

Heroin Addiction and Related Clinical Problems



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Psychological performance and sedation following injectable opioid administration

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Summary

Injectable opioid treatment (IOT) can be an effective strategy for heroin users who respond poorly to treatment with oral methadone, but its safety profile is yet to be fully characterised. This study assessed the risks of sedation and impaired psychological performance in 13 IOT patients following injection of their regular dose of heroin (n=7) or methadone (n=6). Measures of psychological performance (digit symbol substitution task, DSST; cancellation task, CT) and sedation (visual analogue scale, VAS) were taken at baseline and 15, 30 and 60 minutes post-injection. Comparisons were made between the methadone and heroin groups, with reference to data collected in control groups maintained on oral methadone or sublingual buprenorphine. Results indicated that performance and sedation did not change significantly in the hour after injection. However, patients prescribed injectable heroin or injectable methadone showed significantly worse psychological performance at the time of peak effect compared to patients prescribed oral methadone or buprenorphine. These findings suggest that further research is required to characterise possible psychological performance deficit in IOT patients

Key Words: Methadone, Diamorphine, Safety, Performance, Pharmacodynamics

1 Introduction

Randomised controlled trials indicate that medically-supervised injectable opioid treatment (IOT) may be a useful treatment option for heroin users who respond poorly to oral methadone maintenance [6, 11]. However, there is limited evidence regarding certain risks of IOT that could offset these benefits in some patients.

One potential hazard of IOT is that patients will become sedated and experience impaired psychological functioning after their regular injection of heroin or methadone. Opioid agonist side effects (including sedation and impairment) affect many patients receiving oral methadone, particularly at times of peak plasma methadone concentrations (typically 2–3 hours after dosing) [3, 4]. Several studies have demonstrated impaired cognitive performance in patients receiving oral methadone compared to abstinent heroin users and drug-free

controls [7, 8, 12].

Few studies have explored the potential for IOT to cause problematic sedation and impairment, despite the fact that injectable routes of administration are associated with a rapid and intense profile of effects [9, 10]. It is also unclear whether the risks of sedation and impairment vary between individuals prescribed different injectable opioids (heroin vs. methadone). Knowledge of these risk factors would lead to better evidence-based safety protocols for IOT, particularly regarding the need to monitor patients' safety before they leave supervised IOT facilities.

The objectives of this study were to determine whether measures of sedation and impairment in IOT patients (1) show significant changes over time in the 60 minutes after patients self-inject, (2) differ according to the maintenance drug (heroin versus methadone), and (3) differ in comparison to data collected in control groups receiving oral methadone

or sublingual buprenorphine. It was hypothesised that opioid injection would be associated with (i) increased sedation and (ii) decreased psychological performance relative to pre-injection baseline.

2. Methods

2.1 Subjects

Subjects were recruited from an outpatient drug treatment service within the South London and Maudsley NHS Trust. Eligibility criteria required subjects to be aged 18 years or over and currently prescribed injectable methadone or heroin (diamorphine) for IOT. All subjects gave written informed consent. The Research Ethics Committee of the Institute of Psychiatry approved the study. The study has been conducted in accordance with the Declaration of Helsinki.

2.2 Design and procedures

Measures of sedation and psychological performance were taken before subjects' self-injected their regular dose of heroin or methadone and subsequently at 15, 30 and 60 minutes post-injection. All procedures took place in a supervised injecting facility with the subject seated throughout the testing session.

2.3 Measures

Psychological performance was assessed using the Digit Symbol Substitution Task (DSST), a measure of coding skills from the Wechsler Adult Intelligence Scale [13], and the Cancellation Task (CT) [1], which measures focused attention. Sedation was assessed using factor 1 from the Mood Rating Scale [2], which consists of 9×100 mm visual analogue scales, upon which subjects mark the position that best describes their present feelings. The mean score was recorded. Subjects' recent use of drugs was assessed by self-reported use in the previous 7 days and urinalysis.

2.4 Statistical Analyses

Repeated-measures analysis of variance (ANOVA) was used to assess the effect of time since dosing (TIME) on sedation and performance. Secondary ANOVA analyses investigated interaction effects for TIME × DRUG. Linear mixed-models (LMM) were used to assess differences in response according to DRUG and DOSE. An autoregressive covariance structure was used and DOSE was treated as a nested covariate within the DRUG factor (to examine separate dose response relationships for methadone and heroin). Univariate ANOVA with Bonferroni post-hoc tests were used to compare sedation and psychological performance

outcomes for the IOT sample in this study with data collected previously in control groups receiving oral methadone or sublingual buprenorphine [5]. This earlier study used the same measures of sedation and psychological performance, which were collected at baseline, 60, 120, and 300 minutes after patients received their regular dose of methadone or buprenorphine (i.e., to capture peak effects 1–2 hours after dosing). Comparisons between these 4 treatment groups (injectable heroin vs. injectable methadone vs. oral methadone vs. sublingual buprenorphine) were made for (1) baseline outcomes prior to dosing and (2) 'peak effect' responses, defined as maximum VAS sedation, maximum CT score, and minimum DSST score (i.e., across all observed time points).

3 Results

3.1 Description of subjects

Thirteen IOT patients (11 male, 2 female) with a mean±SD (range) age of 42±3.6 (36–51) were recruited. Seven subjects self-administered injectable diamorphine (mean dose 169±44mg, 100–230mg ; 3 IV : 4 IM) and six injected methadone (mean 110±17mg, 100–140mg; 1 IV: 5 IM). With the exception of one subject in the injectable diamorphine group, all subjects were also prescribed oral methadone to be taken at night (mean doses: injectable methadone group 32±4.9mg, 20–50mg; injectable diamorphine group 32±4.9mg, 10–50mg). None of the subjects had taken their oral methadone dose within 12 hours of their testing session. Mean doses for the control subjects, described in detail previously [5], were 55±21mg (35–100mg) for the oral methadone group (n=8) and 10.5±3.2mg (6–16mg) for the buprenorphine group (n=8).

3.2 Changes in sedation and psychological performance over time

ANOVA revealed no significant TIME effects for DSST, CT or VAS sedation. Figure 1 shows that mean performance for the DSST and CT tended to be slightly higher for patients prescribed injectable methadone compared to the injectable heroin group. However, there were no significant effects for DRUG or DOSE on any measure.

3.3 Comparisons of injectable and non-injectable treatments

At baseline, one-way ANOVA indicated a significant main effect for treatment group on baseline DSST scores ($F_{3,26}=3.84$, $p=0.02$), with Bonferroni post-hoc tests indicating significantly worse performance for the heroin group compared to the buprenorphine group ($p=0.03$). There were no differences between the 4 groups at baseline for CT ($F_{3,26}=1.14$, $p=0.35$), or VAS sedation ($F_{3,26}=1.26$, $p=0.31$).

At the time of peak response, there were significant dif-

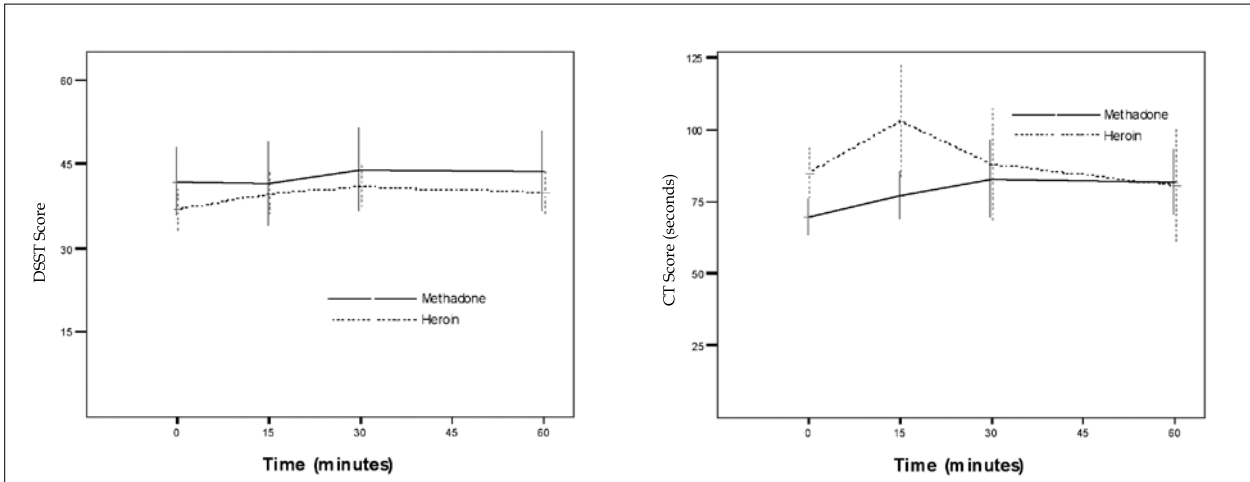


Figure 1. Psychological performance on the digit symbol substitution task (DSST: higher scores indicate better performance) and cancellation task (CT: lower scores indicate better performance) for patients prescribed injectable heroin or methadone. Data represent mean ± SE.

ferences between the treatment groups for minimum DSST ($F_{3,26}=4.57, p=0.01$), and maximum CT scores ($F_{3,26}=4.37, p=0.01$). For the DSST, post-hoc tests indicated that performance was worse for both injectable heroin and injectable methadone compared to oral methadone and buprenorphine ($p<0.001$ for all analyses). There were no significant differences between the two injectable groups ($p=0.40$) or the two non-injectable groups ($p=0.61$). For the CT, post-hoc tests indicated that the injectable heroin group performed significantly worse than the injectable methadone ($p=.004$), oral methadone ($p<0.001$) and buprenorphine ($p<0.001$) groups, and the injectable methadone group performed significantly worse than the buprenorphine group ($p=0.01$). There were no significant differences between groups for VAS sedation ($F_{3,26}=0.52, p=0.67$). Figure 2 summarises differences between the 4 treatment groups at the time of peak effect for CT and DSST.

4. Discussion

Contrary to hypothesis, this study found no evidence that IOT patients experience significant changes in sedation or psychological performance in the hour after their injection. The lack of significant changes in performance is notable given the relatively high mean doses of injectable heroin (169mg) and methadone (110mg) that were used. No significant differences in sedation or psychological performance profiles were found between patients prescribed injectable heroin or methadone.

However the results of this preliminary study also suggest that the safety of IOT with regard to psychological performance effects could differ from that of first-line treatment options using non-injectable routes of administration. Patients prescribed injectable methadone or heroin showed

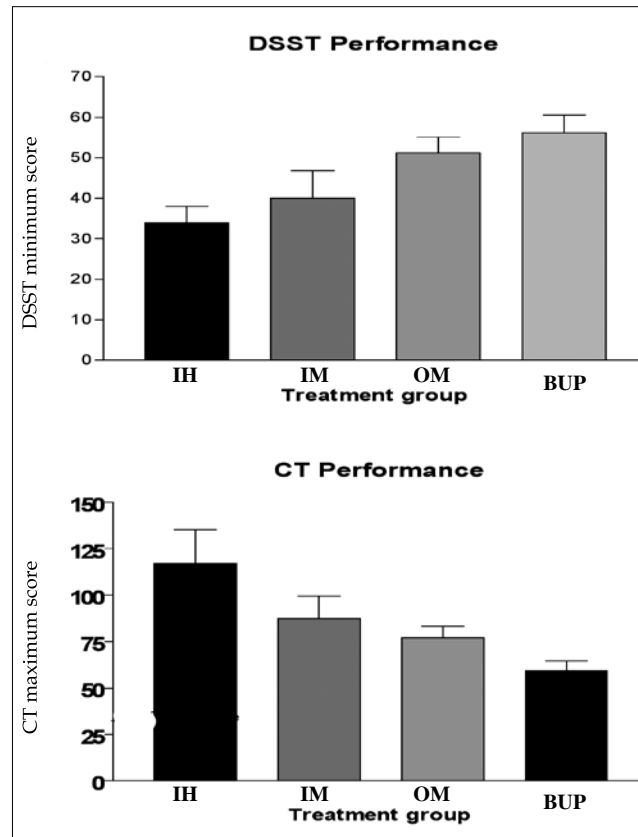


Figure 2. Psychological performance at the time of peak effect for the digit symbol substitution task (DSST, minimum score) and cancellation task (CT, maximum score) in groups of patients receiving injectable heroin (IH), injectable methadone (IM), oral methadone (OM) or sublingual buprenorphine (BUP). Data represent mean ± SE.

poorer performance compared to patients prescribed non-injectable treatments, both at baseline (DSST only) and the time of peak effect (CT and DSST). These performance differences were detected despite the use of only two very short tasks and were particularly marked for the focussed attention task which indicates that injectable maintenance treatment slows down performance rather than impairing accuracy. However, these performance deficits needed to be weighed against the potential benefits of IOT in patients who continue to inject illicit opioids whilst prescribed methadone or buprenorphine [11].

The use of an open-label non-randomised design prevents strong conclusions regarding differences between treatment groups. Other study limitations include the small sample size, variable treatment regimens (i.e., dose, route of administration, co-prescription of oral methadone), the use of self-report measures of sedation, the limited selection of performance tasks, and the potential practice effects that may apply to performance tasks. It is also possible that stimulation of patients through their involvement in the study procedures at regular intervals after their injection may have counteracted the potential intoxicating and sedating effects of injectable opioids.

In conclusion, larger studies are needed to confirm possible differences in psychological performance, especially involving higher cognitive processes, between injectable and non-injectable pharmacotherapies.

