Heroin Addiction and Related Clinical Problems

the official journal of

Europad
European Opiate Addiction Treatment Association
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Swedish Use and Misuse of the Dole & Nyswander Treatment

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Summary

For 23 years (1966-1989) Sweden had a National Methadone Maintenance treatment of opioid addicts, delivering 70-80 % vocationally rehabilitated patients, taxpaying citizens, with no drug abuse and a great reduction in mortality rates. This treatment was changed in 1990 into a short-term methadone program, resulting in numerous discharges for disciplinary reasons, a high mortality rate among the newly discharged and poor rehabilitation results. Politically, the short-term treatment is called “restrictive”, which is regarded as commendable by the Swedish mass media.

Key Words: Maintenance vs. short-term methadone treatment

1. Introduction

During a one-year visit at the Rockefeller University in New York 1965-66, I had an opportunity to study the Dole-Nyswander treatment of heroin addiction at a time when the initial results were being published [3]. After returning to Sweden I set up a similar treatment system in Uppsala and for 23 years, beginning 1966, I was in charge of a National Swedish methadone program. I remained in contact with both these pioneers in addiction treatment for the rest of their lives and got many helpful suggestions from them on how to develop the Swedish program.

There are two different attitudes among therapists in this field, which may create problems. One is a severe repressive attitude (give them short-term treatment, and then they will have to manage as best they can). The other problem-inducer can be described as permissive benevolence (give them methadone and early retirement pension and let us then be spared the trouble of hearing from them). Both these attitudes unfortunately neglect the normalizing effect of methadone maintenance and both effect a message to the patient that “we are not willing to welcome you back as a normal citizen in our society”. Naturally both therapist attitudes are learned, sometimes during early childhood, and therefore difficult to eradicate. Part of our own good treatment results may have been due to my careful supervision of unwanted tendencies and removal from the MMT program of colleagues with inappropriate reactions.

In my experience it is important to maintain a generous and hopeful view on this clientele and to point out to them that during methadone induction they have become fit for work and stimulate the acquirement of any reasonably well-paid job. These patients have lost many of their best years and it is essential for them to feel support and encouragement, rather than being subjected to time-consuming instruction in more or less sophisticated social or psychotherapeutic training programs, regularly with many elements of confrontational moralizing and punishment. In Sweden we have had during the last 20 years a development which is a good example of the first problem (severe repression), while other countries (the Netherlands, Switzerland and Denmark) are examples of a development into permissive benevolence, eventually leading to heroin maintenance treatment. Since both systems are harmful for the treatment results, it may be worth while describing them. Here follows a description of the Swedish development.

2. A National MMT 1966-89

For more than two decades the National Swedish methadone maintenance treatment (MMT) was subjected
to political and mass media criticism, although functioning well and delivering a stable majority of 70 to 80 percent of our heroin addicted patients as vocationally rehabilitated taxpayers. We had a yearly patient retention between 80 and 100 percent and a mean 89 percent of the patients admitted during the first 23 years stayed at least a year in treatment. Although we had had the same frustrating experiences as other countries with the drug-free treatment of morphine addicts, who seldom managed to break their drug habit, only few cared to notice or comment on our results with MMT. Instead, there was a repeated slander of our efforts, which were said to be just a meaningless switch from one narcotic drug to another. In particular, the political attitude even in conservative newspapers favoured such views and the Swedish Radio described methadone as an invention by Adolf Hitler, who had sold the German patent to the American multi-millionaire John D. Rockefeller, who used it to eradicate the black race in Harlem of New York City. Among the hostile enemies of MMT was the National Board of Health and Social Welfare (abbreviated Board of Health), where a social worker became head of the Division of drug addiction and decided that drug addicts should no longer be treated by psychiatrists, but primarily by social workers. Being head of a psychiatric research unit at Ulleråker Hospital in Uppsalas I could disregard most of the ongoing debate, but I needed some support from the Board of Health each time the MMT program had to be enlarged, otherwise I couldn’t get the necessary resources, nurses, etc. from the county of Uppsalas.

In 1973, when I realized that the Board of Health wished to get rid of our treatment program, I decided to arrange an open randomized controlled trial, comparing MMT with drug-free treatment of heroin addicts, 20-24 years of age, in a two-year study. To be able to monitor the outcome of this study, we applied a sequence analysis system[1], comparing MMT patients and drug-free controls pair-wise with respect to cessation of drug abuse, until a statistical difference was established between the groups. Before this study there had been three uncontrolled American studies of mortality rates [2, 5, 8] presenting altogether 14,250 heroin addicts in MMT and 14,250 in drug-free treatment, with no significant difference between the groups. Unless the results of our study enabled the Board of Health to support our efforts, I intended to close down the treatment program and while waiting for the opinion of a special evaluating committee, there would be no more patients accepted.

The outcome of our study unequivocally showed MMT to be superior to drug-free treatment. The sequence analysis had signalled significant group differences already after 17 patients had been randomized to each treatment group. After two years 71 percent (12/17) of the MMT patients were free of drug abuse and socially and vocationally rehabilitated, while the drug-free treatment group had only 6 percent (1/17). When the two years’ study was concluded, ten of the drug-free treatment group reapplied and were admitted into MMT. After six years of observation there were 81 percent (22/27) who had become free of drug abuse and socially and vocationally rehabilitated. In the initial drug-free treatment group only seven remained, one who was still free of drug abuse and six subjects who were dead. This was the first randomized study clearly proving an advantage in survival rate for MMT over drug-free treatment. There was a committee of specialists elected by the Board of Health and the Medical Research Council to scrutinize the results and after a year they came up with a report which was unconvincing and wavering. Our study was considered to be too small and the entrance criteria were said to be insufﬁciently defined (a minimum of 4 years of intravenous heroin abuse around the clock as documented by hospital records, an age of 20-24 years and a minimum of three unsuccessful attempts in earlier drug-free treatment was not considered enough for the committee). When I presented the results at an international meeting in Stockholm, American participants were impressed and found the results very important. However, the newly elected head of the Division of drug addiction at the Board of Health, remained unimpressed and told me that “now we are going to get the patients out of your MMT program”.

As a result the politicians advised me to close down the programme. They were willing to pay only for the MMT patients already in treatment, but not for additional cases. But I told them “no, you can’t have that”. Either I had been unable to demonstrate efficacy and then the whole MMT should be closed down, or if the programme was efficacious this treatment must be given to all heroin addicts in need of it. Finally, after 5 years of mass media debate, the Director General of the Board of Health arranged a meeting with the irresolute politicians and declared that according to her opinion the MMT program had a proven efficacy. The politicians immediately surrendered and decided to support the program, but within the Division of drug addiction at the Board of Health it was decided to maximize the number of patients treated at 150. In 1989 I retired for age reasons as head of the Psychiatric Research Clinic in Uppsala and soon afterwards the head of the Division of drug addiction at the Board of Health introduced new instructions for treatment. It was decided that MMT should only be given for a brief period of time. Doctors should work to convince the patient that he/she could soon leave the treatment and patients should be informed of this policy before entering. At the same time the National MMT program was abandoned and a number of Drug addiction treatment centres were installed, where doctors were instructed to find out strategies to get rid of their patients. Presently there are 77 such treatment centres. At the same time we published a study of street heroin addicts (our 5-year waiting list) whose mortality rate was 63 times the expected for a group of Swedish citizens of that age and gender distribution, while MMT patients had a much lower mortality rate, 8 times the
expected. In that study we also demonstrated the rapid return to a street addict’s mortality rate after involuntary exclusion from MMT [6]. I was asked to present this study at the Board of Health, but later they called back and cancelled the meeting, explaining that they could read it for themselves.

3. Short-term methadone treatment 1990-2009?

During the nineties the 77 new treatment centres came up with a number of harassment strategies. First, a patient could not be entered on the waiting list unless the social services had so decided, referral to treatment by a doctor was not enough. Patients sometimes had to wait for years before they were entered and after that followed a waiting for months on the list. Before the patients entered treatment, they must sign an agreement to let the police read their medical records. Although the length of treatment had not been specified in the recent Board of Health instructions, many centres decided to maximize treatment at 2 years. Patients were instructed to show up for their daily methadone or buprenorphine dose between 10 and 11 a.m. Those who came between 11 and 12 were given only half the dose and after 12 no dose was given that day. Our earlier patients, who had been transferred from the National program and who were carrying on a paid job, had difficulties to be punctual at the centre, but no exceptions were allowed for them. The nurses who delivered the dose could decide whether the patient looked red-eyed or tired and if so they threw out the dose in the sink, telling the patient that “you have probably been out drinking alcohol”. Some centres introduced compulsory psychotherapy sessions, where patients were invited to ponder over the misery they had caused during their years of drug abuse. Several centres introduced zero tolerance to drug-containing urine tests, including tests positive for opioids. Certain doctors made themselves guardians of their patients and could then decide over the patient’s money, which is distributed back to the owner in a token economy system, for wanted behaviour. The vocational rehabilitation results of the former National MMT were replaced by compulsory work (usually raking of churchyard walkways), with a risk of being excluded from MMT if they fail to come. The resulting attitude of the patients is to regard the treatment period simply as a temporary rest from the stressful street-life of drug addiction. After exclusion they go back to heroin. Few patients apply for a job any more, so vocational rehabilitation rates have gone down, from 80 percent in the National programme, to levels which are no longer recorded in evaluation studies.

As a result of the short-term, decentralized methadone and buprenorphine treatment systems, there are several treatment interruptions due to frequent involuntary discharges for disciplinary reasons and mortality rates are rising, particularly among recently discharged patients [4]. But politicians, both to the right and left, are pleased to notice that the Swedish treatment of addiction has become “restrictive”. In an attempt to question this development we have recently published a critical article in Swedish [7] and presently the Board of Health intends to rewrite its instructions. At the moment we therefore feel that there is hope for the Dole & Nyswander [3] treatment to become reintroduced in Sweden.

References


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No fundings source.

Conflict of Interest
The author has no relevant conflict of interest to report in relation to the present paper.
Methadone-treated Patients After Switching to Buprenorphine in Residential Therapeutic Communities: An Addiction-specific Assessment of Quality of Life

Francisco González-Saiz, Rosario Ballesta Gómez, Izaskun Bilbao Acedos, Oscar Lozano Rojas, and Josefa Gutiérrez Ortega

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Summary

Background: evaluating the addiction-related quality of life of a sample of opiate-dependent patients in treatment with buprenorphine in therapeutic communities after a switch from methadone. Design and participants: observational (descriptive), open longitudinal prospective study (‘before-after’ design); a non-probabilistic consecutive sampling procedure was used. After their admission to five therapeutic communities, a sample of patients in treatment with methadone switched to buprenorphine induction (Subutex®). When considered appropriate, a gradual reduction in buprenorphine dose was begun, so as to bring it down to 0 mg within 16 weeks. The patients met DSM-IV-TR criteria for Opiate Dependence, were adults and had signed an informed consent release. All the patients were evaluated at three times; baseline assessment (M0), after one month of treatment (M1) and after three months (M2). The study protocol was approved by the Andalusian Regional Committee for Clinical Trials, and was conducted in accordance with the Declaration of Helsinki. Measurements: The Objective Opiate Withdrawal Scale (OOWS), the Subjective Opiate Withdrawal Scale (SOWS), the Health Related Quality of Life for Drug Abusers Test (HRQoLDA Test), the General Health Questionnaire (GHQ-28), the Opiate Treatment Index (OTI) and the Schedules for Clinical Assessment in Neuropsychiatry (SCAN). Results: A total of 119 patients met the selection criteria. Of these, 46 subjects transferred from methadone to buprenorphine, while the remaining 73 decided to stay on their methadone maintenance treatment. A statistically significant increase was observed in scores on the quality of life scale after one month of treatment with buprenorphine (from 0.62 to 0.99; p<0.05) and at three months (from 0.43 to 0.77; p<0.05). One month after the start of treatment, statistically significant improvements were observed in “general state of health” (from 10.7 to 4.3; p<0.05), in “severity of dependence” (11.7 to 4.1; p<0.05) and in “psychological adjustment” (from 7.5 to 3.7; p<0.05). At the three-month assessment, statistically significant differences were again observed in the same variables, except for “psychological adjustment”. Conclusions: the patients who were in treatment with methadone after their admission to a therapeutic community and switched to buprenorphine were able to experience ongoing improvement in their quality of life.

Key Words: Buprenorphine; Quality of Life; QOL; Addiction; Therapeutic Community

1. Introduction

In spite of a rising incidence of cases of cocaine abuse and dependence, opiate dependence continues to be the most prevalent addictive disorder treated in specific drug addiction services in our catchment area. Methadone maintenance programmes (MMPs), whose efficacy and effectiveness have been widely documented [44], continue to be the main option for this group of patients. The results of these programmes are, however, subject to variation, depending on factors such as: a) patients’ clinical characteristics at time of treatment admission, and b) a variety of process indicators [9,30,31,34,40]. One of these factors is given by the heterogeneous prognostic profile of patients who begin the programme. The availability of various different opiate substitutes, such as methadone, buprenorphine and diacetylmorphine, allows each of these programmes to be matched to certain patient subgroups. In this way, relative programme effectiveness could be improved for each patient ‘typology’– a
refinement that would enhance the overall effectiveness of the service [32]. Buprenorphine is a partial mu-opioid receptor agonist for the treatment of patients with opiate dependence; there is solid evidence of its effectiveness [23,24,25,26,38]. At the present time it is commonly used and standardized in many countries. It is not, however, marketed in Spain because the National Health System has not yet come to a decision on its financing. Our only experience with it therefore belongs to research contexts [2,3,36]. Clinical research has not yet provided sufficient evidence of the patient profile that best responds to treatment with buprenorphine compared to patients on methadone [4]. Randomized clinical trials that have compared the effectiveness of these two pharmaceuticals suggest that, at equivalent doses, they are equally effective in terms of retention in the programme and in reducing heroin consumption [4,25]. However, both accumulated clinical experience and data from studies performed with observational-type designs, show some situations in which treatment with buprenorphine is advisable [28] (e.g., appearance of side-effects with methadone, fast metabolizers, pharmacological interactions, development of anti-methadone antibodies, rejection of effective doses, prejudice towards the methadone programme associated with poor compliance, perception of the buprenorphine programme as less stigmatizing, expectations and curiosity about a new opiate, easier withdrawal from the methadone programme by taking buprenorphine). With reference to this last point, buprenorphine may be a useful substance in assisting methadone maintenance patients who wish to terminate that kind of maintenance therapy [6]. On the other hand, most of the studies on the effectiveness of buprenorphine treatment have been carried out in an outpatient setting, employing classical outcome indicators such as reduction in heroin use, increased retention rate or reduction in severity of addiction. Therapeutic communities have traditionally been considered drug-free-oriented residential programmes and, even if they have recently begun incorporating methadone therapy [7,46], studies that have evaluated the usefulness of buprenorphine in these residential resources are still a rarity [10]. We think that it is of interest to evaluate the usefulness of buprenorphine in the treatment of opiate addicts in therapeutic communities, as in our catchment area; therapeutic communities are not a last-in-line or last-resort service, but provide an extra link in a wide network of coordinated services. Another point in question is the concept of quality of life, which, compared to traditional outcome indicators, is becoming more widely recognized as a fundamental variable in drug abuse programme evaluation, due to the wealth of information it provides [41,42]. Although there are different operative definitions of the health-related quality of life concept, most authors consider that it deals with a subjective perception of a patient’s level of physical, emotional and social functioning and well-being, as well as its repercussions on daily life activities [8]. Although several articles evaluating the impact of methadone treatment on the quality of life of these patients have already been published [5,37,41,42], there is still little available evidence on buprenorphine treatment [14,15]. All of these publications used general health-related quality of life scales. We have been working on the design and validation of a quality of life scale based on the bi-axial addiction model of Edwards et al. [12] that is specific to a drug addict population [29]. The aim of this study is to evaluate the effectiveness of buprenorphine in terms of addiction-related quality of life in a sample of patients after they have taken the decision to switch from methadone in a therapeutic community.

2. Methods

2.1 Sampling design and procedures

This has been an observational (descriptive), open prospective longitudinal study (‘before-after’ design). A non-probabilistic, non-consecutive sampling procedure was used. Subjects who met the criteria for selection were eligible and signed the informed consent release. Study protocol ethics approval was granted by the Andalusian Regional Committee on Clinical Trials and the study was conducted in accordance with the Declaration of Helsinki.

2.2 Clinical setting

The study was carried out at five public residential therapeutic communities (TCs) belonging to the Andalusian Regional Drug Abuse Programme in southern Spain. These TCs are members of a coordinated service network, so the patients who are admitted to them come from specific public outpatient drug addiction service centres. When a patient is released from a TC, he/she can continue treatment provided by the referral outpatient clinic, or may be referred to daycare centres. Patients on methadone can be admitted to Andalusian TCs. At admission, the general clinical profile is defined by: a) continuous use of heroin in spite of treatment with methadone, b) the concomitant presence of one or more other addictions (especially cocaine, alcohol and/or benzodiazepine abuse), c) whether patients show any form of psychiatric comorbidity (regardless of its degree of severity) and d) whether they are difficult to handle in an outpatient regime. At the TCs, these patients have two therapeutic options: a) clinical stabilization and maintenance with methadone throughout the time they remain in residence, followed by continuing treatment with this opiate afterwards as an outpatient; b) clinical stabilization and gradual methadone dose reduction until complete withdrawal before therapeutic release. This second group is the target group selected to permit the assessment of the effects of switching from methadone
to buprenorphine.

