedication (Items 6a and 6b). For further information on the ODAS, see the general instructions in the Appendix. This instrument includes the five Additional Items that record complementary information that the clinic may take into consideration before making its decision on whether to modify the methadone dose. These items do not form part of the ODAS proper, so they have not been included in the quantitative scoring.

The questions that measure the frequency of symptoms are coded by Likert-type scores from 1 to 5, and the questions that measure severity of symptoms follow an analogical-visual scale with the same range of scores. ODAS scores may be interpreted both quantitatively (dimensional model) and qualitatively (categorical model). First, they provide a total score from the weighted sum of individual item scores. The higher the total score, the more 'adequate' the dose is. Second, at a certain cut-off point, each patient's dose can be categorized as 'adequate' or 'inadequate'. ODAS score derivation is explained at the end in the Appendix.

According to clinical pharmacology nomenclature, the ODAS measures the pharmacological effect, that is, the optimal clinical effect most directly dependent on a certain methadone dose. In our opinion, it is important to differentiate between this pharmacological effect and a patient's stabilization after he/she has been on the MMP for a time (outcomes). An adequate methadone

dose is a necessary condition, but it is insufficient to ensure a good response to treatment, since it depends on a variety of predictive factors (i.e. psychosocial intervention, diagnosis and treatment of the psychiatric comorbidity).

2.2.2 Addiction Severity Index (ASI)

It is a semi-structured clinical interview for the purpose of evaluating drug use-related problems [46]. It consists of six individual scales which assign a score to the severity of each of these problems (medical, legal, substance abuse, employment, family and psychological function). Each scale has two types of total scores called Severity Ratings and Composite Scores. It should be noted that some studies have used the items on each scale that measure the frequency of problems over the last month as outcome variables, since it has been demonstrated that these items are especially sensitive to change [1]. One recent study proposes the construction of an aggregate outcome index derived from the weighted sum of these items on the ASI [29]. In our investigation we have used a simplified form of this Aggregate Outcome Index (SF-AOI) as an overall indicator of addiction severity. The validated Spanish version of the ASI [27] was used for this.

2.2.3 Outcome Clinical Impression Form (OCIF).

The overall clinical condition of each patient and the degree of response to the MMP were assessed using the Outcome Clinical Impression Form (OCIF). First, each patient's case-manager (physician, psychologist or social worker) was asked to qualitatively formulate his impression of the clinical progress of his/her patient and the degree of overall response to the MMP, keeping in mind the severity at time of admission and the individual therapeutic goals posed. This description was not to exceed 100 words. Second, an independent researcher not involved in the MMP coded these descriptions, and classified the level of treatment response as Low, Moderate or Good. Finally, an addiction psychiatrist not working in the treatment programmes supervised this assignment process, reaching a consensus with the researcher on initially conflicting coding. The whole coding process was blind to other clinical measurements.

2.2.4 Data Logbook (DLB).

Sociodemographic variables, drug abuse history, health problems, background of previous treatments and variables related to the current MMP were recorded in a Data Logbook (DLB).

2.2.5 Laboratory tests:

Serum Methadone Levels (SML) (trough level) analysis was performed by homogeneous enzyme immunoassay (EIA) using CEDIA® technology on complete blood samples in a Hitachi 911 autoanalyser from Mycogenics (Boehringer Mannheim Corp.). Methadone metabolite EDDP levels and alpha-1-acid glycoprotein (AAG) concentration in plasma were measured, too.

Urine was tested for the metabolites of abuse substances (methadone, heroin, cocaine, benzodiazepines, amphetamines and cannabis), and general biochemistry.

2.3 Procedure

The study was jointly carried out by the Clinical Pharmacology Department of the Hospital de Puerto Real (University of Cadiz) and by the Information Systems and Research Area of the Andalusian Foundation for Drug and Alcohol Dependence (FADA), in cooperation with the medical staff of the Provincial Drug Addiction Service of Cadiz.

After the sample had been randomized by the researchers and a subsample had been assigned to each of the 10 participating centres, the physician in each service made appointments with the candidate patients for an initial interview and informed them individually of the purposes of the study, performed the testing for the selection criteria and asked each candidate patient to sign the informed consent form. Each physician filled out the Data Logbook with the information contained in the patient's clinical history and the information acquired in the interview, except for the Outcome Clinical Impression Form, which was filled in by the case-manager.

Patients were called for a second interview by a team of researchers not involved in the MMP. This team was made up of a physician specialized in clinical pharmacology and by a nurse. The nurse took the blood samples just before administering the daily dose of methadone (SML trough), then the patient provided a urine sample for the drug metabolite test. The clinical pharmacologist interviewed the patient using the ODAS and ASI (SF-AOI) scales and supervised the entire process. The patients were given 12€ as payment for their participation in the study.

2.4 Statistical Analyses

Chronbach's alpha was calculated for an analysis of ODAS internal consistency. This varied between 0 and 1 (14), which was interpreted according to the

Table 1. Patients with “adequate dose” according to the ODAS and their relationship with the mean dose ranges and mean methadone plasma levels

	n	(%)	Methadone dose (mg/day) ¹		Methadone plasma level (ng/ml)	
			Mean	(s.D.)	Mean	(s.D.)
“Adequate”	179	(59.6)	66.5	(55.4)	215.7	(159.9)
“Inadequate”	121	(40.3)	83.3	(58.8)	251.5	(188.1)

¹. Significant differences for $\alpha=0.05$

criteria of Nunnally [47], who considers values under 0.60 insufficient.

To evaluate inter-rater reliability, the following procedure was employed: The clinical pharmacologist interviewed the patient directly using the ODAS, and the nurse simultaneously assigned a score to the subject’s responses to the questions asked by the main interviewer on a blind parallel questionnaire. This was done for a total of 140 subjects. Analysis of this type of reliability was carried out item by item, estimating the value of the weighted kappa coefficient, which represents the concordance between items corrected for chance agreement (12), for each pair. For k the guidelines for clinical significance are as follows: below 0.40 is poor, from 0.41 to 0.59 is fair, from 0.60 to 0.74 is good, and above 0.75 is excellent (Cicchetti’s criteria)[11]. The Intraclass Coefficient Correlation (ICC) by Shrout and Fleiss [54] (Form [1.1]) was used to calculate the agreement between total ODAS scores. The ICC is derived from summarized information taken from the results of the Analysis of Variance (ANOVA) applied to these repeated measurements. Verification of their reliability was based on the hypothesis that the differences found between the two interviewers for each subject (‘intra-subject’ variability or quadratic mean) must be fewer than the differences between the scores of the subjects observed by the same interviewer (‘between-subject’ variability or quadratic mean). Qualitative interpretations of the ICC were based on the recommended ranges of clinical significance specified by Cicchetti [11].

To evaluate the dimensionality of the ODAS, a factorial analysis was performed using an exploratory analysis (Principal Components Analysis). To determine the number of factors to be extracted we followed the criteria of Kaiser [31], and for the selection of saturating items in each factor, the criteria of Stevens [56]. Varimax rotation was used for solution transformation.

The relationship between the adequacy of the methadone dose (ODAS scores) and a set of variables that define clinical patient stabilization was evaluated. This analysis appears to contribute evidence on the concurrent validity of the ODAS. We also wished to simultaneously test the hypothesis that clinical evaluation of methadone dose adjustment (as measured by the ODAS) predicts the clinical response of the pa-

tient better than the methadone dose alone and than the SML alone, as proposed by Okruhlica et al. [49]. The variables considered as indicators of a patient’s stabilization were:

- 1) Percentage of urine tests positive for illicit opiates in the last week;
- 2) Days heroin was used in the last month;
- 3) Clinical impression of patient progress in the MMP (Outcome Clinical Impression Form: OCIF);
- 4) Severity of use-related problems (simplified ASI Aggregate Outcome Index form ASI - SF.AOI).

Lastly, we analyzed the relationship between the ODAS scores and the other nomothetic variables of this construct, such as:

- 1) Patient’s subjective evaluation of the adequacy of his/her dose (as measured by the corresponding Additional Item A in the ODAS);
- 2) Desire to modify the current methadone dose (as measured by the corresponding Additional Item B in the ODAS);
- 3) Secondary effects of the methadone treatment (Additional Item C).

3. Results

3.1 Sample Characteristics

The subjects in the sample studied have an average age of 38.5 years (s.d. 6.7); most of them were men (83.6%). Before beginning methadone treatment, 68.2% were out of work and 76.8% had committed some kind of crime. The mean body mass index was 23.4 (s.d. 4.5). 79.5% of the sample had previously been in some other type of treatment for their addiction. From the beginning of the methadone programme, the subjects attended an average 82% of the appointments fixed for them (“adherence to MMP” is defined as the ratio between the number of appointments the patient kept and the total number of appointments made). The patients in the sample had been in treatment on methadone for an average of 47.3 months (range: 1-124 months). 30.3% of the patients went daily for a directly observed methadone dose and the remaining 69.7% had authorization for weekly take-home doses (either the patient himself/herself or an authorized family member went

to the dispensing point to collect the corresponding methadone tablets.)

The average methadone dose in the sample was 75.5 mg/day (s.d. 57.8), ranging from 2.5 mg/day to 400 mg/day. Table 1 shows that 59.6% of the subjects in the sample received an 'adequate' methadone dose, and that it is properly adjusted according to the ODAS, while the dose of the remaining 40.3% was considered to be 'inadequate'. The average daily methadone doses are shown in this table, together with the mean SML for each of the two classes of adequacy.

The Additional Items in the ODAS provide complementary clinical information that can be helpful in

Table 2. Distribution of frequencies of secondary effects of methadone treatment

	N	(%)
Constipation	126	(41.9)
Increased sweating	140	(46.5)
Insomnia or difficulty in sleeping	183	(60.8)
Altered sexual functioning	94	(31.2)
Altered menstrual functioning	24	(48%)*
Tiredness	165	(54.8)
Nausea	89	(29.6)
* Percentage of total number of women		

reaching a decision on methadone dose changes. Additional Item A evaluates the subjective perception by the patient of how adequate his/her dose is (the higher the score, the more adequate it is perceived to be). The average score in the sample on this item is 4.2 out of a maximum of 5 (s.d. 1.2). As to user satisfaction with their current methadone dose (Additional Item B), 50.2% of the patients expressed their desire to continue on their present dose, 10.3% wanted to increase it and 39.55% wanted to decrease it. As shown in Table 2, the secondary effect most frequently observed in this sample was insomnia, followed by a feeling of tiredness and increased sweating (Additional Item C).

