Heroin Addiction and Related Clinical Problems

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Methadone maintenance treatment and mood disturbances: Pharmacological and psychological implications

Kyle R. Dyer

Summary

The rationale for methadone maintenance is to stabilise the pharmacological condition of illicit opioid users, thereby providing an opportunity to normalise health and social functioning. The extent to which methadone is effective for any given individual may be governed by the degree to which methadone prevents opioid withdrawal symptoms, in the absence of significant opioid adverse effects. Mood and anxiety disorders are common within opioid-dependent patients, and there is some evidence to suggest that these disorders may affect the response to treatment. This paper will describe the relationship between plasma (S)- and (R)-methadone concentration, opioid withdrawal, and state and trait mood disturbance. A series of studies have demonstrated that significant mood changes occur in response to changes in plasma methadone concentration, and that these mood changes are more pronounced in those who experience opioid withdrawal. Concentration-effect relationships suggest that relatively small changes in plasma concentration result in significant mood change. An important implication from this research is that consideration of individual differences in methadone pharmacokinetics is necessary for understanding the aetiology of observed mood disturbance among methadone dependent patients. Implications for the clinical management of methadone patients, including the assessment of, and response to, mood disorders and the implications for therapeutic drug monitoring within methadone maintenance programs will be discussed.

Key Words: Methadone maintenance treatment - Mood disturbances - Plasma methadone concentration

At the time of commencing methadone maintenance treatment most heroin users display significant tolerance to the positive effects of heroin (e.g. euphoria), and much of the use of heroin is to avoid uncomfortable withdrawal symptoms (including feelings of dysphoria and anxiety). For many, the decision to enter treatment is also made in the context of significant social, legal, medical and psychological problems that

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have developed as a consequence of illicit drug use. It is perhaps of little surprise that clinically significant levels of mood disorders have been observed among opioid users in treatment and non-treatment settings. Methadone can improve the mood of these patients in part by relieving opioid withdrawal, but also by facilitating an improvement in social, legal and health status. However, for many methadone patients mood disturbances persist during treatment. The extent to which methadone is effective for any given individual may be governed by the degree to which the daily methadone dose prevents opioid withdrawal symptoms in the absence of significant opioid adverse effects, and this in turn may affect mood state. This paper presents a series of studies with methadone maintenance patients in which acute mood disturbances were compared with changes in plasma methadone concentrations during the inter-dosing interval. The implications arising from these studies for the diagnosis of clinical depression among methadone maintenance patients will be also presented.

In an initial study (4), approximately one-third of a representative sample of patients in a public methadone maintenance program who had been stabilised on oral methadone doses averaging 60 mg/day regularly experienced withdrawal symptoms toward the end of each inter-dosing interval (designated ‘non holders’). These patients could not be differentiated from those who were responding well to methadone (designated ‘holders’) by demographic, health, other drug use or treatment related variables. In a subsequent study (3), subjective (opioid withdrawal severity, MBG scale of the Addiction Research Center Inventory, pain threshold in response to electrical stimulation to the ear) and objective (pupil diameter, respiration rate) opioid responses were measured at multiple time periods over a single inter-dosing interval and blood samples were collected for the determination of plasma methadone concentration. There were very few pharmacokinetic differences between the holders and non holder patient groups. There were neither significant differences in peak or trough plasma methadone concentrations, nor the relative proportions of patients with trough plasma methadone concentrations below 400 ng/mL. The patients did not differ on oral methadone dose level, demographic or other individual characteristics. The areas under the plasma methadone concentration - time curve were similar between the groups suggesting that total racemic methadone clearance and bioavailability were similar. However, there was evidence to suggest that the volume of distribution (VOSS) was smaller in non holders, suggesting a shortened terminal half-life (t1/2) and corresponding shortened period of direct opioid effect among these patients.

Analyses of plasma concentration-effect relationships for the subjective responses demonstrated that small changes in the plasma methadone concentration translated into relatively large changes in these measures. The differences in withdrawal severity between the holder and non holder patient groups was related to the significantly more rapid rate of decline in plasma concentration during the period from the peak plasma concentration (approximately three hours after dosing) to trough (approximately 24 hours after dosing) among the non holders. We have recently demonstrated that alpha1-acid glycoprotein (AAG) levels were elevated in a sample of non-holders, suggesting
that the plasma protein binding of methadone was greater among these patients. As the free fraction of methadone determines the extent of direct opioid effects, such a finding might explain the more rapid rate of plasma methadone concentration decline in non holders. However, as AAG is a reactant protein, further research is required. Finally, a re-analysis of these data demonstrated that a greater relative exposure to (S)- versus (R)-methadone was associated with a greater intensity of opioid withdrawal, among patients maintained on at least 60 mg rac-methadone.

For many methadone patients, the daily methadone dose is associated with immediate and positive changes in mood state, while signs of anxiety are associated with trough methadone concentrations. In a recent study the mood states of methadone maintenance patients were assessed over a complete inter-dosing interval, and compared with a group of non-opioid using controls. Mood states were assessed using the Profile of Mood States (POMS) which is a list of 65 adjectives corresponding to six empirically derived subscales, five reflecting negative mood states (depression, tension, anger, fatigue, confusion) and one reflecting positive mood state (vigour). Summing these scores, weighting vigour negatively, provides a global estimate of total mood disturbance. It was found that there were significant changes in mood states during the inter-dosing interval, and these were associated with the plasma methadone concentration-time profile. In comparison with the relatively stable intensity of mood states reported by the controls, methadone patients experienced significant fluctuations in the intensity of mood states throughout the 24-hour period. For methadone patients, the period in which positive mood state (vigour) was closest to those of the controls corresponded with peak methadone plasma concentrations, and then declined throughout the remainder of the day, returning to baseline levels approximately 6 hours after the dose. Negative mood states (such as depression, anger and confusion) showed an inverse pattern, being lowest at the time of the peak plasma methadone concentration and peaking towards the end of the inter-dosing interval. However, even at peak methadone plasma concentrations, methadone patients reported significantly less of the positive mood states and significantly more of the negative mood states than drug-free controls, indicating that patients’ mood state never attained control values. Once again, analyses of plasma concentration-effect relationships demonstrated that small changes in plasma methadone concentrations translated into relatively large changes in mood states. Non holders displayed significantly greater mood disturbance than holders, and this was related to a significantly greater rate of decline in plasma concentration from peak to trough.

Patients reporting significant opioid withdrawal and mood disturbance, despite seemingly adequate oral methadone dose levels and trough plasma methadone concentration, are at risk of a poor treatment outcome. The standard clinical practice when responding to these patients is to increase the level of the daily methadone dose. However, these studies suggest that for a significant proportion of patients, such an approach is likely to be ineffective. This argument is based upon the finding that patients reporting opioid withdrawal toward the end of the inter-dosing interval often have higher peak plasma
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methadone concentrations, and thus more intense subjective direct effect. This is in turn related to a shortened terminal half-life, producing a shortened period of feeling ‘normal’ and withdrawal in the latter part of the 24-hour inter-dosing interval \((3; 2; 7)\). It is hypothesised that a methadone dose increase might not change this situation, and might expose the patients to increased direct opioid effects. Rather the answer might be to either shorten the dosage interval or prescribe a longer acting opioid such as slow-release oral morphine. In a recent study, 10 methadone patients were identified as non holders by assessing subjective and objective opioid responses at multiple time periods over a single inter-dosing interval with concomitant analysis of plasma methadone concentration. These patients then received a divided daily methadone dose (50% of current dosage administered at 10:00 h and 15:30 h) for a period of two weeks and were then re-assessed to examine the relationship between the modified plasma methadone concentration-time profiles and mood disturbance. It was found that such a dosage regimen effectively flattened the plasma methadone-concentration-time profile without changing the trough plasma methadone concentration. Importantly it was found that the severity of opioid withdrawal and the intensity of mood disturbance were significantly reduced by the divided dose regimen, leading to significant improvements in health and social functioning. However, these clinical improvements were lost as patients were returned to the standard once-daily dosage regimen. These data demonstrate significant outcome benefits from reducing fluctuations in the plasma methadone concentration - time profile.