2.3 Subjects

Buprenorphine treatment was offered to all the patients who were on methadone at a dose equal to or less than 80 mg/day admitted to the TC, and who were clinically assessed as being able to begin a gradual dose reduction of this opiate during their time of residence at the TC. Patients were maintained on their current methadone dose for 1 week, during which time they were assessed against the eligibility criteria. All patients were subjected to medical, psychological and social assessment by the usual clinical procedures during the TC admission phase. The opinions and wishes of the methadone users were taken into consideration in this assessment. Those patients who were on methadone doses equal to or less than 40 mg/day were eligible for direct admission to buprenorphine induction. If the methadone dose was between 40 and 80 mg/day, the patient went through a prior flexible individualized reduction stage until the dose was no more than 40 mg/day.

Inclusion criteria for the study were: a) diagnosed as “Opioid Dependence on Agonist Therapy” (“In a Controlled Environment”) by DSM-IV-TR criteria, and currently in a methadone treatment programme at his/her referral centre, b) taking a maximum daily dose of methadone of 40 mg/day for one week before induction to buprenorphine, c) the characteristic of being a patient who is going to start or is currently in the methadone treatment programme’s “tapering off/withdrawal stage”, as assessed by clinical judgment and d) signed informed consent release. Exclusion criteria were: a) subjects with pending judicial sentences or with a pending sentence due to buprenorphine. The psychosocial intervention model accompanying pharmacological treatment with buprenorphine followed the same pattern used in the methadone tapering off/withdrawal stage.

We considered the following criteria for definition of opioid agonist treatment stages: 1. Induction Stage: Period comprising the first month of treatment; the time necessary to get down to the adequate dose and achieve minimum medical and psychosocial stabilization. 2. Stabilization/Maintenance Stage: Beginning after the first month of treatment and lasting for an indefinite period. From the pharmacological perspective, once the therapeutic opioid dose has been established, it is maintained with little modification. In their health-care and psychosocial facets, certain therapeutic goals, depending on patient needs and possibilities, are covered. 3. Tapering off/withdrawal Stage: begins with the decision that withdrawal from opioid treatment is to be the final goal (usually because of therapeutic or voluntary discharge).

2.4 Induction procedure

The principles of buprenorphine treatment (induction, maintenance, tapering off/withdrawal, recording of adverse effects, interactions, etc.) were organized following the criteria proposed by the Australian Department of Health Clinical Guidelines for Buprenorphine Treatment of Heroin Dependence (27). Buprenorphine (Subutex®) was administered in 2 and 8-mg sublingual tablets.

Patients who decided to switch from methadone to buprenorphine were fully informed twice: a) before signing the informed consent release and b) days before the first buprenorphine dose was administered. As stated in the informed consent release, the patients could, at any time, ask anything they wanted to know about the medication and about withdrawal from treatment. The first day of induction to buprenorphine began 24 hours after the last methadone tablet was taken. At that time, the patient was asked to wait until the moment when he/she would report withdrawal discomfort. This process was personally supervised by the medical and nursing staff, who periodically recorded the symptoms using the Handelsman et al. [18] Subjective Opiate Withdrawal Scale (SOWS) and Objective Opiate Withdrawal Scale (OOWS). Patients could participate in any of the therapeutic community activities and receive psychological assistance during this time. The latest records in the SOWS and OOWS, evaluated before administering the first buprenorphine dose, were encoded for statistical analysis. An hour after taking it, the response was evaluated, again using these scales. Symptomatic medication including NSAIDs, clonidine or benzodiazepines were available for withdrawal symptoms as required. During the first five days of induction, withdrawal symptoms before/after taking sublingual buprenorphine were evaluated. The dosing schedule was flexible, with doses modified according to patient response.

2.5 Reduction procedure and follow-up

Patients went daily to the TC infirmary to receive buprenorphine. The psychosocial intervention model accompanying pharmacological treatment with buprenorphine followed the same pattern used in the methadone tapering off/withdrawal stage.

After induction, the patient received an individualized dose which was maintained for a time varying between 1 and 4 months. When considered appropriate, and in agreement with the patient, gradual reduction was begun (no more than 2 mg/week) to reduce the buprenorphine dose to 0 mg within 16 weeks. For assessment purposes, the maximum duration of the programme for each patient was 3 months, from the moment treatment began. After baseline assessment (before buprenorphine induction), follow-up interviews were given one month and three months after the beginning of treatment.

2.6 Outcome measures

The Objective Opiate Withdrawal Scale (OOWS) (18) is a scale evaluating the presence and severity of objective opiate withdrawal symptoms through the observation
of 13 physical signs. A clinician rates the symptoms as being absent (0) or present (1). The maximum score is therefore 13.

The Subjective Opiate Withdrawal Scale (SOWS) [18] is a 16-item checklist that measures the presence of subjective symptoms of opiate withdrawal. Patients rate each item on a scale ranging from 0 (none at all) to 4 (extremely high); scores therefore vary between 0 and 64. The purpose of the Health Related Quality of Life for Drug Abusers Test (HRQoLDA Test) [29] is to assess how addiction to substances affects a person’s daily life by evaluating physical/psychological health and social functioning. It is a quality of life instrument specific to drug abuse and is based on the bi-axial concept of addiction as defined by Edwards et al. [12]. According to this concept, addiction can be defined along two axes – the first, “substance” dependence itself, and the second, “problems” (medical, psychological and social) that result from substance use. The HRQoLDA Test is a self-administered scale comprising 22 items coded on a 5-point Likert-type scale. Low scores on this scale show a poorer quality of life and high scores a higher quality. The Opiate Treatment Index (OTI) [11] is a semi-structured clinical interview, whose purpose is to evaluate the severity of problems related to drug abuse. It consists of six subscales, the total scores on which make it possible to assess the severity of each of these problems. Each of the subscales can be applied independently. In this study, the scale given was for “General State of Health”, which evaluates general medical condition and injection, neurological, cardiorespiratory, genital-urinary, muscular-skeletal and gastrointestinal problems. Low scores on this scale indicate a good state of health. We used the Spanish version of the OTI adapted to and validated in our environment [17].

The General Health Questionnaire (GHQ-28) [16] is a symptom scale that estimates psychological adjustment or distress. The items on the subscales refer to subjective somatic symptoms associated with anxiety and depression, as well as difficulties in relating and adjusting to social and family roles. Low scores on this scale represent a good level of psychological adjustment. On the other hand, the mean cut-off point (total score of 5 or over) for this severity of opiate dependence was measured using Section 12 of the clinical interview, Schedules for Clinical Assessment in Neuropsychiatry (SCAN) [45]. The CATEG0-5 System is a software application that generates a clinical diagnosis from interview scores according to ICD-10 criteria. It also gives severity scores for a certain disorder (in this case, Substance Dependence), and these go to make up the Definition Index (DI). This parameter is the one we used as our indicator for severity of dependence. Finally, using a Data Collection Notebook (DCN), sociodemographic variables, variables on recent drug use and history of substance abuse, prior treatments, and biochemical and serological parameters were all recorded.

3. Results

3.1 Sample description

A total of 119 patients met the selection criteria during the recruiting stage. Of these, 46 subjects (38.7%) chose to switch from methadone to buprenorphine, while the remaining 73 (61.3%) decided to remain on their methadone maintenance programme. This group did not participate in the study, but baseline information was recorded for comparative purposes. 93.5% of the patients that began the buprenorphine treatment were males; their mean age was 36.9 years (SD: 6.8). As observed in Table 1a-b, most of them had not completed primary school, their employment level was very low and almost half of them had a criminal record. The sociodemographic profiles in the two groups is similar. The only statistically significant difference found is for the variable “level of education”. Among the patients in the buprenorphine group, the mean period that had passed since their initial use of opiates and cocaine was over 15 years. These periods are longer than those observed in methadone patients, even if the differences do not reach statistical significance. In the group that stayed on methadone, there was more use of cocaine in the month prior to admission. Only small differences were detected in the case of other substances. The mean number of prior treatments was 1.3 for all patients, whether they began with buprenorphine or stayed on methadone. On the other hand, the mean time they had stayed in the last MMP before the time of the interview was almost double for those on buprenorphine. In spite of this difference, there was no statistical significance. The total time they stayed on MMP was, again, higher than for those who started with buprenorphine, but in this case too the difference was not statistically significant. As can be seen in Table 1, the mean methadone dose at the time of admission to the therapeutic community was considerably higher in the group that stayed in the MMP. The prevalence of HIV infection was low in the buprenorphine group (6.5%), and almost three times higher in the group that stayed on methadone (17.3%), although there was no statistical significance. The prevalence of HBV and HCV infection was also higher in the methadone group, as can be seen in Table 1. There were no significant differences between the groups with respect to the type of drug they had been taking. Assessment of patients’ physical health was carried out using the OTI health scale. As shown in Table 1, health scores were similar for all groups in all of the subscales. In overall terms, if we consider the total score on the state of health scale, the severity of the various problems listed in the OTI was slightly lower than in the buprenorphine group. The mental health profile differs in the two groups. As observed in Table 1, the profile of psychopathological severity is more severe in the patients who continued on methadone treatment. In this group higher general scores are observed in the GHQ-28 scale.
Table 1a. Demographic and clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>With switch toBuprenorphine (N=46)</th>
<th>Staying on Methadone (N=73)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>36.9 ±6.8</td>
<td>34.3 ±6.3</td>
<td>NS</td>
</tr>
<tr>
<td>Sex (Males)</td>
<td>43 (93.5%)</td>
<td>52 (100%)</td>
<td>NS</td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary/no education</td>
<td>26 (68.4%)</td>
<td>55 (75.3%)</td>
<td></td>
</tr>
<tr>
<td>Professional training</td>
<td>10 (26.3%)</td>
<td>8 (11%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Secondary or higher</td>
<td>2 (5.2%)</td>
<td>10 (13.7%)</td>
<td></td>
</tr>
<tr>
<td>Employment (unemployed)</td>
<td>30 (65.2%)</td>
<td>46 (63%)</td>
<td>NS</td>
</tr>
<tr>
<td>Living with drug-using relatives</td>
<td>10 (21.7%)</td>
<td>16 (22.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Police record</td>
<td>22 (48.9%)</td>
<td>41 (57.7%)</td>
<td>NS</td>
</tr>
<tr>
<td>Clinics and therapeutics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Years of abuse</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiates</td>
<td>15.3± 6.5</td>
<td>14.7±7.0</td>
<td>NS</td>
</tr>
<tr>
<td>Cocaine</td>
<td>15.7± 6.7</td>
<td>14.2±6.9</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol</td>
<td>23.7±17.3</td>
<td>19.8 ± 6.9</td>
<td>NS</td>
</tr>
<tr>
<td>Cannabis</td>
<td>22.2±7.1</td>
<td>21.1 ± 14.7</td>
<td>NS</td>
</tr>
<tr>
<td>Days of abuse in the last month</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opiates</td>
<td>7.8±11.2</td>
<td>11.7±13.4</td>
<td>NS</td>
</tr>
<tr>
<td>Cocaine</td>
<td>8.3±11.5</td>
<td>15.5±13.5</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Alcohol</td>
<td>10.6±12.8</td>
<td>12.4±14.1</td>
<td>NS</td>
</tr>
<tr>
<td>Cannabis</td>
<td>8.3±11.5</td>
<td>12.9±14.5</td>
<td>NS</td>
</tr>
<tr>
<td>Prior methadone treatment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nº previous treatments</td>
<td>1.3±1.3</td>
<td>1.3±1.6</td>
<td>NS</td>
</tr>
<tr>
<td>Months on current treatment</td>
<td>42.3±40.5</td>
<td>27.1±44.5</td>
<td>NS</td>
</tr>
<tr>
<td>Months on previous treatments</td>
<td>16.6±32.7</td>
<td>25.4±35.8</td>
<td>NS</td>
</tr>
<tr>
<td>Months on all treatments</td>
<td>62.3±55.9</td>
<td>54.2±50.0</td>
<td>NS</td>
</tr>
<tr>
<td>Methadone dose at TC entry</td>
<td>46.6±22.0</td>
<td>53.5±18.4</td>
<td>NS</td>
</tr>
<tr>
<td>Prevalence of</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV +</td>
<td>3 (6.5%)</td>
<td>9 (17.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>9 (19.6%)</td>
<td>8 (15.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>24 (52.2%)</td>
<td>28 (53.8%)</td>
<td>NS</td>
</tr>
<tr>
<td>Current treatment with:</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>19 (41.3%)</td>
<td>20 (38.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>18 (39.1%)</td>
<td>14 (26.9%)</td>
<td>NS</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>1 (2.2%)</td>
<td>6 (11.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>8 (17.4%)</td>
<td>8 (15.4%)</td>
<td>NS</td>
</tr>
<tr>
<td>Antiretroviral</td>
<td>2 (4.3%)</td>
<td>6 (11.5%)</td>
<td>NS</td>
</tr>
<tr>
<td>Tuberculostatics</td>
<td>2 (4.3%)</td>
<td>1 (1.9%)</td>
<td>NS</td>
</tr>
</tbody>
</table>
and the percentage of patients classified as “probable psychiatric cases” is higher. Statistical differences are found between the groups in the “anxiety/distress” and “depression” scales. There are slightly better scores for quality of life in the buprenorphine treatment group.

The average dose of buprenorphine used during the treatment period was 4.8 mg/day (S.D.: 1.02).

3.2 One-month follow-up (M1)

After one month of treatment with buprenorphine, 93.5% of the original sample (43 patients) were still on it. The three patients who abandoned the study during this period did so voluntarily after having remained an average of 3.7 days in buprenorphine treatment. In other words, they were subjects who had failed to complete the induction phase set to last the first week. Table 2 shows the statistics found by comparing the two assessment times (M0-M1). As can be seen from the four variables analyzed, statistically significant clinical improvement was observed in the patients. The Hedges g statistic was used to interpret clinical significance. This follows the interpretation of the Cohen D statistic, according to which an effect is considered “small” if the figures are between 0 and 0.2, as a “medium-low” change if they are between 0.3 and 0.5 and as “moderate to high” if they are between 0.6 and 0.7. When a figure of 0.8 or higher is observed, the change is considered “high”. As a result, and as shown in Table 2, the effect of the variations noted (all were improvements) between the two assessment times may be considered “moderate” for “psychological adjustment” and “quality of life”, and “high” for “severity of dependence” and “general state of health”.

The GHQ-28 subscales measure different dimensions of psychopathological adjustment. Although a considerable degree of general improvement is observed in Subscale A (“psychosomatic symptoms”) and Subscale B (“anxiety/distress”) between the two times, this variation is not statistically significant (Table 3). Conversely, in Subscales C (“social dysfunction”) and D (“depression”) statistically significant differences were observed between the two assessment times. The magnitudes of the effects recorded on the “depression” subscale should be noted carefully.

### Table 1b. Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>With switch to Buprenorphine (N=46)</th>
<th>Staying on Methadone (N=73)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTI-Health Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Scale</td>
<td>3.5±2</td>
<td>4.27±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Problems related to injection</td>
<td>0.26±0.8</td>
<td>0.15±0.5</td>
<td>NS</td>
</tr>
<tr>
<td>Neurological scale</td>
<td>2.33±1.9</td>
<td>2.35±1.3</td>
<td>NS</td>
</tr>
<tr>
<td>Cardio-respiratory scale</td>
<td>1.41±1.6</td>
<td>1.9±1.9</td>
<td>NS</td>
</tr>
<tr>
<td>Genital-urinary scale</td>
<td>0.52±0.6</td>
<td>0.6±0.6</td>
<td>NS</td>
</tr>
<tr>
<td>Muscular-skeletal scale</td>
<td>0.78±0.8</td>
<td>0.94±0.9</td>
<td>NS</td>
</tr>
<tr>
<td>Gastrointestinal scale</td>
<td>1.63±1.2</td>
<td>1.73±1.4</td>
<td>NS</td>
</tr>
<tr>
<td>Total score on the “State of health” scale</td>
<td>10.6±6.4</td>
<td>11.9±5.1</td>
<td>NS</td>
</tr>
<tr>
<td>Psychological Adjustment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychosomatic symptoms</td>
<td>2.5±2.4</td>
<td>2.84±2.1</td>
<td>NS</td>
</tr>
<tr>
<td>Anxiety/Distress</td>
<td>2.7±2.6</td>
<td>3.9±2.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Social Dysfunction</td>
<td>2.5±2.7</td>
<td>2.9±2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Depression</td>
<td>2±2.4</td>
<td>3.2±2.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Severity of general psychopathology</td>
<td>9.7±8.3</td>
<td>12.7±7.7</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Prevalence of probable psychiatric cases</td>
<td>26 (63%)</td>
<td>42 (80.8%)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Quality of life related to total health score</td>
<td>0.4±0.6</td>
<td>0.3±0.6</td>
<td>NS</td>
</tr>
</tbody>
</table>
Three months after starting the treatment, another assessment was made with the remaining patients (comparison M0-M2). These represented 45.7% of those who began (21 patients). Between the one-month and three-month assessments (M1-M2), 14 subjects were released after having completed buprenorphine treatment, 6 left the TC and were switched back to methadone and 2 subjects were withdrawn for disciplinary reasons. The results of this new assessment are shown in Table 4. It may be seen that the scores show improvement in all the variables evaluated (“severity of dependence”, psychological adjustment”, “general state of health” and

| Table 2. Assessment of the results for variables after one month of treatment |
|------------------------|----------------|----------------|--------------|---------|
|                        | Comparison M0 – MPA (Mean and SD) | Diff in means | 95% C.I. I. Low – W. High | p       | Effect Size (Hedges g) |
| Severity of dependence (SCAN) (n=36) | 11.72 (3.4) - 4.1 (2) | 7.61 | 6.36 – 8.86 | <0.05 | 2.7 |
| Psychological adjustment (GHQ-28) (n=43) | 7.58 (8.2) - 3.74 (4.4) | 3.84 | 1.19 – 6.49 | <0.05 | 0.57 |
| General state of health (OTI) (n=43) | 10.77 (6.5) - 4.37 (4.5) | 6.4 | 4.38 – 8.41 | <0.05 | 1.13 |
| Quality of life related to health (TECVASP) (n=43) | 0.62 (0.6) - 0.99 (0.6) | -0.37 | -0.57 – -0.17 | <0.05 | 0.58 |

| Table 3. Comparison of GHQ-28 subscales |
|------------------------|----------------|----------------|--------------|---------|
|                        | Comparison M0 – MPA (Mean and SD) | Diff in means | 95% C.I. I. Low – W. High | p       | Effect Size (Hedges g) |
| Psychosomatic symptoms (n=43) | 1.88 (2.4) – 1.37 (1.9) | 0.51 | -0.27 – 1.29 | NS | 0.24 |
| Anxiety/distress (n=43) | 2.1 (2.4) – 1.35 (1.8) | 0.72 | -0.1 – 1.54 | NS | 0.34 |
| Social dysfunction (n=43) | 1.84 (2.5) – 0.7 (1.3) | 1.14 | 0.31 – 1.97 | <0.05 | 0.57 |
| Depression (n=43) | 1.79 (2.6) – 0.3 (0.7) | 1.49 | 0.7 – 2.28 | <0.05 | 0.8 |

| Table 5. Assessment of variables after three months of treatment |
|------------------------|----------------|----------------|--------------|---------|
|                        | Comparison M0 – MPA (Mean and SD) | Diff in means | 95% C.I. I. Low – W. High | p       | Effect Size (Hedges g) |
| Severity of dependence (SCAN) (n=21) | 11.3 (3.9) – 3.65 (2.2) | 6.45 | 2.77 – 10.13 | <0.05 | 2.4 |
| Psychological adjustment (GHQ-28) (n=21) | 8.62 (8.6) – 5.5 (6.5) | 3.1 | -1.75 – 7.94 | NS | 0.4 |
| General state of health (OTI) (n=20) | 11.25 (7.2) – 4.8 (3.7) | 7.65 | 5.58 – 9.72 | <0.05 | 1.1 |
| Quality of life related to health (TECVASP) (n=21) | 0.43 (0.6) – 0.77 (0.5) | -0.34 | -0.64 – 0.03 | <0.05 | 0.58 |