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Treatment practices and perceived challenges for European physicians treating opioid dependence

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Summary

This survey investigated the current practices and challenges of physicians treating opioid dependence in Germany, France, Italy and the UK. Doses favoured in Europe appeared to conflict with recommended best practice, with low mean methadone and buprenorphine maintenance doses reported (44.3 and 9.5 mg, respectively). Mean time to buprenorphine maintenance doses was longer than recommended at 14.4 days. Respondents also rated diversion and misuse management as their most difficult challenge in treating opioid dependence. These data suggest that prescribing practices are likely to increase this problem, as well as impeding treatment success by decreasing compliance and retention.

Key Words: Maintenance treatment; pharmacotherapy; diversion; misuse; induction; dosing; methadone; buprenorphine

1. Introduction

It is now widely accepted among healthcare professionals that opioid dependence is a chronic relapsing condition that is treatable, and that long-term comprehensive care leads to the best outcomes (41).

Maintenance pharmacotherapy has long been established as an important component in the treatment of this condition and methadone in particular has accumulated several decades of clinical experience. Methadone's pharmacological potential for overdose and diversion necessitated the development of highly regulated treatment systems most often based on daily supervised dosing in specialist addiction centres. This treatment delivery model has been the 'gold standard' since the 1970s and continues to form the basis for much of current opioid-dependence treatment in Europe despite the emergence of new medications, such as buprenorphine

and buprenorphine/naloxone (bup/nx), with substantially different pharmacological characteristics.

Political pressures have led to marked geographical differences in the treatment options available and the restrictions under which physicians are allowed to treat patients. Where some opioid users can access treatment just by walking into a local physician's office (eg, France) or drug treatment clinic (eg, Italy, Spain and the UK), others are required to remain on waiting lists for many months or even years (eg, Greece) or undergo detoxification for all other drugs before being allowed maintenance therapy (eg, Norway).

Variation in the amount of training available to physicians and the availability of national clinical guidelines can exacerbate such differences. For example, doctors wishing to treat opioid users in Germany face a mandatory training

course of 56 hours, whereas in France any physician is allowed to prescribe buprenorphine with no additional training. Also, the vast majority of treatment in France is provided in doctors' offices, whereas 95% of treatment in Italy takes place in specialist clinics.

Inappropriate dosing of opioid pharmacotherapies can put patients at risk of significant complications. Excessive opioid doses can lead to overdose and/or death, whereas prescribing doses that are too low can limit the potential for success and expose patients to the myriad of harms associated with continued illicit drug use.

This study aimed to shed some light on the attitudes of physicians in four large European countries relating to specific aspects of opioid-dependence treatment, how this translates into real-world clinical practice, and the overall impact on the quality of care that opioid-dependent patients are receiving.

2. Methods

2.1 Physician surveys

A structured online questionnaire was developed and circulated to physicians in Italy, Germany, France and the UK in February 2010. The survey was estimated to take about 25 minutes, and respondents received a fee of €20 for completing it. Data for 300 respondents (75 per country) were collected anonymously. The survey was stopped in each country after the quota of respondents who met the inclusion criteria was filled. An additional 246 entries did not meet the inclusion criteria and 82 more submissions were incomplete. Survey data were collated and analysed in the SPSS statistical package.

2.2 Inclusion criteria

Physicians were restricted to those specialising in addiction medicine, emergency medicine, general practice, internal medicine, neurology, pain, psychiatry/psychology or rheumatology. They were required to have at least 2 years of experience in prescribing methadone and/or buprenorphine to an average of 20 or more opioid-dependent patients per month. To ensure representation of all maintenance pharmacotherapies in the survey results, at least half of the doctors from each country prescribed buprenorphine (including bup/nx) to at least 20% of their patients.

2.3 Exclusion criteria

Respondents with less than 2 years or over 35 years experience in their field were excluded.

2.4 Survey overview

Physicians responding to the survey were asked to report

the proportion of their patients who received maintenance pharmacotherapy versus those who underwent short-term detoxification. They also submitted the average dose of methadone and/or buprenorphine on day 1 of induction, the average final maintenance dose and the average time taken to reach that dose. They were also asked to rate the difficulty they experienced in 10 different aspects of opioid-dependence treatment on a scale of 1 (easiest) to 7 (most difficult) and to subjectively estimate the extent of medication diversion and misuse in their local area. These findings as well as the physicians' goals for treatment are discussed herein.

The survey also contained questions about the components of a high-quality treatment programme and the areas of improvement that the respondents identified in their individual countries. These results are not discussed here.

3. Results

3.1 Treatment practices

European physicians treating opioid dependence reported that an average of 61.4% of their patients received maintenance treatment and 38.6% underwent short-term detoxification. Three in five physicians prescribed either methadone or buprenorphine maintenance to at least 60% of their opioid-dependent patients (Figure 1). UK doctors maintained 69.9% of their patients on pharmacotherapy, significantly higher than in other countries ($p < 0.05$).

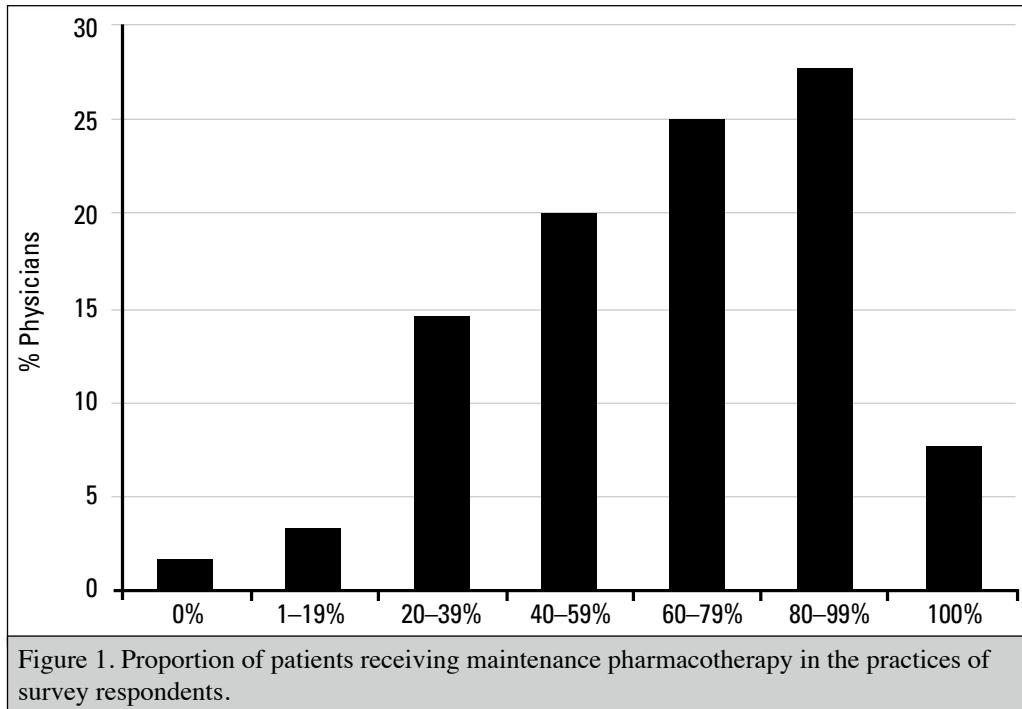
Physicians rated six different goals of opioid-dependence treatment on a 1–5 scale according to how important they were considered in an effective treatment programme (Table 1).

3.2 Dosing practices

The mean reported induction dose of methadone was 31.3 mg. The average day 1 dose of buprenorphine prescribed was 8.7 mg. However, these means mask considerable variability in the doses prescribed. Buprenorphine tended to be inducted at low doses with 58% of physicians prescribing less than 8 mg of buprenorphine on the first day, 48% prescribing 4 mg or less and more than a quarter (27.3%) prescribing 2 mg or less (Figure 2a). Low dosing was also reported in methadone induction with 24% giving their patients less than 15 mg on day 1 (Figure 3a). There was also a marked degree of high dosing in methadone induction, with one in five doctors giving initial doses of 50 mg or higher and 4% routinely prescribing 100 mg or more on day 1 (Figure 3a).

The mean maintenance doses were 44.3 mg for methadone and 9.5 mg for buprenorphine. In total, 41% of patients were receiving less than 40 mg of methadone (Figure 3b) or 8 mg of buprenorphine (Figure 2b) per day on average.

Methadone patients reached their maintenance dose in an average of 16.7 days. Furthermore, 21.3% were stabilised in less than 7 days (Figure 3c). Only 13.4% of patients ar-



rived at their buprenorphine maintenance dose in 3 days or less, while over half took longer than 7 days and a quarter (26.5%) took at least 15 days (Figure 2c). There was also a large variation between the countries in the number of days physicians took – averaging between 9.3 in Germany and 21.5 in France – to get their buprenorphine patients to their target dose (Table 2).

Dosing practices were largely similar across the four countries but national differences did emerge in some areas (Table 2). Italian physicians inducted patients on an average of 41.9 mg of methadone or 12.9 mg of buprenorphine, significantly higher than all the other countries ($p < 0.05$). By contrast, methadone maintenance doses in Italy were significantly lower than the European average at 31.8 mg ($p < 0.05$). In Germany, the average times taken for methadone

and buprenorphine patients to reach their maintenance doses were 9.3 days and 6.9 days, respectively – significantly faster than their European counterparts ($p < 0.05$).

3.3 Physician challenges

Survey respondents overwhelmingly regarded the quality of care that patients in their country currently receive as less than optimal. On a scale of 1–5, where 5 represents optimal care, only 3.7% gave their country’s treatment system the highest rating, while 18.4% felt that the quality of care in their country was less than adequate (1–2 out of 5). Italian and German physicians were the most pessimistic, with 100% and 98.7%, respectively, giving their country’s treatment less than 5. Ratings from the UK and France were 94.7% and

Table 1. The importance of various treatment objectives to the quality and effectiveness of opioid-dependence treatment.

How important do you think the following patient objectives are in determining the quality and effectiveness of a treatment programme? (5 = Very important, 1 = Not important)	Mean score	Very important (5)	Not important (1)
Improvements in patient’s quality-of-life	4.3	46%	0%
Abstinence from street drugs	4.3	46%	0.7%
Optimisation of ORT dosing for each patient	4.1	27%	0%
Minimising harm	4.0	37%	1%
Strict compliance with treatment programme conditions	4.0	28%	0.3%
Achieving a completely drug-free life (including ORT)	3.6	24%	4%

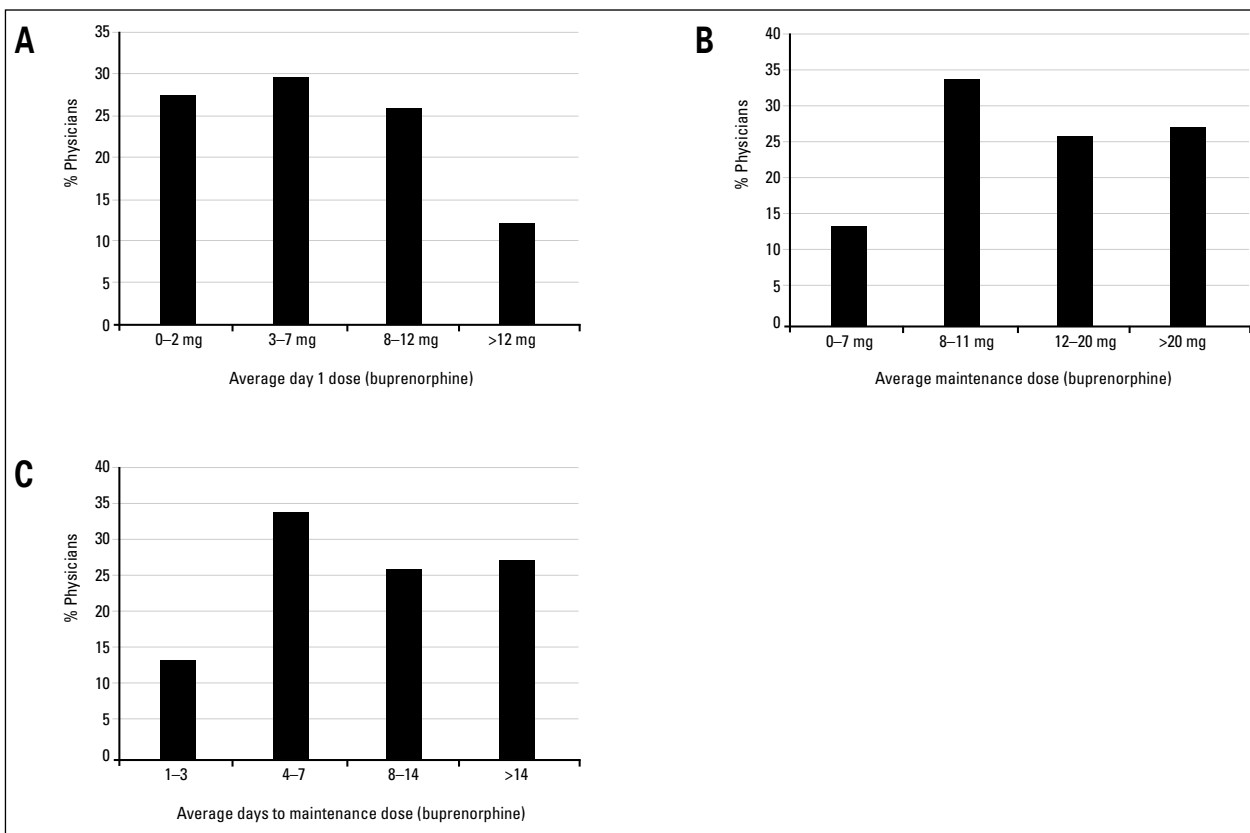


Figure 2. A) Mean induction doses of buprenorphine prescribed by doctors responding to the survey. B) Mean final maintenance doses of buprenorphine. C) Mean number of days taken by the respondents' patients to reach their maintenance dose of buprenorphine.