Such acute changes in mood state during the inter-dosing interval may also have important implications for the diagnosis of primary mood disorders, such as depression, within this population. The effective treatment of people with both mental health problems and drug dependence is contingent upon accurate diagnosis, but it is necessary to differentiate primary psychological disorders from the psychological disturbances associated with the pharmacological sequelae of opioids, as these two aetiologies require very different therapeutic strategies. However, the majority of current systems and instruments used in the assessment of people with both mental health and drug use problems have been developed within population representing only one of these conditions, making the validity of diagnoses uncertain. The Beck Depression Inventory-II (BDI-II) \((1)\) is a valid and reliable 21-item self-report instrument that assesses the symptoms of depressive disorders as defined by the DSM-IV. In a current study, 520 methadone patients completed the BDI-II and the Subjective Opioid Withdrawal Scale. Confirmatory factor analyses on BDI-II data indicated that a 3 dimensional model with cognitive, affective and somatic symptoms loading on separate factors provided the best fit. It was found that the mean total BDI-II score for these patients \(21.8\pm12.7\) was at the lower end of the “severe” range and similar to that obtained for males entering residential drug detoxification treatment \(22.1, p=.619\), but significantly higher than: college students \(12.6; p<.001\), and psychiatric patients with anxiety disorders \(19.4; p<.001\) or adjustment disorders \(17.3; p<.001\) \((1)\). However, regression analyses demonstrated that opioid withdrawal \(b=1.46, P<0.01\), the number of days of health
problems (b=.29, p<0.01), and the total number of illicit drugs used in the previous month (b=1.59, p<0.05) were significant predictors of scores on the BDI-II for these methadone patients. The model had significant predictive power (F(4,77)=11.6, p<0.001) and accounted for 37.6% of the variability in depression scores. Furthermore, for the non-holders receiving a divided daily methadone dose there was a 48% reduction in BDI-II total scores, which then reverted to original levels when the patients resumed the once-daily dosage regimen. In conclusion, these studies suggest that the use of the BDI-II by itself cannot distinguish between depression and opioid withdrawal, highlighting the difficulty in measuring diagnostically relevant psychiatric conditions among methadone patients.

Methadone patients display considerable mood disturbance, with the severity of this disturbance being associated with fluctuations in plasma methadone concentration, rather than a function of time in treatment or other factors. An important implication from these studies is that consideration of individual differences in methadone pharmacokinetics is necessary for understanding the aetiology of observed mood disturbance among methadone dependent patients. Methadone patients will display significant depression, anxiety, anger, confusion and fatigue toward the end of each dosage interval and for non-holders such mood disturbance will persist during the day. These patients might best be considered as in an almost chronic state of opioid withdrawal that is diminished partly by the administration of the daily methadone dose. In terms of the diagnosis of psychological disorders, these data demonstrate that reliance upon single interviews and self-report forms may be affected by transient symptoms, and will thus overestimate the prevalence of these disorders among this population. Nevertheless, chronic pronounced negative mood coupled with significant daily fluctuations in mood state, may make normal social functioning extremely difficult. As such, to identify primary mood disorders we need to be mindful of opioid withdrawal severity and the patients’ response to methadone. Accurate diagnosis of clinical depression among methadone patients requires individualised behavioural, psychometric and psychosocial assessment (including assessment of opioid withdrawal symptomatology). Although intensive, such an assessment will provide the necessary information to develop an effective individualised treatment program.

References


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Long-term treatment for patients with severe mental illness and substance abuse

Olof Blix and Ulf Eek

Summary

Drug and alcohol addiction is common among patients with severe mental illness. Those patients often fall between different treatment systems. Since 1994 a long-term treatment for patients with this kind of “Dual Diagnosis” has been going on in the city of Jonkoping, Sweden. It is a joint programme with staff both from the local social services and the psychiatric clinic. A team of six people, three social workers and three nurses with special education in psychiatry, are working with a group of at most 35-40 patients. A stepwise treatment lasts for a minimum of 3 years, after a model constructed and evaluated in the U.S. (Meuser and Drake, New Hampshire). The aim of the treatment is enduring retention leading to the stabilization of both problem areas. The treatment goals are set by each client. Great attention is given to training in social skills. Between 1994 and 2004, 82 patients in all were in the treatment programme. The results of the treatment programme are presented.

Key Words: Double Diagnosed Patients - Opiate Dependence - Long Term Treatment - Opioid Agonists - Drug Dependence - Alcohol Dependence

Background

The main responsibility for the treatment of alcohol and drug addiction in Sweden belongs to the department of social services in each community. The treatment of mental disorders is organized by the county’s department of psychiatry. As in many other countries, the organization of psychiatric treatment has, during the last few decades, been considerably modified. Some psychiatric hospitals have been closed down and the numbers of beds have been substantially reduced. The need for an expansion of
outpatient treatment facilities was obvious. Patients with a dual diagnosis are often rejected by both treatment systems, and the DD team in Jonkoping was set up as a response to this problem.

Jonkoping is located in the middle of south Sweden, at the southern tip of lake Vattern, and has approximately 120,000 inhabitants.

In 1994, following an inventory of the prevalence of people with severe mental illness and co-occurring addiction in the community of Jonkoping, the regional Social Insurance Office, together with the Department of Psychiatry at the Ryhov Hospital, started a project to treat those persons. After 18 months the National Board of Health and Welfare in Sweden initiated similar projects in 2 counties and 8 cities in Sweden. At the same time it took over economic responsibility for the Jonkoping team for 3 years. During this period the project developed into a joint programme between the local social services and the Department of Psychiatry in Jonkoping. Starting in 1998, it was taken over permanently by those authorities. The team is staffed by 3 social workers and 3 psychiatric nurses. A part-time psychiatrist is associated with the team. All team members are specially trained to treat both addiction and severe mental illness.

**Inclusion criteria**

- The following criteria must be fulfilled for admission to treatment:
- Any addiction to alcohol, illegal drugs and/or tranquillizers, combined with at least one of the following mental disorders according to DSM III R:
  - Schizophrenia;
  - Other psychotic disorders including schizoaffective disorders;
  - Bipolar disorders;
  - Major depression;
  - Borderline personality disorder;
  - Schizotypal personality disorder.

**The treatment**

All patients referred to the programme are evaluated according to strict admission criteria as described above. Participation in treatment is voluntary. Treatment goals are set by each patient. Drug abuse during treatment is not an exclusion criterion. Urine tests are not mandatory, but can be administered if requested by patients.

Simultaneous treatment of the mental disorder and the addiction is needed. It is crucial that this should be delivered by staff who is familiar with both sides of the patient’s problem areas. The minimum recommended treatment time is 3 years. To set up a treatment alliance in this patient group normally takes 6-12 months.

The team is working according to the ground principles laid down by professors Kim Mueser and Robert Drake \(^{(1,2)}\). Patients in treatment are assessed on the substance abuse treatment scale (SATS) (table 1) described by McHugo, Drake et al. \(^{(1)}\) during the
Table 1 Substance Abuse Treatment Scale

Instructions: this scale aims to assess a person’s stage of substance abuse treatment, not to determine diagnosis. The reporting interval is the last 6 months. If the patient is in an institution, the reporting interval is the time period prior to institutionalization.

1. **Pre-engagement.** The patient is not in contact with the case manager, mental health counsellor or substance abuse counsellor.

2. **Engagement.** The patient has set up contact with an assigned case manager or counsellor but does not have regular contacts. The lack of regular contact implies the lack of a working alliance.

3. **Early persuasion.** The patient has regular contacts with a case manager or counsellor, but has not reduced substance abuse over a period of more than a month. Regular contacts imply a working alliance and a relationship in which substance abuse can be discussed.

4. **Late persuasion.** The patient is engaged in a relationship with a case manager or a counsellor, is discussing substance use or attending a group, and shows evidence of reduction in use over a period of at least one month (fewer drugs, smaller quantities or both). External controls (e.g. Antabuse) may be involved in reduction.

5. **Early active treatment.** The patient is engaged in treatment, is discussing substance use or attending a group, has reduced use over a period of at least one month, and is working towards abstinence (or controlled use without associated problems) as a goal, even though he or she may still be abusing.

6. **Late active treatment.** The patient is engaged in treatment, has acknowledged that substance abuse is a problem, and has achieved abstinence (or controlled use without associated problems), but for less than 6 months.

7. **Relapse prevention.** The patient is engaged in treatment, has acknowledged that substance abuse is a problem and has achieved abstinence (or controlled use without associated problems) for at least 6 months. Occasional lapses, not days of problematic use, are allowed.

8. **In remission or recovery.** The patient has had no problems related to substance use for over one year and is no longer in any type of substance abuse treatment.

period between establishing contact and discharge from treatment. Patients entering the programme are by definition in stage 1, and stage 7 is “graduation”, which means that they are successfully discharged either when they have stabilized, or passed stage 7. Patients can also be discharged to institutional care, when the DD-team treatment is insufficient.

Patients see their counsellors with a frequency between 3 times a day and twice a week. The clinic is located downtown, and is easily reached by patients. The contact between counsellor and patient is non-confrontational. At every session both problem
areas are discussed. When needed, patients are given appointments with other professionals, such as dentists, psychologists, physiotherapists and occupational therapists. The team members also see their patients in their homes, especially when patients have not shown up at the clinic in line with the agreed treatment plan.