### 3.3 (Three-month follow-up) (M2)

Three months after starting the treatment, another assessment was made with the remaining patients (comparison M0-M2). These represented 45.7% of those who began (21 patients). Between the one-month and three-month assessments (M1-M2), 14 subjects were released after having completed buprenorphine treatment, 6 left the TC and were switched back to methadone and 2 subjects were withdrawn for disciplinary reasons. The results of this new assessment are shown in Table 4. It may be seen that the scores show improvement in all the variables evaluated (“severity of dependence”, psychological adjustment”, “general state of health” and
Addiction to substances is a chronic condition of relapse. The health-related quality of life is a clinical parameter which is being used more and more in evaluating outcomes in this field, since, compared to traditional indicators, it provides relevant information on the impact of treatment on a level of general patient functioning [5,37,41,42]. The data from our work contribute new evidence on the effectiveness of treatment with buprenorphine measured in terms of health-related quality of life.

In this sense, we have observed that both at one month and at three months of treatment with buprenorphine, the level of patients’ quality of life had risen. Although one study has found similar results in evaluating the quality of life in patients on treatment with buprenorphine [14,15] and another reported the usefulness of this partial agonist in facilitating admission to therapeutic communities [10], our work is the first to combine these two characteristics. On one hand, it provides the first evidence that we know of on the effectiveness of this opiate measured in terms of quality of life in a therapeutic community. On the other, we have for the first time employed a scale for the health-related quality of life that is specific to a population of drug addicts. General scales measure the patient’s subjective perception of his/her “disease” and its repercussions on the general level of functioning. These general scales come up against problems when they are applied to drug abusers, as they are oriented to the physical concept of “disease”. The HRQoLDA Test proposes that the concept of “disease” be replaced by that of “disorder” (addictive disorder) made operational by the bi-axial addiction model. Another strong point in our work is the use of the Hedges g statistic as an estimator of the effect size, that is, the magnitude of the difference that is recorded between the base-line time and at each of the follow-up assessments for a specific variable. In this sense, the clinical distinction between a “statistically significant difference” and a “relevant clinical improvement” should be borne in mind. From the perspective of clinical epidemiology, both conditions are desirable [35]. Although the criteria for considering an improvement “clinically relevant” are relative and based on knowledge of the indicator assessed, the Hedges g statistic provides an additional criterion for clinical interpretation of outcomes. Concerning the other outcome variables studied (“severity of dependence”, “psychological adjustment” and “general state of health”) we have observed an improvement at both one and three months of treatment. The magnitude of change at both follow-up times is greater for “severity of dependence” and “general state of health”. This can be explained as a direct consequence of intervention in the therapeutic community, as the patient remains abstinent and receives adequate medical attention. The severity of psychopathological symptoms has fallen significantly at one month of treatment; this is especially noticeable for symptoms of depression. Although a further decrease is observed at three months, it is less noticeable. Data on these complementary variables abound in a tendency observed with other types of treatment that aim to improve the psychophysical health conditions that accompany a reduction in drug abuse. Working from the paradigm of harm reduction, apart from abstinence from substance abuse, an improvement in quality of life and in physical and mental health problems constitutes a basic treatment goal. It can be observed that all of these variables behave in the same way during follow-up. On one hand, an improvement at one and again at three months of treatment was verified, but the magnitude of this improvement was

Table 5. Assessment of GHQ-28 Subscales at three months

<table>
<thead>
<tr>
<th>Subscales</th>
<th>Comparison M0 – MPA (Mean and SD)</th>
<th>Diff in means</th>
<th>95% C.I. I. Low – W. High</th>
<th>p</th>
<th>Effect Size (Hedges g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychosomatic symptoms (n=21)</td>
<td>1.95 (2.4) – 1.9 (2.5)</td>
<td>0.05</td>
<td>-1.35 – 1.45</td>
<td>NS</td>
<td>0.02</td>
</tr>
<tr>
<td>Anxiety/ distress (n=21)</td>
<td>2.29 (2.5) – 1.81 (2.2)</td>
<td>0.48</td>
<td>-0.95 – 1.9</td>
<td>NS</td>
<td>0.2</td>
</tr>
<tr>
<td>Social dysfunction (n=21)</td>
<td>2.24 (2.8) – 0.81 (1.4)</td>
<td>1.43</td>
<td>-0.16 – 3.02</td>
<td>NS</td>
<td>0.64</td>
</tr>
<tr>
<td>Depression (n=21)</td>
<td>2.14 (2.8) – 1 (1.9)</td>
<td>1.14</td>
<td>-0.18 – 2.46</td>
<td>NS</td>
<td>0.46</td>
</tr>
</tbody>
</table>
greater in the first follow-up assessment and more moderate in the second. This tendency in outcomes, called the “hit-bottom effect” by Apsler and Harding [1], is common in most longitudinal opioid addiction treatment follow-up studies. According to this phenomenon, when the subject is in an active heroin abuse situation, the most likely outcome is that the variable level of severity of the problems that are related to abuse will tend to gradually increase. This gradual increase will motivate the baseline treatment demand, and the patient’s initial levels of severity are likely to be relatively high. From this point onward, these levels undergo significant reduction, especially during the first month, partly due to decreased consumption. During follow-up, the figures could continue to improve somewhat, but, predictably, to a lesser degree, with variations depending on the circumstances. These falls in severity might be influenced by the “regression to the mean” phenomenon, which cannot be monitored in studies on a single group such as this. This same phenomenon has been observed by Giacomuzzi et al. [14,15], who evaluated quality of life in a sample of 29 patients in buprenorphine treatment for three years.

Generally speaking, the sample in which we have observed these outcomes has a medium-low addiction severity profile compared to the patients who decided to stay on MMP. More specifically, the patients who chose to switch to buprenorphine showed lower baseline levels of cocaine abuse and psychopathological severity. These differences in severity profiles have also been observed in comparative studies on the long-term outcome effects of methadone and buprenorphine maintenance treatments on quality of life [14,15]. Although there is no consensus on a definite clinical profile [4], it does seem clear that treatment with methadone will continue to be the first-line alternative therapy for a majority of opiate-dependent patients, especially for those with higher levels of heroin use and greater heroin-related problems. This is at least partly determined by the different pharmacological profile of the two opioids (partial agonist vs. complete agonist) [13].

More studies are now needed to identify the characteristics of the subgroups of patients that best respond to methadone or buprenorphine [39,43]. As described in “Patients and Methods”, treatment with buprenorphine was offered to all of the patients who were admitted to the TC with a dose equal to or less than 80 mg/day. Of the 119 patients who met the selection criteria, 46 accepted buprenorphine treatment and the remaining 73 rejected it. It is, therefore, a self-selection process. Almost all of the subjects who rejected buprenorphine explained their decision in terms of their uncertainty and fear towards a pharmaceutical unknown to them. This is understandable, since it should be borne in mind that sublingual buprenorphine treatment (Subutex®) is not yet marketed in our country and this study is experimental. These patients, who have the worst kind of addiction severity profile, are the most suspicious of the benefits that buprenorphine could bring them. In Spain, it has still not been decided whether the National Health Service should finance buprenorphine; nor is it available for treatment at private centres because of the strict legislation regulating it. Fortunately, this is not true of methadone treatments.

4.1 Limitations

Our work has two main limitations. The first is the small size of the sample – a factor that makes outcomes statistically less powerful and less representative; besides this, as in all observational designs without a control group, we cannot provide any guarantee that the improvements in quality of life were not due to factors other than buprenorphine. More specifically, we cannot be sure that they would not have appeared in other patients who were admitted to the TC but did not receive buprenorphine. Secondly, the 73 patients who decided to stay on their MMP were not evaluated at one and three months because the study lacked the required funding. In this sense, we cannot discard the possibility that in this group an improvement in quality of life might have been similar, lower or higher with respect to the group that switched to buprenorphine.

5. Conclusions

The patients in treatment with methadone who, after admission to a therapeutic community, switched to buprenorphine, were able to experience ongoing improvement in their quality of life. The results of this study argue in favour of buprenorphine treatment programmes being extended to drug-dependent populations with an appropriate profile.

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Contributors

The authors contributed equally to this work.

Conflict of Interest

There are no conflicts of interests. This study was done without any pressure from the Pharmaceutical Industry or Government political interests. The authors of this work declare their desire for buprenorphine treatment to be made definitively available in Spain with the same level of equality and accessibility as methadone treatments.

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Clinical Trial on the Use of Olanzapine in Reducing the Consumption of Cocaine in Methadone Maintenance Programmes

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Summary

The consumption of cocaine among people included in Methadone Maintenance Therapy (MMT) is a widely identified phenomenon, but clinical experience and the literature have highlighted the difficulty of finding an effective pharmacological alternative for cocaine abusers. The aim of this study was to assess the use of olanzapine as a therapy for reducing the use of cocaine in MMT while implementing a more controlled design. A randomized clinical trial has been applied to 60 subjects assigned to three MMT programmes. The independent variable was treatment with olanzapine at three dose levels (0, 5 and 10 mg/day), with three treatment groups being formed; they comprised 20, 21 and 19 subjects, respectively. The outcome variable was the percentage of positive urine tests for cocaine consumption, as estimated by means of urine monitoring using immunoassay, during the first three months after the start of treatment. For the data analysis, MANOVA and the hierarchical regression model were used. The mean proportion of previous cocaine consumption was 25.8% (S.D. = 26.4; range 0-100), with no differences between the treatment groups (F(2,57) = 0.167; p = 0.845). Hierarchical regression analysis showed a significant model in final step (F(5,54) = 8.61; p ≤ 0.001), with an explained variance of 44.3% (R² = 0.443). The semi-partial correlation coefficients (rspm) indicated significant effects on the variables: methadone dose (rspm = -0.229), previous cocaine consumption (rspm = 0.345) and treatment with 5 mg/day (rspm = -0.469) and 10 mg/day (rspm = -0.514) of olanzapine. The mean proportion of positive control results in the untreated subjects was 21%, whereas, in the patients receiving olanzapine therapy, it was 8.8% in those taking a dose of 5 mg/day and 9.5% in those on a dose of 10 mg/day. The prior consumption of cocaine is shown to be a risk predictor for subsequent consumption, whereas an increase in the dose of methadone or treatment with olanzapine both show a protective effect. Specifically, the 10 mg dose of olanzapine, when followed by the 5 mg dose shows the highest degree of explained variance in post-treatment cocaine consumption, after checking the effects induced by the remaining variables.

Key Words: Cocaine; Methadone Maintenance Therapy; Olanzapine; Clinical trial

1. Introduction

Nowadays, the most widespread and effective forms of treatment for addiction to opiates [2,28,38,47,48] are replacement therapy or methadone maintenance therapy (MMT); a major complication is that many users of these programmes are consumers of multiple other substances [30,20]. In this respect, the consumption of cocaine in patients receiving MMT is a widely described phenomenon that tends to rise over earlier consumption levels and significantly hinders patients’ evolution [6,12,19,21,23,35,41,43]. Among the variables associated with cocaine consumption during MMT, the consumption of cocaine prior to treatment with methadone has been described as the main risk factor [6,19,21,41]; on the other hand, the larger the amount of the methadone dose, and the longer the time the patient has stayed in an MMT programme, the greater the protective effects, even if each of these two parameters has been proposed as a risk factor [8,14,42].
With respect to treatment, both clinical experience and the literature have highlighted the difficulty of finding an effective drug for cocaine abusers [1]. Basic research has presented evidence suggesting the involvement of the dopaminergic and serotoninergic systems, among others, in the action mechanism of cocaine and the use of dopaminergic antagonists to reduce the self-administration of cocaine in animal models [31,36]. In this connection, atypical neuroleptics such as olanzapine, which is able to block dopamine D2 receptors, as well as serotonin receptors 5HT2A and 5HT2C, may be able to reduce the euphoric effects of cocaine and attenuate reinforcement and cocaine craving [29,30,32,37,49]. In this sense, some clinicians have mooted the idea that olanzapine may be able to reduce cocaine use in patients who abuse this substance [4,22,24,25]. In addition, olanzapine may be superior to traditional neuroleptics in treating cocaine dependence, due to its less severe side-effect profile [5,26].

There is evidence both for [9,18,27,40] and against [22] the usefulness of atypical neuroleptics in reducing cocaine consumption in humans. Previous studies by our group using less well-controlled designs [24,25] offered promising results on the use of olanzapine in patients addicted to opiates who were receiving treatment with methadone after there had been an increase in cocaine abuse while they stayed in the MMT programme. In this paper our aim is to offer results based on a better controlled design that allows olanzapine therapy to be assessed for its capacity to reduce cocaine abuse in patients without psychotic symptoms who are still on an MMT programme.

2. Materials and methods

2.1. Subjects

The study sample comprised 60 people with DSM-IV criteria for opiate dependency and receiving MMT, where there had been an increase in cocaine consumption after...
stabilization of the methadone dose.

Of the 60 participants, 48 were male and 12 were female (80% versus 20%), ranging between 23 and 46 years of age (mean = 35.5; SD = 4.8), and they were mainly single (58.4%) or separated (16.7%). The mean time on the MMT programme was 6.3 months (SD = 2.4), with the longest participation stretching to 11.7 months. The doses of methadone dispensed varied between a minimum of 10 mg/day and a maximum of 150 mg/day (Mean = 66.4; SD = 28.5).

The research protocol was approved by the health services’ ethics committee. All the participants partook in the characteristics of the trial and their informed consent was obtained prior to participation.

2.2.- Procedure

The trial has involved the participation of 3 Drug Abuse Treatment Centres (CTT in their Spanish acronym) located in the Basque Country (Spain). From the total number of patients receiving treatment in the MMT programmes present at these three CTTs (n = 528), after applying the inclusion and exclusion criteria, an eligible sample of 71 subjects was obtained, with 62 of them (87.3%) giving their consent to participation. CTT-1 contributed 15 subjects, CTT-2 21 and CTT-3 24. Lastly, one subject from CTT-1 and another one from CTT-2 withdrew before starting the study, so the final sample comprised 60 participants (Figure 1).

One of the inclusion criteria for admission to the trial was that the participants had to show an increase in their consumption of cocaine after the start of treatment with methadone compared with that recorded previously. During the three months prior to the start of the study, there was a selection of those subjects who had delivered more than 15% of cocaine-positive samples (237/528) during the routine substance detection tests.

The exclusion criteria applied were:
1) the presence of psychotic symptoms, dementia disorders, major or bipolar depression;
2) alcohol consumption in excess of 20 standard units per week for men and 30 standard units a week for men;
3) pregnancy in women; and 4) known hypersensitivity to olanzapine.

After selection, participants were randomly assigned, in a proportion of 1:1:1, to three treatment modes with olanzapine: ‘0’, ‘5’ and ‘10’ milligrams a day. For the randomization process, each participant was given a consecutive number, and the distribution of patients among the treatment groups was performed using Epidata software [33]. The outcome of this randomization was as follows: 0 mg (n=20), 5 mg group (n=21) and 10 mg group (n=19). No masking techniques were used for the administration of the therapy i.e. neither the patients nor the physicians were blinded, but blinding was used for the data analysis.

A study period of 3 months was set. Every day, each participant was given the appropriate prescribed dose of methadone, and the treatment with olanzapine assigned to them; both doses were taken in situ, except in the case of doses intended for the weekends, which were delivered on Friday for self-administration on the scheduled days. Furthermore, all the subjects received a weekly counselling session where the effects of the therapy and the prevention of relapses were discussed. These sessions were homogeneously structured and administered by the clinicians at each of the participating CTTs. On the other hand, all the participants were being medicated with benzodiazepines in a variety of pharmacological formats and doses that had been prescribed prior to the start of the trial. This variable was not systematically controlled in view of the diversity of subgroups that might arise from this classification, and the randomized assignment was assumed to have distributed the resulting effects homogeneously.