92%, respectively. Measuring withdrawal severity, titrating to a therapeutic maintenance dose and understanding side-effects and drug–drug interactions were rated as the easiest aspects of treatment (Table 3). Induction also ranked among the easier aspects of treatment provision despite the disparity of induction practices reported. Identifying diversion and misuse and transferring between opioids were reported as the most challenging activities by the survey respondents, with between one-third and one-fifth of doctors finding them very difficult (1–2 out of 7).

3.4 Diversion and misuse of medication

There was considerable concern over misuse and diversion reported by responding physicians, with 70.3% agreeing that it is a significant issue and that physicians themselves have a responsibility to address it (rating 4–5 out of 5). Responses were similar across the four countries, although concern was highest in Italy at 78.7%. Using the same scale, 65% agreed that prescribing formulations with the lowest misuse potential was essential for reducing diversion and misuse. French

Table 2. Mean day 1 and maintenance doses of methadone and buprenorphine, and mean time to maintenance across four European countries.

Country	Mean day 1 dose (mg)		Mean maintenance dose (mg)		Mean time to reach maintenance (days)	
	Meth	Bup	Meth	Bup	Meth	Bup
All	31.3	8.7	44.3	9.5	16.7	14.4
Germany	25.6	6.9	45.7	9.0	9.3	6.9
UK	27.9	6.3	51.3	11.0	16.1	12.4
France	29.8	8.7	48.2	9.0	19.6	21.5
Italy	41.9	12.9	31.8	9.0	21.9	16.8

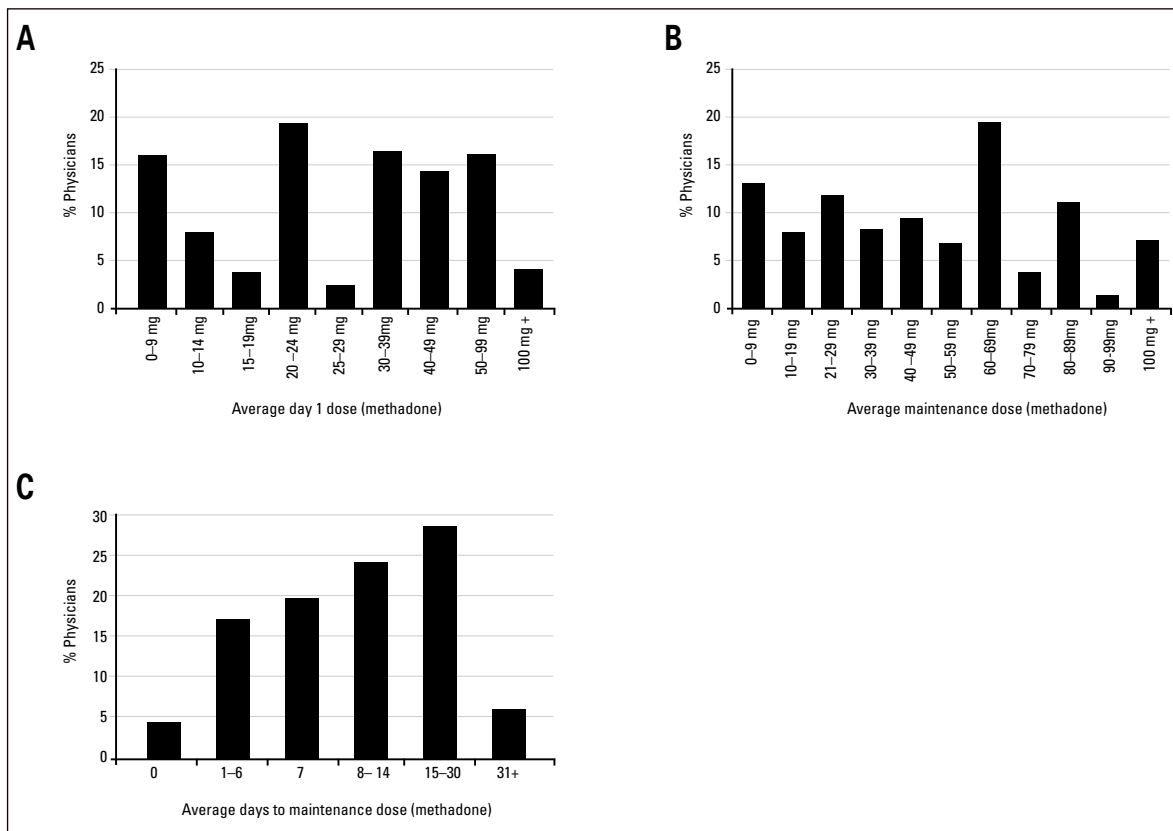
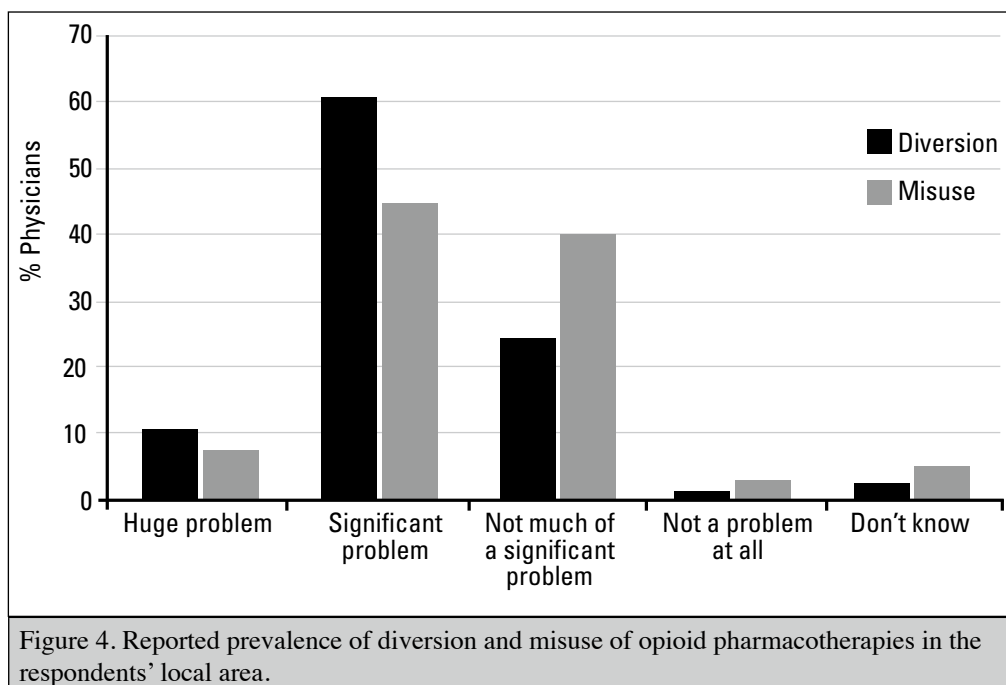


Figure 3. A) Mean induction doses of methadone prescribed by doctors responding to the survey. B) Mean final maintenance doses of methadone. C) Mean number of days taken by the respondents' patients to reach their maintenance dose of methadone.

Table 3. Doctors rated the difficulty they experienced with 10 aspects of treatment on a scale of 1–7, with 7 representing the easiest tasks and 1 the most difficult.

How easy do you find the following... (7 = Very easy, 1 = Difficult)	Mean score	Very easy (6 or 7)	Very difficult (1 or 2)
Measuring withdrawal severity based on physical signs	4.2	16.7%	9.0%
Understanding the safety, side-effects and drug–drug interactions of the different pharmacotherapies	4.1	12.7%	11.3%
Titration therapeutic maintenance doses	4.1	12.0%	9.3%
Smooth induction onto methadone	3.9	10.3%	14.3%
Smooth induction onto buprenorphine or buprenorphine/naloxone	3.9	8.3%	14.0%
Building an open relationship with patients so they will talk about their drug use, cravings and problems	3.8	11.0%	19.0%
Selecting the most suitable pharmacotherapy for each patient	3.8	9.3%	17.7%
Switching buprenorphine patients to buprenorphine/naloxone	3.6	7.7%	19.0%
Transfers between the different pharmacotherapies	3.4	4.3%	22.7%
Detecting and responding to misuse and diversion with the patient	3.1	3.0%	33.0%



doctors felt significantly more strongly about this than the other countries, with 77% agreeing that the prescribing of the least divertible medications is essential ($p < 0.05$).

When asked how prevalent diversion or misuse of medication was in their local area, 72% of doctors said diversion was a 'huge' or 'significant' problem while 52% said the same about medication misuse (Figure 4).

4. Discussion

4.1 Limitations

This survey has uncovered a wide range of treatment practices among European doctors treating opioid-dependent patients, a proportion of which are at odds with clinical evidence and treatment guidelines around the world. While the data have revealed much about how European doctors currently practice, it should be noted that the dosing data are self-reported recollections from the physicians themselves rather than a review of physician prescribing records. Questions on the prevalence of diversion and misuse were also subjective, so do not necessarily reflect the exact extent of the problem in any of the four countries.

4.2 Treatment modalities

Despite the advantages of long-term pharmacotherapy over abstinence-oriented treatment in retaining patients and reducing drug use and its associated harms (5, 9, 13, 18, 21, 27, 31), these findings suggest that as much as 39% of patients across Europe are still receiving detoxification rather than long-term treatment. Clinical evidence sug-

gests that between 60 and 72% of detoxified patients can be expected to relapse to drug use within 1 year (14). They are also subject to further risks compared to maintenance patients. For example, medication-assisted treatment reduces opioid-related mortality by about eight-fold (5) and non-fatal overdoses are also reduced by maintenance therapy but not by detoxification (9). Patients who undergo single detoxification episodes do not alter behaviours that put them at risk of contracting HIV (27). Even among maintenance patients, HIV prevalence and infection rates are inversely correlated to the duration of treatment (31). Long-term treatment leads to improved outcomes including lower illicit substance use, fewer psychiatric problems and an enhanced quality of life (23), while detoxification is associated with substantial psychological distress (21).

While short-term detoxification may be suitable for some patients, particularly those with high motivation and family support, the WHO recommended that it not be promoted as an evidence-based treatment option due to the poor associated outcomes (41). Indeed, the persistently high rates of detoxification seem to be at odds with the physicians' stated priorities for treatment, where improvements in quality of life and abstinence from street drugs were reported as much more important than complete abstinence. One possible reason may be the influence of patients who often may not understand the chronic relapsing nature of opioid dependence and therefore have unrealistic expectations of being drug-free quickly. A lack of awareness of the available treatment options could also lead a patient to prefer detoxification. A recent study has shown that patients' own preferences are one of the most important determinants of which treatment they receive (36).

4.3 Induction and titration

Where patients do receive maintenance treatment, the survey revealed extensive under-dosing with both methadone and buprenorphine combined with relatively fast methadone induction and slow buprenorphine induction. The principles of methadone induction have long been a low initial dose followed by slow titration to stability ('start low, go slow'), due to the risks of respiratory depression. A range of international guidelines generally recommend an initial methadone dose of 10–30 mg and maintenance doses of 60–120 mg per day (11, 25, 32, 40). Dose increases are generally recommended to be no more than 10 mg every 3 days (or 30 mg per week) depending on the patient's opioid tolerance. However, while the mean induction dose was close to the recommended maximum, more than half of responding physicians prescribed higher doses. Indeed, one in five respondents inducted on at least 50 mg of methadone and 4% even reported using 100 mg or more. Most methadone-related deaths occur in the first 2 weeks of treatment (6, 20, 43) and the majority of those are associated with doses of just 40–60 mg (25). This indicates that one-fifth of European methadone prescribers may routinely be putting their patients at serious risk of overdose death. The time taken to reach maintenance also appeared short given the slow dose increases recommended for maintenance. It is unclear whether this is really due to rapid dose increases or simply a function of the low maintenance doses prescribed. At the rate of increase generally cited in guidelines, a doctor could titrate from a starting dose of 10 mg to the average reported methadone dose of 44 mg in just 9–12 days.

Buprenorphine has very different pharmacological characteristics to methadone, and thus a very different recommended induction strategy. Unlike methadone, buprenorphine guidelines generally advocate reaching the target maintenance dose in 3 or 4 days at most (11, 25, 32, 40, 42). Recommended doses are 8 mg on day 1, 12–16 mg

on day 2 and maintenance doses are 12–24 mg (11, 25, 32, 40, 42), with up to 32 mg being cited as necessary in some cases (11). However, buprenorphine prescribers in the four countries surveyed appear to be following the 'start low, go slow' induction principles of methadone treatment. Almost three-fifths of doctors prescribed less than 8 mg on day 1 and 48% prescribed 4 mg or less. Meanwhile, the average of 14.4 days to reach maintenance doses is far higher than the recommended buprenorphine induction time of 2–3 days (11, 25, 42). Such cautious induction protocols have been acknowledged as potentially leading to lower treatment retention by the Cochrane Review Panel and the UK National Institute for Clinical Excellence's Healthcare Technical Assessment (7, 29), and the importance of rapid induction is underscored in the best practice published in more recent treatment guidelines (11, 32). Clinical data support this; trials that allow patients to reach 8 mg sooner tend to retain patients better, particularly if they achieve this level within 1–3 days (Figure 5). Studies that take longer than 3 days to reach 8 mg appear to retain fewer patients (22, 34, 35).