Patients entering treatment commonly have a very low level of social functioning. Training to teach them social skills is an important part of the treatment. Patients often lack proper housing and almost all are unemployed on admission to treatment.

Pharmacological therapy is offered on a regular basis, both for mental illness and, when applicable, for the treatment of addiction (e.g. maintenance treatment of opioid addiction, Antabuse for alcohol addiction). The tapering of benzodiazepines is commonly offered, as most patients have a mixed abuse involving those drugs. When needed, patients are admitted to the detoxification unit of the Department of Psychiatry, as well as other wards of the clinic.

Results

The 1994 inventory revealed approximately 100 individuals who fulfilled the criteria for inclusion in treatment. Since the start in 1994, 82 patients (20 females, 62 males) at an average age of 33 years at admission have been included in the programme. It is of interest to mention that the patients admitted during the first two years (1994-
Patients entering later on have been considerably younger on admission than early entrants. This probably reflects the fact that there had been an accumulation of patients needing this treatment when the programme opened.

Six patients dropped out of the treatment within 4 months after admission; none of them had set up a treatment alliance. Five out of those 6 had a personality disorder: 2 borderline, 1 schizotypal and 2 had no diagnosis within the inclusion criteria (they had an antisocial personality disorder) and were more or less “forced” into the programme by referring colleagues. The sixth had a schizoaffective disorder. This group of 6 did not differ from the whole group with respect to preferred drugs.

Nine patients have died during the 10 years of the programme operation. Three main causes have been recorded: suicide, accidents/violent deaths and overdoses, where it is unclear whether they were intended or not.

In Figure 1, the distribution of diagnosis is presented. Personality disorders account for the largest group, comprising 54% of the patients, followed by psychotic disorders, including schizophrenia, comprising 40%.

Only 5 individuals (6%) had affective disorders. Four had a bipolar disorder and one had major depression.

Figure 2 shows the preferred drug(s) of abuse on admission. As in most Western countries, alcohol is the most common drug of addiction in the Jonkoping area. Legal
and/or illegal prescription drugs come next, with benzodiazepines and pain-killers commonly found in a mixed abuse pattern. On the illegal scene, cannabis and central stimulants, especially amphetamines, dominate. Heroin has only recently been introduced in the region on a wider basis, and, so far, in most cases it is smoked or snorted. It is often a part of mixed abuse, and few “pure” heroin addicts are to be found in this region.

Figure 3 shows the status of all 82 patients admitted since 1994 in July 2004. Since the start of the programme, 37 individuals (28 males and 9 females) have been discharged from the programme, after an average treatment time of 41.2 months. In this group, 10 have moved to other communities for continued treatment. Another 6 have moved to institutional treatment, due to criminal activities followed either by forensic psychiatric treatment (4) or imprisonment (2). Eleven individuals were discharged to continued psychiatric follow up, since they had reached SATS stage 7, i.e. were completely drug-free and had their psychiatric symptoms under control. Another 11 were either in SATS stage 5 or stage 6 when leaving the programme, and can be described as showing clear improvement.

Patients discharged to institutional treatment or treatment in other regions were at a considerably lower SATS stage than “graduates” from the programme.

In figure 4, the SATS scores for the 37 patients who have left the programme is shown. Figure 5 gives the SATS scores for subjects who were still in treatment in July 2004. As Hugo et al. report, the SATS scores of patients rise from entry to discharge.
Discussion

The introduction of the DD team has clearly met a need for treatment among this group of patients with co-occurring severe mental illness and substance abuse. It has improved the collaboration between the Psychiatry Department and social services. It has also led to fewer admissions to in-patient treatment at the Department of Psychiatry and an improvement in patients’ general health and in their ability to receive a combination of social support and psychiatric treatment. Pharmacological treatment for both addiction and mental illness has been provided under controlled conditions. The fact that patients meet their counsellors daily, or almost daily, increases the safety and efficacy of the treatment. Patients with opioid addiction can receive substitution treatment (Buprenorphine or Methadone) under safe and controlled conditions. It must, however, be mentioned that there may be a conflict between the need for control measures in these pharmacological therapies and the generally non-confrontational treatment ideology applied. So far, only 2 patients have received opioid substitution therapy, and in one of the cases the two worlds did not meet comfortably.

Conclusion

By identifying individuals with severe mental illness and addiction and by customizing treatment for both conditions, improvements can be achieved in both problem

Figure 4. Stages on discharge (N=37)
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areas. It is important to address both sides of the problem simultaneously, through the same counsellors. By offering this stepwise programme for a period of at least three years, considerable improvements have been achieved in the target group. In this study, it has been found that as many as 30% of the patients leaving treatment have become drug-free and remained so for at least a year when proceeding from this programme to continued treatment of their mental disorder. The patients still in treatment show increasing stability over time. Mortality in the group of 82 patients, 11%, indicates a yearly rate close to 1%, a figure close to other reports of drug addicts in general; this is surprisingly low, considering the severity of the problems and co-occurring diseases in this patient group.

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Good practice, good results.
Maintenance treatment outcomes in France

Anne Coppel

Summary

In 2004, a public debate emerged on the misuse of, and trafficking in, prescribed drugs. Because of their positive outcomes, maintenance treatments were not officially questioned. A national evaluation showed that the decrease of 80% in fatal overdoses and of 67% in arrests for heroin use (1994-1999) were directly connected with treatment accessibility. This assessment resulted in a consensus among addiction and public health experts. These good results have not, however, been published by the mass media, and the general public still is unaware of them. Nor were the causes of these good results were not discussed among health professionals. They are not only due to the medications involved, but to good clinical practices. The first practitioners who started to prescribe maintenance treatment had followed extensive training, and were networking and building relationships of trust with their patients. Against the background of this public debate, a consensus conference on maintenance treatments organized in 2004 recommended that the prescribing GPs should be better trained, and that they should be included in professional networks. Although these recommendations gave priority to the improvement of clinical practices, the authorities have decided to implement control measures over patients. These measures might make access to treatment more difficult, and they fail to support the involvement of GPs and pharmacists. The effectiveness of substitution treatments could be affected.

Key Words: Maintenance treatment - Treatment accessibility
- GPs training

Over the last 3 years, the misuse of, and trafficking in, prescribed drugs has given rise to public debate. It began with a Senate report published in 2001, but at that time the extent of the misuse was not known (4). In 2004, a study by the French Health Insurance (Caisse Nationale d’Assurance Maladie) showed that 5 to 10% of the patients, depending on their regions of origin, had been supplying most of the black market trade,
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with the help of more than three prescribing doctors and with a dosage that was much higher than needed. The cost of the treatment created a scandal, mainly because the treatments are reimbursed by French Health Insurance, but both the cost of treatments and the cost of diversion have been considered. No journalist, however, has noted so far that 90% of all patients have been following their treatment on a regular basis, a far higher percentage than had been estimated earlier. Nor did any journalist mention the national decrease in fatal overdoses linked with maintenance treatment, as demonstrated by a national evaluation study. Initially, the senators ignored the good results published in this official evaluation; within the framework of their inquiry, they had to admit that there was no controversy over the results among the experts.

In the light of the consensus among health professionals, the Senate report could not question the maintenance treatment or the harm reduction policy that have both been introduced in France; it only requested the introduction of controls.

Anational consensus conference was organized in June 2004 by the ANAES (National Agency for Health Evaluation) and the FFA (French Federation on Addictionology). The conference recognized the positive outcomes of maintenance treatment.

The essential problems have been confused in the public debate. The good results documented in the national evaluation study are only known to the experts. Collective beliefs hostile to these treatments still prevail because of the widespread moral or purely psychological conception of addiction.

When public opinion has been consulted about maintenance treatment, 70% of those interviewed state that they are in favour of medical treatment for addicts, but do not understand why the diversion of drugs has not been stopped. The silence of the experts after years of violent debates did raise suspicions and questions, such as: ‘Is this a business affair or are some other interests being hidden?’

In 2001, senators had recommended a better control of patients, but this might impede access to patient care. Can we control medical prescriptions without affecting the positive outcomes of substitution treatment? This is the question I am addressing.

First, I will present the main data, then I will discuss the different explicative theories and conclude with proposals about how to improve the results.

High dosage buprenorphine and methadone were legalized in 1995. During the first four years, maintenance treatment underwent a sizeable expansion. There are now approximately 100,000 patients. Subutex is prescribed for 83,000 patients and methadone for 12,000; other drugs like morphine and codeine are still prescribed for some patients. Subutex is the most frequently prescribed medication, as it can be delivered by any GP, without any special control. Methadone treatment can only be initiated by specialized care centres. Nine out of ten patients are followed up by GPs. Both treatments are reimbursed by the French Health Insurance.