The main outcome parameter assessed in this trial was the proportion of cocaine during the last 2 months of the study period after therapy with olanzapine had been initiated. Estimations were made based on urine samples collected for the determination of cocaine metabolites. As part of the protocol, each of the participating CTTs collected urine samples weekly and selected the collection day at random. The analyses were performed using homogeneous enzyme immunoassay techniques (EMIT) in a COBAS-MIRA analyzer, using SYVA reagents, calibrators and control samples, and an external control of DOA at two negative and positive levels, with the results stored in a computerized database. For each subject the number of tests performed was noted, along with the number of positive results in each case, so as to give an estimate of the ratio between these 2 variables (Npositives / Ntests); this procedure yielded an index expressing the Proportion of Consumption (PC) of this substance. For example, a subject for whom 20 determinations of cocaine have been made, with none of them positive, will have a PC of 0 (0/20); this expresses the subject’s situation in terms of his/her degree of abstinence from cocaine; if, on the other hand, there had been 8 positive tests recorded, the PC would be 0.4 (8/20), in other words the subject has presented consumption of cocaine on 40% of the occasions analyzed. PC values vary between 0 and 1, with the level of substance use increasing as the value comes closer to 1.

2.3.- Statistical analyses

All of the analyses were performed using the SPSS software. Tally and proportion procedures were used, together with central trend and dispersion statistics for the description of the sample.

In order to verify whether the random assignment had produced a compensation effect, an analysis was carried
out on the contrast between the differences in the pre-treatment characteristics of the sample, depending on the assignation groups they belonged to. To do so, the Chi square test was used for category data and a variance analysis for continuous data.

The effect of treatment with olanzapine on the reduction of cocaine consumption was assessed through two procedures. First of all, a multiple analysis of variance model (MANOVA) was used to compare the inter-group, intra-subject and interaction effects. In order to determine where the differences between the treatment groups occurred, the post hoc contrasts based on the Bonferroni test were used; for the post hoc comparisons found in the change in each group between the baseline and post-treatment values, the t-test for paired data was used.

Secondly, a hierarchical multiple regression model was used to determine the direct and indirect effects of each level of treatment with olanzapine and the possible co-variables (the percentage of cocaine consumption in the pre-treatment period, the duration of participation in the methadone programme and the methadone dose dispensed) on cocaine consumption after treatment. Model 1 includes the treatment with olanzapine variable in a dummy format, taking the no-treatment group as its term of reference (0 mg of olanzapine). Models 2, 3 and 4 include, in order, the aforesaid co-variables in order to check the effect of the main variable and assess the contribution of each of these co-variables.

The results of all regressions were presented through semi-partial correlation coefficients for each predictor variable, along with overall F values and adjusted \( R^2 \). Semi-partial correlation coefficients were chosen over other possible coefficients (e.g. partial correlation, beta weights) because they represent the proportion of variance in the dependent values uniquely associated with a particular predictor variable [11].

3. Results

There were no withdrawals from treatment nor was it necessary to intervene or alter the therapy in any case. Nor were any significant side-effects noticed, except for weight gain in 16 of the participants (26.6%).

The randomized assignation of the subjects to the treatment groups allowed a homogeneous distribution of the pre-treatment variables to be obtained. None of the variables assessed has shown statistically significant differences (Age: \( F_{(2,57)} = 0.088; p=0.916 \) / Gender: \( \chi^2_{(2)} = 1.91; p=0.384 \) / mean time with MMT programme: \( F_{(2,57)} = 1.780; p=0.178 \) / Methadone dose: \( F_{(2,57)} = 0.180; p=0.836 \) / Proportion of positive cocaine consumption tests during the three months prior to the start of treatment: \( F_{(2,57)} = 0.167; p=0.845 \).

Figure 2 represents the degree of cocaine consumption before and after treatment through the prevalence of positive results in the cocaine consumption tests, and
the $F$ values in the MANOVA. Both the intra-subject effect and interaction have been shown to have statistical significance. A post hoc analysis concluded that the differences between the groups after treatment [$F_{2,50} = 6.17$; $p = 0.004$] were between those treated with olanzapine (5 or 10 mg) and those who were not treated (0 mg). Furthermore, a fall in the consumption of cocaine before and after treatment occurs in the groups treated with 5 mg [$t_{18} = 5.04; p< 0.001$] and 10 mg of olanzapine [$t_{19} = 6.03; p< 0.001$], but not in the untreated group [$t_{19} = 1.86; p= 0.078$].

Table 1 presents the semi-partial correlation coefficients of the treatment variable and other co-variables of interest, as well as the $R^2$ and the increase in $R^2$ produced at each step in the hierarchical regression used. The first step included the main variable under study, and this alone was enough to account for 25.3% of the variance. The semi-partial correlation coefficients for the 5 mg and 10 mg doses are negative, above the value of 0.40 and very closely bunched. Step 2 includes the variable ‘months of participation in the methadone programme’ and fails to produce any significant changes. Step 3 incorporates the variable ‘prevalence of cocaine positive tests in the three months prior to the start of the study’ and there was an increase of 0.137 in $R^2$, with a semi-partial correlation of 0.37. The incorporation of this variable promotes a change in the semi-partial correlation values of the 5 mg (-0.47) and 10 mg (-0.52) doses. Step 3 incorporates the variable ‘months of participation in the methadone programme’ and fails to produce any significant changes. Step 4 incorporates the ‘methadone dose’ and promotes an increase of 0.05 points in $R^2$, which in this last model reaches a value of 0.44. The semi-partial correlation coefficient associated with the methadone dose is -0.23; it does not substantially alter the magnitude of the coefficients attained by the other variables included in the model.

4. Discussion

The results obtained provide evidence in favour of acceptance of the hypothesis that the use of olanzapine may be useful in reducing cocaine consumption, at least in subjects on MMT who continue to use this substance.

The bivariate analysis of the study factor has shown statistically significant differences in favour of the groups treated with olanzapine over the control group, although it has not allowed differences to be established in terms of the olanzapine dose used (5 mg versus 10 mg). Subjects treated with olanzapine show a much lower mean proportion of cocaine use after treatment than those not treated (a reduction of 16.15% versus 5.9%, respectively). Olanzapine is a powerful antagonist of 5-HT2a receptors (saturating them with a dose of 5 mg [15]) located in the glutamatergic pyramidal neurons of most of the cortical regions [30]; agents with significant affinity for 5-HT2a receptors antagonize hyperactivity, reversing the symptoms produced by the non-competitive antagonists of the NMDA receptor [30,49]. It is likely that the combined action of olanzapine on the dopaminergic, serotoninergic and glutamatergic systems [7,16], and its probable ability to reduce depression [44,45], may help to reduce cocaine consumption.

It must be noted that other studies [13,17,34] with serotoninergic drugs (SSRIs) were inconclusive on the issue of the reduced consumption of cocaine, although they did report a decline in depressive symptoms, probably through its sole serotoninergic action. Furthermore, those studies [4,5,9,18,24,25,26,27,39,40,46] showing the effects of the atypical antipsychotics on symptoms of schizophrenia, particularly the negative symptoms, will prove to make these medications useful to cocaine-dependent patients with schizophrenia. At the present time, it is probably not appropriate to seek a global or

<table>
<thead>
<tr>
<th>Table 1. Hierarchical linear regression on the percentage of cocaine consumption after treatment (semi-partial correlation coefficients)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step 1</strong></td>
</tr>
<tr>
<td>Olanzapine Dosage: 5 mg/day (Dummy variables) 10 mg/day</td>
</tr>
<tr>
<td>Previous Cocaine Consumption (% positive controls)</td>
</tr>
<tr>
<td>Time with MMT</td>
</tr>
<tr>
<td>Methadone Dosage in mg/day</td>
</tr>
<tr>
<td>$F$</td>
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<tr>
<td>$R^2$</td>
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<tr>
<td>$\Delta R^2$</td>
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</table>

* $p<0.05$; ** $p<0.001$; all regressions significant ($p<0.001$)
universal treatment for all consumers of cocaine, but, rather, to undertake a selective search for patients with specific characteristics, where these or other drugs might be effective in such dependencies.

Other authors in our setting have described an increase in the plasma levels of methadone in patients participating in MMT programmes treated with SSRIs [3] and/or OLZ [4], which may allow reductions in daily doses of methadone – reductions that may have a subjective positive effect on patients in MMT programmes as they relate dose reduction to improvement.

It is noteworthy that 100% of the patients included in the study completed it, indicating a scant incidence of side-effects deriving from olanzapine administration, unlike what happens with typical neuroleptics in addiction clinics where cases of early withdrawal due to side-effects were a majority. Attention should be drawn to the scant incidence of side-effects, except for weight gain, but in this kind of patient, with many years of cocaine use, mostly infected with HIV and with considerable organic deterioration, weight gain might almost be considered to be a beneficial effect.

The multivariate analysis, on the other hand, allows certain important observations to be drawn. First of all, the findings obtained in the bivariate analysis are ratified, with the first step in the hierarchical regression presenting a very similar effect between the doses of olanzapine used (semi-partial correlations of -0.44 and -0.43 for the 5 mg and 10 mg doses, respectively); in addition, it is the variable that shows the greatest protective effect on the consumption of cocaine after treatment (25% of the variance explained).

The risk factor with the second greatest effect on the outcome variable is the prior consumption of cocaine, which turns out to be a factor predicting future consumption or continuation of consumption ($r_{sp} = 0.37$). This risk effect was already well-known [6,14,19,21], but the inclusion of this variable in the model has brought about an effect on the main variable: a modification in the magnitude of the semi-partial correlations of the doses of olanzapine. When the effect of prior consumption of cocaine is controlled, an increase in the protective effect of olanzapine is observed; this effect is greater in the case of the 10 mg dose ($r_{sp} = -0.43$ to $r_{sp} = -0.52; \Delta = 0.09$) than for 5 mg ($r_{sp} = -0.44$ to $r_{sp} = -0.47; \Delta = 0.03$).

A third variable that, like the first two, shows a significant effect on the reduction of cocaine consumption among users receiving MMT is the dose of methadone dispensed. The effect is moderately low (an increase of 5.2% in the variance explained by the regression model and an $r_{sp} = -0.23$), yet it indicates that a greater dose of methadone is likely to be associated with a lower consumption of cocaine during MMT. Furthermore, this variable does not interact with the other variables included in the model, because the magnitude and the sense of the semi-partial correlations of those other variables are not altered by it.

On the other hand, the longer or shorter participation in MMT programmes, in other words the duration of the period spent in methadone treatment, does not influence cocaine consumption during the programme.

Although the results obtained provide evidence of an appropriate degree of effectiveness in the use of olanzapine for the reduction of cocaine use among patients receiving MMT, we feel that further studies are now required to corroborate these findings. The use of randomization for the assignation of subjects and the composition of the treatment groups have, we feel, neutralized the impact of variables not assessed in our study. No doubt a wider-ranging assessment, capable of taking into account other predictive variables analysed in other studies [21,22], would allow us a greater degree of breakdown regarding the factors involved in cocaine consumption during MMT.

As clinicians, we have given priority to flexibility and the naturalness of treatment in order to avoid instrumentation effects through the assessment of a few relevant variables measured indirectly; as proponents of scientific knowledge, we are aware of the limitations implied by proceeding in this way. For this reason, further studies should be undertaken to overcome these limitations; this would allow an answer to be given, while the hypotheses put forward by us to account for our results could then be accurately assessed.

5. Conclusions

The previous level of cocaine consumption proves to be a risk predictor for subsequent consumption, whereas an increase in methadone dose or in the treatment with olanzapine has a protective effect.

Treatment with olanzapine, whether at a dose of 10 mg/24 hr or at a dose of 5 mg/24 hr, is the factor which has the greatest effect on the reduction of cocaine consumption in patients currently in methadone maintenance programmes who are addicted to opiates and who continue to consume cocaine during treatment.

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Conflict of Interest

The authors have no relevant conflict of interest to report in relation to the present study.
Voices of Experience: Attitudes and Opinions of Recipients of Unsupervised Injectable Opiate Treatment in the Northwest of England

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Summary

Aims and Methods: To describe the views and experiences of drug users receiving unsupervised injectable opiate treatment (IOT) for opiate addiction, the most common current form of injectable treatment in the UK. Semi-structured interviews were completed by 29 IOT recipients from two Community Drug Teams in northwest England.

Findings: Attitudes of most respondents were positive with personal and social benefits: reduction or cessation of illicit drug use; health gains; more “normal” lifestyle; reduced criminal activity. IOT recipients were not a homogeneous group and had different needs and goals.

Conclusions: Individuals valued the stability IOT had brought to their lives. The treatment challenge is how to maintain stability without allowing drift into inertia. Much of the IOT debate has been led by service providers and academics. IOT recipient views have been neglected and this study adds a new voice.

Key Words: Attitudes; Injectable Opiate Treatment

1. Introduction

In the UK, injectable opiates have been prescribed as part of the management of drug dependence since the start of the twentieth century (30). Although some other countries have conducted research into the use of injectable diamorphine treatment (21, 22, 33, 34), the UK is almost alone in prescribing injectable methadone on a maintenance basis (27, 16). The number of people being prescribed injectable opiates in the UK has varied over time and across locality. There is a dearth of statistics relating to individual prescriptions. The best estimates available indicate that in 2001 injectable diamorphine accounted for 0.5% of all prescriptions for opiate dependence (28) and that, in 2005, injectable methadone accounted for just short of 2% of all methadone prescribed in England and Wales (32).

It has been argued that the decision to prescribe injectable opiates is based more on the personal viewpoint of the prescriber than on research evidence or systematically collected clinical data (13, 36). Indeed, despite its history, injectable opiate treatment (IOT) had, until recently, attracted relatively little research interest in the UK. Of the earlier published studies of IOT, two excluded injectable methadone (6, 10) and one included only a small number on injectable methadone scripts only (2). Studies covering injectable methadone treatment (14, 15, 31) focused on comparing two or more different treatment modalities and had acknowledged design difficulties that made drawing firm and general conclusions difficult. Findings from an audit of IOT patients and a cross-sectional survey (26, 27) suggested both benefits from, and dissatisfaction with injectable methadone treatment, most of which was, and, still is provided on an unsupervised basis. Recent policy interest has shifted to focus on the prescription of diamorphine (16) and on the provision of IOT under supervision. Drawing on the experience of work in the Netherlands and Switzerland (33, 21), the current Randomised Injecting
Opioid Treatment Trial (RIOTT) study will compare supervised methadone and diamorphine injecting as well as oral methadone treatment (8).

A detailed discussion of the debate concerning IOT has been presented by Zador (36). The main rationales for IOT are harm reduction and retention in treatment. It is argued that IOT is justified when other treatments have failed and the injecting drug user’s health or well-being is at serious risk (5, 36). IOT is said to provide a way of minimising illicit drug-related harm for those who are unable to respond to other treatment interventions while also retaining injectors in services until they feel able and willing to make changes to their drug using behaviour.

The effectiveness of harm reduction approaches (which encompass IOT) has been questioned (11) by pointing to the continued spread of HCV, and the impact of drug use on drug users families and host communities. Opponents of IOT argue that providing injectables merely condones and perpetuates injecting practices. The provision of such treatment is said to make the injector’s behaviour even more entrenched, to take away any motivation to cease drug use and to delay significantly the decision to give up injecting (36, 1).

British policy on treatment for opiate addiction has in the past acknowledged that a small number of long term injectors may benefit from IOT (3, 17). The current UK clinical guidelines (4) maintain the 2003 recommendations that injectable heroin and methadone should be considered for a minority of individuals who are genuinely unresponsive to oral maintenance treatment. In an annexe to the guidelines it is suggested that Metrebian (16) provides evidence that “quality of care planning and treatment” for patients receiving unsupervised prescriptions is “variable and often poor” (4: 117). The advice does not go as far as recommending that all patients should be placed on the same footing; instead, current treatment should be continued but it should be reviewed regularly. The 2008 UK Drug Strategy (7) continues to include the option of “rolling out the prescription of injectable heroin and methadone to clients who do not respond to other forms of treatment”.

There are many unanswered questions concerning the practice of treating opiate dependent individuals with prescribed injectable opiates. While injectable treatment is still included in the options available to clinicians, the most recent national guidelines recommend that any patients new to treatment and deemed to require an injectable prescription must have this administered in a supervised environment. This is a new departure for the UK and could in the future be seen as allowing a comparison to be done with the current unsupervised modality.

There are few readily traceable published studies on the opinions and experiences of those receiving IOT (27, 35) and both are based on structured, self-completion questionnaires. The current study used a different approach and sought to explore the recipient perspective in more depth by using a semi-structured interviewer-administered method allowing scope for respondents to expand on their answers. More qualitative explorations such as this have not been widely used in looking at IOT (19, 20). The aim was to add a new dimension to the current debate on prescribing injectable opiates by providing information from the recipients of IOT concerning the following research questions:

- How do IOT recipients perceive the process of being put on IOT?
- Is IOT viewed as beneficial by those who are receiving it?
- Are there ways in which IOT is unhelpful to its recipients?
- Do IOT recipients think it was the best form of treatment at the time?
- Are IOT recipients planning to come off IOT?
- Do IOT recipients want help other than their prescription from services?
- Do IOT recipients receive other help from services?

2. Methods

2.1 Study Population

The study was carried out at two Community Drug Teams within the Morecambe Bay NHS Primary Care Trust area in the north west of England between July 2002 and May 2003. Approximately 420 individuals were receiving opiate substitution treatment (with a further 110 being prescribed for by their GPs and supported by the Drug Teams under “shared care” arrangements) at the time of the study. IOT had been initiated by a variety of different doctors at different times in the history of the Service. Thirty-six of the 420 (nearly 9%) were receiving injectable opiates. The target population was these 36 individuals.