The Pearson correlation coefficient between methadone dose and plasma level is 0.57 ($p < 0.05$). Between methadone dose and total ODAS score (degree of adequacy), the correlation observed is -0.13 ($p < 0.05$). Lastly, between plasma level and total ODAS score, a correlation coefficient of -0.025 ($p < 0.05$) is observed.

3.2 Reliability

3.2.1 Internal consistency

The Chronbach Alpha coefficient observed is 0.70, which is sufficient according to the Nunnally criteria [47]. This means there is acceptable covariance among the items in the ODAS, which appears to support its

Table 3. Inter-rater reliability analysis kappa coefficients.

	Weighted Kappa
1. Continued heroin use	1
2. "Narcotic blockade" (Crossed tolerance)	1
3a. Frequency of objective OWS	0.98
3b. Intensity of objective OWS	0.95
4a. Frequency of subjective OWS	0.96
4b. Intensity of subjective OWS	0.96
5a. Frequency of craving heroin	0.98
5b. Intensity of craving heroin	0.98
6a. Frequency of overmedication	0.94
6b. Intensity of overmedication	1

internal consistency.

3.2.2 Inter-rater reliability

Table 3 shows the weighted kappa coefficients for each of the items in the ODAS. It may be observed that these values are very high, all of them within the category of "excellent" according to the criteria of Cicchetti [11], which supports the inter-rater reliability of this scale. The intraclass correlation coefficient, too, is very high ($ICC = 0.98$), which indicates close concordance among total scores on the scale to be administered by different evaluators.

3.3 Validity

3.3.1 Factorial analysis

Analysis of the main components shows a four-factor structure which coincides precisely with the dimensions of the "dose adequacy" construct proposed a priori (see Table 4). The first factor, which we call "OWS", clusters the four items that evaluate the frequency and intensity of the objective and subjective opiate abstinence symptoms and explains 29.7% of the variance in the correlation matrix ($\lambda = 2.9$). The second factor (which we call "craving") saturates the items that evaluate the frequency and intensity of craving for heroin, and accounts for 21% of the variance. The third factor clusters the items that evaluate "overmedication" and the fourth and last factor, which we call "consumption", saturates the items on consumption frequency in the previous week and the degree of narcotic blockade.

Once the dimensional structure of the scale had been identified, we carried out a reliability analysis for each of these dimensions. Thus, the "OWS" factor turned

Table 4. Factorial analysis of items on the ODAS

	Factor 1	Factor 2	Factor 3	Factor 4
1. Continued heroin use	0.032	0.313	-0.021	0.802
2. "Narcotic blockade" (Crossed tolerance)	0.008	0.004	-0.016	0.900
3a. Frequency of objective OWS	0.793	0.107	-0.021	-0.057
3b. Intensity of objective OWS	0.819	0.090	-0.030	-0.013
4a. Frequency of subjective OWS	0.849	0.033	-0.059	0.026
4b. Intensity of subjective OWS	0.836	-0.045	-0.059	0.107
5a. Frequency of craving heroin	0.064	0.944	-0.023	0.172
5b. Intensity of craving heroin	0.083	0.950	-0.020	0.101
6a. Frequency of overmedication	-0.062	-0.022	0.971	-0.022
6b. Intensity of overmedication	-0.065	-0.020	0.970	-0.016
Eigen value	2.97	2.10	1.82	1.17
Percentage of variance	29.73	21.04	18.16	11.65

out to have a Chronbach's Alpha Coefficient of 0.84, the "craving" factor 0.92, "overmedication" 0.92 and, lastly, "consumption" had a coefficient of 0.67. As may be observed, these values support high internal consistency for each of the scale's dimensions.

3.3.2 Relationship of the construct measured with the ODAS and clinical stabilization variables

The mean ODAS score is higher for patients who are abstaining from heroin, as measured by urine analysis, than for those still consuming it; this difference is statistically significant. On the other hand, no significant differences were observed between average

methadone doses in the two groups of patients. Nor is there any statistically significant difference in plasma levels (see Table 5).

What is more, there is a statistically significant negative correlation ($r = -0.29$) between ODAS scores and the number of days when heroin was consumed during the previous month (that is, the more adequate the dose, the lower the consumption frequency). Conversely, no significant association can be found between the mean methadone dose or plasma levels, and the number of days when heroin was consumed during the last month (Table 5).

Among patients showing better clinical progress, as measured by their case-managers using the Outcome

Table 5. Analysis of the relationship of the construct measured with the ODAS and clinical stabilisation variables

	Heroin use			Outcome Clinical Impression Form (OCIF)			Aggregate Outcome Index (ASI)
	Opiate metabolites in urine (ANOVA)		Nº of days used in the last month (C. Pearson)	Low N=34	Moderate N=42	Good N=129	
	Positive N = 42	Negative N = 258					
Methadone dose adequacy (Total ODAS score)	26.1	27.4 **	R = -0.29 **	25.4	26.9	27.4**	R = -0.30**
Methadone dose (mg/ml)	70.5	73.6 (ns)	R = -0.006 (ns)	82 (ns)	67.1	71.3	R = 0.07 (ns)
Methadone plasma level (ng/ml)	219.4	249.1 (ns)	R = -0.04 (ns)	242.7 (ns)	213	240.1	R = 0.07 (ns)

* $p < 0.05$; ** $p = 0.01$; ns = not significant

Clinical Impression Form scale, the mean scores on the ODAS are higher, too, and these differences are statistically significant. However, there are no significant differences between these three groups of patients based on methadone dose or plasma levels.

Lastly, a statistically significant negative correlation can be observed ($r = -0.30$) between ODAS scores and scores on the ASI Aggregate Outcome Index. In other words, the better adjusted the methadone doses measured by the ODAS, the fewer heroin use-related problems there are. On the other hand, no significant correlation is found between average methadone dose or plasma levels and the Aggregate Outcome Index.

3.3.3 Relationship between the constructs measured using the ODAS and other nomothetic variables (Additional ODAS Items)

3.3.3.1. Subjective patient evaluation of the adequacy of his/her methadone dose (Additional Item A)

A statistically significant correlation ($r = 0.47$; $p < 0.01$) can be observed between the total ODAS score and the subjective evaluation which the patient himself makes of how well his methadone dose is adjusted. In other words, there appears to be an acceptable concordance between the adequacy as evaluated by the clinician on the basis of the information supplied by the patient, and the subjective evaluation of the patient himself.

3.3.3.2. Patient's desire to modify his/her methadone dose (Additional Item B)

The multiple Bonferroni test comparisons indicate that there are statistically significant differences ($p < 0.05$) between those who wish to increase their methadone dose (worse average adjustment [24.4]) and those who wish to maintain (27.5) or decrease it (27.7). There are no significant differences between these last two categories..

3.3.3.3. Secondary effects of methadone taken during the last week (Additional Item C)

Lastly, a moderate statistically significant negative correlation ($r = -0.37$; $p < 0.01$) can be observed between the total score on the ODAS and the number of secondary effects of the methadone treatment. That is, there appears to be an association between good adjustment of the methadone dose and fewer secondary effects.

4. Discussion

The data contributed by this research work provide sufficient evidence of the reliability and validity of the

ODAS when it is used as an instrument of measurement and assessment of the adequacy of the methadone dose taken by a patient in the context of an opiate dependence treatment programme.

The internal consistency of the scale is sufficient according to the criteria of Nunnally [47] and according to the recommendations of Dennis et al. for the requirements for an addictive disorder evaluation instrument [19]. This seems to indicate that all the items on the ODAS are strongly related to each other, and in the same direction. Moreover, the degree of agreement observed between clinicians is very high (inter-rater reliability), which helps minimize the different sources of diagnostic variability described by Spitzer et al. in the use of a measurement instrument in clinical practice or research [55].

Our theoretical proposal of the construct 'dose adequacy' is, on one hand, based on a review of the literature and the opinions of relevant authors [22, 50, 36, 37, 43, 49] and, on the other, on our own clinical experience subjected to reflection and review. Factorial analysis of the ODAS identifies four factors ("OWS", "craving", "overmedication" and "heroin consumption"). In our opinion, it is worth mentioning the coincidence of this structure with the dimensions proposed a priori for this construct, which we interpret as empirical support for it [28]. All of the items on the scale, bar none, saturate the four factors identified by the model as a solution for the matrix of correlations. In other words, all of these items appear to be "necessary" in explaining and defining the 'adequacy' construct. This, along with the internal consistency, go to indicate that the ODAS appears to measure a homogeneous (as a whole) and, at the same time, multidimensional construct. Each of these dimensions, in turn, appears to display a very high degree of internal consistency.

Another outstanding fact in this factorial analysis is the distribution of the percentages of variance accounted for by each of the factors. Percentages are observed to be well distributed, which implies that all of the factors have an excellent 'weight' within the construct. The OWS items explain a major percentage of the instrument's variance, followed by the items that saturate the 'craving' and 'overmedication' factors. To a certain extent, this weighting and this order may also be observed in clinical practice during the process of induction into methadone treatment. The goal of the early doses is to decrease or eliminate the symptoms of the objective OWS, and with each successive increase after a steady state is reached, a reduction in the subjective OWS symptoms and craving can be observed [65, 36, 51, 43]. In our opinion, an 'adequate' dose appears to fall within a hypothetical 'individual therapeutic range', that is, a dose that is high enough to achieve an 'anti-craving' effect, but not high enough to induce

symptoms of overmedication. In our experience, it is clear that this therapeutic range (regardless of the dose that defines it in each patient) varies widely. For example, for some patients the 'anti-craving' dose is very near to the dose at which overmedication symptoms begin to appear, whereas other patients tolerate the drug well when it is given at effective doses. Situating the patient within this therapeutic range is a crucial concern, since a reduction in the continued consumption of heroin usually takes place when he/she reaches the 'anti-craving' dose, which is usually (but not always) associated with achieving a narcotic blockade.