An evaluation by the National Health Surveillance Institute has been published (Institut National de Veille Sanitaire, 2001). It is mainly based on the evolution of national statistics on fatal OD and heroin use arrests, as attested by the police and HIV national statistics.
Between 1994 and 1999, the national statistics show:

◊ An 80% decrease in fatal overdoses;
◊ A 67% decrease in arrests for heroin use;
◊ A 2/3 decrease in IDU Aids-related deaths.

These decreases are most impressive; this is the first time that the drug policy has achieved good results. From 1970 to 1995, each year was worse than the previous one, with a continuous increase in arrests and fatal overdoses. Of course, the decrease in HIV deaths is due to HIV treatment, but it proves that heroin users do get proper access to health care. These positive outcomes also show that the damage done to the health and social status of heroin users over these last two decades was due not only to addiction itself, but, in a measure as high as 80%, to drug policies and lack of treatment.

Why is this information not made more widely available? First, these results go against popular beliefs about drugs. The second point is the contradiction between the results and the actual Drug Scene. Field studies show that Subutex can be bought on the black market. It can be injected, sniffed or misused together with other drugs, specially benzodiazepines.

That is what outreach services or field researchers can observe, but we must not forget that once a patient is stabilized, he is no longer part of the Drug Scene. He has become invisible.

In France as in other countries, scepticism is rampant, and everyone has their own interpretation of the decrease in arrests and cases of fatal OD. For some, this phenomenon can be explained by the fall in heroin use; for others, the available studies do minimize the Subutex black market and misuse in injections, as they do not follow a rigorous methodology. For anti-prohibitionists, it is access to the product that managed to reduce the harm.

Each interpretation has good arguments on its side. There are several factors that contribute to these good results. I will now discuss these explicative theories.

1) *The fall in heroin use*: actually, stimulants like cocaine and synthetic drugs are now being used more often, and this new trend creates a favorable context. Heroin users get age; most of them are ill and this certainly favours the demand for treatment coming from them, but users did not stop using heroin because it was no longer a fashion, but because treatment became possible. It is supposed that approximately one out of every two heroin users took this opportunity and about 100,000 of them are now being treated. This too contributed to the fall in heroin use, but this is not a major factor in the fall recorded in the national statistics. A comparison between the outcomes for the various French regions shows that the main factor giving rise to the fall in numbers of fatal overdoses is improved treatment accessibility: the more patients there are in treatment, the greater the fall in overdoses and arrests for heroin use.

2) *Legal access to the product*: of course, prohibition does a great deal of harm by creating problems like unsafe injection and the adulteration of drugs;
currently, drug users’ behaviour is largely patterned by prohibition. Actually, providing access to the product is not enough to change behaviour. The drug prescribed can be used with other drugs, with no change in behaviour or very little. International evaluations of methadone treatment show that positive outcomes are mainly due to good clinical practices, such as adequate dosing policies, individualized treatment, comprehensive services and adequate training (5). It is clear that within any treatment, inadequate dosing destroys effectiveness, but, indirectly, evaluation studies on maintenance treatment have also shown that the product itself is not enough to change behaviour. The crucial factor is how to use it. This is true for prescribed medicines as well as for street drugs.

3) Faults in methodology: there can be no question about the national statistics reported by the police: the annual statistics are collected each year in the same way. Actually, misuse and injection may have been minimized in some follow-up studies. Seven follow-up studies have been synthesized by a library-published series (TOXIBASE, 2000). The outcomes are comparable with international ones, with a reduction of 70% in heroin use (national average). Percentages for the fall in the number of injection users vary from 46% to 12%, depending partly on the length of treatment. Even taking errors in methodology into consideration, the fall in the use of injections is incontrovertible. This has been documented by the important fall in HIV contamination through the use of injection (3% of HIV contamination in 2003 versus 27% in 1991).

In the follow-up studies, patients followed by GPs organized as a network showed better results than those with isolated GPs. The retention rate averaged 70% but it reached 82.7 and 96% in two follow-up studies carried out with patients treated by doctors organized as a network. There is no doubt that the network system has reinforced the successful pattern. Ten years ago, French practitioners had no experience in maintenance treatment. Rapid development with a new medication and inexperienced GPs could have been a disaster. That has not been the case. Because GPs had no experience and because they had to overcome prejudice and fear, networking was the answer. Guidelines were elaborated and discussed in the networks.

The most significant fact over the last ten years has been «the interactional change» in the behaviour of doctors and drug users (3). The first step was the change in their relationship. Nowadays heroin users have much better access to care, as the 2/3 decrease in IDU HIV deaths shows. Heroin users no longer die in front of hospitals as they once did, thanks to prescribing doctors. «Drug users should be patients like any others» was the real fight to be fought by prescribing doctors.

At the same time, heroin users changed their behaviour, as has been shown by the fall in HIV contamination. AIDS and self-help organizations play an important role in spreading harm reduction behaviours.

The temptation is to control most patients and exclude bad ones, those who still inject or resort to misuse. We have to bear in mind that stabilization is a process, not
Considering first the need to conserve financial resources and then the need to avoid risks such as non-opiate dependent use, the Social Security services should not reimburse clients with multiple prescriptions. Administrative controls are necessary for the 5 to 10% of drug traffickers identified by the study, but the remaining 90% of all patients are the concern of practitioners. Easy health-care access should be preserved. Essentially, clinical practices should improve. Doctors’ training and network organizations must be given priority. In France, we need better access to methadone treatment. My opinion is that when GPs are organized in networks, they should be able to prescribe methadone for non-stabilized buprenorphine patients.

Heroin prescription would be useful when heroin users have not yet been stabilized with a current treatment. The Swiss experiment shows that a low rate of patients are in need of heroin medical prescriptions when current treatments have been adapted to individual patients.

Unfortunately, a new law has imposed a declaration of treatment for each single patient to the director of French Health Services. Nobody knows what the results of these new measures will be, but they have already limited the involvement of health professionals, instead of supporting it.

The honeymoon with maintenance treatment that had experienced in France until recently is over. Patients and doctors now have to live together for years. So the therapeutic alliance must be protected. The effectiveness of treatment depends on it.

References


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The endogenous cannabinoid system: 
Physiological modulation of neuronal activity

Giovanni Marsicano

Summary

The endogenous cannabinoid system in the brain consists of the seven trans-
membrane cannabinoid receptor type 1, its endogenous lipid ligands (endo-
cannabinoids) and the enzymatic machinery for their synthesis and degradation. 
By genetic, pharmacological, biochemical and behavioural approaches, our 
group has recently described several physiological functions of the endogenous 
cannabinoid system, such as processing of aversive memories, neuroprotection 
against excitotoxicity and regulation of energy balance. These and other results 
indicate that the endogenous cannabinoid system is centrally involved in many 
physiological functions and that pathological alterations in defect or in excess 
of its activity might participate in the progress of several diseases

Key Words: Cannabinoid system - Neuronal activity - 
Memory - Neuroprotection -

Extracts of Cannabis sativa have been well known for their therapeutic and psycho-
active effects for more than 5000 years. Δ9-Tetrahydrocannabinol (THC) was identified as 
the most active component in Cannabis sativa. The cannabinoid receptor type 1 (CB1) 
constitutes an endogenous receptor for THC in neurons and other cell types, whereas 
the cannabinoid receptor type 2 is mainly expressed in immune cells. These receptors 
are activated by endogenous fatty acid derivatives, the so-called endocannabinoids (e.g. 
anandamide and 2-arachidonoyl-glycerol). CB1 receptors exist abundantly in the brain 
and in peripheral organs, and this expression accounts for many of the pharmacologi-
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cal effects observed after treatment with cannabinoids (THC, synthetic or endogenous compounds). However, the existence of receptors and endogenous ligands, together with the machinery for their synthesis and degradation, indicates that the endogenous cannabinoid system may participate in the modulation of many different physiological functions. The long history of therapeutic and experimental use of cannabis derivatives and of synthetic or natural CB1 agonists has led to the formulation of several hypotheses concerning the physiological functions of the endogenous cannabinoid system. However, such pharmacological treatments lack spatial and temporal specificity, which are fundamental characteristics of the activation of the endogenous cannabinoid system. In recent years, the advent of new tools, including the generation of mutant mice lacking CB1 receptors (CB1-KO) and the use of specific CB1 antagonists, have paved the way towards a better understanding of the physiological roles of the endogenous cannabinoid system.

The aim of this short review is to present three recent examples of how the use of CB1-KO mice, together with pharmacological and biochemical approaches, has shed new light on the physiological roles of the endogenous cannabinoid system in the modulation of memory processing, in neuroprotection against excitotoxicity and in the regulation of energy balance.