4.4 Maintenance dosing

Mean methadone maintenance doses were markedly lower than the advocated range in all countries and nearly three-fifths of doctors maintained their patients on less than 60 mg, with 42% prescribing less than 40 mg. Even these doses may represent an improvement in some countries. UK physicians prescribed an average of 51.3 mg of methadone, up from just 36.9 mg reported in a 2005 survey of nearly 1900 general practitioners (39). Low maintenance doses are associated with decreased treatment retention, putting patients at risk of relapse and the associated harms of drug use, including mortality (3).

Buprenorphine maintenance doses in Europe also appear to be sub-therapeutic, as trials using similar doses have shown only modest outcomes (17, 24, 38). Indeed, 58% of

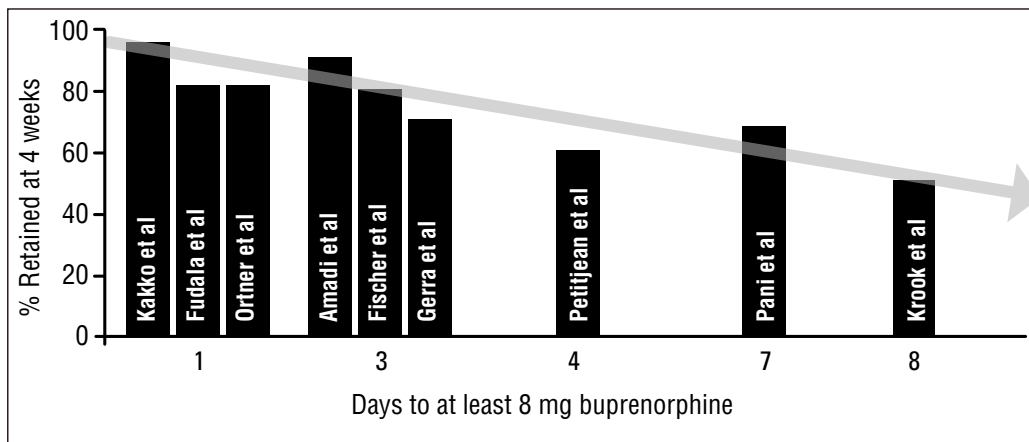


Figure 5. Rapid induction increases retention on buprenorphine maintenance treatment.

European patients are being maintained on 8 mg or less per day, many on doses lower than the generally recommended day 1 dose. Low buprenorphine doses markedly reduce retention and abstinence in a range of early studies (Figure 6). The wider adoption of rapid induction protocols at therapeutic dose levels could make a considerable difference to retention rates for patients in buprenorphine therapy. A 6-month patient retention of nearly 80% has been reported using a titration strategy where patients receiving either methadone or bup/nx had their dose increased fortnightly until drug use, withdrawal symptoms and cravings were eliminated (19). In addition, bup/nx patients reached 16 mg in 2 days. This 6-month retention rate is markedly higher than that typically reported in opioid-dependence studies (28, 29).

Remarkably, although the dosing practices revealed by these data diverge from best practice guidelines in many countries, titrating to therapeutic maintenance doses was rated as one of the easiest aspects of treatment by physicians. Induction on to methadone and buprenorphine were also not identified as a difficult area even though a proportion of physicians appear to follow induction protocols that could lead to drop-out in their buprenorphine patients and potential fatalities in their methadone patients.

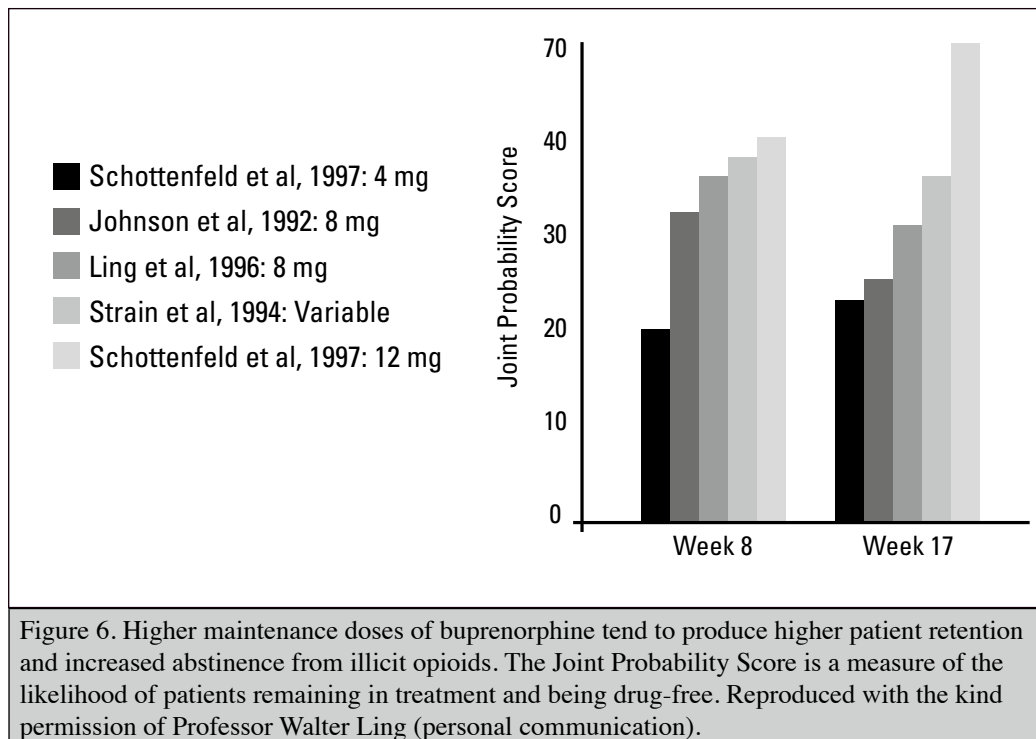
Possible explanations for these deviations from best practice in Europe are that prescribers may be under-dosing with methadone due to a fear of overdose while those using buprenorphine may be erroneously following the 'start low, go slow' practices advised with methadone because they are unaware of buprenorphine's distinctive safety profile as a partial mu-opioid agonist. Since early research with

buprenorphine tended to use lower doses (30), it is also possible that clinical practice has yet to completely align with currently recommended best practice. Some mistrust of patients claiming to need higher doses may also be a factor, particularly as patients who feel they are under-dosed may inject their treatment or seek additional prescriptions from other doctors (ie, 'doctor shopping') (12). A vicious circle, where doctors become even more fearful of giving higher doses, may result.

4.5 Misuse and diversion

As well as the implications for patient retention, low and slow dosing of buprenorphine can be a driver for diversion and misuse. In a survey of 298 patients receiving take-home buprenorphine in France, 70% of those using illicit buprenorphine reported doing so to supplement inadequate dosing by their physician. Low dosing also emerged as the second-highest risk factor for misuse of prescribed buprenorphine (37). Thus, the dosing practices revealed in this research, may also contribute to the level of diversion and misuse reported, although the data are purely subjective.

Concern over the diversion and misuse of medication is already high among survey respondents; 72% thought that diversion is a problem in their area and 52% felt the same about patients misusing their own medication. Although 70% felt it was their responsibility to address diversion and misuse, this was rated as the most difficult area of opioid-dependence treatment. Only 3% reported being very confident in this area while 33% of respondents found it very difficult.



This presents additional challenges for physicians, as all four countries allow the prescribing of take-home buprenorphine and methadone, although the restrictions under which this is possible vary widely.

The common response to diversion and misuse in many countries is to require supervised dosing. However, mandatory supervision appears to not correlate well with overall rates of diversion and misuse (1, 10, 16, 33, 37), can be a drain on limited treatment resources and may further serve to restrict patients' quality of life. Improving dosing practices to more closely match internationally accepted guidelines would be an important first step in addressing diversion and misuse given the that inadequate dosing appears to be a noteworthy risk factor (2, 8). Treatment options such as volume-expanded methadone and bup/nx may also be useful in this regard, and the evidence suggests that they can make a marked difference to diversion rates (4, 10, 15, 25). In total, 65% of physicians surveyed agreed that the prescribing of the least divertible medications is essential.

5. Conclusions

These results paint a troubling picture of opioid-dependence treatment in Europe. Prescribing practices are widely divergent from the clinical evidence base, with widespread non-therapeutic induction and maintenance dosing. Excessively slow buprenorphine induction times are also common. Evidence suggests that these practices may lead to diversion and misuse of medication, poor retention in treatment, and ultimately a lower quality of patient care. Indeed, the overwhelming majority of physicians in this survey felt that the quality of care in their countries is currently sub-optimal. This underscores a significant need for further education and training for physicians treating opioid dependence in Europe.

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Contributors

JB designed the questionnaire, contributed to the design of the study and drafted the manuscript. SR contributed to the design of the questionnaire, implemented the survey and analysed the data. AP conceived of the study, contributed to the design of the questionnaire and the drafting of the manuscript.

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Conflict of Interest

PCM Scientific has previously received untied educational grants from RBP and Merck Sharp and Dohme/Schering-Plough for educational activities related to opioid dependence.

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FORUM

Pre-Conference Session

Hilton Chicago - Illinois, USA

Sunday, October 24, 2010

EUROPEAN OPIATE ADDICTION TREATMENT ASSOCIATION (EUROPAD) -

TIME: 1:00 PM - 5:00 PM

Chairmen: Icro Maremmani, MD (Pisa, Italy, EU) - Marc Reisinger, MD (Brussels, Belgium, EU)

- 1:00 PM** *Opioid maintenance treatment (OMT) and patterns of crime reduction during treatment*
Clausen, T. (Oslo, Norway)
- 1:15 PM** *Is it possible to provide a democratic treatment in a non-democratic environment?*
Dvoryak, S. (Kiev, Ukraine)
- 1:30 PM** *Compared analysis of representations of needle exchange program in prison in France between inmates, medical team and prison staff*
Ferrer-Borras, D., Remy, A., and Sistach, D. (Perpignan, France, EU)
- 1:45 PM** *Philosophy of treatment and standards of care: the Bulgarian way*
Kantchelov, A. (Sofia, Bulgaria, EU)
- 2:00 PM** *Treating drug users with co-occurring mental disorders*
Kastelic, A. and Segrec, N. (Ljubljana, Slovenia, EU)
- 2:15 PM** *Are methadone and buprenorphine associated with a dramatic increase of fatal cardiac arrhythmias?*
Leonardi, C. (Rome, Italy, EU)
- 2:30 PM** *Drug users mortality in Slovenia: sociodemographic characteristics*
Lovrecic, B. and Semeri, J.S. (Ljubljana, Slovenia, EU)
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Clinical foundations for the use of methadone in patients with infectious diseases

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Summary

The immune system is an organization of cells and molecules with specialized roles in defending against infection. Communication between the central nervous and the immune system lies at the heart of the neuroimmune axis. There are several data indicating that opioids drugs may influence the immune system. One of the main features of opioid induced alteration of immune function is the development of immunosuppression. However, evidence has been provided to suggest that different opioids drugs may have distinctive effects on the immune system. Methadone is a widely used synthetic 3,3-diphenylpropylamine opioid which primarily acts at the μ opioid receptor. Its most common use is in the therapy for opioid dependence. Besides to their therapeutic efficacy, opioids can produce several well known adverse events, and, as has recently been recognized, can positively interfere with the immune response. Infact, data obtain from animal and human studies have demonstrated that long acting opioids drugs such as methadone is devoid of any intrinsic immunosuppressive activity. This effect may partly depend on the ability of methadone to restore the HPA axis function, that is altered in heroin dependent patient, or by the long-lasting activation of opioid receptors both in the central nervous system and on immune competent cells. HIV and HCV infections are the most frequent infectious disease seen in drugs users. Opioids may facilitate the outbreak of infections through marked immunomodulating effects on the immune responses against a virus. The enrolment of heroin patient in MMT programs represents a particularly effective measure for the prevention of HCV and HIV virus transmission and the immunorestoring properties of methadone are particularly relevant in the treatment of concurrent infectious such as HCV frequently associated with heroin addiction. It is evident that the possibility to reach an adequate control of addiction and of concomitant infectious diseases choosing either immunosuppressive drugs or drugs characterized by immunoneutral or immunostimulating effects could represent an important point to be considered in the future in opioid therapy.

Key Words: Methadone maintenance; HCV Infection; HIV Infection

The immune system is an organization of cells and molecules with specialized roles in providing defence against infection, There are two fundamentally different types of response against infections. However many times an infectious agent is encountered, innate or natural responses occur to the same degree, whereas acquired or adaptive responses improve on repeated exposure to a given infection. Methadone is a widely used synthetic 3,3-diphenylpropylamine opioid which acts primarily at the opioid receptor. Its most common use is in therapy for opioid dependence, but it is

also being increasingly used in the management of chronic pain. Besides their therapeutic efficacy, opioids can produce several well-known adverse events, and, as has recently been recognized, can interfere with the immune response. Morphine may decrease the effectiveness of several functions of both natural and adaptive immunity, while significantly reducing cellular immunity, too. The first demonstration that the activation of opioid receptors within the Central nervous System (CNS) was capable of modulating peripheral immune parameters was presented many years ago following the in

vivo administration of morphine in rats. Since then, a great deal of effort has gone into determining not only which immune parameters are modulated by the CNS, but also the specific action sites that mediate these responses, and how central opioid regulation influences the immune response.