This is precisely one of the hypotheses that we are trying to test: that is, an 'adequate' dose, as measured by the ODAS, should be related to clinical stabilization of the patient. In this sense, the data in this research work support the existence of a clear and significant relationship between a more adequate methadone dose and a reduction in heroin consumption, a favourable evaluation by the case-managers and fewer heroin use-related problems. These results appear to contribute evidence on the validity of the ODAS construct. In addition to this conclusion, the data reported in this paper provide empirical support for the hypothesis proposed by Okrulika et al. [49], that is, neither the methadone dose nor the SML alone appear to satisfactorily account for the patient's clinical stabilization. As shown by our clinical experience and common sense, it is the clinical assessment of the patient (individual response to a certain methadone dose) which must be considered in deciding whether it should be changed; in addition, this assessment seems to be associated with the patient's clinical improvement.

Moreover, the relationship between the 'adequacy' construct and other variables of interest has been explored, too. The patients in the sample are observed to have a subjective perception of the methadone dose they are taking as 'adequate', that is, they perceive that their dose is helping them to reduce their continuing consumption of heroin, because they do not experience withdrawal symptoms or craving for heroin, but do not feel overdosed, either. It is precisely the patients that record the highest scores on the ODAS who evaluate the adequacy of the dose they are taking most positively. Similar results have been observed by Pérez de los Cobos et al. [53], in employing an analogical-visual scale to evaluate the overall adjustment of the methadone dose perceived by patients. Lastly, it is observed that the more adequate the methadone dose is, the fewer the secondary effects it has. Conversely, it is interesting to note that higher doses are associated with more secondary effects ($r = 0.13$; $p < 0.05$) and higher plasma levels, too, correlated with more secondary effects ($r = 0.12$; $p < 0.05$), even if the correlation coefficients are lower.

As shown in Table 1, there is considerable over-

lapping of the methadone dose between patients with 'adequate' and 'inadequate' doses (see s.d. values). For example, there appear to be patients taking a 70 mg/day dose that is considered 'adequate' (effective) according to the ODAS, whereas in other patients, this same dose may be assessed as 'inadequate' (ineffective) and it would therefore have to be increased. Trafton et al (62) find this same overlapping and arrive at the same conclusion by employing as their criterion for an "effective dose", a dose that enables a patient to stay off heroin for longer than one month. This, along with the above discussion on secondary effects, again provides support for the hypothesis that there is no such thing as 'high' and 'low' methadone doses in absolute terms, but only 'adequate' ones. In other words, what is really important from the clinical viewpoint is not that the patient should take the highest dose possible, but, whether the dose is 'high' or 'low', that it should be the most 'adequate' one for each individual patient.

In the sample studied, almost 60% of the subjects appear to have received an 'adequate' dose. In our health-care network there is no policy on methadone dose limitation and, in general, the philosophy of the staff is oriented towards maintenance in line with the paradigm of harm reduction. If a patient does not receive a higher methadone dose, it is generally because he or she does not want to increase it. In our environment, it is usually patients who request a methadone dose that is relatively low', in the sense of being sufficient to avoid objective OWS symptoms, but not high enough to implement a narcotic blockade. This enables them to start the day without any urgent need to take heroin, but, independently of whether it is consumed together with alcohol or benzodiazepines (generally alprazolam), they experience an effect of euphoria/sedation. In this context, we distinguish between an 'adequate dose' and a 'dose accepted by staff', that is, a dose which in principle is pharmacologically 'inadequate' but which, owing to patients' retention in the methadone programme, actually allows them to meet intermediate health goals (treatment for HIV infection and HCV, tuberculosis, psychiatric treatment), social integration, employment and quality of life.

In the sample studied, the correlation coefficient observed between methadone dose and plasma levels is considerably lower than those found by other authors [67, 33, 34]. In our opinion, this is due to the 'naturalistic' design of our study since, unlike other authors, we did not exclude any patients because they were taking antiretroviral agents, tuberculostatics or other types of drug, or because of their medical or psychiatric condition. That leads us to believe that a correlation coefficient of 0.57 must be a figure close to to the clinical reality in which we work. On the other hand, the correlation between methadone dose and its

“pharmacological effect” (as measured by the ODAS) can be acknowledged to be insufficient. Even more evident is the absence of linkage between the SML and the “pharmacological effect”. The most important requirement for a drug to be subject to monitoring is that there should be linkage between its concentration in plasma and its pharmacological effect, because otherwise it would be pointless to try to measure it [3]. Thus, the data reported in this study do not justify systematic monitoring to determine the SML (that is, as a dose adjustment tool for placing the dose to be prescribed within the therapeutic range). In any case, our data fail to provide grounds for considering the clinical assessment of patients - in the attempt to achieve adequacy as measured by the ODAS - the most useful instrument for making a decision on whether to modify the methadone dose. Even so, we believe that determining the SML could offer a useful way to a) evaluate compliance with the dose, as pointed out by Torrens et al. [61], and b) facilitate the diagnosis of a fast metabolizer (that is, a case in which the peak/trough ratio is over 2). In this context, Baño et al [38], propose a promising algorithm for the integration of clinical information with that contributed by the SML in making methadone dose adjustment decisions.

One of the basic hypotheses of our research work was that among the patients with the highest methadone doses, we would find the highest ODAS scores, or at least a higher percentage of subjects with ‘adequate’ doses’. Unexpectedly, we did not observe this in our sample (see Table 1 and the correlation coefficient between methadone dose and ODAS scores). In our opinion, this result may be due to the sample studied being made up of stabilized patients who had been on treatment with methadone for quite some time. For example, many of the patients with doses under 60 mg/day had been gradually reducing their dose. This same phenomenon has been observed by Willenbring et al. [66], who found that treatment centres with a low level of patient turnover and a high percentage of stabilized patients in maintenance may achieve good results despite the prescription of relatively low doses. We should not forget that in these cases there has been a gradual reduction in tolerance and neuroadaptation, so that, for example, a dose as low as 30 or 40 mg/day might prove to be ‘adequate’. Another factor that could explain relatively low ODAS scores in patients with high methadone doses is the high prevalence of cocaine abuse. In our environment, heroin is preferentially inhaled-smoked (95%) in combination with cocaine (a mixture called “rebujao”). This type of patient would try to experience the effects of cocaine more than those of heroin, and in the therapeutic approach this is usually associated with an increase in the methadone dose. These ‘unexpected’ effects often turn out to be quite

common in treating patients with multiple substance abuse [23].

One of the limitations of our study is precisely that it was performed on a sample of very stable patients who had been in an MMP for a long time. It would be of interest for future studies on this scale to perform an evaluation of patients during their first few weeks in the programme (methadone induction), up to the moment of their stabilization. Furthermore, more evidence on the concurrent validity of the EADO is required. Specifically, it would be worth studying the relationship between the items on this scale with parallel measurements and then going on to analyse it with a multi-method-multi-trait matrix, for instance, the objective and subjective OWS items with specific OWS scales or the craving items with another scale on craving.

Another limitation of our work is its transversal design. Future longitudinal studies should attempt to incorporate ‘adequacy’ sequentially and relate it to measurements of treatment outcomes. Although this study was performed on a sample of patients already on methadone treatment, the ODAS is also designed to evaluate the adequacy of buprenorphine doses. Therefore, future studies should aim to provide evidence on patients taking buprenorphine.

This research work contributes more evidence on ODAS dimensional scoring than on its categorical scoring. Our recommendation is that dimensional scoring

Appendix 1. ODAS Scoring Code

Dimensional Scoring

Item 1: Scores from 1 to 5

Item 2: Scores from 1 to 5

Item 3 (objective OWS):

Item 3a: Scores from 1 to 5

Item 3b:

If the score on 3b is 1 or 2 (that is, a very intense objective OWS), one point is subtracted from Item 3a (example: if 3a scores 4 and 3b scores 2, then “Item 3” scores 3).

If the score on 3b is 3, 4 or 5: the score in Item 3a is not changed (and this will therefore be the score for “Item 3”).

Items 4, 5 and 6: score using the same procedure as for Item 3.

Therefore, the total score on the ODAS is the sum of the scores of each one of the 6 items in a range of 6 to 30 points.

Categorical scoring:

A patient is considered to have the “adequate dose” when the 6 items in the ODAS (scored following the procedure defined in “Dimensional scoring”) SCORES 4 OR 5. Those who do not meet this condition are not classified as patients with an “adequate dose”.

should always be employed, both for both clinical and research applications. The transformation of a dimensional measure into a categorical one always means a loss of information, in addition to the difficulty of deciding on a cut-off point (44). The categorization of a measurement may be worthwhile when a diagnostic or therapeutic decision depends on it. We have chosen a clinical criterion based on the literature to establish the cut-off point by differentiating between 'adequate' and 'inadequate', but we understand that other colleagues may not concur with this criterion.

This work contributes sufficient evidence on the psychometric quality of the ODAS, and we believe that it constitutes a good working tool, whether in clinical practice or in research; in addition, it opens up new lines of study.

5. Conclusions

This study provides sufficient evidence for the reliability and validity of the ODAS as a tool for measuring methadone dose adequacy. The results of the construct validity test support the hypothesis put forward by several authors that an individualized clinical assessment of methadone dose adequacy is better able to account for a patient's condition than either the methadone dose or the patient's serum level.

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Contributors

The authors contributed equally to this work.

Conflict of Interest

The authors have no relevant conflict of interest to report in relation to the present study.