The endogenous cannabinoid system and the extinction of fear memories

In fear conditioning experiments, animals learn to react with fear to a neutral stimulus (e.g. a tone: conditioned stimulus, CS), after its pairing with an unpleasant stimulus (e.g. a footshock: unconditioned stimulus, US). In the absence of the US, repeated presentations of the CS has lead to a decrease in the fear response, through a mechanism known as extinction or adaptation. Recent work by our group has shown that the endogenous cannabinoid system plays a central role in modulating the fear response during extinction. Mutant mice lacking the CB1 receptor showed no alteration in the ability to acquire fear memories, but did show strong impairment in extinction. The treatment of wild-type mice with the CB1-specific antagonist SR141716A mimicked the phenotype of the CB1-deficient mice, and revealed that activation of CB1 receptors is required at the onset of memory extinction. Consistently with this, tone presentation during extinction trials resulted in elevated levels of endocannabinoids in the basolateral amygdala complex of wild-type mice, one of the brain regions implicated in extinction of aversive memories, strongly indicating that the endogenous cannabinoid system is necessary for a proper extinction of aversive memories.

The endogenous cannabinoid system and protection against excitotoxicity

Mnemonic processes require intense neuron activity in the brain. When this activity exceeds a certain threshold, however, neurons encounter a series of molecular changes, which can eventually lead to the death of the neuron itself and to the spreading of the
damage to other neurons. This pathological phenomenon, known as excitotoxicity, plays an important role in the pathophysiological development of several diseases of the central nervous system, including many forms of epilepsy.

Evidence was recently presented that CB1 receptors and endocannabinoids constitute a physiological system providing on-demand protection against excitotoxicity. Kainic acid (KA) is a seaweed-derived amino acid, which is able to induce excitotoxicity by the excessive activation of glutamate receptors. In animals, injection of KA provokes epileptiform seizures, which can be scored, so allowing excitotoxicity levels to be measured at the behavioural level. CB1-KO mice are much more sensitive to KA-induced seizures than control wild-type littermates, indicating that CB1 receptors play a role in physiological protection against excitotoxicity. In wild-type mice, injection of KA induces increased levels of anandamide in the hippocampus, and pre-administration of the CB1 antagonist SR141716A mimics the phenotype of the CB1-KO mice. At cellular level, KA, when applied to the hippocampus of wild-type mice, induces a series of intracellular events (e.g. activation of extracellular regulated kinases and increased expression of immediate early genes), which might contribute to protection against excitotoxicity. All these events are abolished in the hippocampi of CB1-deficient mice after treatment with KA, indicating that the endogenous cannabinoid system might use these intracellular signalling pathways to protect neurons from excitotoxicity. From these results, a model emerges in which the excitation of a given neuron, once it has reached a certain threshold, induces the activation of the endogenous cannabinoid system, which then dampens the excitation itself and triggers the protective intracellular mechanisms.

The endogenous cannabinoid system and food intake

It is well known that extracts of Cannabis sativa can induce an increase in food intake in humans and animals. Using CB1-KO mice, we were recently able to show that the endogenous cannabinoid system actively participates in the maintenance of the energy balance. CB1-KO mice show decreased body weight and reduced fat mass compared with wild-type controls. Brain neuropeptides, which are centrally involved in the regulation of food intake (e.g. Corticotropin Releasing Hormone, CRH) present alterations in their expression levels in CB1-KO mice. This, together with the decrease in food intake of CB1-KO mice, strongly indicates that the endogenous cannabinoid system is directly involved in the central regulation of food intake at the level of the brain. However, the endogenous cannabinoid system might also participate in energy balance through a peripheral function at the level of fat tissue. In fact, adipocytes express CB1 receptors and their lipogenic activity is regulated by cannabinoids. These results show that the endogenous cannabinoid system is a very interesting physiological regulator of energy balance, functioning both at the central (brain) and peripheral (fat tissue) levels.
Concluding remarks

The experiments briefly reported here present three examples of the physiological roles of the endogenous cannabinoid system in mammalian physiology. Considering these and other important functions of the endogenous cannabinoid system, it is conceivable that a pathological decrease in the activity of the endogenous cannabinoid system might contribute to certain pathologies (e.g. through the extinction of fear, to phobias; through protection against excitotoxicity, to certain forms of epilepsy). At the same time, an increase in the endocannabinoid system activity is likely to be involved in other pathological states (e.g. obesity). Thus the enhancement or blockade of the physiological activation of the endogenous cannabinoid system might each offer promising therapeutic tools for the treatment of particular pathological states in which this system appears to play a key role.

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Substitution treatment in European prisons.
A study of policies and practices of substitution treatment
in prison in 18 European countries

Laetitia C. Hennebel 1, Heino Stöver 2, Joris Casselman 3

Summary

The objective of this study was to examine policies in place for the provision
of substitution treatment in prisons and existing practices in 18 European
countries. The report presents findings per country through 'country reports',
together with 'emerging issues' across the countries, which inform the recom-
mandations made at the end.

Key Words: Substitution treatment - Prison - Methadone
- Buprenorphine

Introduction

Since July 2004, Cranstoun Drug Services’ networks (ENDSP and CEENDSP)
have merged with ‘The European Network on HIV and Hepatitis Prevention in Prison’
managed by the German Health Institute to create the ENDIPP network: the European
Network on Drug and Infections Prevention in Prison. Cranstoun Drug Services and
the German Health Network on HIV jointly manage ENDIPP.

ENDIPP combines the activities of these three European Networks, establishes a
multi-disciplinary network, conducts various activities, partly funded by the European Commission, and is active in all 25 EU Member States.

The ENDIPP Network’s overall aim is the protection and improvement of Public Health by promoting the adoption of integrated, inter-sectoral drug-demand reduction and infections prevention strategies in European Prisons. This is to be achieved by promoting the implementation of the “principle of equivalence” between health care in prison and in the community and by encouraging cooperation between countries to reduce drug related health damage and related negative social consequences.

ENDIPP will carry out its work in a number of different ways including conferences, several research projects, training, educational exchange visits between member states, publication/dissemination of information, cooperation with other European and International Organisations such as EMCDDA, Council of Europe, the World Health Organisation, Open Society Institute, Aids Foundation East West.

Within the context of the activities of the ‘European Network of Drug Services in Prisons’ (ENDSP), Cranstoun Drug Services managed a research project on ‘Substitution Treatment in European Prisons’ over a period of 18 months (December 2002 to May 2004) in 18 countries (the 15 EU member states prior to 1 May 2004, the Czech Republic, Poland and Slovenia).

The researchers were Dr. Heino Stöver (University of Bremen, Germany) and Laetitia Hennebel (Cranstoun Drug Services - ENDSP/ENDIPP, U.K.). Professor Joris Casselman (Catholic University of Leuven, Belgium, and member of the Scientific Committee of the European Monitoring Centre of Drugs and Drug Addictions (EMCDDA) for Belgium) acted as the scientific peer-reviewer.

The study was carried out with the support of the ENDSP’s national contacts.

The research objective

The research had the following specific objectives:
- Conduct a literature review on substitution treatment in prisons;
- Elaborate an inventory of the substitution policy and practice in prisons;
- Provide an overview of the national and regional developments of health care standards with regard to substitution treatment in prisons;
- Point out issues related to cessation and continuation of substitution treatment prescription from the community into the prison setting;
- Initialise an exchange of information of medical doctors and health care workers in charge of prison health care services; and
- Identify ‘Good Practice’ where substitution treatment is offered in prisons.

Methodology

The research involved collecting national data and qualitative data. National data were collected with the support of the national contact in each country. The majority of
national contacts were ENDSP (and CEENDSP) representatives, as well as key individuals working in the national prison service. Furthermore, ongoing examination of research reports, national governmental and non-governmental websites was conducted.

Qualitative data were collected through interviews conducted during field visits and organised with the support of the national contacts. The group of participants was made up of Group A: prisoners and professionals working in prison, and Group B: key individuals within governmental and non-governmental institutions located outside of the prison. In total, 17 countries were visited. Prison visits took place in 33 prisons, with an average of two prisons visited in each country. In each case focus groups were organised to obtain information from prisoners, with 184 prisoners (132 men, 52 women) in total taking part.

Results and discussion

Substitution treatment is managed by the Ministry of Justice (Prison Administration, Health Care Service) in all the countries visited, with the exception of France, where the Ministry of Health is in charge of substitution treatment and health care generally in prison.

It was found that methadone (as administered as a drinkable syrup) is the most used substitute. In most of the countries, buprenorphine (administered as a sub-lingual pill) has only recently been introduced in prisons, except in France where substitution treatment is predominantly provided with Subutex® (buprenorphine).