1. Methadone and Immune function

It is well known that opioids, especially heroin and morphine, suppress the immune system and lower resistance to various infections [83]. Human and animal studies have, in fact, shown that both innate and acquired immunity are significantly affected by these drugs [70, 91]. The acute and the chronic administration of opioids both induce inhibitory effects on humoral and cellular immune responses, including antibody production, natural killer (NK)-lymphocyte activity, cytokine expression and phagocytic activity. The possible mechanism(s) of morphine-mediated immunosuppression may reside in the drug's ability to regulate the immune system either directly, by activating mu opioid receptors located on immune cells, or through an indirect central pathway, by activating mu opioid receptors in the CNS [69]. Receptors for opioids are expressed on the cell surface of mature lymphocytes, and are involved in mediating autocrine or paracrine types of response [13, 35, 53, 58]. Since the biochemical and hormonal perturbation that takes place during opioid withdrawal or intoxication has been implicated in opioid-induced immunosuppression [61, 62], it is possible that improvements in immune responses could partly depend on the constant activation of Mu Opioid Receptors (MOR) that is present with methadone in contrast to heroin-injecting subjects. Consistently with this hypothesis, it was shown in a monkey model of AIDS that the administration of morphine according to an experimental design that prevented intoxication or withdrawal conditions, did not exert any negative impact on immune responses and HIV disease progression. These authors also reported that a structured discontinuation of opiate administration precipitated immune alteration [14], indicating that the tonic activation of the opioid receptors on the lymphocyte cell surface did not produce any immunosuppressive effect [80, 81]. In agreement with these data is the observation that short-acting opioid drugs such as morphine and heroin produce severe changes in the immune system [55], while long-acting opioid drugs such as methadone are able to progressively restore immune function and cytokine concentrations [46]. The significant decrease in NK cell activity observed after the administration of morphine directly into the rat right lateral ventricle was blocked by the central administration of the opioid antagonist, naltrexone, suggesting that the opioid agonist suppressed the NK cell function primarily through opioid receptors located in the CNS [26]. In addition, the suppression of mitogen-induced whole blood lymphocyte proliferation in rats was demonstrated in the presence of

morphine, but not of its analogue, N-methyl-morphine, which cannot readily cross the blood-brain barrier [26]. Another mechanism that underlies the opioid-mediated modulation of the immune system is the ability of these compounds to influence immunocompetent cell production, as shown by the dose-dependent reduction in the numbers of T- and B-lymphocytes, NKs and monocytes/macrophages observed in the presence of morphine [72]. Opioids may also influence the immune function through activation of the descending pathways of the hypothalamus-pituitary-axis (HPA) and the sympathetic nervous system [83]. Activation of the HPA axis elicits the production of immunosuppressive glucocorticoids in the periphery, while activation of the sympathetic nervous system induces the release of epinephrine, nor-epinephrine and dopamine from adrenal medulla as well as from sympathetic nerve terminals innervating primary and secondary lymphoid organs [7, 16]. Both nor-epinephrine and glucocorticoids modulate the immune functions negatively by their action on leukocytes. In particular, the glucocorticoids play an important role in decreasing and regulating cellular immune responses [5]. Studies have shown that morphine treatments suppress immune parameters in mice through the HPA axis [60]. The ability of a centrally administered acute dose of morphine to inhibit either lymphocyte proliferation or NK cell activity appears to be primarily mediated by the sympathetic nervous system, whereas a more prolonged exposure to opioids alters the immune system predominantly by activating the HPA axis. In this respect it is interesting to note that longlasting treatment with methadone can normalize the HPA axis – the axis that is altered in heroin abusers – as demonstrated in various clinical studies [21]. The normalization of HPA after prolonged treatment with methadone could play an additional role in restoring the altered immune function observed in heroin abusers. A receptor-mediated increase in the production of the transforming growth factor, an immunosuppressive cytokine, is another possible indirect mechanism which may account for the ability of opiates to suppress immunity [11].

A variety of changes induced by chronic exposure to opioids have also been observed in the human immune system, by means of studies carried out in heroin addicts and in heroin withdrawal subjects. Govitrapong and colleagues documented a decrease in the immune system functions of both heroin addicts and subjects undergoing a short period of heroin withdrawal (between 15 to 21 days and 6 to 24 months). On the other hand, longer withdrawal periods, lasting over two years, were associated with a gradual return of some immunological parameters, such as the CD4/CD8 ratio and the absolute number of NK cell count, to normal levels [22]. From a pathophysiological viewpoint, the ability of heroin to induce immunosuppression may have some bearing on the higher rates of infectious diseases that are observed in heroin addicts, although the high percentage of infections among injecting drug users is probably related to

drug injection procedures and life-style practices [18, 82]. In this connection, one interesting issue is how long-acting opioids are able to restore the immune system. In fact, both preclinical and clinical studies appear to indicate that not all opioid receptor agonists share the same immunosuppressive properties [70]. The hypothesis that significant abnormalities of cellular immunity in heroin abusers can be normalized by using long-term methadone treatment was formulated many years ago, in a pivotal paper that analyzed the T cell genetic damage induced by various opioids [40]. Follow-up studies evaluated several immune parameters, such as NK activity, T lymphocyte subset numbers and function and phagocytic physiology, in methadone-maintained patients in comparison with heroin abusers [52]. More recently, further studies attempted to find out whether the improvements observed in immune responses in the course of methadone treatment were due to the drug profile or to the lifestyle changes that take place in maintenance treatment [1]. Accordingly, a randomized clinical trial recently reported that methadone was able to activate the immune systems that had formerly been inhibited by heroin in addicted patients [47].

The most surprising result was that cytokine levels in subjects on methadone treatment were higher than those observed in healthy volunteers. This may suggest that methadone, unlike heroin, has a stimulatory effect due to the immunologic hyperactivation of an immune system that was formerly inhibited by heroin. Recently, our group has investigated the immune system function in former heroin addicts who have been in maintenance therapy with methadone for at least six months, comparing them with untreated heroin addicts who are still injecting heroin, and with healthy controls [71]. The proliferation rate of peripheral blood monocytes induced by phytohemagglutinin in untreated heroin addicts was significantly lower than that observed in methadone-treated patients. Further, alterations of the Th1/Th2 balance and reduced levels of IL-4, TNF-, interferon -were reported in untreated heroin addicts, with respect to methadone-treated patients.

Because of the AIDS epidemic, interest in investigations on how drugs of abuse, especially opiates, affect the immune system has greatly increased. Clinical studies that aim to evaluate the immune function of HIV+ subjects have shown that MMTs prevent the progression of HIV, which, however, does take place in those who continue to use substances of abuse such as heroin, cocaine and morphine [67, 77]; in fact, the relative risk ratio (RR) of developing AIDS is higher in HIV+ drug users who do not take methadone (RR of 1.78) than in patients in treatment with methadone. Remission from drug use is in itself a protective condition, even in the absence of pharmacological treatment (in this case RR is 0.66, much lower than that of active drug users) [87], but still greater protection is provided by MMT (RR 0.44).

Against the background of these epidemiological data, which are enough by themselves to justify the elective indi-

cation of MMTPs for HIV-positive drug users, in this kind of population some issues are left open in connection with certain alterations in lymphocyte functions during MMTPs. MMTPs make it possible to improve some immune system functions, but a number of dysregulations that are hard to interpret are observed in the immune parameters of these patients. In particular, the lymphocyte subsets CD2, CD3, CD4, CD8 and NK cells are better represented in patients during MMTP than in heroin addicts who are still injecting heroin [52]; furthermore, during MMT there is an increase in lymphocyte subpopulations – in particular, of CD4 CD26, CD2, CD26 and CD8 – which are also functionally hypoactive [28]. These abnormalities of the immune system are most likely a result of acquired immunopathy due to chronic liver disease or to other infectious diseases that occur in this population [29] and, as such, have a tendency to decrease with the time spent in treatment [30].

The immune abnormalities which may be present in HIV+ subjects during their MMTP are probably associated with HIV infection itself, rather than with an immunosuppressive/immunodysregulatory effect of the drug. However, some aspects related to the management of therapy in patients moving towards AIDS as well as to humoral anti-methadone immunity (88% of HIV+ patients in MMTP have antimethadone antibodies [19, 20], are points of interest that should be investigated further. In the current state of knowledge we can say that MMTP is able to improve the immune system functions in heroin-addicted patients who are not users of other substances and are not affected by other causes of immunodeficiency, such as HIV infection. Therefore any alteration in the immune system observed in this kind of patient during an MMTP deserves further clinical investigation [31, 50, 54].

2. Methadone maintenance and HCV infection

Hepatitis C virus infection (HCV) is a clinical disease often (64-88%) associated with heroin addiction [12, 24, 54, 59]. The chronic character of hepatitis C and its evolution towards hepatic insufficiency causes 9% of all deaths associated with methadone maintenance treatment (MMT) [2]. The increased infectiveness of the virus and the existence of modes of transmission that cannot be neutralized by the clinical control of drug addiction most probably underlie the increased infectiousness of HCV, compared to other infectious diseases related to addiction, such as HBV and HIV [6]. The major risk factors that are the basis of infectiousness in patients in MMT are the frequent inadequacy of methadone doses, resulting in the continuation of the use of heroin, and the intravenous use of cocaine. Retrospective studies have pointed out that seropositivity for HCV is associated with elements of the clinical picture that reflect both the duration and the severity of addiction [24]. In fact, in many heroin addicts, especially those who experience intravenous addiction, there

is the co-presence of one or more viral infections, such as HCV and HBV [24]. This finding in particular suggests that during the active phase of the disease, sources of infection associated with drug abuse practices are the main channels of infection for different pathogens. In HCV infection, cellular and humoral immunological mechanisms participate in viral clearance in the liver, peripheral blood and lymphatic organs. However, the role played by the immune system in the progression of chronic hepatitis is not completely clear and the mechanisms responsible for the persistence or viral clearance are still largely unknown. The activation of T cell responses is considered one crucial mechanism in the antiviral immune response against viruses [9, 15]. It is generally accepted that opioids may facilitate the outbreak of infections through marked immunomodulating effects on the immune response against a virus. Conversely, opioids seem to exert a biphasic action on cytokine production, as this action is mediated by endogenous opioids. In any case, opioid receptor overexpression or deficiency would predispose aberrant defensive mechanisms [57, 68]. Interferon in combination with ribavirin is currently the most effective therapy for patients with HCV infection, and the positive effects of this combination therapy may not be directly antiviral but mainly immunomodulatory [9, 15]. In this connection it is important to note that opioids are able to interact with the immune system, and different types of opioid receptors have been detected on various cell types, including blood mononuclear elements which differentiate as macrophages in tissue. In fact, suppressed NK activity was demonstrated in heroin and in polydrug abusers and NK antibody dependent cell-mediated cytotoxicity (ADCC) was present in injecting drug users. Conversely, some experimental data have shown that the opioid effects on the immune system are not necessarily deleterious; in fact, the endogenous opioid met-enkephalin was seen to determine immunostimulatory activity on T cells. These different effects (inhibitory or stimulatory) of opioids on immune system functions could be explained by the method or duration of chronic drug use [56, 88]. However, it has been observed that the immune functions that become normalized in drug abusers on long-term methadone maintenance as a result of methadone's longlasting action comprise the normalization of the HPA axis, the consequent persistence of the drug level, and the greater endurance of receptor stimulation [32, 45, 71]. Heroin addicts presented significantly low levels of NK cell activity, whereas patients treated with methadone over a long period, from 5 to 8 years, showed a progressive and constant normalization of NK cell activity. Likewise, data presented in the literature suggest that IL-2 and TNF-alpha production is a predictive index of a good response to IFN-alpha treatment in patients affected by a chronic hepatitis C virus, even in non-drug users. The plasma levels of TNF-alpha, IL-2 and IFN-gamma in patients affected by chronic active virus C hepatitis rose significantly in patients during methadone treatment [48]. Because of their

poor compliance, drug users with HCV are usually treated for only a few months after the end of methadone therapy. Nevertheless, specific IFN therapy may be recommended in drug addicts during methadone treatment, since this period is immunologically favourable for antiviral treatment.

2.1 Methadone maintenance for HCV-positive patients

Chronic Hepatitis C, in its natural history, alternates between periods of persistence of the virus without clinical evidence of hepatic suffering, and periods of increased infectiveness, with or without the presence of specific or non-specific symptoms. In any case, the presence of severe chronic hepatopathy is not a clinical counterindication for beginning and/or continuing a pharmacological treatment with methadone [51]. The belief that people suffering from hepatitis C are intolerant to methadone and/or are more sensitive to unspecified hepatotoxic effects of methadone itself, is unmotivated. In any case, pharmacological treatment with methadone has a positive impact on the liver function of patients with HCV-related liver disease; in fact, plasma transaminase levels are higher in non-treatment than in cases of methadone treatment [39]. The lowering of plasma transaminases is probably related to the clinical remission of drug behaviours, and any direct hepatotoxic damage from a drug (as in the case of naltrexone) appears to be clinically less significant for the liver as compared with a clinical addiction not treated pharmacologically. Furthermore, long-acting opioids seem to improve the outcome of the viral infection, as suggested by the ability of methadone to significantly reduce the relapse rate of patients undergoing interferon and ribavirin treatment [48]. With hepatopathic patients, the choice of using a daily dosage of methadone below the levels recommended in the international literature has a clinical rationale only when there is a rapid progression of liver disease towards a form of cirrhosis. This clinical attitude has a pharmacological rationale, considering that in such situations, the sudden reduction of liver function resulting in a reduction of the hepatic absorption of methadone, will gradually develop tolerance to the amount given, with a subsequent increase in plasma concentration, when the quantities being administered remain constant. Normally, in a patient who has cirrhosis *ab initio*, the best recommendation is to use appropriately reduced posology and patterns of introduction [49, 51], whereas in patients undergoing active hepatitis, an increase in daily dosage may be required, since the activation of C infection can actually lead to an increase in the enzymatic activities that are responsible for the hepatic metabolism of methadone [42]. After all, the inclusion of HCV+ subjects in methadone maintenance programmes appears to be a priority, not only for the remission of the underlying disease but especially since the progression rate of hepatitis C is lower in these treatment conditions. The clinical measures to be taken in managing drug addicts suffering from HCV,

should include: (1) the enrolment of the patient in an MMT as quickly as possible; (2) the initiation of a parallel treatment to reduce the possible consumption of alcohol and cocaine; (3) verification of the presence of antibodies to HAV and HBV and possibly an immunoprophylaxis treatment through vaccination; (3) an assessment of the desirability / feasibility of starting a specific antiviral therapy for HCV [85].