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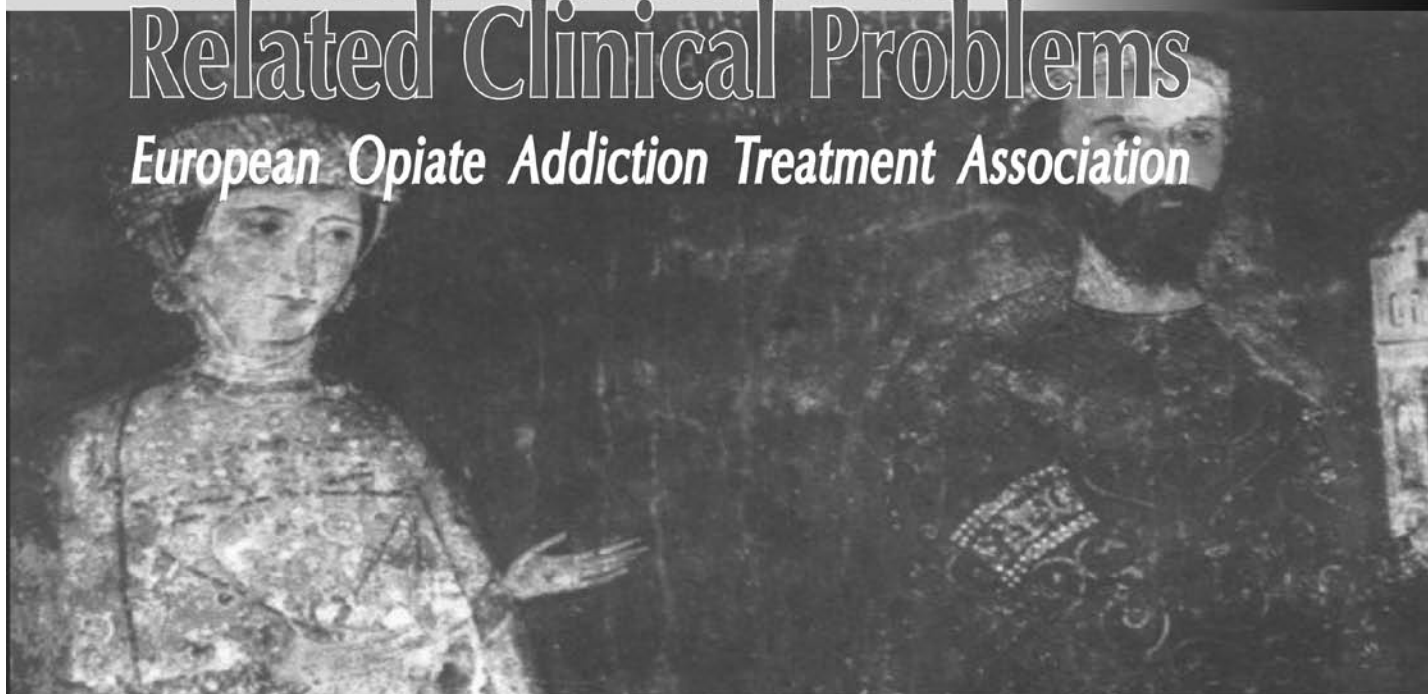
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Improvement in the Quality of Life in Heroin Addicts: Differences Between Methadone and Buprenorphine Treatment

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Summary

The main goals of opioid treatment in heroin addiction are to eliminate or reduce the use of heroin and other substances of abuse, to promote patients' social rehabilitation and to improve their quality of life. The purpose of this study is to evaluate the efficacy of buprenorphine and methadone on the quality of life of patients. These subjects were sampled on the basis of the same severity of illness and the same impairment of quality of life at the start of treatment. 50 patients (41 male and 9 female) in buprenorphine treatment and 83 patients (63 males and 20 females) in methadone treatment, were evaluated regarding their retention in treatment, the use of substances, their clinical improvement and their quality of life over a one year period. In markedly ill patients buprenorphine and methadone both successfully and similarly reduce substance abuse and the severity of illness. Patients treated with buprenorphine show a better improvement of quality of life especially regarding improvements in jobs, leisure activities, income and self-acceptance. We conclude that Buprenorphine is a good choice for markedly ill patients with severe impairment in their quality of life parameters.

Key Words: Methadone treatment, Buprenorphine, response predictors to treatment outcome, retention, psychiatric comorbidity, quality of life

1. Background

The main goals of opioid treatment in heroin addiction are to eliminate or reduce the use of heroin and other substances of abuse, to promote the patients' social rehabilitation and to improve their quality of life [10, 13, 15, 17]. Buprenorphine and methadone, mainstay of pharmacological management of heroin dependence, have different pharmaceutical properties (mechanisms of receptor action and opiate activity)

[9, 20, 21]. While these medicines have comparable efficacy in controlling substance abuse, they may have different impact on patients' quality of life, especially in the long term and for patients' social rehabilitation. Usually pharmacological studies do not use "the impairment of quality of life" as sample selection criteria and often both patients with good and poor life quality are divided in groups to be evaluated in unbalanced way, which could significantly bias the results. The purpose of this study is to evaluate the efficacy of buprenorphine

and methadone regarding the quality of life of patients sampled on the basis of the same levels of severity of illness and the impairment of quality of life as judged at the initiation of the treatment.

2. Methods

2.1 Subjects

A re-evaluation of patients that have participated in a previous observational study with the following characteristics was undertaken [12].

The old multi-site cohort study was designed in order to evaluate treatment outcome (in terms of retention in treatment, substance use, psychopathology and quality of life) of patients staying in treatment beyond the early attrition stage (3 months) in a methadone or buprenorphine program. This was an open, non-randomized, observational study.

Follow-up evaluation was carried out at 12 months, one year after the beginning of treatment. All the patients gave their informed consent for participation in the study. Study procedures were approved by appropriate ethics committees, in accordance with internationally accepted criteria for ethical research.

All 213 patients participating in the study have been considered.

In order to be included in this study, except for satisfying inclusion and exclusion criteria reported in the reference study, patients needed to satisfy in addition the following criteria;

- a) Life quality, assessed with QoL questionnaire to be not superior than 350 points. A total score of 350 or more means fairly successful living conditions and quality of life.
- b) disease severity corresponding to 5 points in the CGI scale (markedly ill) at the beginning of the observation lead to exclusion. So the most extremely ill patients were excluded.

The two samples treated with buprenorphine and methadone were subsequently balanced according to demographic and clinical characteristics. In the group treated with buprenorphine 50 patients were selected, 41 male and 9 female, with mean age of 32 years (sd=6). In the group treated with methadone 83 patients were selected, 63 males and 20 females with mean age of 32 years (sd=6). the two samples were extremely homogenous regarding demographic, clinical characteristics and quality of life subsequently to balancing (Table 1).

2.2 Instruments

The following instruments were used to collect data on the variables to be studied:

2.2.1 Clinical Global Impression (CGI).

Clinical Global Impressions (CGI) consists of 3 global scales (items). Two of the items, Severity of Illness and Global Improvement, are rated on a 7-point scale (from normal to among the most extremely ill for the Severity of Illness and from very much improved to very much worse for Global Improvement); while the third, Efficacy Index, requires a rating of the interaction of therapeutic effectiveness and adverse reactions. Efficacy Index is an attempt to relate therapeutic effects and side effects. Therapeutic effect is regarded as gross profit (from 1-Unchanged or Worse to 4-Marked); side effects as cost (from 1-None to 4-Outweighs). The index, then, is analogous to net profit. The index is derived by dividing therapeutic effect score by side effect score.

2.2.2. Drug Addiction History Rating Scale (DAH-RS)

The DAH-RS [11] is a multi-scale questionnaire comprising the following categories: sociodemographic information, physical health, mental health, substance abuse, treatment history, social adjustment and environmental factors. The questionnaire rates 10 items: physical problems, mental problems, substance abuse, previous treatment, associated treatments, employment status, family situation, sexual problems, socialization and leisure time, legal problems. (The specific clinical variables addressed are: hepatic, vascular, haemo-lymphatic, gastrointestinal, sexual, dental pathology, HIV serum status; memory disorders, anxiety disorders, mood disorders, aggression, thought disorders, perception disorders, awareness of illness; employment, family, sex, socialization and leisure time, legal problems; use of alcohol, opiates, CNS depressants, CNS stimulants, hallucinogens, phencyclidine, cannabis, inhalants, polysubstance abuse; frequency of drug use, pattern of use, previous treatments; current treatments). Items have been constructed in order to obtain dichotomous answers (yes/no).

2.2.3. Quality of Life Questionnaire (QLQ)

QLQ is a semi-structured interview investigating the following life dimensions: job, leisure, appetite, sleep, social relationships, social involvement, income, parental role, romantic relationships, self-acceptance. It was chosen for its minimal overlap and good fit with the other instruments [1, 19]. The scales included were: working, earnings, leisure, eating, sleeping, social relations, romantic relations, parenting, environment and self acceptance. Each scale was measured on the

Table 1. Demographic, clinical and quality of life characteristics at study entry

	BUP N=50	MET N=83		
	M±s	M±s	T	p
Age	32±6	32±6	0.21	0.83
Age 1st use	19±4	19±5	-0.12	0.90
Age of dependence onset	21±5	22±5	-0.06	0.95
Dependence length (months)	101±7	103±7	-0.17	0.86
Age 1st treatment	24±5	25±5	-0.53	0.59
N abused substances	3.26±1.4	3.39±1.5	-0.51	0.61
Psychopathological Areas Total	2.54±1.9	2.73±2.0	-0.54	0.58
Somatic Areas Total	1.52±1.2	1.60±1.2	-0.37	0.71
	N (%)	N (%)	Chi	P
Sex (males)	41 (82.0)	63 (75.9)	0.68	0.40
Education (more than 8 yrs)	15 (30.0)	28 (33.7)	0.19	0.65
Marital status (married)	22 (44.0)	33 (39.8)	0.23	0.63
Job (employed)	28 (56.0)	33 (39.8)	3.31	0.06
HIV positivity	3 (6.1)	9 (11.1)	0.90	0.34
Family Issues	27 (54.0)	44 (53.0)	0.01	0.91
Legal Issues	20 (40.0)	36 (43.4)	0.14	0.70
Heroin Daily Intake	32 (64.0)	46 (55.4)	0.94	0.33
Late Phase of Addiction*	39 (78.0)	69 (83.1)	0.53	0.46
Dual Diagnosis	35 (70.0)	53 (63.9)	0.52	0.46
	M±s	M±s	T	p
Job	25.20±5.0	26.02±9.2	-0.66	0.50
Leisure	27.20±9.6	29.63±10.0	-1.39	0.16
Appetite	37.20±7.0	36.86±7.3	0.26	0.79
Sleep	32.40±9.8	30.60±10.0	1.01	0.31
Social relationships	28.00±14.8	26.98±14.9	0.38	0.70
Income	26.80±9.5	25.54±9.0	0.75	0.45
Parental role	40.00±0.0	36.66±9.6	1.80	0.08
Romantic relationships	29.80±14.3	29.51±14.3	0.11	0.91
Environment	28.80±3.2	28.43±3.6	0.60	0.55
Self acceptance	34.00±4.9	33.25±5.6	0.80	0.42
QOL Total Score	301.82±33.1	298.83±39.1	0.47	0.64
QOL Positive Area Total	5.16±1.3	5.01±1.6	0.56	0.57

*So called “revolving door stage”. The patient underwent a series of relapses and repeatedly failed to maintain abstinence.

following metric: 0=non-existent or no opportunity. 10=Minimal; 30=Adequate; 50=Best possible. Intermediate values are 20 and 40. A total score of 350 or more means fairly successful living conditions and quality of life. A total score of 250-350 suggests a situation of painful but adequate ability to cope, and a total score of 100-250 is found among people who suffer a lot and seek immediate help. Institutionalized mental patients fall below 100.