2.2 Study Instrument and Administration

A semi-structured interview schedule was devised that included selected closed-response questions used in a descriptive study of IOT in Manchester (26). The qualitative element was developed following a review of the relevant literature, discussions with experienced clinicians working in the field and informal interviews with a range of clinic staff and service users. The resulting open-ended questions covered the following topics: reasons for, and views on, being put on IOT; benefits and unhelpful aspects of IOT; views on coming off IOT; perceptions concerning help received from the service.

Ethical Approval was sought and obtained from the Local Research Ethics Committee. Following a pilot of the instrument, participants were interviewed between July 2002 and May 2003. Interviews were conducted by an experienced independent researcher (AW) who...
was not associated with the clinics or with respondents’ treatment. Subjects were given written and verbal information and the chance to ask questions about the study. It was made clear that participation was voluntary and that agreement or refusal to take part would not affect their treatment in any way. Participants signed a consent form. The majority of interviews were conducted in a room in one of the drug services; two were conducted in the interviewees’ homes and one took place in a doctor’s surgery. Length of interviews varied from thirty minutes to three hours.

2.3 Study Cohort

During the study period, 36 people receiving IOT were eligible for inclusion: 20 attending Lancaster and Morecambe Drugs Service and 16 attending South Cumbria Drugs Service. Three were discharged before they could be interviewed, one moved out of the area and three refused to take part in the study. A total of 29 subjects were interviewed; a response rate of over 80%. Sixteen participants were interviewed at Lancaster and Morecambe Drugs Service and 13 were interviewed at South Cumbria Drugs Service.

2.4 Cohort Characteristics

Twenty-one (72%) men and 8 (28%) women were interviewed. The mean age of the sample was 40 years (range 31-52). All participants described their ethnic group as “white”. The vast majority (27; 93%) were dependent on social security benefits. Only 2 (7%) said their main source of income came from employment. Over half (16; 55%) were married or living with their partners, 3 (10%) were in relationships but not living with their partners and just over a third (10; 35%) were not currently in a relationship. The mean age at which respondents began injecting was 20 years (range 14-50; median 18). The mean duration of injecting any drug was 21 years (range 14-50; median 18). The mean age at which respondents began injecting was 20 years (range 14-50; median 18). The mean age of the sample was 40 years (range 31-52).

2.5 Qualitative Analysis

Responses to the open-ended questions were audio-taped and then transcribed verbatim. Initial analysis involved reading and re-reading the transcripts and conducting a preliminary categorisation of the data. After summarising and indexing the data, emerging themes were identified and existing categories refined (12, 23). This process was undertaken separately by members of the Project Team (RL, MO and AW) and also by an independent researcher (IP). Results were compared and, after some discussion, a consensus was reached on the main concepts and themes. Quotations were then selected to represent the range of views expressed by participants, including the untypical, whilst aiming to avoid repetition and redundancy. Interviewees’ words are largely unedited.

3. Results

3.1 Reasons for receiving IOT

When asked why they had been put on IOT, participants’ responses varied from one-line answers to in-depth explanations. While several suggested they had been put on IOT simply because they had “asked for it”, a couple described the process as having been long and drawn out.

The majority of participants (24/29) had been prescribed oral methadone at some point prior to being put on IOT. The average length of time on methadone mixture before getting an injectable prescription was three years, with a range from 0 to 16 years. One of the most common reasons given for being moved to injectables was having a bad physical reaction to the oral preparation:

“Every time I had the green, it was a case of being sick or I ended up with ulcer burns in my mouth. I hated the taste of it. It was horrible.” [MB14, M, 32, 18, 5]

Another recurrent explanation for being moved to IOT was the practice of injecting their prescribed liquid methadone. Sometimes this behaviour was linked with, what participants called, “needle fixation”:

“I couldn’t handle the linctus cos I was picking it up and I had a needle fixation and I was injecting the linctus and it’s dangerous so that’s why they ended up putting me on the injectables.” [MB11, F, 31, 17, 6]

An equally common though more vague theme was that oral methadone “was not working” [MB1, M, 36, 19, 2] or “wasn’t doing anything for us” [MB10, F, 34, 16, 6]. As one participant put it:

“The oral wasn’t enough. It was sorting me bones out but my head was still buzzing.” [MB16, F, 52, 11, 1]

Others put it in more specific terms: “I wanted to get the hit faster.” [MB6, M, 32, 16, 14]

The frequency with which they had been injecting illicit drugs was also seen as a major reason for being put on IOT.

While the term “harm minimisation” was not used, many indicated that it had played an important part in the decision to prescribe injectables:

“If they’d given me the mixture I would’ve injected that so it was safer I suppose to give me the amps… I was injecting a lot and my arms were quite bad at the time you know.” [MB2, M, 37, 21, 10]

“If she hadn’t put me on it I would’ve ended
3.2 Perceived benefits of IOT

As the IOT had helped them, most participants perceived a variation of benefits. These ranged from the decreased sense of security: “It has stopped me from dying or killing myself” [MB2, M, 37, 21, 10] to the less vivid: “It gives me a sense of security” [MB8, M, 44, 23, 10]. Comments like “It's changed my life completely” [MB24, M, 48, 31, 20] were not uncommon.

From their accounts it was clear that IOT had helped participants to cease or significantly reduce heroin and other illicit drug use. This was borne out by examination of each user’s reports of past drug taking and current drug taking. Several stressed the point that if they had not been put on IOT they would still be injecting either “street gear” or oral methadone.

“I'd either be dead or in prison if I wasn’t taking these drugs. I would definitely have carrier on injecting. I have no doubt in my mind.” [MB3, M, 50, 33, 30]

“It has kept me off street drugs for long periods of time. If I wasn’t getting them, I would probably be doing smack every day. I just know I’ve benefited from it. I don’t know.” [MB12, M, 32, 16, 10]

IOT helped some because it meant they no longer had to mix with certain people:

“I have met people I didn’t even know existed. People wrecked out their heads with heroin. I’d never seen stuff like that in my life, now I’m on an injectable script. I can keep away from it. No one knows I’m on it. It gives you a bit more pride. I feel very anti-heroin now.” [MB22, F, 38, 13, 7]

Hand in hand with this response, it was often stated that IOT had given them a chance to lead a more “normal” or “stable” life:

“I was a single parent for years looking after my children and it helped me to get on and have a life. Get up, get my daughter ready and take her to school and come back and go to the chemist. It helped me have a normal life. I get into the garden, do whatever instead of just spending all my time out stealing and lying and cheating.” [MB18, M, 38, 23, 10]

“My life is a lot calmer now. I don’t have to spend all day running around looking for gear. The drugs I used to take would make me out my head. I’m a lot calmer now. I’m allowed to see my children now, when they come over, they stay now. I don’t know where I’d be actually now if I hadn’t got on this prescription.” [MB25, F, 41, 14, 10]

“Just knowing that it’s there and I’m not having to run out and I can spend time with my family instead of chasing drugs. It gave me the time to have quality time with my mother. It’s helped me with looking after my father.” [MB19, F, 44, 28, 9]

Not having to commit crimes to fund their drug use was perceived as a very important benefit by many. Several said they would have been serving custodial sentences if they had not been given IOT:

“It enabled me to live a reasonably normal life without ending up in jail for the last 15 years. In the last 15 years, I’ve not been in trouble for anything.” [MB15, M, 46, 30, 15]

“It’s taking a lot of weight off my shoulders... I don’t have to do any bad things to get money or anything. The money I get is just mine, for food and whatever I want. It really has helped me.” [MB16, F, 52, 11, 1]

Some participants were emphatic that, without IOT, they would be dead. Less extreme health gains were noted:

“I look after myself a lot better. I’m a lot healthier person. And not only that, I’m getting constant medical attention as well, you know, and care. Which before I wasn’t. When you’re using street gear, you don’t go to the doctor at all for anything.” [MB29, F, 42, 23, 12]

For four, who had problems with chronic pain, an important beneficial effect of IOT was its pain relieving properties.

3.3 Ways IOT had been unhelpful

There were ways in which IOT had been unhelpful. The dominant concern was not with the treatment itself but with the way it was administered. Participants complained that prescription collection severely restricted their movements:

“It ties you down. Having to pick it up every day. You can’t just get up and disappear for a week. Get a holiday. You have to be there 9.15 every morning.” [MB18, M, 38, 23, 10]

Several participants complained about how difficult it was to get off injectable methadone:

“If I’d known all this shit was going to happen it would’ve been easier to get off street gear. It’s easier to get off street gear than methadone. Methadone gets into your bones. The only way to alleviate it is to get sun into your bones. I feel cold even if my body seems warm.” [MB4, M, 51, 36, 11]

“I get really annoyed with myself for taking it because it doesn’t do anything for me. All it does, it makes me feel normal. I don’t get stoned off it. It’s the dependency really - dependency on the drug. The withdrawal from methadone is very severe and I find that the longer I take them,
the quicker I get ill in the morning.” [MB15, M, 46, na, 15]

A range of other issues was raised including problems with profuse sweating and serious concerns about the effects of IOT on the veins. One participant said it had interfered with his sex drive and that this was causing difficulties in his relationship.

3.4 Thinking about coming off injectables

When participants were asked if they thought they would reach a stage when they might consider coming off injectables, responses tended to fall into three broad groups.

The first group was currently reducing their prescribed doses. Some were doing this in a planned way with a definite end date in mind:

“I’m doing it now. I’m reducing now. You’ve got to want to do it yourself. It’s up to me. I’m going on holiday next March so my plan is to get off it by then, for when I go away.” [MB11, F, 31, 17, 6]

Others were reducing over a longer time period with no set date for coming off:

“Soon. In the next year or two I’ll probably be off it. It’s only the last year that I’ve been reducing. I’ve come down 50 mls so far. I do get help off a counsellor and he listens to what I say and we compromise about the best thing to do. I reckon I’ll be off it in the next year or two definitely.” [MB13, M, 32, 7, 6]

The second group said that they thought they would reach a stage of coming off but dates and timescales were usually indeterminate:

“Yes, hopefully not too far away. It depends on the situation. If something turns up and I’ve got a good incentive to change me habits, then hopefully I’ll be able to do it.” [MB4, M, 51, 36, 11]

“I’ll be ready to come off one day but not in the near future. I need to get my life sorted out. I’ll know when.” [MB7, M, 33, 13, 10]

“Obviously, there’s going to be a stage when I’m going to come off. I don’t really know. I don’t want to be an old man having to shove needles in my body.” [MB12, M, 32, 17, 10]

“yes. Every day I make a little promise to myself. I got goals. I started with that job and I had all good intentions to carry on with it. Getting up and putting on a shirt and tie was hard but if I could manage it for two months then I could stop the ampoules or pills like my wife. If I don’t get it, I don’t miss it. I don’t just get up for my methadone in the morning. I don’t go to the chemist till the afternoon to get it. I don’t bother with it until the evening and I wonder why I am bothering. It’s just that little bit of

security. Because I always get anxious just after my son goes to bed at about 8:30 to 9 o’clock. I get anxious. I start thinking too much. I draw a lot to keep my mind off it. When I was at work I was too tired to think about it. I enjoyed work. I drive her mad at home. I’d work for the same money you get on the dole. You don’t meet anyone at home do you? I hate going to work but once I’m there I like it.” [MB8, M, 44, 23, 10]

The third group comprised individuals who said they could not envisage stopping injectables. Some put this down to an inability to give up adding that they would only come off if forced to:

“There will probably be a time when I come off when my body will make me come off. If I could stay using but they said I’d die in the next 6 months then, of course, I’m going to go for something else. I’d only come off if I had to.” [MB27, F, 51, 35, 34]

Others put it in terms of choice:

“Ideally, I’d like what I’m on now to take me through. I know of people in their 60s and 70s who have been using methadone in London and are still going strong. There is the possibility of the injection site getting traumatised but other than that, the actual drug … I really think there is more damage from smoking and alcohol.” [MB24, M, 48, 31, 20]

3.5 Was IOT the best form of treatment

The majority of participants said that, looking back, IOT had been the best form of treatment for them at the time and some stated they should, in fact, have been put on IOT earlier. Comments from those who said IOT had not been the best form of treatment included complaints about the type of opiate they had been prescribed and that detoxification would have been a preferable option although this participant admitted that “I don’t know if I would have gone or not” [MB14, M, 32, 18, 5]. Some participants were ambivalent. As one put it:

“Yes and No. Yes, because it got me through some really bad times but no, because I didn’t think I’d be doing it this long.” [MB8, M, 44, 23, 10]

3.6 Other help received from Service

Participants said they had valued help, other than their prescription, received from the Drug Service. The main type of help was variously described as: “someone to talk to”, “someone who listens” and “support”. Two said they had received “counselling”. The degree of importance placed on this kind of help ranged from people who saw it as relatively peripheral - “The script is the main thing but it’s nice to talk as well” [MB28, M, 42, 12, 6] - to those who perceived it as being central to
their existence:

“Over the years, I’ve lost my kids, my home and everything over drugs. I don’t know what I would have done without someone to talk to in here. It’s the only place you can go really if you need to talk to someone.” [MB25, F, 41, 14, 10]

“Apart from my addiction, [Key worker] has been there and even though I’ve had other relationships in my life, I’ve moved, I’ve done things - he’s been a constant in my life for the last ten years. I can tell him anything.” [MB29, F, 42, 23, 12]

A number of participants talked about assistance with practical problems:

“He’s tried to help me and he has helped me a lot. Getting housing and that, letters of support and that.” [MB6, M, 32, 16, 14]

“Yes. Well, problems like doctors’ appointments. It can get very hard to get them. [Key worker] will phone around for you. They help with just about anything really if you ask them.” [MB26, M, 45, 27, 10]

“He’s helped me with everything. With my children, with housing, with social security, sickness benefits. At times, I get really bad agoraphobia and that’s when things go wrong. [Key worker] is good at helping sort out my housing benefit.” [MB29, F, 42, 23, 12]

There were those who said they had not, in fact, required any other help from the Service:

“I have not needed help. I can’t wait to get off it. It feels like they are playing God with my life and I don’t like it. The attitude is “f*** them, they are only drug addicts”.” [MB4, M, 51, 36, 11]

Several pointed out that they would rather not have to attend the Service although a couple of them made contradictory statements:

“I’m sorry, but I’ve got no choice. I’d rather not have to come. I’m glad, I come sometimes. I build stuff up and some days I’ll be more happy and everything and some days, like today, I feel shit.” [MB14, M, 32, 18, 5]

3.7 Help wanted from Service but not received

While some said they had got all the help they needed or wanted, there was a range of complaints from others.

Several were unhappy about the lack of access they had to Drug Service staff:

“I find the service does not provide an adequate in, off-the-street service. If you’ve got an immediate problem there is no provision for helping you here. There’s no one on standby, no nurse, no one who can write a script on standby.” [MB3, M, 50, 33, 30]

“When I first started here… they had loads of time and you could go in and see them whenever you wanted and if you had a problem you could talk to someone. If I phone up now they are always busy or in a meeting. I leave messages and they never seem to get passed on. I don’t blame them for it, I can understand how busy they are and how many people they have to see.” [MB15, M, 46, 30, 15]

Three participants reiterated previous complaints about their prescription dose or type. Other kinds of help not received included: a lack of support or understanding from a key worker or doctor; more help with after-care; the service not being orientated towards self-help.

4. Discussion

The prescribing of injectable opiates is a controversial treatment option. While the debate concerning the rights and wrongs of IOT continues (36,5,11), it is surprising that such scant research interest has been paid to the experiences and views of those on the receiving end of this intervention. The aim of the current study was to explore IOT from the recipient’s perspective. The results show that those receiving IOT in the Morecambe Bay NHS Primary Care Trust area between July 2002 and May 2003 area were not a homogeneous group of people. There was a wide range of attitudes to, and perceptions of, IOT.

Reasons for being put on IOT were not always clear in individual cases but harm minimisation played a large part in the decision. The majority had initially been prescribed oral methadone but for a variety of reasons they said they could not give up injecting. Attitudes to receiving IOT were overwhelmingly positive with many personal and social benefits noted including: a reduction or cessation of heroin and other illicit drug use; a range of health gains; leading a more “normal” lifestyle; and not having to commit crimes. The vast majority had no hesitation in saying that, looking back, it had been the best form of treatment for them at the time.

Attitudes to coming off injectables were varied. Some were actively reducing their doses with the aim of abstinence. The largest group said they planned to stop but timescales were usually vague. Others stated they had no intention of coming off unless forced by service providers or other circumstances and a small minority said they would choose to stay on injectables indefinitely.

Many said that they had received help in addition to their prescription. The value placed on this help ranged from those who saw it as being “nice to talk” to those who perceived it as having been crucial to their survival. Several said they had neither wanted nor needed help other than their prescription. A few insisted that they would rather not have to come to the service.

The results of the study show that there were clearly distinguishable extremes of opinions and attitudes to
IOT with a range of views between these positions. At one extreme, were those who perceived themselves as having significant psychological and social problems in addition to requiring an injectable opiate prescription. They felt that they had needed, and continued to need, a great deal of support and help from the service. IOT was viewed as treatment. Both the prescription and the input from service staff were of central importance. IOT, they said, had literally saved their lives. They wanted to come off injectables at some stage in the future but were fearful about making this change.

At the other extreme were individuals who did not perceive themselves as having problems other than needing access to free, pharmaceutically safe, injectable, opiates. The main benefit of IOT was not having to commit crimes in order to purchase street heroin. Their main complaint concerned the restrictions that collecting their prescriptions placed on their personal freedom. They did not see themselves as needing or wanting help other than their opiate prescription. They did not perceive IOT as being “treatment”. They would rather not have had to come to the service and only came in order to get an opiate prescription. They would choose to stay on injectable opiates for the rest of their lives.

In spite of the differences in research approach, some results from the current study were similar to those found by Sell and Zador (27). Participants in both studies reported problems with previous oral methadone treatment in terms of it making them vomit, disliking the effect and the continuing desire to inject. In each study the benefits of IOT included: keeping out of trouble with the police; helping with family relationships; having a drug supply of known dose and purity; improvements to health. Participants tended to perceive IOT as a long-term intervention. Coming off injectables was often viewed as something to be done in the indeterminate future and some wanted to stay on them indefinitely.