2.2 Antiviral Therapy in MMT patients

The treatment of HCV infection with interferon and ribavirin proved feasible in patients who had good compliance with methadone treatment, regardless of the presence of a dual diagnosis (62% of the sample) or the continued use of alcohol (21%) and drugs (31%) during the antiviral therapy itself [79]. The data reported in the literature indicate the presence of a satisfactory and stable clinical response to the antiviral therapy among heroin addicts in MMT – a response which is quite similar to that observed in non-addicted patients treated for HCV infection (40%) [79]. In a population of non-selected patients, a number of factors such as older age, prevalence of significant psychiatric disorders, a more advanced hepatopathic stage and the use of opioid drugs have a negative impact on the response to antiviral therapy (29%) [12, 79]. In the selection of patients to be directed to an antiviral treatment, it should be borne in mind that a priority should be given to those for whom methadone therapy is not only able to determine the remission of drug addiction, but also control over the use of other drugs, so avoiding any indication of suitability for the treatment of patients with a low probability of clinical response to antiviral treatment. From this perspective, pharmacological treatment with methadone offers the most effective therapeutic strategy for drug-addicted patients to get anti-HCV treatment. The incidence of mood disorders, states of anxiety and depressive symptoms in patients secondary to treatment with interferon and ribavirin in patients in MMT is similar to that seen in non-addicted patients, but the severity of the sequence of symptoms is less marked in patients treated with methadone [73]. In order to reduce the side-effects of antiviral treatments on mood, the following are effective: a) an increase in the daily dosage of methadone during antiviral treatments; b) the preventive use of antidepressant drugs (SSRIs). In patients in MMT, cases of drop-out from antiviral treatments are not correlated with therapeutic status nor with the presence of mood disturbances, depression in particular.

3. Methadone maintenance and HIV infection

3.1 Methadone and prevention of serum conversion

The enrolment of heroin patients in MMT programmes is a particularly effective measure for the prevention of HIV virus transmission [4, 17, 84]. Indeed, several retrospective

epidemiological studies have provided evidence that in a population of people addicted to heroin, those who had been enrolled in MMT before 1981 showed a //lower incidence of death caused by AIDS than those who received pharmacological treatment after 1981 [75]. During the period corresponding to the epidemic diffusion of HIV infection, the terminal phase of the viral infection was the most important cause of death among those treated with MMT, in spite of the decline in the importance of other causes of death related to drug addiction [2]. In this sense, MMT seems to have played a protective role, especially in patients who were enrolled before the epidemic diffusion of HIV and who presented a condition of serum negativity to the HIV virus. Those patients have consequently maintained a negative serological status as a result of their pharmacological treatment in the years when the HIV epidemic was spreading. The hypothesis of protective action from MMT is strengthened by the observation that some patients who had been enrolled in MMT before 1981 and left the treatment for 1 year during the period when the epidemic was active, after which they re-enrolled in MMT, died of AIDS [75]. In order to reduce the spread of HIV among addicted people, optimization of the strategy should aim to achieve early enrolment in the treatment, so reducing their exposure time to risks of infection. Once enrolled in an MMT treatment, the protective role of these agents tends to persist in proportion to the rate at which good therapeutic results, especially withdrawal from the endovenous use of drugs of abuse, are achieved. Indeed, when starting MMTs, HIV-negative subjects maintain serum negativity both in the short [27], medium [92], and the long term, providing that the treatment is carried out uninterruptedly [50]. As already stated, continuity in treatment is the main feature on which the protective role towards serum conversion for HIV is based: subjects suspending the treatment tend to show a higher degree of serum conversion [3, 10, 90] with respect to those who remain for longer periods in pharmacological treatment. This effect is already clear-cut as little as 18 months after the interruption of methadone treatment, (3.5% vs 22% of serum conversions for HIV among subjects treated with respect to those who have interrupted the treatment) [43]: any relapse in the use of abuse substances is thus readily followed by the reappearance of the use behaviours that facilitate the spread of the HIV virus. However, one noteworthy underlying factor is that, even in MMT-treated subjects, rates of serum conversion are not completely suppressed [44, 76]: indeed, an epidemiological investigation carried out in the United States showed a serum conversion rate of 1.3% even among patients who were treated for at least one year during the epidemic diffusion of HIV infection between 1985 and 1990. In this connection, it can be presumed that some of these subjects have relapsed into using drugs of abuse at the end of their pharmacological treatment, with the consequent adoption of risk behaviours for the transmission of infectious diseases related to dependence. From a clinical viewpoint,

the real evaluation of MMT efficacy in preventing HIV from spreading among people addicted to heroin is correlated with the efficacy of this treatment in controlling possible relapses into any recourse to drugs of abuse. Short-lasting pharmacological treatments or those carried out with inadequate and/or sub-therapeutic dosages fail to provide satisfactory protection from the risks of contracting the infection. Lack of protection may become evident both during the treatment, in the case of sub-therapeutic dosages, and after the end of the treatment, in the case of unduly short-lasting programmes – those carried out below the “security limits” [34]. Furthermore, the use of subtherapeutic treatments, based on doses that are ineffective in reducing heroin craving, must itself be considered a negative feature that weakens retention in treatment [25, 74] and predisposes the subject to a relapses into heroin use. Reduction of the risks of infection in subjects addicted to heroin with unsafe behaviours is extremely important, especially for the kind of population being considered, since the subjects who are a target for the infection also represent the ‘reservoir’ of the infection itself. Consequently, in this population the probability of transmission of the disease is quick to show the typical features of an epidemic diffusion. In this regard, a study carried out in Vienna has shown that all the subjects entering an MMTP from the second half of the 1980s onwards displayed a progressive increase in the rate of positivity to the infection (from 8.5 to 29.7%); this increase abated in conjunction with the growing use in the district of Vienna of methadone treatment, which led to a reduction, even if modest, of the rates of infection (from 29.7% to 26.9%) [36]. This reduction does not seem to be exclusively due to fall in the availability of subjects who might have been infected, since one distinctive feature of the addicted population is the high turnover of subjects. This observation is confirmed by a comparative analysis carried out in several European countries, which reported that the high percentage of intravenous drug users (IDU) treated with MMT is inversely proportional to the prevalence of HIV infection. In addition, countries with a low prevalence of HIV infection are characterized by a rise in the number of cases between 1987 and 1992. During that time lag period, the European countries which had both a low prevalence and a low incidence of the infection were further distinguished from the other European countries by having a much higher percentage of drug addicts enrolled in MMTs [63-65, 86, 92].

3.2 Behavioural targets in methadone maintenance

The appearance of a full response to methadone therapy, as a consequence of withdrawal from taking drugs of abuse, induces a reduction in risky behaviours [75, 90]. However, a beneficial effect on the risk of contracting infectious diseases related to dependence can also be recognized in heroin addicts who respond, even if partially, to treatments. Even if these

individuals do not stop taking heroin during MMTP treatment, it is well documented that in these cases patients who are still heroin-addicted at least reduce syringe interchange significantly [78, 89]; from a behavioural viewpoint this is interpretable as an increase in attention towards their own safety (the tendency “to borrow a syringe” is, indeed, weaker than the tendency “to loan a syringe”) [78]. It is also evident that a reduction in the frequency of taking drugs of abuse is paralleled by a reduced tendency to interchange syringes [8]. This last phenomenon can be partly related to a higher tendency to take drugs occasionally and on their own, with a less recurrent use of drugs taken together with those who are defined as “needle mates” [23, 33, 90]. However, some data in the literature suggest that even when greater attention is given to rules on hygiene, such as the washing of used syringes, this may not be accompanied by behavioural changes in the habit of interchanging syringes [3]. A limitation of sexual promiscuity is another important issue to be considered in preventing the spread of HIV infection. MMT subjects reported having had fewer partners in the period preceding the interview [23, 37, 38, 86, 90], even if, from this standpoint, there are conflicting data in the literature [3, 33, 78]. Furthermore, the number of partners in the year preceding the interview proved to be inversely proportional to MMTP duration [38], confirming the importance of treatment retention as a stabilizing factor. Viewed as an isolated factor, retention in treatment seems to be directly proportional to the daily dosage of methadone. The sexual activity of subjects undergoing treatment persists as a result of the search for personal satisfaction, while prostitution tends to become less common. Although there is no general consensus on the possibly higher attention displayed by MMTP patients to condom use [23, 37, 41, 86], the concept of sexuality for these patients is mostly oriented towards the search for personal satisfaction, with the consequent exhaustion of a series of phenomena which favour promiscuity, such as prostitution [86]. An indirect, but significant, demonstration of the usefulness of methadone treatment as a tool for the prevention of the spread of HIV infection is the fall observed in serum conversion between sexual partners in MMTP patients [76]. A possible explanation for the discrepancies in the data on risky sexual practices is based on the presence, among MMTP patients, of subgroups of patients with unsafe behaviours, which are not directly related to the use of heroin, but to the use of other drugs of abuse, such as cocaine and/or patients with mental diseases unrelated to dependence [10]. There is, however, a common consensus on the evidence that MMTP treatments are effective in reducing the risks of HIV infection risk that derive from risky behaviours [65].

3.3 Methadone and the reduction of infection risk in low threshold programmes

Harm Reduction (HR) traditionally sets a premium on

handling the contingencies of a specific case or of an illness by adopting measures that aim to prevent and/or reduce risks deriving from drugs of abuse, rather than planning a specific therapeutic programme that aims for a clinical resolution of the illness itself. By contrast, when the path chosen is that of a specific intervention on drug dependence, the dominant idea is that the use of sub-therapeutic dosages of methadone or of non-continuous cycles of methadone therapy are useless, since these interventions will not lead to recovery from the illness. One outcome of this dichotomy has been that the tool 'methadone' has been segregated exclusively for use in specific, structured programmes. Furthermore, "HR" programmes are prevalently based on non-pharmacological interventions, such as the distribution of condoms, contingent support, or, when intervention is pharmacological, it is exclusively carried out with symptomatic drugs. In our opinion the true intrinsic difference in HR does not depend on the means to be used, but on the need to use both pharmacological and non-pharmacological approaches, in relation to the therapeutic needs of a target patient who displays poor compliance and/or is characterized by having to face degrading psychosocial conditions. In any case, HR programmes should refrain from excluding a pharmacological tool such as methadone. Indeed, even in subtherapeutic dosages, besides its contingent usefulness in combating the anti-withdrawal syndrome, pharmacological treatment with methadone could be particularly useful in reducing some risky behaviours that may lead to a rise in the transmission of infections. In general, infections transmitted in this way are a consequence both of a partial effect on craving, and of a 'cooling' effect on peaks of psychopathological distress, which are often associated with impulsive behaviours that themselves lead to leading to risky behaviours. In most cases such behaviours are not under the patient's control and therefore place him/her in a condition of higher vulnerability to the transmission of infectious diseases related to dependence. In addition, any reduction in the need to consume drugs of abuse, as well as in ideation in their favour, allows the 'on the road' drug abuser not only to participate more advantageously and directly in informative campaigns, but also to take in what can be learned on these occasions. The utility of prevention campaigns, which is already evident in the absence of pharmacological adjuvants [6], might therefore be enhanced, even in the absence of any drastic reduction in the chronic use of drugs of abuse. When the impact of MMTP is reduced, that is undoubtedly linked to a significant increase in the risks and the damage associated with drug dependence [23, 66].

4. Conclusions

Although many advances have been made in understanding the effects of opioid drugs on immune response, the real clinical relevance of these effects has only emerged recently. It has been definitively shown that not all opioid drugs share

the same immune profile. Chronic morphine administration in animals and long-term heroin in humans have consistently been associated with immunosuppression and a higher rate of infection. Conversely, it has now become clear from human and animal studies that methadone is not only devoid of any intrinsic immunosuppressive effect but that it is able to progressively restore immune system functions. This effect may partly depend on the ability of methadone to restore the HPA axis function, which is altered in heroin-dependent patients, or by the longlasting activation of opioid receptors both in the central nervous system and on immune competent cells. The immunorestoring properties of methadone are key factors in the treatment of concurrent infections, such as HCV, which are frequently associated with heroin addiction. In fact, evaluation prior to, during and after methadone treatment has revealed that heroin addicts with HCV can be successfully treated with pegylated interferons and ribavirine, suggesting that therapy should be initiated during the MMT to achieve a more sustained response. Indeed, it is evident that the objective of achieving adequate control of addiction and of concomitant infectious diseases by choosing either immunosuppressive drugs or drugs characterized by immunoneutral or immunostimulating effects could become an important focus of attention in the future in opioid therapy. It must be added that further clinical studies are needed to gain a better understanding of the impact of chronic opioid treatment on the immune system.