2.2.4. Psychiatric Diagnostic Evaluation.

Psychiatric disorders were investigated on the basis of the DSM-IV Decision Trees for Differential Diagnosis. Each decision tree starts with a set of clinical features. When one of these features is a prominent item of the current clinical picture, the clinician will ask a series of questions to rule in or rule out a number of disorders. The questions are just approximations to the diagnostic criteria and are not meant to replace them. Three decision trees have been used: “Differential Diagnosis of Psychotic Disorders” (initial clinical features: delu-

sions, hallucinations, disorganized speech, or grossly disorganized behaviour); “Differential Diagnosis of Mood Disorders” (initial clinical features: depressed, elevated, expansive or irritable mood; two separate items record the presence of depression and/or any tendency towards the bipolar spectrum as testified by an elevated, expansive or irritable mood); “Differential Diagnosis of Anxiety Disorders” (initial clinical features: symptoms of anxiety, fear, avoidance, or increased arousal).

We considered there to be a “dual diagnosis” when we have determined the presence of both heroin dependence and an autonomous psychiatric disorder.

2.2.5. Urinalyses

Urine drug testing was performed for opioids and cocaine and cannabinoids. Sample collection was supervised by a nurse in order to prevent fraud. Urine samples which were skipped because of patients’ unavailability were registered as positive for opioids.

2.3. Data analysis

Analysis of the results was made on completion of the 12 months of treatment. The two groups of patients undergoing treatment, with buprenorphine and with methadone, were compared for sociodemographic and addiction history by means of the Chi-square test for categorical variables, and Student’s t test for continuous variables.

Retention in treatment was analyzed by means of the survival analysis and Leu-Desue statistics for comparison between the survival curves. For the purpose of this analysis, “completed observations” refer to patients who left the treatment and “censored observations”

refer to patients still in treatment at the end of the 12-month period or who discontinued treatment for reasons unrelated to treatment itself (patients moving to other towns, imprisonment for old crimes, and so on).

The toxicological urinalyses were expressed as the percentage of the total number of urinalyses positive for each patient. Comparisons between the two groups used Student’s t tests. (for cross-sectional evaluation) and MANOVA repeated measurement (for longitudinal evaluations).

3. Results

3.1 Retention in treatment

12 patients undergoing treatment with buprenorphine and 18 in methadone treatment had abandoned the program with negative outcomes during the 12 months of observation. Consequently 38 with buprenorphine treated patients and 65 methadone treated patients had completed the observation period.

The cumulative proportion of patients remaining at the end of the observational period was 0.76 for buprenorphine patients and 0.77 for methadone patients. This difference is not statistically significant (Le-Desu statistics 0.24 DF=1 p=0.61. The maximum risk for drop-out occurs in the seventh month both for patients treated with buprenorphine as for those treated with methadone. For details see table 2.

3.2 Longitudinal analysis

Longitudinal analysis was carried out for patients who were still in treatment at 12 months. Table 3 shows the differences between buprenorphine and metha-

Table 2. Survival in treatment

Months	N° exposed to risk		N° of terminal events		Cumulative survived		Hazard rate	
	BUP	MET	BUP	MET	BUP	MET	BUP	MET
1	50	83	0	0	1.00	1.00	0.00	0.00
2	50	83	0	0	1.00	1.00	0.00	0.00
3	50	83	0	0	1.00	1.00	0.00	0.00
4	50	83	1	0	0.98	1.00	0.02	0.00
5	49	82	2	1	0.94	0.99	0.04	0.01
6	47	80	2	1	0.90	0.98	0.04	0.01
7	45	78	3	7	0.84	0.89	0.07	0.09
8	42	71	1	1	0.82	0.88	0.02	0.01
9	41	70	2	2	0.78	0.85	0.05	0.03
10	39	66	0	2	0.78	0.83	0.00	0.03
11	39	64	1	4	0.76	0.77	0.03	0.06
12	37	60	0	0	0.76	0.77	0.00	0.00

Le-Desu 0.24 DF1 P=0.61

Table 3. Differences at 12 months between patients treated with buprenorphine and methadone.

	BUP N=38	MET N=65		
Urinalysis	M±s	M±s	T	p
Clean urine for opioids	91.66±25.5	88.58±23.6	1.57	0.12
Clean urine for cocaine	86.25±32.0	74.96±39.5	1.57	0.12
Clean urine for cannabinoids	77.27±40.7	70.00±40.3	0.68	0.50
CGI				
Severity of illness	2.58±1.0	2.38±1.0	0.92	0.36
Global improvement	2.05±1.1	2.20±1.2	-0.60	0.55
Efficacy index	2.88±0.9	2.64±1.0	1.18	0.24

done treated patients at the end of the observational period.

Regarding the clinical global index evaluation after 12 months, patients treated with buprenorphine and methadone achieved similar good results. The average severity of illness rated from borderline mentally ill and mildly ill, while average global improvement was measured as much improved. As for efficacy index, the therapeutic effect and side effects ratio, the subjects achieved average scores indicative of a good therapeutic effect-side effects ratio. The therapeutic effect is positive and the side effects are either absent or do not significantly interfere with the patients' functioning.

Regarding the urinalyses, the results relate to a total of 4944 analyses (1824 for patients in buprenorphine

and 3120 for those in methadone treatment, once-a-week analysis), not considering the initial analysis for heroin, which were positive. by definition. Clean urines for opioid were found in over 90% of patients in buprenorphine treatment and 88% of patients in methadone treatment. Percentage of positivity to cocaine remains slightly lower and corresponds respectively to 86% (buprenorphine) and 74% (methadone). Effectiveness is less on the cannabis use which continues to be used by 23% of subjects in buprenorphine treatment and 30% of patients in methadone treatment. These differences are not statistically significant and therefore buprenorphine and methadone have proven equal efficacy in controlling the use of heroin, cocaine and cannabis.

Table 4. Repeated measurement analysis of variance. Differences between 1-12 months in completing patients

	Buprenorphine N=38		Methadone N=65		Manova repeated		
	Baseline	12 months	Baseline	12 months	Group	Time	Group by time
	M±s	M±s	M±s	M±s	F	F	F
Job	25.12±5.0	37.17±5.1	26.66±9.5	33.00±5.6	1.55	96.51**	9.34**
Leisure	27.69±9.8	36.15±4.9	30.00±10.0	33.00±5.9	0.10	31.48**	7.15**
Appetite	36.41±7.7	38.94±6.4	36.66±7.5	35.66±6.7	2.08	0.59	3.07
Sleep	32.30±9.8	39.74±6.6	29.00±10.0	36.50±7.5	6.03*	39.14**	0.00
Social relationships	29.23±14.5	37.69±5.3	28.50±14.7	36.16±7.8	0.42	25.73**	0.06
Income	26.15±9.3	37.17±5.5	26.66±9.5	32.16±5.2	3.55	63.61**	7.11**
Parental role	40.00±0.0	42.50±4.6	40.00±0.0	41.66±5.7	0.12	2.90	0.12
Romantic relationships	28.46±14.7	35.64±5.9	28.50±14.7	34.83±7.2	0.05	17.46**	0.07
Environment	28.71±3.3	37.94±5.7	28.50±3.6	36.33±6.8	1.29	148.51**	1.00
Self acceptance	33.33±4.7	40.25±5.3	33.00±5.9	35.83±6.9	6.90*	34.92**	6.14**
QOL Total Score	299.91±33.0	379.31±37.8	300.16±40.7	349.81±40.04	5.49*	173.61**	9.23**
QOL Problematic Areas Total (<40)	5.16±1.3	2.71±2.7	4.96±1.6	5.70±2.4	15.02**	12.02**	38.99**

* p<.05 ** p<0.01

3.2. Improvement of quality of life

Quality of life shows a substantial improvement over time, both in patients treated with methadone and those treated with buprenorphine (Table 4). In fact 10 of the 12 indexes used improved in a statistically significant way. Only the appetite and the parental role dimensions failed to show significant improvement.

The index “QOL Problematic Areas Total” pinpoints all the areas where the life quality is less than optimal (at least “problematic, but with adequate coping”). At the beginning of the observation the two groups showed the same characteristics (around 5 areas), but at the end the individuals in buprenorphine treatment showed improved but not an optimal situation only in 2-3 areas, while for the individuals in methadone treatment the number of areas considered (more than 5) remained unchanged. The two groups differ significantly at 12 months for this index (in the benefit of patients with buprenorphine), both show an improvement over time but with a group-time effect still in favor of patients with buprenorphine.

The total scale score shows how the mean of patients in buprenorphine treatment reached, after 12 months, a higher score than those in methadone treatment, this is indicative for a high quality of life. Indeed, a score superior to 350 indicates fairly successful living conditions and life quality. Those treated with methadone remained at the border of this value suggesting that for some of them the situation remains painful but with adequate ability to cope. A group effect, a time effect and a time for group effect exists for this index as well. Patients treated with buprenorphine show greater improvement in work, leisure, earning ability and self acceptance areas. Despite the fact that most indexes improve over time both for patients treated with buprenorphine as for those in methadone treatment after the 12 months of observation period, patients treated with Buprenorphine have manifested larger improvement than their colleagues in methadone treatment under. This was noted in different aspects of investigation such as work, leisure time activities and their degree of overall self-acceptance

Similar improvements have been obtained regarding sleep, social relationships, emotional-sexual life, and relationships with domestic, work and life environment in general.

4. Discussion

Buprenorphine and methadone appear equally effective in maintaining patients in treatment, reducing the use of opiates, cocaine and cannabis in patients who meet the criteria for markedly ill patients. We

have intentionally selected this type of patients avoiding “severely ill” and “most extremely ill” subjects since the comparative effectiveness of methadone and buprenorphine for these individuals is still being researched [2, 6, 7, 16]. In our markedly ill subjects, therefore, the effect of the two drugs on the addiction illness is very similar.