In the current study many had been receiving IOT for a long period of time. Some of those interviewed said they had never made a serious voluntary attempt to come off IOT. It could be argued that these findings lend support to the view that the provision of IOT makes injecting practices even more entrenched. Equally it could be argued that, without IOT, this group would have carried on injecting with all the attendant risks of illicit drug use. While the exact personal and social cost in terms of criminal activity, incarceration, family break-up, health problems and even deaths that may have ensued had they been refused injectables cannot be known, respondents themselves felt that the costs would have been high.

Retention in treatment is seen as key to achieving more positive treatment outcomes (18) and it is acknowledged that IOT is a long-term intervention requiring long-term commitment from services (24). It was clear that many valued the stability that IOT had brought to their lives and the reluctance to give up injecting may reflect the fear of jeopardising that situation (25). However, the challenge is how to maintain the stability gained through treatment retention without allowing it to drift into inertia (25). This study indicates that ongoing IOT with its multiple components did not result in inertia in this challenging group but allowed some to make positive progress. As Strang (29) pointed out the ambivalent drug user’s motivations may alter over time and services need to work to exploit the resolve to change by providing the most appropriate intervention at any given time.

The findings from this study cannot provide answers to questions concerning the optimum service delivery of IOT. However, many respondents valued the relationships they had developed with staff and clearly valued the “support” they had received in addition to their injectable opiate prescription. The NTA (18) has acknowledged the importance of empathy and support in establishing better rapport with service users. Involving service users is crucial to providing relevant, successful interventions.

This study of one treatment service highlights the fact that those receiving IOT were not a homogeneous group but comprised individuals with differing needs and goals. Services must be adequately resourced, skilled and responsive in order to work with people who have different motivations and a varied readiness to act. How services work with those who do not view IOT as a treatment or are even openly antagonistic towards the idea of treatment, poses a difficult question that is beyond the scope of this paper to address.

This study was based on all recipients of IOT within one UK NHS Primary Health Care Trust. Clearly, the characteristics of the subjects and of the drug services within that Trust may differ from those in other parts of the country so the findings cannot be generalised to all those receiving IOT in the United Kingdom. Also, the majority of subjects were prescribed injectable methadone and only a few prescribed injectable diamorphine. This study cannot therefore comment authoritatively on current debate in UK and Europe about heroin prescribing. However, a major strength of this study is that it allowed IOT recipients to talk about issues that were relevant to them in their own way. Much of the debate concerning IOT has been led by service providers and academics. Although IOT recipient needs are mentioned, their actual views are rarely documented. The findings from this study add a new dimension to the IOT debate.

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Substitution Therapy. A New Problem of Biomedical Ethics and Medical Law

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Summary

Substitution maintenance therapy can be judged from different perspectives focused on its medical, legal, social, economic and ethical aspects. A subject that attracts special attention is the ethical side of substitution therapy. In the opinion of the opponents of substitution maintenance therapy, there are several key ethical problems that make this therapy immoral. From our point of view, it is unethical to refuse a patient this kind of help (substitution therapy). Substitution therapy for opioid dependence should be seen as the most ethical and humane of all methods. The absence of substitution therapy in the Russian Federation puts Russian patients in an awkward position.

Key Words: Substitution Therapy; biomedical ethics; medical law.

Every year a wide range of new medical problems become the object of ethical evaluation. The reasons for this are: the invention of fundamentally new research methods, therapies and technologies, as well as ongoing changes in social morality. Still, the problems of transplantology, genetics, reproduction, cloning and manipulation with stem cells, moral problems connected with “The End of Life” (old people’s homes and death by lethal injection), abortion, ethical aspects of psychiatry and of providing help to people living with HIV/AIDS remain pressing questions for biomedical ethics [7, 26].

In the context of biomedical and legal problems within the field of psychiatry, the main topics are: confidentiality, the stigmatization and decriminalization of patients, and the provision of patients’ rights. Narcology, which has come close to being an essential part of psychiatry, has never – unlike psychiatry – been given serious consideration from the viewpoint of biomedical ethics, up to and including the present time. This may be because it has been linked with the status of people having problems with alcohol and drugs, who were not treated as real patients. For example, for many experts a drug-addicted person was not on the same level as a person with schizophrenia. As a result, critical ethical and legal problems of narcology in the context of biomedical ethics were avoided and were not taken into account. (This is especially true of Russian narcology.) There were attempts to ignore operating standards in the ethics of psychiatry and lawful criteria in the sphere of narcology.

As a result, in Russian narcology there were (and continue to be) repressive non-medical strategies practised in the sphere of providing help to patients, which are hard to compare with anything that can be found in psychiatric strategies. The most striking example of that is the mandatory therapy for drug- and alcohol-addicted people in the conditions applied in administering treatment in labour camps; this has been practised for years and still receives wide support. In fact, patients were sent there not to receive treatment, but “for correction and for deliverance from a bad habit, and from a parasitic and immoral way of life”. Officials responsible for Russian narcology, as well as narcology experts, put forward the idea that “drug-addicted people should not receive relief from the withdrawal syndrome, because that might decrease their social dangerousness”. In this way the tactic of “torture for edification” was confessed. It was suggested that drug addiction should be viewed as a mental disorder of psychotic type, which would make it possible to hospitalize
a narco logical patient against his/her own will, according to the 29th article of the Law of the Russian Federation “About Psychiatric Help...” [29].

Being under the pressure of society and remedial organizations that cancelled the practice of mandatory treatment more than ten years ago, the area covered by ethical problems in the field of modern Russian narcology has been greatly enlarged after the problem of opioid addiction appeared. There are several critical problems involving biomedical ethics and medical law in this sphere now:

1) The problem of implementing the principle of “informed consent”;
2) The existence of the principle of “straight away refusal of psychoactive substance (PAS) usage” as the condition for giving a patient the right to enter treatment and rehabilitation programmes (as well as the problem of providing ARV treatment to HIV IDUs);
3) The existence of the principle of “paying for anonymity” in administering therapy for narcomedical diseases;
4) The problems that arise from using scientifically unjustified methods (for example, stereotoxic operations on a brain [33], “birch therapy” [31], methods based on forming a mythological mode of thinking and instilling irrational fear (for example, with the help of what is known as ‘coding’);
5) Neomoralistic approaches;
6) Bans on the use of substitution maintenance therapy [13, 22]. This is last of the problems we have listed here, but it is actually present in all of them, so it is worth making the effort to analyse all these ethical problems in Russian narcology.

The problem of the principle of “informed consent” is that a patient who continues to be addicted to alcohol or drugs during treatment does not get all the information that he/she urgently needs to be able to take deliberate decisions about the choice of the therapy, or can only get this information in a strained way. First of all, this relates to the practice of “coding”, when ‘informed consent’ is based on providing a patient with false information about the essential mechanisms that come into play in applying this method. A patient is told that “a substance that blocks opioid receptors will be given”, or “the activity of the brain will be changed, and that will lead to a lowering of the craving for a substance”, or that “a coding of a dosage” will be performed, or “a subconscious form of an illness will be demolished”. In cases like these, ‘informed consent’ is implemented when a patient signs a document where it is stated that the person who is signing agrees that in the case of a voluntary breach of a treatment regimen, when a dose of alcohol (or a drug) is taken, the person’s health could be damaged, or a lethal outcome might be caused. Scientists ground this method on its psychotherapeutic effect – the new attitudes a patient forms because of his/her fear of taking a psychoactive substance. In reality, that patient’s health is in no danger, while the practical result is that an expert knowingly misleads a patient. According to ethical principles, and because of its unscientific character, this method is prohibited by the World Narcological Community [18].

One of the basic principles regulating Russian narcology is the principle of “straight away refusal of psychoactive substance (PAS) usage”. As a matter of fact, a person’s wish to fulfill this condition determines the amount of help that a person can get from official medicine, and is a crucial factor in deciding whether a patient will be able to get into a hospital or be included in rehabilitation programmes. This condition is an independent refusal by the patient, before treatment is prescribed, to take psychoactive substances. However, the ethical question arises of whether a person can be expected to get rid of a pathological craving for psychoactive substances before treatment starts. It can be supposed that the existence of such a condition is based on the position of narcology experts who see a PAS-craving symptom as a “bad habit” or “moral defect”, which could be got rid of by simply by making an effort of the will. Could this, perhaps, turn out to be a way that is used by these doctors to exclude “unpromising patients” from the therapy if they have no motivation or only a weak motivation for entering treatment? A paradox arises here: if someone could independently get rid of a pathological craving for psychoactive substances, what role could a doctor play?

No other medical profession makes such severe demands on its patients. For example, if the demand was made on a person with schizophrenia to get rid of a state of delirium “through his/her own will-power” before hospitalization, that would be considered a bad joke, at best.

Russian narcology demands a patient’s “straight away refusal of psychoactive substance (PAS) usage” without taking into account the existence of another principle – the step-by-step lowering of the dose and graduated admission to a remission schedule. This conspicuous lack of understanding may have as its most immediate effect a patient’s refusal to admit traditional narcological help or his/her independent decision to regulate these questions by gradually reducing the dose of a drug or looking for a drug substitute. In the case of opioid addiction, the role of a substitute is very often played by alcohol or illegal “street” drugs, which are less addictive. It can be said that the principle of “straight away refusal of psychoactive substance (PAS) usage” contradicts ethical rules, which require a doctor “to help all patients without making any distinctions between them”.

HIV-positive active IDUs face the same problem. These people are not allowed ARV therapy because they break hospital rules (by continuing to take PAS). This leads to the outcome that the number of patients who are able to get ARV therapy on the basis of the principle of refusal is very low. In addition, this practice lowers...
patients’ compliance with HIV therapy and boosts the spread of the HIV epidemic.

Another ethical problem that arises in Russian narcology is the problem of “paying for anonymity”. According to the existing rules, a person addicted to alcohol or drugs who would like to receive treatment anonymously, without any narcological registration, has to pay for the therapy. The same therapy could, after all, be provided to that person for free in the case of a refusal of anonymity. So, the question of biomedical ethics is how the anonymity of therapy can be correlated with payment for that therapy.

Undoubtedly, beyond the limits of bioethical norms and medical rights, it must be recognized that, currently, narcological treatment sometimes takes the form of inflicting physical pain (activating a pain syndrome) on a patient. In any case, the “birching therapy” proposed by scientists from Novosibirsk working at the Research Institute of Hygiene and the Research Institute for Therapy (Russian Academy of Medical Science) is based on these principles. It includes “series of birchings on the buttocks, from 5 to 60 birchings during one treatment session” [31]. The authors of the method say that “this progressive method” leads to the “activation of endorphin receptors as the result of the sensation of pain and leads to a rise in the production of endorphins after the birching”.

One of the most critical and controversial ethical problems is the issue of the ban on substitution maintenance therapy in the Federation. Substitution therapy consists of the prescription to patients with opioid dependence of fixed doses of medications that are opioid agonists (analogues of drugs from the same pharmacological group). These prescriptions should be made out in the hospital under medical control and should be based on a patient’s mental condition. The goals of such a treatment are: normalization of the mental (narcological) condition of a patient; the blocking of a pathological craving for drugs, on the basis of aetiology and pathogenetics; lowering the likelihood of overdosing and lethal outcome; reducing the chances of taking illegal ‘street drugs’ or absolutely stopping the taking of illegal drugs; lowering the criminal activity of a patient, connected with his/her need to get money to buy drugs; preventing the spread of HIV by increasing compliance with therapy [17, 19-21].

The factors that regulate the choice of patients who can join substitution therapy programmes are: repeated lack of success in applying opioid treatment, concomitant pathology (first of all, HIV-infection), age over 18-21, having previously participated in substitution programmes (including substitution therapy) take up “a more respectful attitude to drug users than that adopted by any other medical approach”.

It should be mentioned that many arguments against substitution therapy are based on an incorrect idea about the method’s essence. Thus, the treatment of drug addiction with a view to making a person completely stop taking drugs, while his/her health undergoes a definitive improvement, is not the main aim of substitution therapy. People who support substitution therapy see the idea of a complete refusal to take PAS, for most patients with opioid addiction, as being impossible to achieve (as has been proved by many studies, and in line with common sense). Opioid addiction is proclaimed to be a chronic disease, so the goal is to help patients stop taking all PAS, or at least, to reduce the frequency and the amount of taking PAS, or to refuse the intravenous usage of PAS. So, there is an attempt to attain two goals – a minimum one and a maximum one. If the latter goal is impossible to achieve, then an attempt can still be made to achieve the former. Therefore, the argument that describes the
substitution therapy usage as unethical (entailing a refusal to allow drug addiction treatment, on the grounds that the disease will continue) is unfounded, because substitution therapy does not imply a total or definitive refusal of any other form of drug. It can be related to the group of palliative therapies. In some cases, what a patient is offered is a way forward to a step-by-step (rather than an immediate) refusal of opioids; that means providing ‘treatment’ in the authentic sense of the term. From our point of view, it is unethical to refuse a patient this kind of help (substitution therapy). According to one definition [7], a common demand made by biomedical ethics is that all patients should be helped without making any differences between them; the principle of imposing a refusal of PAS usage, as required in Russian Narcology, is, in fact, almost impossible to apply, because the nature of the illness itself is incompatible with that principle. A patient who is given no chance to enter a substitution therapy programme, because doctors cannot provide it, is, in practice, deprived of the opportunity to receive any kind of treatment (apart from a regime prescribed to block the withdrawal syndrome, so as to improve the “quality of life”). It seems paradoxical that opponents of the substitution therapy say that it is unethical because “patients who enter substitution therapy programmes continue, in fact, to have dependence problems; and the doctor who treats them does not give them any other treatment, which he could give when he treats drug addiction”. To agree with such a position means to blame all palliative therapy and to say that it should be evaluated from the ethical point of view. (It might be better to say “unethical”!).

It is also a doubtful argument to say that substitution therapy is unethical only because it is incorrect “to offer a person a drug that is new to him/her, which might induce that person to refuse other drugs and so become less dangerous to society”. The substitution of a drug whose use belonged to a criminal setting with a legal medicine (even if this medicine contains a PAS), is only one of the many goals of the therapy. There are also humane goals, such as those of improving a patient’s “quality of life”, and reducing the risk of overdosing, suicidal behaviour and lethal outcomes; these are, in fact, the most important points, and they should be taken into account by a doctor who prescribes a substitution therapy. These goals cannot be judged as immoral from the viewpoint of biomedical ethics.

It would be astonishing to conclude that the substitution therapy approach is unethical, because of the adoption of “a more respectful attitude to drug users than that adopted by any other medical approach”. A major question arises here: who could possibly consider a surplus of medical humanism (if that is possible in general) to be immoral? Moreover, it is not at all clear, either, why doctors applying other methodologies do not respect their patients so much (I am referring to the view taken by opponents of substitution therapy). Could it be that the problem lies not only in the attitude to patients who have narcological (dependence) problems, which could be considered to be the standard (if one listens to these opponents), but also in traditional attitudes to patients in all the various spheres of medicine?

It is known that more than one million patients currently participate in substitution maintenance therapy programmes in all parts of the world. The number of such patients has grown from 73,400 in 1993 to 450,000 in 2004 in the European Union [8, 9, 25, 27, 30]. So, over a period of 11 years, access to the programmes has grown more than 6 times. The models available for substitution maintenance therapy evolve in the course of time. One of the reasons for the spread of buprenorphine programmes in world narcology is not disappointment over methadone projects, but an attempt to escape the need to ‘bind’ a patient to the hospital, and to make everyday visits to a doctor unnecessary [14]. Another modern trend is that of widening a circle of specialists who are able to prescribe medicines for substitution maintenance therapy. This trend means attracting the doctors of general practice to this problem.

The countries that have been actively introducing these methods in the last few years are China and Iran. The growth in the numbers of patients receiving substitution maintenance therapy ranges between 500% and 1000%, according to the official data of the Health Departments of these countries, who initiated their programmes in 2003. According to the same data it is predicted that the increase in numbers of patients by 2008 will be 350,000 in China and 150,000 in Iran [1].

In most countries located within the former Soviet Union (Lithuania, Latvia, Estonia, Ukraine, Kyrgyzstan, Moldova and Azerbaijan) the number of patients who get an opportunity to receive substitution maintenance therapy is growing. In other countries within the former Soviet Union (Belarus, Georgia, Armenia, Uzbekistan), there is a legal basis for the implementation of such programmes. Pilot projects are now under way in these countries to determine the place and role of substitution maintenance therapy in the narcological treatment system.

Because of the alarming trend for HIV/AIDS to spread, WHO, together with UNODC and UNAIDS, has formulated the official report after a series of researches and analyses on the effectiveness of substitution therapy based on randomized experiments in 2003. In this report substitution maintenance therapy is called one of the most effective ways of treating drug dependence and preventing HIV/AIDS. Methadone and buprenorphine were included in the WHO’s “List of Basic Medicines”, which includes “medicines that are needed to provide minimal health care standards in all the countries...” and that should be made “available every time, in adequate amounts and at an adequate price, which society itself can support” in 2005.

As is known, substitution therapy is prohibited in the Russian Federation (“it is prohibited to treat drug dependence with PASs included in list II”) and, for that
reason, it is not applied. By contrast, in most countries of the former Soviet Union there is a legislative basis that gives the opportunity to use substitution therapy. These laws appeared after the fall of the Soviet Union, in response to the need to overcome high levels of drug addiction, the low effectiveness of traditional treatment methods, and the widespread presence of HIV/AIDS among IDU’s.