Differences were reported between methadone and buprenorphine, the latter being seen as offering advantages that methadone does not have, and vice versa. It was mainly reported that:

- Buprenorphine offers less risks of overdose, and no risk of overdose with non-topped up (i.e. taken on its own) high doses of buprenorphine.
- Stocking tablets is easier than bottles.
- Delivering buprenorphine was seen as easy when delivered ‘in hand’ twice a week (e.g. France) and did not require a high number of staff; however, this resulted in some misuse (not reported with methadone).
- Delivering buprenorphine tablets under supervision was seen as both time and resource consuming, as sublingual intake requires 5 to 10 minutes per person. Methadone intake was seen as easier and more time effective, except in France where methadone is only delivered in an intensely supervised way, due to the fatal risks (a single dose of 1 mg per kg may be lethal for any “naive” patient) linked to abuse and misuse of methadone.
- The withdrawal and craving effects are stronger with methadone; some prisoners reported ‘being hooked’ on methadone.
- Buprenorphine and methadone were seen as complimentary, as some prisoners could be switched from one to the other according to individual needs.

Substitution treatment was positively associated with:
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◊ Identification of and reaching out to drug users in prison, using imprisonment as a key period to offer health care and refer to community services.
◊ A reduction of self-harm and overdoses in prison and on release.
◊ Overall, an efficient harm reduction measure.
◊ Softer’ and more humane detoxification (versus ‘cold turkey’) and stabilization of prisoners.
◊ An improved health care (decreased feeling of ‘helplessness’ for doctors) and follow-up of drug users.
◊ Achievement of abstinence and/or detoxification for some prisoners, and stability through maintenance for others.
◊ Prisoners’ increased responsibility, awareness of and involvement in health care.

Substitution treatment was negatively associated with:
◊ Being a substance (a drug) rather than a treatment, which relates to the idea that substitution treatment is just replacing one drug with another one and ‘preserving’ the drug dependence and drug use.
◊ Buprenorphine was seen in France as a new drug used for traffic within the prison (entering the existing black market licit drugs); the pill is crushed and sniffed or injected, similar to the practise out of prison. This misuse concerned a minority of prisoners but was of concern.

It was reported that substitution treatment is provided in prison primarily as part of a detoxification regime (reducing the dose over a fixed time period). Maintenance was less commonly offered and involved maintaining the same dose for an unlimited time period.

It was found that substitution treatment is provided in a heterogeneous way in the different countries. These differences seemed to reflect the historical, cultural, social, economic and political differences across and within European countries.

Access to and continuity of substitution treatment in prison in many countries in Europe, compared to service provision in the community, was reported as inadequate, as the principle of the equivalence of care was seen as not being respected.

It was also found that the provision of substitution treatment in prison varied from one country to another, from one prison to another, within a medical team, and from one doctor to another. The heterogeneity of the treatment raised difficulties for the continuity of care within the prison settings and from or to the community.

Although psycho-social care was seen as an additional and necessary part of substitution treatment, it was found that such a support was rarely provided, resulting in rare cases of the provision of ‘therapeutic’ treatment. It was reported that many doctors ‘simply’ prescribed substitution treatment.

Finally, it was found that throughcare (linking with the community) was limited in most of the countries except in Slovenia where the involvement of the ‘National Addiction Institute’ was fruitful.
Conclusions and recommendations

Recommendations were put forward, reflecting recommendations made by international bodies and experts and drawing on the study’s results, observing the need to take the national, regional and local differences into account.

It was suggested to expand the availability of and access to substitution treatment, as well as the quality of services. Continuity of care between prisons, throughcare (i.e. linking with the community) and community-based services (quantity wise) should be improved. Training and support to staff, as well as psycho-social support to prisoners should be ameliorated and offered on an on-going basis. Finally, variety of treatment options (detoxification, maintenance, buprenorphine, methadone) were seen as necessary and beneficial in order to answer individual needs.

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Medical meaning of psychosocial issues of heroin addiction

Matteo Pacini¹ and Icro Maremmani¹,²,³

Summary

Drug addiction is often characterized by psychosocial highlights, so that it has been repeatedly depicted as a social disease, although to differing degrees. A variety of interventions have been proposed and applied as therapies, more on the basis of intentions than of scientific prospects of success: in fact, they all seem to share common roots in conceptions of addiction as being the outcome of a vicious social dynamic. The scientific vision of addiction as a medical issue allows a more reasonable evaluation of addiction-related social issues, both on pathophysiological and therapeutic grounds. To date, advisable first-line interventions for drug addiction have not been of a psychosocial kind. On the other hand, psychosocial markers have been crucial in assessing the effectiveness of pharmacological treatments since the very earliest stages of research in the field of methadone treatment. Furthermore, psychosocial adjustment and well-being should always be measured when newer approaches are tested, since they are crucial in allowing meaningful comparisons between treatment options. Lastly, a subgroup of heroin addicts, who suffer from severe psychosocial impairment, partly unrelated to addiction, should be offered psychosocial facilities as soon as they have been stabilized on an agonist treatment: predictably, their psychosocial well-being will not, as happens with others, follow the remission of drug abuse, but maintenance treatment will make them suitable for so-called pharmacologically assisted rehabilitation programmes.

Key Words: Drug Addiction - Rehabilitation - Psychosocial Intervention - Methadone

The need to include psychosocial features within a comprehensive clinical view

Descriptions of core addictive symptoms are usually made independently of the portrayal of drug-related phenomena. In addition, psychosocial aspects are often presented and highlighted as crucial to an understanding of drug addiction, but their
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medical meaning and roots are usually neglected. Lastly, on therapeutic grounds, there is a trend to pursue social rehabilitation regardless of what control has been achieved over addictive symptoms up to that point. Indeed, addictive symptoms are mostly of a behavioural kind, and craving is best rated by the assessment and measurement of drug-seeking behavioural automacies. Social decay, the disruption of relationships and ties, deviance, with a drifting away from social pathways, and drug-related crime, develop to the degree to which craving for the substance has overwhelmed the individual’s freedom of choice. In parallel with the addictive buildup, the individual’s brain is progressively damaged by undergoing exposure to the substance, and the resulting disease is expressed through social disadjustment.

Clinical evaluations should always include psychosocial features, to take into account the ways in which addictive symptoms are expressed on social grounds. Addiction should not be faced as if it could be split into two different pictures, one individual and one social, but be interpreted as a single disease active on two different levels of clinical expression that are rooted in a common neurobiological core.

Psychosocial features of addiction: what is directly disease-related?

Of the psychosocial features to be recorded among heroin addicts, some are strictly dependent on addictive dynamics, whereas others are not always present and are, in any case, variable. In statistical terms, we could say that some features are displayed as dependent variables, and are the social consequence of what started out as, and remains, an individual disease. Other elements can be better interpreted as dependant, and constitute the environment’s reaction or adaptation in responding to addictive behaviours. The latter can be subdivided into two categories: on one hand environmental addictive features, which correspond to addictive behaviours viewed from a social standpoint. On the other hand, post-environmental addiction-related elements are the community’s response to the presence and the behaviours of an addicted individual.

Only those who have a thorough knowledge of addiction from a clinician’s point of view, and are accustomed to treating addiction at an individual level, can easily assess addiction-dependent variables when examining addiction-related phenomena. At an individual level, in fact, craving is the drive which leads to addiction construction, and underlies its recklessness and relapsing course. If, in describing addiction, we distinguish between symptoms of overactivity and symptoms of dysfunction (a plus vs. minus dichotomy), core addictive symptoms would certainly fall into the first category. Craving is, in fact, first and foremost a pleasure-seeking drive, strongly and exclusively aiming at a precise objective. The incapacity to grant on self pleasure from other sources, because of a craving’s monopoly over one’s choices, comes second, on the minus side. The very first abnormality in pleasure feelings is an extreme drive towards the substance which ends up by actually thwarting the consumption of the substance, because of an intrinsic imbalance. In fact, the urge to consume the substance is such as to make it less likely that the individual will be able to take advantage of the environment for his
or her purposes: the only choice left is to accept continuous risk-taking, to undergo individual collapse and detachment from significant others, and progressive erosion of personal resources. Relapses into drug use cannot be opposed or resisted, because they are the pathological behaviour unleashed by this uncontrollable urge. Thus, the condition of an individual who is condemned to crave for a high-cost substance is the cognitive basis for an understanding of addiction as a social phenomenon. The loss of control over one’s behaviour occurs through an excessive desire (craving) that affects the relationship between the individual and the substance: as a result, it is predictable that any social elements that mediate that relationship will be affected too.