Regarding the quality of life, however, buprenorphine appears to have superior beneficial action. This fact has been demonstrated in our data, after a 12-month protracted period of treatment, mainly by global scale scores that for patients in buprenorphine treatment exceeds the average score of 350, indicative of fairly successful living conditions and quality of life

For subjects in methadone treatment scores around, but less than 350 suggests a situation of painful but adequate coping abilities. Even the areas where the patient does not feel completely at ease remain high (around 5-6) in patients in methadone treatment, while decreasing significantly (between 2 and 3) in patients in buprenorphine treatment. After a year of observation, improvement of quality of life is significant for both groups, however buprenorphine treated patients show major improvement in job, leisure and earning capacity. Generally beneficial effects of the maintenance treatment programs using both buprenorphine and methadone with regard to satisfaction with QoL and all specific life domains among heroin-dependent outpatients are reported in the literature [4, 14, 18]. On the contrary, our data suggest buprenorphine has a better impact than methadone on selected areas of quality of life linking a social dimension like working to a personal one like leisure time.

Particularly interesting is the evidence, in this study, of major self acceptance of patients treated with buprenorphine when compared to those treated with methadone. Methadone treated patients with limited resources, few social connections, and negative self-concept tend to see methadone as an addiction, and as a highly stigmatizing and disempowering intervention [3, 5, 22]. It appears that patients treated in the buprenorphine arm of the study limit their sense of stigma which more regularly affects patients treated with methadone. Buprenorphine seems, in fact, to be better accepted than methadone; especially for patients having sufficient income and a satisfying job. This fact supports that buprenorphine can be more largely used in primary care settings [8]. In fact when the patients reach the stabilization/rehabilitation phase the role of general practitioners becomes crucial because they represent a reentry in to the “normality” of the general health care system therefore limiting the “stigma” of Methadone Clinic attendance.

4.1 Limitations

There might be some valid criticism for the open manner in which patients were selected for each arm of the study based on achieving a balanced levels of Quality of Life. The researchers have attempted to extract information regarding the differential effect of these two medications on the main outcome of Quality of Life. In essence this was a method of using a “Naturalistic Treatment” sample where there was no initial random assignments to each arm of the study. Important demographic and clinical dimensions had proven to not be significantly different at the initiation of the observation time. We therefore feel that meaningful conclusions can be reached regarding this investigation.

5. Conclusions

In markedly ill patients buprenorphine and methadone both successfully reduce substance abuse and severity of illness. Patients treated with buprenorphine show a better improvement in their quality of life, especially regarding dimensions reflecting job, leisure, income and self acceptance parameters. Buprenorphine represents a good choice for markedly ill patients with severe impairment of quality of life. Its utilisation in a user friendly primary care setting is recommended and should be developed.

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Contributors

The authors contributed equally to this work.

Conflict of Interest

The authors have no relevant conflict of interest to report in relation to the present study.

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Methadone: A Fast and Powerful Anti-anxiety, Anti-depressant and Anti-psychotic Treatment

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TO THE EDITOR: On the brink of retirement, I find it useful to raise certain important points about the treatment of drug addiction, most particularly the observation that methadone exercises fast and powerful anti-anxiety, anti-depressant and anti-psychotic effects.

For 30 years, with my colleagues at the Phénix Foundation - now 60 in number - we have followed more than 2000 heroin addicts. We have often been surprised by the almost miraculous action of methadone in stabilizing important psychiatric disorders that had responded poorly to medication such as antipsychotics and to psychotherapy. To illustrate this observation, I present four particularly interesting clinical cases.

During the Seventies, most heroin addicts were still socially integrated, intelligent and cultivated people, in search of new sensations through opiate use. This was perceived as a sensorial search, an exploration of pleasure, a semi-mystical enlargement of awareness within a private and elitist sphere. Trapped by heroin, with their autonomy and quality of life threatened by their dependency, these addicts sought out substitution treatment. Many among them were subsequently able to wean themselves off methadone, successfully and without relapses, after a few years of medical and psychosocial treatment. Part of this success must, of course, be attributed to what was often a fairly solid personality structure and a favourable psychosocial environment.

Sadly, owing to the ever-increasing prevalence and profitability of drug trafficking, heroin is now

available at every corner of town. Its most powerful impact has been on the more fragile among our young people, those with affective, social and psychiatric problems. Suffering its side-effects, these unfortunates have spontaneously discovered ways to alleviate their pain, first through nicotine, alcohol, benzodiazepines and opiates, then, more recently, through cocaine. All of these substances increase the concentration of dopamine in the brain, to different degrees and in different ways [15].

A number of studies postulate that genetic particularities in certain individuals lead to a dysfunction of dopaminergic systems owing to an insufficient number of dopamine receptors or an excess of 'recapture pumps'; this might explain certain psychological disorders such as attention deficit hyperactivity disorder (ADHD). When a cocaine addict says he takes the drug in order to be calm and concentrated, ADHD is sought out and is nearly always found.

By using the 15-question Connor test, we have evaluated the severity of ADHD symptoms in 371 of our patients in methadone substitution treatment. What emerged was a marked over-representation of symptoms in our population, including 25% hyperactivity compared to the 5% norm. The hyperactivity group, compared to the non-hyperactivity group, proved to have twice as many problems with the police and to use double the amount of heroin before treatment (3 grams per day).

We also divided patients into groups according to

their degree of pathology, and found that the group with the highest psychiatric comorbidity used double the amount of heroin before treatment (2.9 grams per day compared to 1.4 grams per day) and had suffered seven times more overdoses.

When one prescribes morphine to a normal individual in care, even over a long period of time, not only does the person feel no particular pleasure, but also often suffers disagreeable side effects, such as nausea. When treatment ends, the person does not become an addict.

The same can be said of thousands of American soldiers who became heroin addicts in Vietnam owing to the availability of the drug, the need to compensate for factors such as combat stress and their distance from loved ones. Once home, back in reassuring and affectionate surroundings, far from military conflict and, most importantly, sheltered from the drug, a majority of the soldiers remained abstinent. Among those that continued heroin use in America and remained addicted, severe psychiatric comorbidity or psychosocial complications were often observed.

Based on our longstanding clinical experience and numerous evaluations, we have concluded that the most important factor — the factor best correlated with addiction development, maintenance and treatment failure — is the presence of psychiatric suffering accompanied by psychosocial complications [16, 17, 33].

Numerous recent studies inquiring into the origins of psychiatric disorders have shown, more often than not, an important genetic and neurobiological component. In this case, psychiatric difficulties come to the surface, in different forms, as early on as childhood. They entail numerous affective, social and psychological complications. If the hypothesis of a primary neurobiological disorder is confirmed for these patients, it is understandable that medication specifically balancing cerebral dysfunction is more efficient than psychodynamic treatment alone.

In such patients, psychiatric suffering is not always conscious and may often be denied, but the first time they take an opiate, it will emerge, and leave an indelible mnemonic impact. For the first time in their lives, these patients will feel well, 'feel normal', as an ordinary person would put it. They then realize that they have been suffering for many years, without ever knowing what it is like to be normal. They will then naturally seek to reproduce and maintain this state of equilibrium, but at the cost of risking chronic addiction. In these cases, any weaning attempts are bound to lead to the reappearance of underlying psychiatric disorders.

It is like the experience of a short-sighted child, who thinks his blurred world is normal, but, on discovering glasses during adolescence, discovers the pleasure of precise and colourful vision. He will never want to go

without glasses again.

Such is the problem of substitution treatment in many cases where the patient is one who suffers from a chronic disorder, most often triggered by a dysfunction of one or many neurobiological cerebral systems, due to genetic factors and aggravated by an abuse of drugs that permanently modifies the functioning of the brain [18,19,21,26,32].

The search for drugs to alleviate psychological suffering has been well documented over the last decade [2,5]. As early as 1970, studies refer to this concept of automedication to explain the use and maintained use of drugs. Numerous observations have described the calming and stabilizing virtues of opiates in aggressive or psychotic patients and in those with bipolar disorders [11,13].

Published research showed spectacular improvements in non-addicted patients with paranoid schizophrenia who had not benefited from the effects of the usual anti-psychotic treatment [1,3,28].

Other studies made over a long period have demonstrated the marked anti-depressant effect of methadone in patients with depression who were resistant to the more usual anti-depressants. One must recall that opiates, especially laudanum, were used at the beginning of psychiatric history to treat severe forms of depression such as melancholia and manic-depressive psychoses [5,7,10,24,25,29].

During a trip to study drug problems on the paths of Kathmandu in 1970, I was impressed to see travellers successfully using a little opium to treat young people in complete delirium after they had taken LSD.

The anti-anxiety effect of methadone is widely recognized. Methadone blocks the stress hormone at a cerebral level, which allows severe anxiety states to be durably stabilized. Conversely, the interruption of methadone treatment entails a dysfunction of the stress axis, and leads to long-term anxiety disturbances.

How can the speed and efficiency of the anti-anxiety, anti-depressant and anti-psychotic action of opiates and methadone be explained? The very little research carried out so far leaves scope for an explanation. The effect is probably due to complex interactions between endorphinic, dopaminergic and glutamatergic systems [6,12,22,23,27,30]. Quite a few studies have demonstrated the anti-depressant effect of NMDA receptor agonists in animals [8,14].

In 2004, Sanacora and colleagues found significantly higher levels of glutamate in the occipital cortex of 29 patients with major unipolar depression, when compared with 28 control subjects. One explanation for mood disorders would therefore be the dysfunction of the glutamatergic system. On this view, antagonist substances of the latter would have anti-depressant effects.

Very recently, in August 2006, Carlos Zarate and colleagues [34] published a study that showed a marked and speedy anti-depressant effect following a single dose of an NMDA antagonist, Ketamine, in patients with major depression disorders. This anti-depressant effect was present among some as early as two hours after the Ketamine injection and remained significant throughout the next seven days.

Buprenorphine, an opiate agonist-antagonist, at an adapted dose, has also shown anti-depressant, anti-dysphoric and anti-psychotic properties. An agonist action on the Kappa receptors has been hypothesized in order to explain this psychotropic effect [4,9,31].

The remarkable progress made over these last few years in the field of animal research, cerebral imagery and the neurosciences should enable us to find further answers to this fundamental question.

One can only hope that research will lead to the development of new and efficient medication able to offer patients suffering from addiction better stabilization.