Substitution maintenance therapy programmes are included in the system of narcological help provided to people with opioid dependence as an additional measure. These programmes did not lead to the closing of any other programmes in any of these countries. Still, discussions continue on the topics: ‘How often should they be used?’; ‘For how long can a patient participate in these programmes?’; ‘What doses should be made available?’. Discussions about the ethical side of substitution therapy ended long ago.

The absence of substitution therapy in the Russian Federation puts Russian patients in an awkward position. They cannot receive all the help they would receive if they were in any other country. It should be also considered unethical that the dominant rule of the “straight away refusal of psychoactive substance (PAS) usage” discriminates 70% of patients who cannot receive any form of professional, scientifically based help (such as substitution therapy).

Substitution therapy for opioid dependence should be seen as the most ethical and humane of all methods. The current ban on this kind of therapy should be seen as a violation of the norms of biomedical ethics and medical law.

Therefore, in evaluating the substitution supporting therapy as a question intrinsic to narcology while respecting the rules and basic principles of biomedical ethics: independence, justice, the principle “do not hurt”, it can be concluded that, from the viewpoint of biomedical ethics, the analysis and evaluation of real narcological theory and practice should not be avoided. In this connection, it should be noted that, while narcology is part of psychiatry, it does, in fact, promote other principles and ethical rules that are based on ambivalent attitudes to a narcological patient (i.e., one with alcohol or drug dependence). And this attitude differs from the attitude taken towards a patient with schizophrenia, neurosis, or mental backwardness. All the points mentioned here make it clear how important it is to activate the discussion in the medical sphere and so get to the point of working out new norms of biomedical ethics and medical law in response to the peculiarities of the current situation in narcology.

The existence of “special ethical conditions” in Russian narcology and the existence of special attitudes to drug-addicted people can be explained because of the appearance of the “neomoralistic” approach (to quote a term proposed by Meilachs [16]) that is specific to the "post-perestroika" period in the Russian Federation. Many authors characterize the situation in the sphere of attitudes to drug-users (including patients) as a state of moral panic that has led to the appearance of neomoralism. As P. Meilachs says, the central moral dividing line in neomoralism was the dividing line that regulated relations in the public sphere. So this dividing line determines “what is permitted in a public sphere and what is not. The main strategy of neomoralists is to protect this public sphere”.

In conclusion, it can be said that the special attitude of the medical community to the problems of narcology (especially drug addiction) is caused by the official strategy of enforcing what are thought to be 'civilized standards’, while suppressing the strategy of biomedical ethics based on concepts of humanism, justice and the welfare of patients. This should become a subject of discussion and analysis among medical professionals.

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New Approaches in the Treatment of Opioid Dependency During the Pregnancy.

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Although methadone maintenance therapy has been used in pregnant women for over 40 years, no randomized trials comparing dosing regimens have been published on which to base specific therapeutic recommendations. It has been recommended that dosages should be individually determined which will keep the woman and fetus subjectively comfortable and clinically stable. Although the health and comfort of the pregnant opioid dependent woman remain paramount considerations, higher dosages of methadone (60-150 mg/day) early in pregnancy have been reported to be associated with more normal fetal growth. Data on the relationship between maternal methadone doses, especially late in pregnancy, and subsequent severity of neonatal abstinence have been variable causing considerable confusion for clinicians involved in treating these women. The development of neonatal abstinence has precipitated much controversy and emotional reactions by parents and medical staff. Studies have shown the variability of methadone pharmacokinetics in pregnant women in comparison to non-pregnant individuals. Plasma methadone levels during pregnancy show marked intra-patient and inter-patient variability and usually

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are somewhat lower than those prior to pregnancy. This decrease can be explained by an increased fluid space, a large tissue reservoir, and altered drug metabolism by the placenta and fetus. These data suggest that pregnant women may need increasing methadone doses during gestation and that lowering the dosage in an attempt to minimize neonatal abstinence would be medically inappropriate. During labor, the patient can be managed like any other parturient and conduction anesthesia should commence as early as possible.

In summary, perinatal opioid dependence is a problem of major public health importance for women and children throughout the world. Societal moral attitudes which have stigmatized and dehumanized women who use drugs during pregnancy have placed barriers in the way of obtaining optimal medical and obstetric care. These considerations apply to women of all races and socioeconomic status. The best public health result can be obtained once these barriers have been removed and women are provided appropriate services in a supportive, multidimensional treatment facility with the addition of well managed pharmacotherapy.

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2. Buprenorphone in the Treatment of Opioid Dependent Pregnant Women

Bernadette Winklbaur and Gabriele Fischer

Continuous abuse of illicit opioids during pregnancy is associated with adverse consequences for mother, fetus and neonate [1]. The main risk factor originates in the fluctuation of opioid concentration in the maternal blood, which may lead to withdrawal symptoms in the neonate as well as to symptoms of overdose. In addition, heroin use in pregnancy is often related to difficult psychosocial environmental conditions, malnutrition of the pregnant women and subsequently poor outcome in newborns.

Methadone maintenance of pregnant opioid dependent women has been found to reduce complications of pregnancy and childbirth, and leads to improved neonatal outcome [2]. However, methadone maintenance during the course of pregnancy is associated with potential side effects. Based on recent findings its administration appears to alter fetal activity and heart rate [3,4]. Moreover, neonatal abstinence syndrome (NAS) frequently occurs following methadone exposure.

With the increased propagation of buprenorphone treatment in opioid dependent patients, supportive data for this agent has been published consecutively. However, most trials on maintenance treatment of opioid dependence exclude pregnant women by definition, since these patients require specialized treatment programs in order to minimize potential harm to the fetus. Although data from more than 500 neonates prenatally exposed to buprenorphone have been published with no related physical teratogenic effects and a low rate of prematurity [5], it has to be emphasized that these findings are limited due to several possible confounding factors: in many cases results are based on retrospective data, the use of concomitant consumption of other substances is rarely reported in detail, no appropriate control groups or different NAS scoring systems used. Until today the majority of information has been gained through French publications, where buprenorphone has been available for more than 10 years. As a result of their office-based prescription policy, many pregnant patients in France have been treated with buprenorphone. These mainly naturalistic data indicate the safe use of buprenorphone in pregnant opioid dependent women [6,7,8,9]. However, to date limited data from prospective open-label controlled studies of neonates born to buprenorphone-treated mothers are available.

The first open-label, flexible-dosing, study on buprenorphone during pregnancy was carried out by Fischer et al. [10]. Overall 15 opioid-dependent pregnant women have been included; based on their findings buprenorphone was well tolerated during induction and mean birth outcome measures were within normal range. In eight of the neonates no NAS was observed, while mild NAS occurred in four and moderate symptoms, requiring treatment, in three cases. The mean duration of NAS
treatment was 1.1 days. A case report by Schindler et al. analyzed 2 buprenorphine-maintained pregnant women in a prospective manner and found both newborns to be healthy, not requiring NAS treatment [12].

Until now, there have been only two prospective double-blind, double-dummy randomized controlled trials comparing buprenorphine with methadone in pregnancy. Both studies, one from Europe and one from the US, used similar methodology to show the safety and comparability of both substances. The study by Jones et al. investigated 18 pregnant opioid dependent women [12]. Based on their results buprenorphine was at least comparable to methadone in regard to maternal and neonatal outcome measures with some items in favour of buprenorphine: The total amount of opioid agonist medication for the treatment of NAS in methadone-exposed neonates was three times greater than for those prenatally exposed to buprenorphine. In addition, a significantly shorter hospital stay was found in the buprenorphine exposed group. In terms of peak NAS total scores or neonatal birth weight, no significant differences between the groups have been revealed. In order to minimize possible confounding effects of concomitant drug use, patients received voucher payments (“contingency management”) in return for negative urine samples and negative ethanol-breath samples. As a consequence, both groups had low rates of illicit drug consumption prior to delivery.

Fischer et al. included 18 opioid dependent pregnant women into a clinical trial, using as well a double-blind double-dummy design [13]. The mean methadone dose was 47.5 mg, and 13.5 mg per day for buprenorphine, whereas doses where slightly increased during the last trimester (+5 mg for methadone, +0.5 mg for buprenorphine). In regard to neonatal outcome no significant differences between both groups were found. Overall 43% of the neonates did not require NAS treatment. NAS occurred 12 hours later (mean) in the buprenorphine group, while the mean duration of NAS treatment was 4.8 days for those babies born to buprenorphine maintained mothers and 5.3 days in the methadone group. No difference has been observed with respect to the dose of medication needed to manage NAS. As eight women of the buprenorphine versus six of the methadone group completed the study, the retention rate was somewhat higher in the buprenorphine group. Methadone, however, was significantly more effective in preventing concomitant opiate consumption, while both groups showed low concomitant consumption of cocaine and benzodiazepines.

Based on preliminary data, it appears that buprenorphine induces a milder withdrawal syndrome in newborns, compared to methadone [14]. The onset of NAS is usually observed within the first 12 to 72 hours after delivery reaching its maximum within approximately 66 to 96 hours, lasting approximately 120 to 168 hours, although considerable individual variability occurs. To date, only one paper reports a correlation between buprenorphine dose and the severity of NAS [15]. This finding, however, was based on the maximum Lipsitz score, while most publications on NAS refer to the Finnegan score [16]. More recent reports [6,12,13] did not find a correlation. Further investigations are needed in that regard.

A recent comparative, multicenter clinical trial on the comparison of high-dose buprenorphine versus methadone maintenance in 259 pregnant women reported no major difference in perinatal prognosis. Base on their results a higher level of prematurity in the methadone group was found, which could also be explained by other confounding factors. In addition the mean onset of NAS for the methadone group was 81 h versus 66 h for the buprenorphine group [6].

Another recent prospective study by Ebner et al. [17] aimed at the comparison of three neonatal groups being prenatally exposed to either methadone, buprenorphine or slow-release morphine with no concomitant consumption: Overall sixty percent of newborns required treatment for NAS: 68% in the methadone-exposed group, 82% in the morphine-exposed group and 21% in the buprenorphine-exposed group. As a result, a significantly lower incidence of NAS appearance was observed in the buprenorphine group compared to the other groups.

However, large randomized clinical trials in pregnant opioid dependent women are indispensable in order to document safety and efficacy, as currently both medications, methadone and buprenorphine, are classified as FDA pregnancy category C medications [5].

As a consequence, a new multi-site study has been designed. This large randomized double-blind, double-dummy study comparing the efficacy of buprenorphine to methadone treatment is still going on, whereas first results are currently published [18]. The Maternal Opioid Treatment: Human Experimental Research (MOTHER) project is an eight-site randomized, double-blind, double-dummy, flexible dosing and parallel group clinical trial hypothesizing that buprenorphine may lead to superior neonatal outcome. This study will also address research questions in regard to the influence of pregnancy on pharmacokinetics and pharmacodynamics of both, buprenorphine and methadone.

Conclusion

Over the past years an increasing number of results in favour of buprenorphine have been published emphasizing that NAS after intrauterine buprenorphine exposure might be less severe than that of methadone exposed newborns. However, further research is required to support these early findings which are limited to some extent due to several methodological flaws. Future investigations have to consider concomitant consumption, as, for example, nicotine dependence in opioid dependent pregnant women seems to be connected with smaller babies for gestational age-factors, compared to opioid dependence alone. Furthermore, concomitant consumption of illicit substances
influences neonatal outcome and may be reduced by contingency management. In general, monetary vouchers given to patients as reward for opioid- and cocaine-negative urines have been found to be successful. Pregnancy provides a perfect model for the use of this behavioural intervention as contingency management is provided for a limited time-course throughout pregnancy in a highly motivated group [19].

However, a novelty in the field of pharmacological studies in opioid dependent pregnant women is the multi-site, MOTHER trial, which might serve as a role model for future medication trials in this field of research.

References

3. Comprehensive Treatment for the Pregnant Opioid Dependent Women: Traditional Approaches and the New

May Olofsson

Children born of mothers using alcohol or drugs in pregnancy are at high risk of developmental disturbances, neglect and abuse. These infants are at risk of birth defects, premature deliveries, low birth weight, perinatal death, asphyxia, brain damage, neonatal withdrawal symptoms (NAS), fetal alcohol syndrome (FAS) and other neonatal morbidity. Furthermore, these children are often growing up under bad circumstances with deprivation, neglect and abuse, which may enhance the consequences of the congenital damages in the development of these children. The children are normal from the very beginning of foetal life and have the potential for normal development if they are not exposed to drugs and other detrimental risk factors during foetal life. On that background, all the above mentioned complications for the children can be prevented if their mothers are provided with counselling, comprehensive treatment and support during pregnancy, delivery and the first years of the infants’ life. Experience from USA and Denmark has shown that all the above mentioned complications for the children can be prevented by multidisciplinary, comprehensive prenatal and postnatal care. The risk for the children is a combination of their mother’s health, her life situation and her lifestyle, including her consumption of alcohol, tobacco and drugs (Table 1).

Family Center at the University Hospitals of Copenhagen, Hvidovre Hospital and Rigshospitalet, is a specialized multidisciplinary department for alcohol and drug using pregnant women and their children up to the age of 6 years. The program was inspired by Family Center at Thomas Jefferson University Hospital in Philadelphia, USA, and by Dr. Loretta Finnegan’s research and treatment methods. Family Center in Copenhagen offers comprehensive prenatal care, counselling, outpatient and inpatient treatment, opioid agonist therapy with methadone, psychosocial support, outreach, induced abortion and contraception (Table 2). After delivery, the infants are examined and treated in the neonatal department if they are suffering from neonatal abstinence syndrome (NAS) or other neonatal morbidity. Family Center is using Loretta Finnegan’s method for the treatment of NAS. The mothers are inpatients as long as their infants need special care and the early attachment between mother and infant is supported. Table 3 lists the disturbances of early mother-infant attachment. From the beginning of pregnancy, Family Center collaborates with the Social Authorities and other professionals in the community so that the infants are provided with all the care, treatment and support that they need during the first years of life. After discharge from the hospital, the children are followed in Family Center including health care and developmental assessment in continued collaboration.
with the Social Authorities. Some of the infants are discharged to their own home with their mother, some to a foster family with or without their mother, and some of the infants are discharged to a residential placement with or without their mother.

During the years 2003 – 2006, 288 pregnant women were referred to Family Center (Table 4). 115 were
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dependent on opioids. 110 of these women were treated with methadone during pregnancy (Table 5). Table 6 shows the neonatal data and Table 7 shows the discharge status of the infants.

Family Center has reduced the number of children suffering from congenital damages, low birth weight, premature delivery, perinatal asphyxia, NAS and other neonatal morbidity. Most of the children are growing up under stable home environments and are seen by pediatricians and child psychologists in Family Center. The number of children suffering from developmental disturbances, neglect and abuse are reduced compared with the children born of drug dependent mothers in Copenhagen before Family Center was established (Tables 8).

As a result of the good outcomes of mothers and babies...

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<tr>
<th>Table 5. The Opioid Dependent Pregnant Women (N=115)</th>
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<tr>
<td>Methadone Treatment</td>
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<td>Buprenorphine Treatment</td>
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<td>Without Medical Substitution</td>
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<tr>
<td>Detoxified to 0</td>
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<td>Detoxified to a lower dose</td>
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<td>Maintained on the same dose</td>
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<th>Table 6. Neonatal Data 2003 – 2006 Pregnant Opioid Dependent Women (N=115)</th>
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<td>Birth weight</td>
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<td>Birth length</td>
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<td>Head Circumference</td>
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<td>Gestational Age</td>
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<tr>
<td>Premature (≤37 weeks)</td>
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<tr>
<td>Low Birth weight (≤2500 grams)</td>
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<td>NAS</td>
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<th>Table 7. Discharge Status of the Infants (N=114)</th>
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<td>Home with the mother</td>
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<td>Residential care with the mother</td>
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<tr>
<td>Residential care without mother</td>
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<td>Foster family with the mother</td>
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<td>Foster family without the mother</td>
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<th>Table 8. Follow-up Study of 89 Children Born to Drug Dependent Mothers in Copenhagen (1970-1978) (Average age at follow-up 4 years (Range 1 – 10 years))</th>
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<tr>
<td>PREMATURE BIRTH</td>
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<td>PERINATAL ASPHYXIA</td>
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<td>NEONATAL WITHDRAWAL SYMPTOMS</td>
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<td>IMPAIRED PSYCHOMOTOR DEVELOPMENT</td>
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<td>BEHAVIOURAL AND EMOTIONAL DISTURBANCES</td>
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<td>NORMAL DEVELOPMENT</td>
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<th>Table 9. Results of Comprehensive Prenatal Care Program. Family Center of Copenhagen</th>
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<tr>
<td>1. Pregnant women are coming earlier into prenatal care (counselling about abortion, hepatitis, HIV, etc.)</td>
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<td>2. The perinatal health of infants is improved (the number of premature and low birth weight infants and infants with asphyxia are reduced).</td>
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<tr>
<td>4. Reduction in FAS and other ARBD</td>
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<td>5. Reduction in developmental disturbances, neglect and abuse</td>
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<tr>
<td>6. Infants are discharged to stable home environments.</td>
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<td>7. The infants are followed-up by professionals during infancy. Developmental problems, neglect and abuse are prevented.</td>
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<td>8. The mothers receive contraception.</td>
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and the long experience of Family Center of Copenhagen, the Danish Government has decided to establish Family Centers all throughout Denmark during the years 2008-2012. (Table 9)

With the funds granted by the Danish Government, Family Center in Copenhagen has commenced a research program which includes a cross-sectional follow-up study of 196 children who are 12-14 years of age. There will also be an evaluation of the multidisciplinary interventions for the pregnant women and their children who participated in Family Center from 1993 –2004 (1400 pregnant women and 1200 children).

References


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Conflict of Interest

No relevant conflict of interest to report in relation to the present paper.