**Plus side: overactive behaviours of drug addicts**

The risk behaviours of an addicted individual belong to the sphere of sexual life, criminal acts, the neglect of hygienic and health care precautions, as well as the methods and settings used in drug-taking itself. Addicts may take advantage of the environment (by pilfering or theft, for instance), fail to protect themselves, and become vulnerable to whatever dangers may derive from the environment. In any case, the addictive behavioural plus is always crucial in interpreting addiction-related risk: it is not substance use that is abnormal in itself, nor the purpose of pleasure that is sought from the substance, but the incapacity to take hold of one’s desire. Non-addicted users may put up with the controlled use of the same substance and face possible risk situations; unlike them, addicted users are blind to risk, are not free to draw back from their drug-seeking behaviour, regardless of looming danger. In other words, non-addicted users act in response to the physiology of novelty-seeking and pleasure-seeking, while addicts are affected by the overwhelming dynamics of craving and behavioural recklessness.

Drug consumption itself takes place in conditions that endanger the very possibility of keeping up the habit. Heroin injectors are not concerned about infections, may not worry about using dirty equipment (or, at an earlier stage, about the quality of the substance they have bought), do not disinfect or keep clean paraphernalia or injection sites.

Loss of control is prominent during relapses, too. The main risk for detoxified subjects is not relapse itself, but overdosing when a relapse occurs. This phenomenon is peculiar to those who have been released into their environment from jail or therapeutic communities, and is mostly interpreted as accidental. Although addicts actually make a mistake when overdosing, when first injecting again after detoxification is likely to be due to a bout of craving, rather than to a re-emergence of physiological desire. As the desire is extreme and urgent, injectors will be blind to the condition of a lack of tolerance, and crave for doses as high as the last dose they injected, or a high quality mixture, or even accept an accidentally polluted mixture just because it is right at hand.

Sexual behaviours bring with them non-physiological hazards, beyond the possibly illegal context. Sexual activities often take a particularly hazardous form (another addict as a partner, unsafe sex, promiscuous sex with needle-mates), and prostitution may
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be abnormal, too: craving-affected prostitutes are unable to negotiate, and are easily exploited in a qui pro quo relationship. Addicted prostitutes, because of their disease, have lost the ability to handle their sex-trading activity so as to achieve satisfactory incomes and protect themselves as earners.

Similarly, criminal addicts are unlikely to handle their criminal business soundly or successfully. While non-addicted criminals may make choices in order to continue as before, to make a profit and avoid being caught, criminal addicts cannot help exposing themselves, in line with their craving: when risks increase, their precautions will not, so that the risk/reward ratio deteriorates. It often happens that former successful criminals become disorganized and have their criminal skills impaired when they develop addiction.

If methadone treatment reduces the likelihood of engaging in criminal activities in general, as a trend, this effect turns out to be even stronger when non-organized crime alone is taken into account. In other words, an anticraving agent reverses certain behaviours when they mirror craving-related loss of control, whereas similar but organized behaviours tend to persist.

Minus side: residual states and dysfunctional remission

Apart from risk behaviours and acts of aggression, the other side of the psychosocial impairment of drug addicts consists in the loss of productive ability and relational skills. A history of addiction is a good enough reason for that, but chronic opiate intoxication may also lower the stress threshold, so making even common social challenges too stressful to overcome. Martin portrayed detoxified addicts as suffering from a type of dysthymic condition he named hypophoria, which foreruns relapse and mirrors long-term acquired opioid damage. Key symptoms of hypophoria are a low pain threshold, a low tolerance to stress both before and during efforts, isolation and apathy, boredom and discomfort in one’s natural environment. Patients who undergo agonist treatment programmes show quite a rapid recovery in their productive capacity and recuperate their tolerance to stress. On the other hand, they remain hypophoric as far as motivation and drive are concerned, even when work and family status show significant improvements. When effective treatment keeps craving suppressed, patients experience a state of emptiness due to the widened gap between their substance-heightened pleasure threshold and the stimuli available to them. As a result, no available stimuli are able to raise the former addict’s interest, or be subjectively rated as motivating. When no specific treatment is provided to keep craving under control, this hypophoric state is likely to lead to a relapse sooner or later, regardless of possible improvements in one’s productive and relational status (15-18).

It may be appropriate to draw a comparison with another psychiatric disorder, panic disorder: for subjects who have experienced panic attacks, agoraphobic avoidance of certain places or settings may develop into a pathological solution to feared panic crises. Thus, panic is kept under control by self-limitations to social, working and individual
activities. So too, drug addicts undergoing periods of clinical remission may learn to prevent relapse by self-isolation from a wide range of common occasions of social stress, engagement and effort. In some cases, early clinical remission is achieved by segregation within CT walls, or a change of environment. To tell the truth, environmental isolation may be just temporarily effective and necessary in handling craving in such a way that abstinence is maintained. As a rule, when craving persists despite stable environmental control, in the absence of any specific treatment targeting the core of drug addiction, a drug addict can be expected to break environmental bounds by experiencing craving overshoots and an eventual relapse.

As long as abstinence is the crucial measure of the effectiveness of treatment against addiction, residual dysfunctions due to unrepaired opiate damage, or unstable craving control through environmental restrictions are acceptable solutions. On the other hand, if treatment philosophy aims to reverse the natural course of the addictive disease, the target sought after will go beyond abstinence, by comprising the restoration of impaired opiate-related brain functions. Abstinence without rehabilitation, in other words, does correspond to the loss of a possible missed therapeutic gain and brings the prospect of further interventions to provide pharmacological support for addiction-related brain damage, so as to compensate for missing functions and favour spontaneous repair.

**Psychosocial variables and retention in treatment**

Data analysis performed on the PISA-SIA (Study and Intervention on Addiction) Group sample showed some noteworthy relationships between psychosocial variables and retention in treatment. Between 1993 and 2004 the Pisa-SIA Group ran three pharmacological maintenance programmes, employing either naltrexone (149 enrolments), methadone (175 enrolments) or buprenorphine (the latest programme to be initiated, with 81 enrolments). These programmes provided pharmacological treatment both for addiction and for possible concurrent psychiatric disorders, plus counselling if requested by the patient. The outcome was rated as positive or negative according to treatment retention and opiate use status: patients who stayed in treatment for one year and showed at least a 90% decrease in their opiate use (with a maximum of one positive urinalysis during the latest sixty days in a weekly evaluation schedule) were rated as stabilized and therefore labelled as responders (i.e. with a positive outcome). Dropping out or failure to stabilize by the twelfth month of treatment was assessed as to a negative outcome. The naltrexone treatment programme employed naltrexone at standard dosages (100 mg/day), while agonist dosages was managed on a flexible schedule, according to which increases were decided to counteract persisting opiate use and achieve eventual stabilization. Mean dosage in 2-year retained patients was around 8 mg/day for buprenorphine-treated subjects and around 130 mg/day for methadone responders.

With respect to buprenorphine patients, methadone patients are more severely impaired at treatment entrance, in the field of work and family relationships, but show a
greater retention rate as a group. Buprenorphine responders reach a more satisfactory level of psychosocial adjustment, which also accounts for their lower grade of impairment at treatment entrance.

In the naltrexone programme run by the PISA-SIA Group (149 subjects), work and leisure time impairment predicted dropping out (14). Nevertheless, naltrexone-treated patients, regardless of baseline psychosocial status, had all been able to interrupt their heroin consumption as a habit, since a negative naloxone challenge was required for them to be able to start on naltrexone. In the PISA-SIA Group methadone maintenance programme sample (129 subjects), family life impairment proved to be the only feature to hamper treatment retention, whereas other fields were irrelevant (13).

In the studies reported above, patients were admitted without accounting for past treatment history, so that treatment-naïve patients were grouped together with already treated peers. Looking further, we evaluated 63 consecutive heroin addicts who were at their first treatment attempt, among those admitted between 1999 and 2002, and who had stayed in treatment for at least 36 weeks. These subjects had either been sent to our unit after being discharged from the psychiatric ward (N = 10, 15.87%) or come directly from the general psychiatry outpatient unit (N=53, 94.13%). They were assigned to buprenorphine (n=35) or methadone (n=28) treatment programmes with no predefined rule for patient-treatment matching (Pacini and Maremmani, unpublished data).

The retention rate proved to be higher for the methadone group. Logistic regression analysis did not provide indications for any sharp discrimination, but revealed that for some categories of patients retention is more likely if they belong to the methadone group: patients with children, with a stable partner, those who live with a partner, and those who keep on working or find a job during treatment. Curiously, retention in treatment was related to higher dosages for the methadone group, and lower dosages for the buprenorphine group, in a comparison with dropouts from both groups. One possible explanation is that rehabilitation, far from being a therapy in itself, acts as a stressor on the patient’s brain. Opiate agonists counteract rehabilitation-related stress, make rehabilitative pathways viable on neurobiological grounds, and favour the accomplishment of rehabilitative goals. Buprenorphine supplies an amount of agonist which is fixed and limited, due to its peculiar ceiling effect; this pharmacological mechanism may mean that buprenorphine provides no more than partial relief or a buffer against increasing levels of stress.