In order to illustrate the anti-anxiety, anti-depressant and anti-psychotic effect of methadone, I will now present clinical cases summarizing the treatment of four patients suffering from significant psychiatric comorbidity. In all four cases, methadone demonstrated remarkable success in stabilizing the patient.

Case David

An occasional hashish smoker, the 22-year-old David was discovered in a city park stark naked and masturbating. Taken to the psychiatric hospital, he exhibited a hypermanic state which evolved to the frankly manic. Bipolar disorder with psychotic characteristics was diagnosed and Haldol (200 mg by injection) prescribed. When discharged, he was given a prescription for 10mg per os of Haldol daily.

Suffering from the side-effects of neuroleptics, he discovered one day that he felt much better psychologically if he took heroin. He stopped taking Haldol and developed a rapid dependence on heroin, graduating to injection. After a few months of submission to heroin, he successfully undertook a first methadone cure of one full year, remaining well balanced on the psychological level. At 28, eager to live normally and without drugs, he decided to end methadone support. One month later, a new manic episode occurred, and as a result he lost his job. He started self-medicating with heroin again, in a major way, and stabilized on the psychological level, but with many financial and legal disadvantages. That is why he decided to take a long-term methadone cure with a private doctor.

Over six years, with a dosage of 100mg of methadone per day and without any other drug, he remained perfectly stabilized on the psychological level, enjoyed

a good quality of life, worked regularly and got married.

In 2002, he became an administrative civil servant, working in a government building very close by our treatment centre. He transferred the responsibility for his treatment to us and we continued his dosage of 100mg per day. He continued to be very well stabilized in his mood.

One year later, again very eager to live without chemical help, he insisted on being progressively weaned off the treatment. I set out to discourage him reminding him about the events that had lead up to his first psychiatric hospitalization when he was only 22. He minimized their importance and persisted in his idea. Over the next months he steadily reduced his dosages. Three years later, when it had reached just 20 mg, I got a telephone call from David's boss. He was extremely concerned. David, in a half-naked state, had made sexual advances to a secretary, tried to buy an elephant over the telephone and otherwise behaved in a generally agitated and incoherent manner. It amounted to a manic decompensation — all his defence mechanisms had collapsed so completely that, for the first time in many years, I had to organize his urgent admission by ambulance to a psychiatric hospital. The scandal was great, since David had a service apartment in the building itself and was entrusted with confidential assignments.

Even after treatment at the psychiatric clinic with 100mg of Depakine and neuroleptics, he remained agitated and threatening. Finally, the psychiatrist treating him agreed to re-establish an adequate methadone dosage — 50 mg — and the patient quickly and successfully restabilized.

Over the last three years, first in monotherapy with methadone, then with MST (slow-release morphine tablets) because of certain methadone side-effects — sweating and oedema — he has been able to lead a normal life, maintaining a satisfactory level of mood stability. We were able to save his job by explaining to his employers the exceptional character of his outbreak, related to the fall in his methadone dosage, just as surely as an epileptic would collapse into crisis if dosages of his stabilizing medication were to fall below a certain level. He is now holding down his job to the complete satisfaction of his superiors, besides practising several sports and other leisure activities.

He now accepts his need to take a daily opiate dose for the rest of his life. In the long run he is proving much more stable, enjoying a better quality of life and experiencing far fewer side-effects than do bipolar patients treated with classic medications.

Case Alain

Alain has been a heroin addict since he was 17. Psychiatric antecedents were found in his family. After some attempts at weaning him off the habit failed, he began a methadone treatment with us when he was 22. During the early years, dosage was limited to between 20 and 50mg, the result being that he continued to take heroin once or twice a week, in spite of the psychosocial support he was receiving.

He then agreed to accept an increased dosage of 120mg of methadone. From then on he remained completely abstemious by maintaining good psychosocial balance and holding down a stable job.

One day he decided to wean himself progressively off methadone and left soon afterwards to spend some weeks in Crete with his girl-friend. When the time came to return to Switzerland, he vanished at the airport and his friend had to come back without him. He was found several days later wandering around the island, half-naked and confused, in a disturbingly paranoid psychotic state. He saw the sea as totally black, bubbling with a multitude of crabs ready to attack him. Once he was back in a psychiatric hospital, he spent several weeks under treatment with neuroleptics, showing only feeble signs of improvement.

On being discharged, he relapsed immediately into heroin addiction, with a clear increase in his psychiatric disorders as a consequence. Following this relapse, he returned to us again to follow a methadone treatment that would be appropriate to his needs. He stabilized perfectly in three days and remained so for several years, maintaining normal regular working habits and leisure activities.

In 1987 came another relapse, when he cut his methadone dosage to 50mg — with destabilizing results — and started taking cocaine. One Thursday afternoon, I was at home when I was warned that the burglar alarm had gone off at our clinic. When I arrived on the spot, I saw that the glass outer door had been smashed in and that Alain was hacking the furniture to bits with an axe. I firmly asked him to hand it over and he did so without argument. He was in a full psychotic crisis, confused, no longer able to remember that the centre was closed on Thursday afternoons. I called an emergency ambulance and he was again taken to a secure psychiatric ward. He restabilized in a few days with the appropriate dosage of 120mg of methadone, without neuroleptics. For almost 20 years now, Alain has continued his daily treatment with an adequate quantity of methadone. He continues to abstain completely from drugs. He is married and works full time, to the complete satisfaction of his employers. An HIV-seropositive of long date, he has looked after himself carefully, so much so that he has been able to father a seronegative

child. As a result, he is able to lead a normal family life; he enjoys his leisure hours and a good quality of life. He now realizes the importance to him of keeping to a long-term treatment plan.

Case Christian

Christian's parents divorced when he was six years old. His mother suffered from serious chronic depression and made several suicide attempts. Christian started to sniff heroin when he was 16 and rapidly developed dependency. For three years he alternated outpatient and inpatient weaning processes, with immediate relapses into heroin addiction. At 18 he was hospitalized with septicaemia, arising from an abscessed vein. At 19 he was hospitalized for the first time in a psychiatric ward for a depressed and anxious condition displaying problems of a psychotic nature. After this episode, he spent two years in a home for adolescent boys before relapsing into heroin addiction.

It was here that he first requested help from us, and it was then that a serious burden of psychosocial responsibility descended on our shoulders — and has remained there up to the present day. In the early years he refused to accept the increases in methadone dosages we recommended, took only inadequate amounts and even then took them only irregularly. He behaved in the same way with the antipsychotic medications we were obliged to prescribe for him. This disobedient behaviour partially explains why he was hospitalized eight times with psychiatric decompensations up until 2003.

At 24, he was living alone, turned in on himself. He was found on private property. He broke into the houses of strangers, slept in their beds and used their showers. Several times he smashed down his mother's door while she was out, on the pretext that he was hungry. At the psychiatric hospital he was diagnosed with intense psychotic problems — polymorphous and schizophrenic in nature. He fled from the clinic and was found wandering barefoot in the countryside, beset by auditory hallucinations.

Rehospitalized, he underwent crises of violence and needed to be injected with neuroleptics.

During his sixth psychiatric commitment, owing to his pathological wandering, he set fire to his room. Some time later, he turned up in Zurich, where he committed burglaries — and set fire to his hotel room. He was committed on the spot before being readmitted to the psychiatric clinic of Geneva.

It was at this time that we persuaded him to increase his methadone dosage to 120mg and, especially, to take his neuroleptic medication (Risperdal, 4mg) more regularly. To achieve this we also persuaded him to take it in liquid form, after putting it in his methadone bottles.

In this way he was stabilized on the psychiatric level for a year or two. But in Summer 2003, when he left for a week's holiday in Majorca, he forgot his bottles of "Methadone/Risperdal". He compensated with alcohol and cocaine. When he returned to Geneva, in a semi-maniacal state, he presented himself at his mother's door half-naked and, pushing her towards the bedroom, insisted that he wanted to have sex with her. Confronted by her refusal, he started to strangle her, telling her to "Die". Hearing her screams, the neighbours intervened to save her. Christian was immediately arrested for attempted murder.

The resumption of an adequate intake of methadone and 4 mg of Risperdal made possible the rapid stabilization of his psychological state. The psychiatric reports confirmed the psychotic disorders and the psychiatric decompensation caused by his failure to take methadone. The judge declared him irresponsible, without penal judgment, but with the obligation to have a daily consultation at our centre for the controlled administration of methadone and Risperdal. For the last three years, with our assumption of intensive responsibility — medical, social and psychotherapeutic — Christian has remained well stabilized, without psychiatric relapses and/or drug-taking. He currently takes 110mg of methadone, to which we add 4 mg of Risperdal in drops. He has been able to retake a carpentry training course in a readjustment centre. He has a girl-friend, with whom he lives and has a satisfactory relationship.

Case Albert

Albert's case is a very good illustration of the need for adequate dosages of methadone, and particularly for its regular administration in cases of serious psychiatric comorbidity underlying heroin addiction.

I first met Albert when he was 14, at the psychiatry unit for adolescents where I was working as a doctor. His father was being treated with drugs such as lithium for a bipolar disorder. Albert very quickly presented behavioural problems and anxious-depressive states. He already smoked hashish quite regularly and rapidly developed heroin addiction by the time he was 15. More than once he cut his veins at home. On several occasions he saw us arrive in all urgency at the call of his parents; he ran away each time, and we had to run after him to ensure he did not fall under a truck. He was first hospitalized for psychiatric reasons at the age of 16.

Following thefts of money and cars, driving without a licence and causing accidents, the judge dealing with minors ordered him to be placed for six months in a secure centre for adolescents. He escaped in search of heroin. The institution's psychiatrists were the first to hypothesize that he might have a psychotic personality

structure; they placed him under clinical observation.

Upon discharge from the centre, he relapsed into serious heroin usage and made several unsuccessful efforts to wean himself off the drug with the help of various doctors and specialized institutions. Because of these failures he decided to return to his family in Italy. Once there, however, he dived back once more into heroin use — to a disturbing degree. As a result of an overdose, he was committed for two years to the care of a specialized therapeutic community.