The Guideline Process and the Norwegian Key Questions

Gabrielle Welle-Strand

Medication Assisted Treatment (MAT) started in Norway in 1991. By the end of 2007 there were 4550 patients in treatment, 39 % with buprenorphine (Subutex(r) or Suboxone(r)) and 61 % with methadone. Approximately one third of the patients were women, mostly in child bearing age. Approximately 160 women have given birth to babies while they were in MAT from 1996 up to now. The last 3 years between 25 and 35 babies have been born every year to women in MAT.

Concerning heroin dependent pregnant women, it is still common to medically withdraw or taper them off the opiates with methadone or even none-opioid medications during pregnancy. Qualified in-patient treatment is available in most regions in Norway, and the whole family can stay there during the entire pregnancy and until the child is 1-2 years old. Norway also has had a law since 1996 making it possible to compulsory treat pregnant drug or alcohol abusing women. Approximately 35-50 women are treated according to this law every year and most of these women are illicit drug users. Pregnancy is not an indication in Norway for starting MAT in heroin dependent women, unlike many other western countries and as stated in the up-coming WHO Guidelines on opioid dependence [4].

The present recommendations for treating pregnant MAT patients in Norway are: Family planning is part of the program and pregnancies are discouraged for unstable patients. When a woman becomes pregnant, thorough information on pregnancy and MAT-issues are given to the woman and her partner. These women and families need long-time multidisciplinary follow-up. No drug use is tolerated for pregnant MAT-patients and couples responsible for children. Alternatives concerning the pregnancy will be discussed, for example the possibility of tapering off the medication and/or getting more extensive treatment, either out-patient or in-patient. The main policy is that methadone or buprenorphine should be continued throughout the pregnancy and the lowest efficient dose of the medication should be administered. Methadone used to be the drug of choice because it is well documented to be safe in pregnancy, but the evidence for the safety of buprenorphine is also good. If tapering off is to be conducted, it should be done gradually between week 14 and 32 of the pregnancy and a possibility of in-patient treatment should be available when needed. If the woman gets very abstinent, the dose of the medication should be stabilized and if necessary, increased. Towards the end of the pregnancy it is recommended to split the dose of the medication.

A counselling and coordinating group is supporting each patient in MAT and when a woman becomes pregnant, the group will be supplemented by professionals responsible for the follow-up of the pregnancy. Prenatal visits are provided either by a midwife or a doctor, both in the municipality and at the hospital where the baby will be born. There will be close cooperation with the obstetric and paediatric ward. Urine tests for all drugs and alcohol will be taken 1-2 times a week and methadone concentrations will be taken once a month. The follow-up is primarily out-patient, but if necessary, in-patient treatment can be provided. After birth, the babies are transferred to a paediatric ward. In Oslo, many families stay at a specialised institution (Aline) for 2-6 weeks after the hospital stay. Aline is for babies and families with special needs and the parents will learn to care for their abstinent baby during their stay and other parenting skills if needed.

We performed a national evaluation of women who had babies in MAT from 1996 to 2003. The evaluation was undertaken in 2004 and we managed to trace almost all women in MAT who had given birth during this period through our network of regional contacts. A standardised questionnaire was made in close cooperation with other specialists in the field covering variables used in the international literature. The weaknesses of this evaluation are: There were relatively few patients interviewed, they came from different parts of the country with different treatment philosophies, many different professionals filled in the questionnaires and it was not possible to get hold of all the information for all the respondents. The evaluation covered 56 babies and 55 pregnancies, as there was one pair of twins. 51 women were involved, three women had two children and one woman had three children during the period. The mean age of the mothers at birth was 31.7 years, ranging form 22 to 40 years of age. 59 % of the respondents had older children, on average 1.8, ranging from 1 to 4 older children. Most of the women did not have custody of these older children. 37.5 % of the partners were in MAT and 77 % of all partners had no current drug abuse problem. 77 % of the women were in MAT prior to this pregnancy, on average 16 months before they conceived, of those 36 received methadone and 8 buprenorphine. 21 % of the women started MAT in the pregnancy, 5 on methadone and 6 on buprenorphine.

The last month before the pregnancy was confirmed, 52 % of the women had all their urine screens negative for all drugs and alcohol, 7 % had one to two positive tests and 18 % had more than three urine screens positive. The average number of cigarettes at this stage was 17.2 a day and there were only two non-smokers. The last month before birth, 75 % of the women had no positive urine screens, 9 % had one-to two and 7 % had more than three positive urine screens. The number of cigarettes smoked daily was reduced to 11.7 and there were still only two
no-smokers. A positive urine screen could be positive only for cannabis, for example. In conclusion, there was very little abuse of drugs during these pregnancies, but there was a lot of nicotine exposure for the foetus.

The average methadone dose was 97.9 mg (range 30 to 160 mg) the last month before the pregnancy was confirmed and the average through serum methadone was 706 nmol/l (range 297 to 1100). The recommended serum level is ranging from 600 to 1200 nmol/l. The last month before birth the average methadone dose was 93.3 mg (range 0 to 240 mg) and the average serum methadone was 505 nmol/l (150 to 1399). This shows that there was a great variability in the dosages at birth, two women tapered down to 0 before birth, while some women increased their dose during pregnancy.

There were 66% boys and 32% of girls in the sample. The average gestational age was 38.1 weeks, ranging from 29 to 42 weeks. 21% of the babies were preterm, meaning babies born before the 37th week of pregnancy. The birth weight for all the babies averaged 2927 g (1460 to 3745), the "methadone babies" weighed 2870 g (1460 to 3700 g) and the "buprenorphine babies" weighed 3126 g (2300 to 3745 g). 12 babies had low birth weight, meaning they weighed less than 2500 grams at birth. 48% of the babies needed medication because of Neonatal Abstinence Syndrome (NAS). 48% of the "methadone babies" needed treatment for an average of 46.2 days and 50% of the "buprenorphine babies" needed treatment for an average of 31 days.

We also investigated the present situation for the families. The children were on average two years of age, ranging from 0.2 to 7.9 years. 38% of the children lived with both their parents, 30% were living with their mother and 18% lived with their father. 23% of the children had been put in foster care. Two children of the same mother had died due to Sudden Infant Death Syndrome. Of the 39 children who lived with one or both their parents, 85% of the mothers had no sign of drug abuse, while 13% of the mothers used some benzodiazepine. Of the 13 children who were placed in foster care, 46% of their biological mothers were using drugs to a varying degree.

The Norwegian Directorate of Health has been commissioned by the Ministry of Health to make National Guidelines and Recommendations for the pregnant women in Medication Assisted Treatment and the follow-up of the children and families until school age. The reason for this is partly because the current recommended policy is not followed nationwide. There are variable treatment practices in different parts of the country concerning dosing policies, tapering-off medication, the degree of in- and outpatient treatment offered, the treatment of NAS and the policies concerning breastfeeding. There is also a lot of political, professional and public interest in this issue and the Norwegian parliament spent an hour discussing tapering-off in pregnancy less than two years ago. There is also a lack of knowledge about pregnancies and MAT amongst professionals from different disciplines and the women and children suffer varying degrees of stigmatization. The aim of the guideline process is to give clear and knowledge based recommendations for the whole period from conception until the child starts school. Our knowledge base is knowledge based on research (evidence), knowledge based on experience (the project group of experts and the reference groups) and the users' knowledge. This knowledge has to be put into a Norwegian context. Most of the research is from US and is not always relevant for Norwegian settings [2, 3].

The Directorate of Health is responsible for the guideline process. A project group of experts was appointed in the autumn of 2007 consisting of two doctors and one psychologist from addiction treatment, one obstetrician, one midwife, one paediatrician, a general practitioner, a social worker, four representatives for the child custody services at different levels, one child psychiatrist, one developmental psychologist and a user's representative. We have asked the Norwegian Knowledge Centre to do a review of the relevant literature. One problem we are encountering is that the search of literature focuses mainly on RCT's and other controlled studies. This has the consequence that studies focusing on the developmental aspects have been left out, an issue we have to address in our ongoing work. We also will have reference groups' meeting twice during the guideline process and we will arrange a separate meeting on the treatment of Neonatal Abstinence Syndrome and also a separate meeting to get the views from many of the users. We aim at a transparent process, where drafts are put out on our web-page, welcoming anybody to comment. When the final draft is ready, we will have a formal consultative round among bodies entitled to comment. The plan is to finish the guideline process by the summer of 2009.

In November 2007 the Directorate arranged an Advisory Conference with International and National Experts. Each of the Norwegian key questions was addressed by an international and a national expert, followed by a discussion in plenary on each topic. The Norwegian key questions addressed at the conference were:

* What should be the aim of Medication Assisted Treatment in pregnancy?
* What should be the policy concerning tapering-off during pregnancy?
* Should methadone or buprenorphine be used during pregnancy?
* How should the recommendations for breast-feeding be?
* How and by which hospitals should NAS be treated?
* What are the long-term results of children born to mothers in MAT?
* How should the follow-up of the children and family be done in a Norwegian setting?

The project group of experts went on a study-trip to the MATER project in Philadelphia, the CAP project at John...
Hopkins Hospital in Baltimore and to the Comprehensive Health Service Centre in New York City. Several of the group members have previously visited several relevant clinics in Copenhagen and Vienna.

There is interesting research going on in Norway in this field at the Centre for Addiction Research at the University of Oslo. Research on the whole cohort of approximately 160 families has commenced. Data is being collected on the pregnancies and birth outcomes. The second part of the study will be a follow-up study, focusing on how the children and families are doing. The 2005 and 2006 cohort has been followed prospectively from the pregnancy and up to the age of 2 years by Monica Sarfi and Brittelise Bakstad. The treatment group consists of 38 families with mothers in MAT and there is a similar normal control group. The mother and father are interviewed during the pregnancy and the child and the mother-child dyad is being assessed and the parents fill out questionnaires at 3, 6, 9, 12 months and at 2 years of age. A follow-up is presently being planned for the 4 year old children. Another research group led by Vibeke Moe is doing similar investigations on a group of mothers who have used opiates illegally during pregnancy and a group of mothers with psychosocial problems.

References


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Conflict of Interest

The author has no relevant conflict of interest to report in relation to the present report.

Received and Accepted February 2, 2009
TO THE EDITOR: Opioid Treatment Programs (OTPs) should be responsible and vigilant about assessing for the risk of cardiac conduction disturbance in methadone maintained patients and policies should be guided by the evidence of risk for QTc prolongation and Torsade de Pointes (TdP). The threshold for determining guidelines for screening and monitoring must be balanced with the potential barriers to treatment access and the financial burden that routine screening places on patients and programs. AATOD takes the risk for QTc prolongation and TdP in methadone treated patients very seriously. While the literature argues for and against routine testing prior to admission to an OTP, the evidence does not justify routine electrocardiographic (ECG) screening for all methadone treatment patients and does not conclude at which dose level patient should obtain ECG screening [4, 14]. The recommendations below represent our best guidance informed by more than 40 years of methadone treatment experience and the research to date.

Laboratory studies [9, 20] and case reports [2, 6, 10, 11, 17, 19, 22] suggest that methadone, whether prescribed for pain or addiction, has the potential for cardiac arrhythmia complications specifically QT-prolongation and TdP. Methadone alone, however, did not account for the majority of these complications. Contributing factors include pre-existing cardiac disorders, i.e. cardiomyopathy, genetic predisposition, hypokalemia, and taking multiple drugs of abuse or other medications known to prolong QT interval [8, 12, 21]. Studies that examine methadone dose and QTc prolongation have mixed results [13-15, 17, 19, 22]. Opinions about management of this potential risk vary from aggressive intervention including ECG prior to administering any QTc prolonging medications [7, 15], to screening only patients on “high” doses of methadone, although there is no clarity what defines a high dose level [1, 16, 18, 22]. Others recommend only screening high-risk patients [3, 7, 11].

After a review of the evidence-based research, CSAT consensus panel draft recommendations and our experience, AATOD recommends the following for the assessment of cardiac conduction risk in methadone treatment patients:

1. Physicians and other medical staff working in OTPs and Pain Management programs should be educated about the risk of QTc/TdP in methadone maintained patients.
2. OTPs and Pain Management programs should develop a Comprehensive Cardiac Arrhythmia Risk Management Plan that includes the type, threshold and frequency for screening and monitoring. The plan should include a review of:
   - A personal medical history of long QT syndrome, cardiac conduction defects, arrhythmias, syncope episodes, seizures, palpitations, dizziness and lightheadedness, and a family history of long QT syndrome, cardiac conduction defects, arrhythmias, syncope episodes, seizures and sudden or unexpected death should be part of a medical assessment prior to admission to an OTP.
   - Electrolytes disturbances, in particular hypokal-
mia and hypomagnesemia and medications that can induce these conditions (diuretics and laxatives) should be included in the medical assessment.

- The assessment should note any history of clinically significant bradycardia or other relevant cardiac disease.
- A review of all prescribed medications prior to induction onto methadone treatment with particular attention paid to those medications that are substrates of CYP3A4/CYP2D6, CYP2B6 and those that block HERG channel currents. New medications including over-the-counter (OTC) agents, herbal preparations, and dietary supplements should be reviewed with the program physician. (www.Torsade.org)
- A review of toxicology screens for the presence of illicit drugs particularly cocaine and amphetamines.

3. Medically frail patients, patients prescribed additional opioids for chronic pain management and patients with a history of poor, extensive or rapid metabolism of methadone should be closely monitored.

4. Consent to methadone treatment should include information about the risk of using illicit drugs particularly drugs diluted with quinine.

AATOD recommends the following for management of cardiac conduction risk in methadone maintained patients:

1. Consider a baseline and follow-up 12-lead ECG for patients with "a history of arrhythmia, prolonged QTc, a family history of premature death, and/or other significant arrhythmia risk factors" on admission or for suspected arrhythmia risks in ongoing methadone maintained patients [14].
2. Referral should be made for cardiac consultation for "known or detected cardiac conditions affecting heart rhythm, unexplained syncope or seizures or a significant increase in QTc from the baseline if known [14].
3. Patients at-risk should be educated on cardiac symptoms to watch for e.g. "racing" heartbeat, dizziness, seizures, or fainting spells and encouraged to contact the clinic and medical provider and/or emergency services immediately [14].

AATOD believes that the safeguards outlined above along with individualized induction practices will allow clinicians to optimize safety during methadone treatment [5]. Informed and appropriate clinical monitoring and follow-up will be the best protection for patient safety. Prospective clinical trials are needed before routine ECG screening can be endorsed.

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The 4th EUROPAD-Italia
Conference 2009
October 29-31, 2009
PIETRASANTA, (Lucca), Italy, EU
Sala dell'Annunziata, Luigi Russo Cultural Centre
Piazza del Duomo
Chairmen
Icro Maremmani
Roberto Nardini
Day 1 – Thursday 29th October 2009

9:00  Registration

Meet the expert 1
Alcoholism
Chairmen:
Ubaldo Bonuccelli (Pisa, Italy, EU)
Icro Maremmani (Pisa, Italy, EU)

10:00 Following the concept of blocking dosages. Can we make the brain of alcoholics insensitive to alcohol?
Fabio Caputo (Ferrara, Italy, EU)

11:00 Immune system and treatment of alcoholics
Lorenzo Somaini (Biella, Italy, EU)

12:00 Break

Plenary 1
Heroin Addiction and Related Clinical Problems
Chairmen:
Matteo Pacini (Pisa, Italy, EU)
Pier Paolo Pani (Cagliari, Italy, EU)

16:00 Pain-killers use and their relevance in the management of Methadone Clinics
Mark Parrino (AATOD, New York, NY, USA)

17:00 Do we need a compulsory medical treatment for heroin addicts?
Ambros Uchtenhagen (Zurich, Switzerland)

18:00 Does QTc prolongation really matter?
Matteo Pacini (Pisa, Italy, EU)
Claudio Leonardi (Rome, Italy, EU)

19:30 Break

Welcome Reception and Paolo Picchio Award
Chairmen:
Roberto Nardini (Pietrasanta, Italy, EU)
Icro Maremmani (Pisa, Italy, EU)

20:30 Awarded
Ambros Uchtenhagen (Zurich, Switzerland)
Haim Mell (Jerusalem, Israel)

22:30 End of Session

Day 2 – Friday 30th October 2009

Meet the expert 2
Heroin Addiction and Psychopathology.
Chairmen:
Liliana Dell’Osso (Pisa, Italy, EU)
Alessandro Tagliamonte (Siena, Italy, EU)

10:00 Towards a psychopathology of heroin addiction
Pier Paolo Pani (Cagliari, Italy, EU)
Icro Maremmani (Pisa, Italy, EU)

12:00 Break

Meet the expert 3
Heroin Addiction and Psychiatry
Chairmen:
Guido Intaschi (Viareggio, Italy, EU)
Roberto Nardini (Pietrasanta, Italy, EU)

15:00 Bipolar Spectrum
Andreas Erfurth (Vienna, Austria, EU)

16:00 Bipolar disorder and drug addiction
Icro Maremmani (Pisa, Italy, EU)

17:00 Break

Plenary 2.
Heroin Addiction and Related Clinical Problems
Chairmen:
Icro Maremmani (Pisa, Italy, EU)
Andrea Vendramin (Padova, Italy, EU)

17:30 Is it really necessary transferring patients from subutex to suboxone?
Hannu Alho (Helsinki, Finland, EU)

18:30 Helping heroin addicts in the streets. The Tel Aviv experience
Haim Mell (Jerusalem, Israel)

19:30 End of Session
INFORMATION FOR CONTRIBUTORS

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  Book:

  Book Chapter:

  Journal names should be abbreviated as they appear in Index Medicus, journals not currently indexed there should not be abbreviated.

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Conflict of Interest. ALL authors are requested to disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence, or be perceived to influence, their work. If there are no conflicts of interest, authors should state that there are none.

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Ethics of Experimentations: Authors must declare in the cover letter that their studies submitted to Heroin Addiction & Related Clinical Problems have been conducted in accordance with Declaration of Helsinki.
A Winter Morning... on the Beach, Versilia, Italy, 1998

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