On the other hand, fixed agonism may produce the blockade of possible inner endorphinergic peaks, so that whatever compensation may develop from the brain’s residual endorphinergic activity is choked.

A hierarchical order and a logical sequence for psychosocial interventions

The social disruptiveness of drug addiction has raised the need for relatives and communities to work out methods of psychosocial reconstruction that appeal specifically to long-term addicts. In long-term survivors from drug addiction, the mere interruption
of addictive behaviours may not automatically bring about social rehabilitation. The spontaneous allocation of individual resources to a functional use may be extremely awkward and retarded in cases where addiction has continued from early adolescence through the formative years, and relapses have destroyed whatever had been built or restored in drug-free periods.

It must be remembered that, on scientific grounds, the psychosocial features of recovering addicts were the first to be taken into account in measuring treatment outcome, together with substance use status, from the early study of Dole on a sample of “criminal addicts” (6). In the long-standing traditions of scientific evaluation of drug addiction treatments in the USA, psychosocial interventions were examined later, in an attempt to assess their possible role in optimizing the results of pharmacological treatments alone. Even so, no assumption has ever been made that interventions to favour rehabilitation should be resorted to or assessed as effective unless concrete evidence to that effect has been available. In fact, where psychosocial interventions spread before evidence-based pharmacological treatments were introduced, the supporters of psychosocial techniques failed to design an evidence-based role and preferred to stick to the groundless but popular illusion of a drug-free solution.

On scientific grounds, what makes sense now is to choose and apply interventions of proven effectiveness for standard addicts, and handle therapeutic parameters so as to provide solutions to possible further issues on a case by case basis. Because of the delay in the introduction of therapeutic standards all over Italy, there is now a trend towards putting them forward as simple alternatives to other forms of intervention, or as last choices for more severe cases. On the other hand, we have missed the opportunity to study and develop psychosocial techniques side by side with the biological core of multimodal treatment. It is quite common, too, for supporters of psychosocial interventions to deny sharing any scientific views with managers of pharmacological treatments, so that meaningless conflicts have had to be endured on grounds of belief rather than evidence (7).

The effective control of addictive behaviours and core symptoms may be enough for rehabilitation to proceed spontaneously, which indicates how much social impairment currently depends on addicts’ overwhelming priority to be sure of obtaining continuous supplies of their chosen substance.

Data from the literature allow it to be stated that treatment with methadone or buprenorphine has laid the foundations for further improvement by psychosocial techniques, whereas psychosocial interventions are ineffective for active heroin users.

Psychosocial treatment as a side-intervention for methadone-maintained subjects has, in fact, led to better results (11, 12, 27) than it has as a first-line treatment. Ball and colleagues and Dole agree that the success of methadone programmes in combating drug use basically depends on dosage, but they also remark that a good patient-doctor relationship is crucial to maintaining compliance (2, 3, 5). A combination of methadone treatment and psychosocial interventions is not expected to enhance methadone’s effectiveness in treating heroin use, which can probably be extinguished by methadone
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treatment alone \(^{(26)}\), but its impact upon other medically relevant issues, such as somatic and psychiatric impairment, or the transfer of residual craving on to other substances (e.g. cocaine) \(^{(19,25)}\). Without this wide-ranging perspective, a counselling facility during schedules of medically supervised withdrawal is useless as means of drug use control \(^{(20,24)}\). Kakko and colleagues \(^{(8)}\) confirm that psychosocial intervention is useless in the short term (12 months) for addicts who are not receiving therapeutic opiates (buprenorphine in their case), and suggest that a combination of pharmacological and psychosocial treatments provide an enhancement compared with the effectiveness of pharmacological treatments alone, allowing a 75% retention rate to be reached.

Later studies have hypothesized that special counselling techniques (node-linking and group counselling) may also contribute to the reduction of drug use \(^{(23)}\).

During methadone treatment, the availability of counselling increases the likelihood of compliance, as proved by data from a study where patients were allowed to remain on a programme as long as urinalyses stayed negative \(^{(4)}\). In this case it was ongoing pharmacotherapy that allowed subjects to act so as to avail themselves of the one available psychosocial intervention. In addition, pharmacologically treated subjects become capable of trading their abstinence from addictive drugs for money within these programmes \(^{(21)}\).

Tunis, Delucchi and colleagues clarified whether patients’ attitudes affect ongoing opiate use in response to a schedule of medically assisted withdrawal, a setting where participants are artificially made more prone to a relapse. Curiously, a lower rate of opiate use is linked to a positive relationship with the counsellor but also to a positive relationship with other addicts \(^{(24)}\). In any case, a positive relationship with the counsellor brings with it a specific advantage - an ability to handle risks of infection during relapses - which is not guaranteed by a positive relationship with other addicts. As a result, relapsing addicts who do not have a friendly relationship with their counsellors are expected to relapse with no greater frequency, but with a greater risk to their health.

In English-speaking countries, treatments are currently evaluated in terms of cost effectiveness: some authors report that intensive counselling is the most effective form \(^{(1,19,27)}\), while others deny any advantage with respect to basic counselling \(^{(22)}\). Avants and colleagues have shown that the addition of psychosocial facilities as a side-intervention to a combination of counselling and methadone treatment does not give patients better results. In the same setting, the effectiveness of counselling depends on how often patients resort to it. On the other hand, socially inhibited patients may not be at ease with intensive counselling, and may show greater improvement when that interaction is not a daily event \(^{(1)}\).

Although the biological side of addiction is usually recognized, the correct approach to drug addiction comprises different types of intervention which are all equally important in controlling the disease, and are complementary to one another. On the other hand, scientific evidence indicates that a polyfactorial model should be interpreted as involving a combination of causal factors, all rooted in the same neurobiological core \(^{(20,24)}\) and subordinated to it. On this view, it is crucial to target the biological core by
specific means, so allowing psychosocial interventions to be successful as ancillary factors; by contrast, it is pointless to approach addiction by a variety of simultaneous interventions, each matching one aspect of the polyfactorial model. Failure is likely if there is no hierarchical structure able to mirror the spontaneous structure of the disease and its clinical expression.

Some Centres systematically enrol applicants for treatment in psychosocial programmes with rehabilitative aims. In particular, programmes that take place in residential settings offer little more than a safe environment, on therapeutic grounds. Outpatient Centres, on the other hand, offer a wide range of therapeutic facilities, residential treatment included. In cases that require specific psychosocial treatment, pharmacological treatment must come first and have an anti-craving aim, in order to pave the way for the psychosocial intervention that is to follow (7, 9). In many other cases subjects will rehabilitate autonomously, as long as they have achieved stable remission of addictive symptoms by pharmacological means. Rehabilitation is likely to be required for a subgroup of addicts whose maladjustment is not strictly dependent on addictive symptoms, but is also related to the duration of addiction, including periods when social milestones were skipped and social abilities were not acquired. When rehabilitation takes place spontaneously while patients are on agonist treatment, medically authorized rehabilitation sounds appropriate, whereas the term medically-assisted rehabilitation is more suitable in cases in which additional psychosocial interventions are required.

The distinction drawn above recalls a clinical difference, and allows physicians to select patients who need to have their rehabilitative process boosted by psychosocial interventions, and who should be referred to psychosocial facilities after they have been stabilized by anticraving treatment. Other patients, who still show signs of behavioural impulsiveness and loss of control, should preferably be kept on anticraving treatment until stabilization is achieved, before any psychosocial intervention is attempted.

Conclusions

The clinical evaluation of heroin addiction should always feature social issues, to allow a better assessment of an addiction’s grade of severity, its stage, and an evaluation of whether overactive behaviour or decline is prominent. Pharmacological maintenance may be an effective way to promote and enhance rehabilitation. Programmes exclusively based on psychosocial techniques are likely to be a failure for most addicts in terms of long-term rehabilitation. An understanding of psychosocial issues in medical terms is useful in identifying which addicts need additional psychosocial treatment. To this extent, psychosocial techniques may become part of a rehabilitative process for selected addicts, as side-interventions within a pharmacologically centred programme. Opiate agonism appears to be the crucial feature for pharmacological programmes, in giving patients satisfactory prospects for rehabilitation. Above all, full and flexible opiate agonism such as that provided by methadone maintenance seems to preserve rehabilitation from the risk raised by fluctuating levels of social stress.
References


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