On leaving this centre, he fell back immediately into heroin use and became involved in the business of drug dealing. He was discovered unconscious in a toilet on the Milan-Lausanne train, his pockets packed with drugs. He was sent to prison. When released, and after a new and serious relapse into drugs, he asked to be placed under our authority and in our long-term medico-social methadone programme. He rapidly stabilized with an average dosage of methadone, and followed the course of treatment in the most exemplary way for over four years without any recourse to drugs. It was not even necessary to provide any major psychosocial support — within a few weeks he had got himself a job as a qualified salesman in a luxury Geneva jewellery store. He worked to the complete satisfaction of his boss. He enjoyed a good quality of life. He found a girl-friend who eventually became his wife.

At the end of these successful four years, wanting to live free of any medication, even a safe substitute, he insisted on weaning himself off methadone, something he achieved in a few months. As a post-cure, he went to visit his divorced mother in Italy. Once back there, he felt bad about himself, very anxious and depressed, finding great difficulty in attention and concentration; he nearly killed himself in a collision with a truck.

His mother encouraged him to return to Geneva and resume his course of treatment with us, in order to recover a good level of psychological stability. He did so. Under methadone he quickly became stable again, worked regularly and married his girl-friend.

However, two years later, he once again wanted to quit using methadone and things went wrong very quickly. Some days later, he sprayed phallic images on the walls of his apartment, set fire to his posters, fired an air-rifle at his wife and shut himself in his room after swallowing two bottles of tranquillizers. When taken urgently to hospital for treatment, he worked himself into an extreme fury a few hours later and broke everything within reach. Once again he had to be committed to the Geneva psychiatric clinic, where he was kept for a month, under neuroleptic treatment.

Once out of the clinic, he still felt unstable and, to return to a condition of normality, he wished to resume his treatment with us. We discovered once again how quickly he could return to working regularly and leading

a stable life. He followed the treatment for three and a half years without any heroin; he was perfectly stable, working well with little interruption.

Then again he decided he wanted to reduce his dosage of methadone, despite all our endeavours to dissuade him. His condition deteriorated rapidly, but he refused to go back to a higher dosage of methadone. Similarly, he refused to be hospitalized, on the grounds that the doctors of the time refused to prescribe methadone and because of his past bad experience with neuroleptics.

A few days later he failed to come to take his methadone for fear of being poisoned. That evening, in a disturbing psychotic condition further aggravated by heavy drinking, he set fire to his apartment and wandered aimlessly around the city. After being arrested the next day, he masturbated in front of the police. Once again he was committed to the psychiatric clinic, this time in a near-catatonic condition. When released after several weeks of treatment, he decided to go to stay with his father, who had settled down in Rolle, a village between Geneva and Lausanne. After being completely weaned off methadone, responsibility for him was taken by the psychiatrists of the nearby psychosocial centre of Prangins, who decided on treatment by classical means.

Six months later he returned to see me in Geneva. He was in a disquietingly psychotic state, delirious and presenting all the usual signs of schizophrenia. For this reason he was once again hospitalized in a psychiatric clinic, but this time in Prangins, near where he was then living. There he was scheduled for several months of treatment with neuroleptics by injection, because the medical management of the clinic refused to consider any prescription of methadone.

One month after his discharge from the psychiatric clinic he saw me again, showing severe instability on a psychological level and presenting a disturbingly risky forms of behaviour. As it happened, over the previous few weeks, he had injected himself with air, then with mercurochrome. He had shared syringes to inject himself, so running a high risk of infection with AIDS; even more seriously, he had suffered two overdoses which had called for emergency resuscitation at Nyon hospital.

Because of the high risk of death faced by this patient and because of his psychotic state and despite the refusal of the psychiatrists at Prangins — who had told him that if he returned to methadone they would no longer treat him — we decided to take him back on the understanding that he would take a small methadone dosage.

With a first dosage of 30mg, which was progressively increased to 50mg, Albert once again regained psychological stability almost immediately and within a few days was able to return to work.

To save Albert having to travel daily between Rolle

and Geneva to get his dose of methadone, we arranged for him to be taken on as a patient by a local doctor, a general practitioner in Rolle.

After one or two problem-free years, tragedy intervened. Albert's doctor gave him a full week's series of methadone doses to cover the Easter holidays. Albert mistakenly took one or two doses ahead of schedule and, in the absence of his doctor, filled the two-day gap with alcohol. In this state he fired his air-rifle at some street signs. Arrested by the police, he was once again committed to the psychiatric clinic at Prangins. As the medical management of the clinic refused to consider any prescription of methadone, he was treated by more classic methods and was left in an open ward. It is hardly necessary to say that withdrawal from methadone brought on a rapid and serious psychiatric decompensation. He fled from the clinic, took his car and knocked down a passer-by — not fatally. Now considered to be a serious psychopath, he was imprisoned. The psychiatric expert came to very negative conclusions, as a result of which he was kept in jail for a number of years. Immediately after leaving prison, he died of an overdose.

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Contributors

The authors contributed equally to this work.

Conflict of Interest

The authors have no relevant conflict of interest to report in relation to the paper.

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Letter to the Editor

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Explaining Agonist Treatment Through Movie Language: The Interesting Allegory of 'Videodrome'

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TO THE EDITOR: A number of movies have dealt with the issue of drug abuse. Although several film authors have brilliantly portrayed drug-related phenomena, few have provided any insights into the dynamics of addiction. Sometimes, films 'about addiction' are not reality-movies, and deal metaphorically with the broader issue of addictive behaviour, without focusing directly on one substance or even on chemical addiction. Exceptionally, one movie directed by David Cronenberg, *Videodrome*, succeeds in providing with an explanation of the metabolic nature of addiction and its treatment [1-3]. The story is about a TV manager who discovers an illegal TV channel showing shocking images of sex and violence, transmitting on a 'hidden' wave frequency, which is always changing and is awkward to decode. The manager gradually becomes more and more eager to expose himself to 'videodrome', and as long as he reinforces the habit, something continues to change inside him biologically. Even in the absence of any outer stimulation, his brain produces hallucinations of violent scenes; this scares him, and leads him to search for help. Independently of the videodrome shows, another clandestine transmission is on air on the same frequencies. In it, a man, called Professor O'Blivion, is speaking about the risks of videodrome exposure, and warning the audience that they may mutate physically, without being able to get rid of the videodrome's parasitic influence, as if it were some sort of new organ sucking energy out of the soul. Video-addicted people, in fact, become completely dedicated



Figure 1. The videodrome-addict inserting his head into the image: when desire becomes craving, it can no longer reach out reward. In addiction, the overdrive produced by the deviated function of the reward system creates a 'black hole' into the capability to grant oneself pleasure. The chronic state of discomfort and suffering of addicts is a product of addictive ties to a fading anticipation of pleasure.

to videodrome, and are enslaved to its pushers, who belong to an organization that aims to control people's behaviours for their own purposes (Figure 1).

At a certain point, two videodrome staff people grotesquely appear during one of his speeches and strangle him to death. In the hope of finding a solution to his own disease, the protagonist reaches a therapeutic centre which was founded by O'Blivion where he was trying to cure videodrome-affected individuals and bring them back into social life. The place is called

the “Cathode Ray Mission”: a population of homeless people is hosted in small cells, each containing a small TV, so that they will be saturated by a normal TV signal, with controlled doses of sex and violence. O’Blivion’s theory is that, by the daily and continuous maintenance of a controlled intensive stimulation of brain circuits by visual cues, people may stop craving for over-stimulation by videodrome and escape from enslavement to it. Inspired by this solution, the protagonist eventually rejects his latest videodrome dose, and tries to destroy the organization along the slogan “Death to videodrome; long live the new flesh!”.

This formal representation of addiction offers a much more precise description of addictive dynamics than some textbooks. In fact, the name ‘videodrome’ recalls the idea of an acceleration within a circuit, a rush after something, an excess of attraction towards an object with an overactive appetitive behaviour. Other movies do no more than suggest that addiction originates from some emotional ‘hole’, a handicap, some kind of deficiency to which craving acts in a compensatory way. The video-signal acts by a kindling mechanism, so that the brain ends up by itself producing the spark that lights the craving for more stimulation. The desire

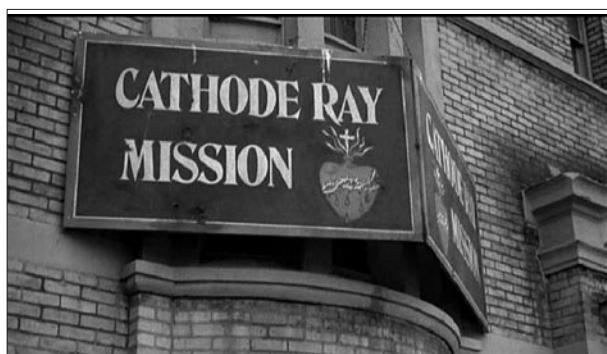


Figure 2. The “Cathode Ray Mission” Headquarter appealing to videodrome street junkies. Cathode rays are the channel by which the disease develops and can also be means of healing, all depending on the modulation of stimuli. A metabolic disease caused by a phasic “cathode ray” cured by the exposure to a “tonic (methadone-like) cathode ray”.

for some videostimulation becomes the prominent idea invading the mind’s room, to the point of overlapping with reality (the metaphor of having hallucinations). The only chance to escape from the video-arena (where you endlessly pursue your craving) is to lose the acquired memory (O’Blivion). This Vincent Dole-type character is a professor who developed an anticraving programme



Figure 3. The inside of the Cathode Ray Mission. Each addict sits in a cardboard-wall cell, in front of a TV screen, to be exposed to controlled doses of stimulating images. Daily attendance of the Mission prevents junkies from dedicating their efforts to ‘videodrome’ doses, allowing them to rehabilitate.

using the same kind of stimulation (visual), i.e. an agonist-based method, to detach people from a toxic stimulus (Figure 2, Figure 3). Acquiring an awareness of losing control is not enough to allow an ill person to escape from their addiction, as symbolized by the video-killers strangling the emerging disease awareness embodied by Professor O’Blivion. The first enemy of treatment is the disease itself, beyond any patient’s motivation. The work we do as addiction physicians is, indeed, similar to that done in his Cathode Ray Mission: a homeopathic struggle against an overactive behaviour which is causing impairment, and is deeply rooted into the brain, as if it were a microscopic parasite made of neuronal flesh. Our treatment programmes aim to make the parasite starve, while feeding the brain’s metabolic gap with an antidote. Eventually, we will be able to see our patients’ new lives blossoming from the ‘new flesh’ we have grown.

Conflict of Interest

The author has no relevant conflict of interest to report.

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