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Bioethical preferences of supporters and opponents of agonist opioid therapy in Russia

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TO THE EDITOR: The question of the bioethical preferences of Russian experts providing drug treatment services has arisen out of an attempt to understand the reasons for a ban on the introduction of agonist opioid therapy (AOT) in the Russian Federation. The reasons for the aversion towards this kind of treatment in law enforcement agencies and in society are clear: they are ideological in character. What is less clear is why the experts in drug addiction treatment possessing scientific knowledge so actively counteract the introduction of AOT.

To understand a situation of how medical care can deal with opioid dependence in Russia it is important to understand the context of the problem. Here are some legislative drug policy initiatives taken over the last few years. In 2006 it was decided to return to the practice of the compulsory treatment of drug addicts. This practice had existed in the Soviet Union and the Russian Federation till 1993. Many experts in addiction medicine advocated the introduction of compulsory treatment, meaning the hospitalization of drug addicts in special centres for 1-2 years and treatment without the patient's consent. The scientific community managed to confine the discussion to a single channel – that of the need for the introduction of the quasi-compulsory treatment that is used in many European countries.

In 2008 a new initiative appeared which will probably become law in the near future. It refers to the introduction of the obligatory testing of all students for drug taking. This initiative had the support of a great number of experts in addiction medicine.

Recently legislators were asked if they wished to introduce

criminal penalties for the use of drugs. At present drug taking is an administrative, not a criminal offence. It is good that this initiative has not been supported.

The application of AOT is still forbidden in Russia by law and it is worth noting that many narcologists support this policy [8, 9].

On the whole drug policy has an impact on addiction medicine around the world. In particular, therapeutic approaches in Russia undergo the effects of the repressive thinking of legislators and public opinion. In many respects the development of this branch of science is defined by the law enforcement agency.

Due to these negative factors it could be stated that, de facto, a drug addict is not considered to be a 'real patient' [7]. This leads to the development of such inadequate practices as an expansion of addict registration (for example, even for those who have only experienced drug taking without any signs of dependence); infringement of the principle of 'informed consent'; infringements of confidentiality when data on a patient are easily accessible to the law enforcement agency; and, certainly, a categorical ban on AOT.

The current situation of addiction medicine in Russia is characterized by the following:

- 1) about 2.5 million people use drugs;
- 2) over 550 thousand are officially registered in narcological dispensaries as drug addicts;
- 3) more than 90% of these are dependent on opiates;
- 4) there are over 30 thousand fatal cases from drug overdoses (to give a comparison, in the European Union, taking into account the difference in population, the

rate of drug-related deaths in 15 times less!);

- 5) there are more than 500 thousand officially registered HIV-infection cases, of which over 67% are injection drug users, with about 60 thousand new cases of infection in 2009.

Official standards of treatment of opioid dependence usually include neuroleptics, antidepressants, tranquilizers, anticonvulsants [13]. These standards essentially differ from the practice of using agonists or antagonists of opioid receptors, as recommended by the WHO. Traditionally in Russia psychotherapy methods, basically with a directive orientation (hypnosis, for example) are widely used. Medical doctors use the given kind of therapy in an overwhelming majority of cases — over 80%. Some years ago scientists from Novosibirsk Medical Academy offered a unique method — therapeutic spanking, having proved the efficiency of the method of treatment by its influence on the endorphin pathway [14]. Fortunately, it was possible to stop anti-human practices of this type. The same concerns arose with the practice of neurosurgical operations, which were used for the treatment of opioid dependence at the St. Petersburg Brain Institute [16].

Such kinds of antiscientific methods are supported by some officials in the Russian public health services. At the same time a categorical ban has been imposed on the introduction and even on the discussion of AOT. The current legislation does not allow the application of opioid agonists for drug treatment.

It is possible to agree with the former director UNAIDS that “In the twenty-first century it is hard to understand that there is a group of countries that do not want to introduce substitution treatment”. It is paradoxical, but the fact is that the overwhelming majority of respondents attribute drug addiction to social deviation, instead of illnesses, and at the same time 80.6% of them are convinced that drug addicts need to be treated, while about 40% consider it is necessary to treat them compulsorily [9].

For an understanding of the situation of addiction medicine in Russia it is important to notice the fact that, along with aversion to AOT in Russian medicine, there is a negative attitude to the use of opioid analgesics even within the limits of palliative help. For example, comparing Russia’s situation with Canada’s, opioid analgesics are prescribed 100 times less.

One other feature is the great influence of Orthodox Church when it comes to choosing treatment techniques and ways of rehabilitating drug addicts in the Russian Federation. This situation has led to the result that 54.5% of narcolo- gists consider religion to be “the most effective method of treatment” [9].

Thus, we are inclined to assume that the ban on the use of OAT in Russian addiction medicine is connected with bioethical barriers — with the specific bioethical preferences of medical doctors [2, 3, 5, 6, 12, 15]. Many international

experts think that OAT is one of the most important bioethical problems [1, 2, 11], like other major ethical problems to be faced in psychiatry [4].

One of the basic conflicts in modern addiction medicine which was defined by Jonass Hartelius in 2006: “the conflict between those who support the lifetime maintenance of opioid addicts by compulsory treatment with those who support the lifetime maintenance of opioid addicts by means of treatment with methadone and buprenorphine».

Many experts in the world ask themselves why Russia says no to methadone. To find the answer to this question it is necessary to know who creates obstacles and who decides whether Russia needs or does not need AOT. Russian medical officials do not hide their opinion and openly oppose AOT. For example, Prof. Gennady Onishenko – chief health care inspector of the Russian Federation – said in 2009 that “substitution therapy is a first step to legalizing drugs” and “there is no scientific evidence of the effectiveness of substitution therapy in the world”.

From our point of view, the basic bioethical problem of modern Russian narcology is the refusal to recognize drug addiction as a real illness. In this connection it is possible to speak about the existence of a new/old paradigm of “antinarcology”. More than 60 years ago similar phenomena existed in the field of psychiatry.

The purpose of this sociological research was the study of the bioethical choices made by the supporters and opponents of AOT. The research group consisted of experts providing drug treatment services. Respondents filled out an anonymous questionnaire that listed 19 questions on various issues in modern bioethics: euthanasia, abortion, cloning, compulsory treatment and testing, surgically produced changes in sex, placebo-controlled trials, patient’s confidentiality, patients’ rights in the field of child-bearing, HR programmes and some others. 246 respondents took part in the survey.

The positions taken by respondents on bioethical problems are shown in table 1.

51.2% of respondents supported AOT, whereas 31.3% opposed it. As shown by the results of the correlation analysis, the attitude to AOT is significantly linked with such bioethical problems as: the attitude to euthanasia, the attitude to compulsory treatment, the attitude to HR programmes, to those with an HIV infection or with drug dependence as to illnesses, and also to a principle of informed consent and even with the attitude to placebo-controlled trials (figure 1).

As was to be expected, the results of sociological research have shown that supporters and opponents of OST took up different attitudes to the compulsory treatment of drug addicts. Authentic distinctions on the given indicators have become apparent. Among supporters of OST compulsory treatment received support from 1.5 fewer respondents than from opponents of OST

Another expected feature was that the overwhelming majority (80.9%) of supporters of OST also supported HR-

Table 1. Positions taken by respondents on bioethical problems

	Agree %	Disagree %	Difficult to answer %
Euthanasia	41.50	38.60	19.90
Surgical change of sex	61.00	27.60	11.40
“Homosexuality as a disease”	21.10	62.20	16.70
Cloning	27.60	44.30	28.10
Abortion	77.70	15.00	7.30
Opioid analgesics	87.00	8.50	4.50
“HIV-infected are responsible for illness”	19.50	43.10	37.40
Transplantology	86.20	6.10	7.70
Compulsory treatment	62.60	29.30	8.10
Ban on mentally sick being allowed to have children	40.60	37.80	21.60
Opioid substitution therapy (agonist opioid treatment)	51.20	31.30	17.50
Harm Reduction programmes	73.50	16.70	9.80
Compulsory testing of drug use	47.20	39.00	13.80
Ban on placebo-controlled trails	28.50	37.40	34.10
Confidentiality guarantees in narcology	35.40	55.70	8.90
Drug addiction as a disease	75.60	16.30	8.10

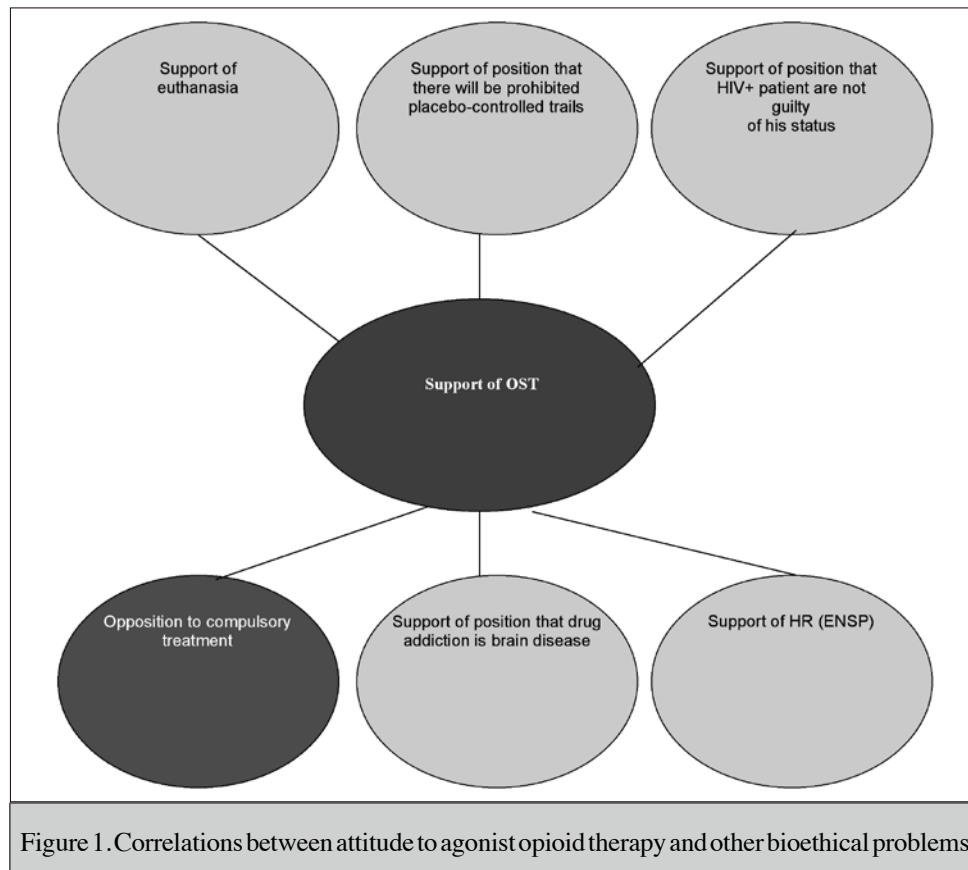


Figure 1. Correlations between attitude to agonist opioid therapy and other bioethical problems

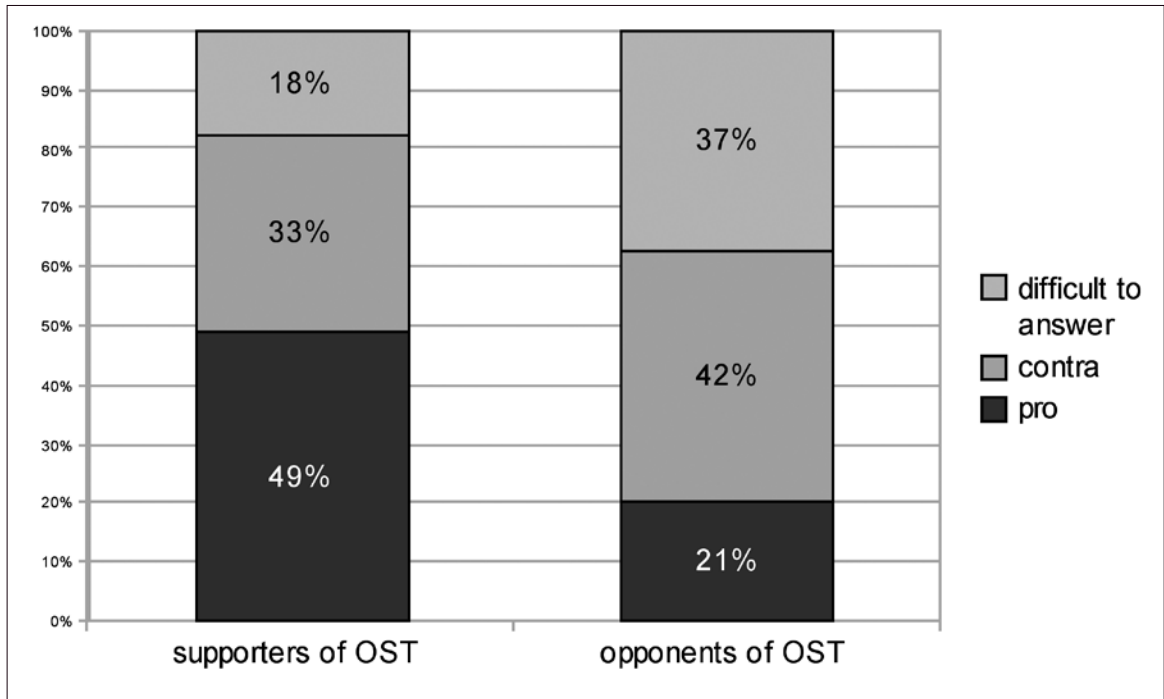


Figure 2. Attitudes to euthanasia procedures

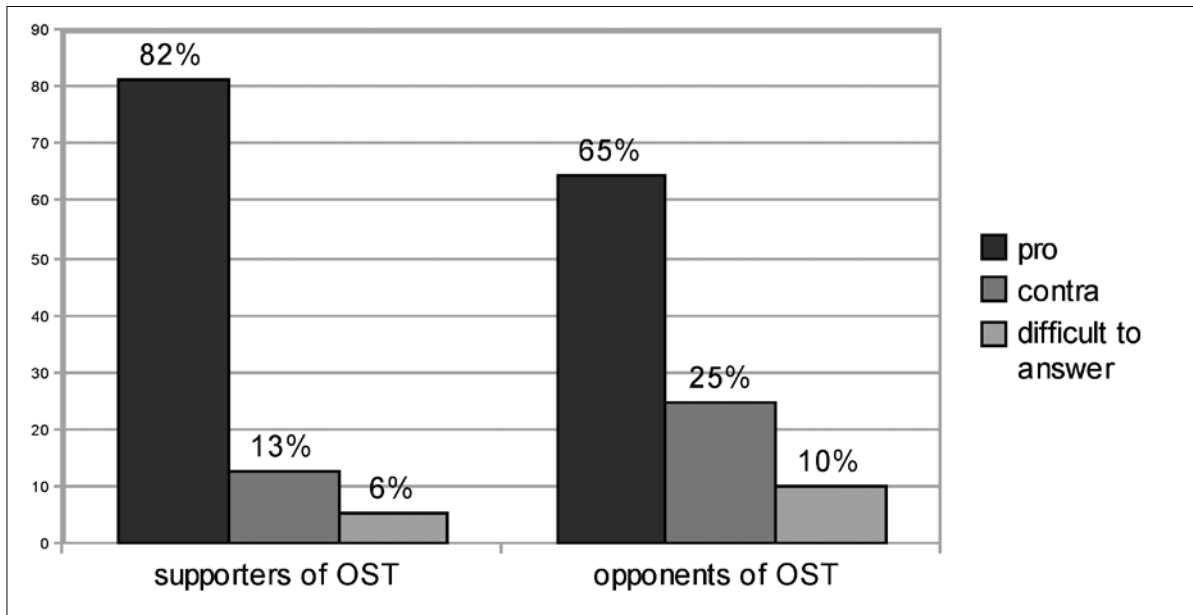


Figure 3. Attitude to needle and syringe exchange

programmes.

One point of special interest was the bioethical preferences of supporters and opponents of OST. The results of research have shown significant distinctions between supporters and opponents of OST in terms of their attitudes to euthanasia. It emerged that among supporters of OST more than twice the frequency of positive attitudes to euthanasia procedures

was recorded (figure 2).

There were no significant distinctions in relation to abortions.

However, among opponents of OST, those who spoke against giving permission to proceed with surgically produced sex changes formed a significant majority.

75% of respondents supported HR programmes in the

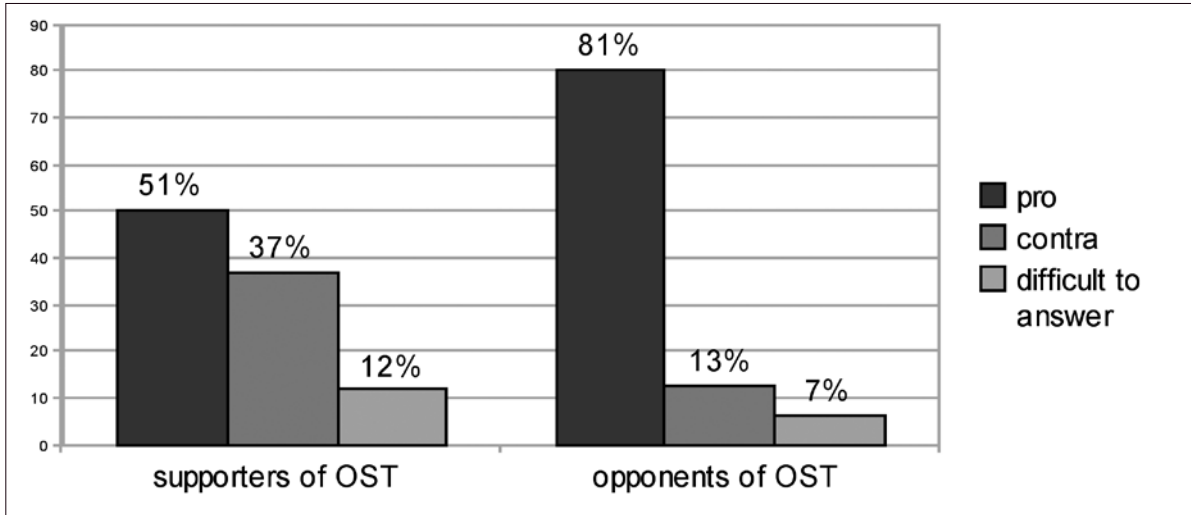


Figure 4. Attitude to compulsory treatment of drug addiction

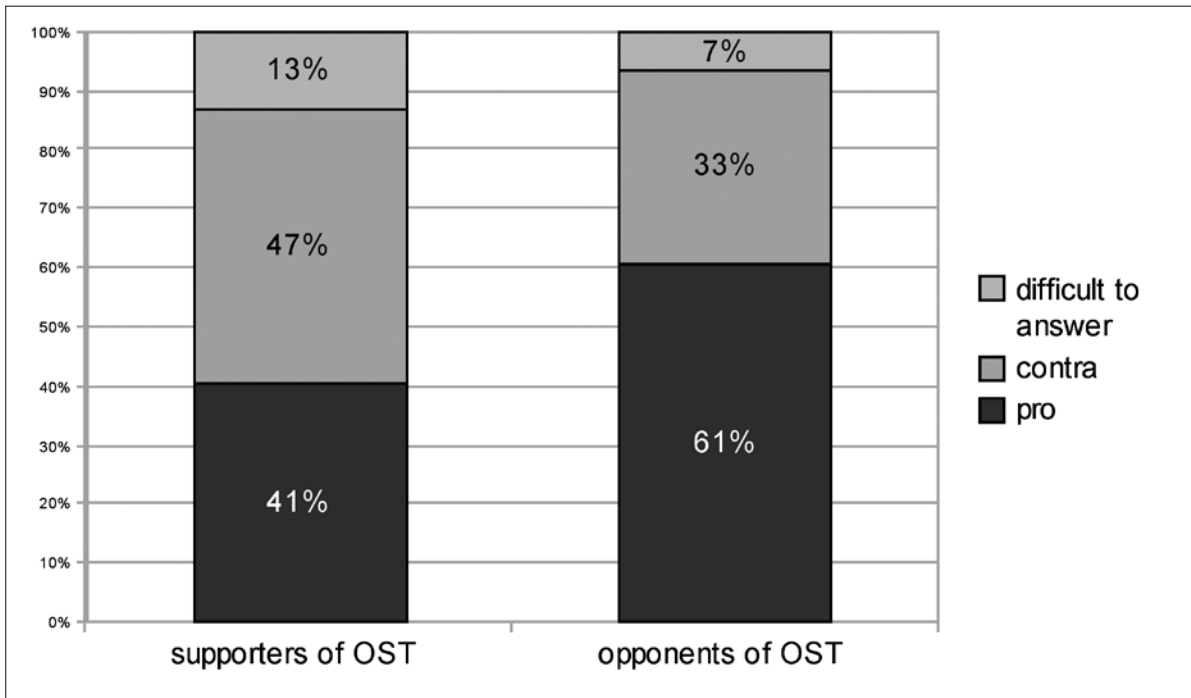


Figure 5. Acceptability that in a narcological clinic data on drug addicts could be transferred to law enforcement bodies

form of needle and syringe exchanges (ENS), 89.8% supported the distribution of condoms. It was therefore evident that different kinds of HR programmes elicit different responses. Among supporters of OST 80.9% supported ENS programmes. More than a quarter of the supporters of ENS programmes opposed OST. Lastly, among the opponents of OST 64.9% supported ENS programmes (figure 3).

Of particular interest is the observation that those supporting OST are less likely to support the compulsory treatment (CT) of drug addiction (50.8% and 80.5%, respectively).

Another point of interest is a high number of those who supported both options (figure 4).

It was interesting that among the supporters and opponents of OST there were significant distinctions in relation to indicators on the compulsory testing of students and school children on the use of drugs and linkage to a strict observance of confidentiality. So it turned out that among opponents of OST there was a significant majority of those who supported compulsory testing and were against a strict observance of confidentiality for patients with drug addiction. Opponents

of OST considered it to be acceptable that in a narcological clinic data on drug addicts could be transferred to law enforcement bodies (figure 5).

No significant results emerged from the indicators related to a ban on allowing the mentally sick to have children.

The answer which from our point of view could throw light on the reasons for support of or opposition to OST, is the answer to a question whether to consider drug dependence as a brain illness or a form of social deviation. It appears from our data that opponents of OST considered a drug addiction as an illness at a significantly lower frequency.

Thus, the sociological research presented here has shown that the relation of medical doctors to AOT is directly connected with their bioethical preferences. This finding should be taken as one more reason for adopting a new approach to this scientifically well-founded technique.

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The pleasure constant

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TO THE EDITOR: Nietzsche says: “life is simply the will to power [...]”. Those working with the addicted can say: life is simply the will to pleasure! Alternatively: where there is displeasure – there must be an addiction!

But pleasure and fun as motives for consumption are overlooked in much of the literature on drug research [1]. Some researchers stress the importance of the development of strategies focused on keeping the needs of health, tranquillity, affection, respect and success satisfied [2]. Others find salty food to be like a new drug [3]. There are valid criteria for recognizing new addictions like the addiction for technology [4]. The role of insula in the brain makes drug addiction like naturally motivated behaviour, such as eating and sex, and being without insula is a critical neural substrate in the addiction to smoking [5,6].

The role of licit and illicit drugs is to provide pleasure: poor smokers in the French inquiry talked about the pleasure they get from smoking, and they highlighted the essential needs that are satisfied by smoking: stress relief, cheap leisure, compensation for loneliness, break-up or redundancy... [7]. We have to rethink some diseases such as anorexia nervosa or define criteria for new ones like the authors of the salted food addiction hypothesis [3].

The pleasure constant hypothesis

Maslow has set up a hierarchical theory of needs. Physiological and safety needs, the need for love, affection and a feeling of belonging, and also the needs for esteem, and self-realization – they all go to make up a pyramid.

But needs are followed by pleasure and only pleasure is important. We do things for pleasure or to avoid dissatisfaction, rather than because of needs. Being human is itself a kind of pleasure.

Every person is capable of enjoyment only in accordance with his or her own capacity for pleasure. That capacity is unlikely to change, so it can be considered almost constant. We use the expression ‘pleasure constant’, which can be interpreted as the multiplication of single pleasures. The pleasure constant is specific for an individual as a personal characteristic. The formula is: $A \times B \times C \times D \times E \times N = \text{const.}$ If one factor decreases the others must increase, and the product remains the same.

The pleasure constant differs in size in different individuals.

The pleasure constant differs in structure in different people.

The pleasure constant and addictions

Those working day by day with addicted people can understand that the single biggest factor in obtaining pleasure is drugs. After taking them, the structure of the pleasure constant has changed. The addicted person needs little or no food, water or sex. All other pleasures count for very little. Pleasures from drugs are often stronger than morality or fear. Theft, robbery, murder, everything is possible to profit from such a strong source of pleasure. It sounds horrible and inhuman, but actually we are daily witnesses to these events. Human beings have only one need – pleasure. If a subject

is hindered in achieving it, everything becomes possible.

Where there is discontent, drugs arrive. In one form or another – alcohol, tobacco, illicit drugs or in the form of obsessive working, exercising, games, gambling, food, religion in an extreme form, and so on.

The pleasure obtainable from drugs or pleasure itself is often stronger than life itself. Heroin changes and destroys everything. In the absence of other pleasures the individual comes to enjoy self-destruction. Pleasure can be taken from altruism, sacrifice and self-destruction for others or for the common good.

Sexual pleasure and pleasure from drugs

I asked a young heroin addict what he would choose between heroin syringes and the prettiest girl. Without any hesitation the answer was the syringe. This example drawn from daily experience shows the importance of drug-induced pleasure for the addicted. The ultimate physiological pleasure is replaced by the pathological one. As previously shown, the structure of the constant has been changed.

Treatment

In applying treatment, we can proceed in the reverse order. We have to ask patients where they find pleasure in everyday life, to encourage them to find new pleasures, or rediscover the old ones. Every single pleasure that can be experienced by an addicted person is a sign of healing. Weight gain is a good sign that the formula of satisfaction is acting on the side of life. If addicts take pleasure in their families, partners, friends or new interests – all that shows that treatment is making progress. Even a switch from one addiction to another (most commonly, from heroin to alcohol) that means a reinforcement of the pleasure constant, even if in a pathological form.

So we can conclude:

1. Every healthy pleasure helps to prevent and heal addiction!
2. Every little step from the ‘pleasure principle’ to the ‘reality principle’ marks a success in treatment.

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Book Chapter:

1. Dole V.P. (1995): Methadone Maintenance. Comes of Age. In A. Tagliamonte and I. Maremmani Eds: *Drug Addiction and Related Clinical Problems*. Springer-Verlag, Wien New York. pp. 45-49.

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