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HEROIN ADDICTION & RELATED CLINICAL PROBLEMS

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How should methadone and buprenorphine treatment be organized and regulated? A comparison between two systems in the context of a EUROPAD Conference in Brussels

Albrecht Ulmer [1], Dominique Lamy [2], Marc Reisinger [3], Martin Haraldsen [4], Icro Maremmani [5] and Robert Newman [6]

1 Vice-President of the German Society for Addiction Medicine (DGS e.V.)
2 President of Alto-SSMG, Mons, Belgium
3 Vice-President of EUROPAD, Brussels, Belgium
4 GP, Member of international networks for OAT
5 President of EUROPAD and World Federation for the Treatment of Opioid Dependence - WFTOD, Pisa, Italy and New York, USA
6 Director, Baron Edmond De Rothschild Chemical Dependency Institute of Beth Israel Medical Center, New York, NY, USA

Summary

Opiate Agonist Treatment (OAT-providing) physicians and pharmacists from the southwest region of Germany and the Wallonian part of Belgium came together with international experts to compare their two different sets of OAT regulations. Both countries mostly rely on methadone, but with an increasing use of buprenorphine, besides a much less frequent recourse to other opioids. German OAT is rather strictly regulated. The aim of these regulations was to ensure quality. That effect is, however, questionable. The regulations make it difficult and legally dangerous to provide OAT. Physicians and patients suffer from these regulations. Most doctors avoid getting involved. No successors are available. The future scenario will be OAT provision at only a few clinics, with a large array of controls and with a customary setting of crowds of addicted people. The Belgian system runs without these regulations. The consequence is not greater chaos, but a much more normal integration of patients into normal medical practice and into society itself. The take-home message of the conference held under the auspices of EUROPAD was that most special regulations point in the wrong direction, and lead into a costly dead end. The whole treatment procedure works better and much more effectively if we treat the patients as normally as possible, with nothing more complicated than normal diligence. Connection with a good support system, networking, regular education and periodic evaluation of how the system functions - all these factors go to constitute a guarantee of the best possible outcome for patients.

Key Words: Methadone treatment; buprenorphine treatment; therapeutic system; regulations

This is a brief report of the Europad meeting that was held in Brussels, Belgium, on October 21-22, 2011 to compare the rules and limitations that affect Opioid Agonist Treatment in Belgium and in Germany.

1. Two Different Ways

OAT is regulated in very different ways in different countries. Opioids have a known abuse potential. Many rumours and reports are afloat on the substitutes that reach the black market and have harmful, sometimes fatal consequences because of their unregulated use. It is comprehensible that, in each nation, society should, as far as possible, try to avoid abuse by imposing regulations, while ensuring high-quality treatment. Most countries show no trust either in doctors or patients, and place treatment under strict regulations and controls. By contrast, a few countries

Correspondence: Albrecht Ulmer, General Practitioner, Schwabstr. 26, D-70197 Stuttgart, Germany, EU
Phone: +49711/62 63 08, e-mail: albrecht.ulmer@gmx.de

have moved in an almost exactly opposite direction, and have revoked most of the regulations that had once been in place. From the viewpoint of the regulating countries, treatment quality in these other countries should clearly be worse. But the OAT-providing physicians working in the former countries report the opposite on all outcome parameters. Therefore, a group of German OAT-providing physicians and pharmacists drove to Belgium, to use the setting of a EUROPAD conference to compare the experiences of two regions which make the complexities of the problem accessible through the documented results of applying the two conflicting philosophies.

2. Germany

Germany has a system which applies rather strict regulations, especially as a result of the Narcotics Act. Doctors have to possess a licence and therefore go through a week of training. Prescriptions can only be made out on special forms with two carbon copies which are distributed to the surveillance authorities; they are subject to many strict regulations, specifying the substances allowed, dosage, duration of validity, limited take-home permissions and many other details. Professional psychosocial care is mandatory, as well as urine controls, which are carried out under personal supervision at many centres and lead to sanctions in case of the continuing use of other substances. In many centres a system of directly controlled intake is applied much more often than that of a take-home prescription. It is also better paid.

The intention behind all these regulations was that of ensuring high-quality treatment. The consequence should have been a crucially better outcome for patients in Germany than in countries that clearly apply fewer, less strict regulations.

3. Belgium

Belgium, especially its Wallonian, French-speaking part, is a country that represents the opposite, less severe attitude. Physicians do not need a licence or have to fill in any special forms there; nor there is regulation of dosage, urine controls, take-home possibilities or all the other details that are subject to meticulous regulation in Germany. OAT patients are accepted in a normal context, in the same way as other patients. GPs who practise as therapists are available all over the region. They have been organizing a collegial network (Alto-SSMG, www.alto.ssmg.be) that has been offering regular training and peer consulting to GPs in many Wallonian towns for 20 years.

4. German Uncertainty

The mood of the German delegates was one of deep dissatisfaction. The burden of extra work brought about by regulations is hard to bear. It has a strong impact on doctor-patient relationships, which are now mainly determined by regulations, fear of sanctions and a great deal of mistrust. Complaints made by patients about insufficient conversations with their doctor are common. The fact that psychosocial counselling is mandatory leads to a further fall in quality: doctors think they are exempt from responsibility for psychosocial aspects. They say something like: “It’s mandatory for you to go to the counsellor”. The patients then go to this counsellor with the attitude: “I have come to you because I need your confirmation that I was here”. This is completely different from an optional service given in addition to an individual, conversation-based treatment, where the doctor would say: “I can recommend a good partner”. Alcohol problems are common, besides which other addictive substances are often shared and sold around treatment centres.

None of the German delegates was aged under 50. The mean age of the group was around 60. They haven’t found any new physicians to share or continue their work for years. Only a very few physicians have the necessary licence, and the others are happy to stay away from this minefield. It is a known fact that treatment under such regulations is frustrating and is also likely to lead to many legal proceedings. The few physicians who do provide OAT live under a cloud of anxiety, and are often accused of violating the law, which is, in any case, almost impossible to observe in an absolutely correct way. The laws and regulations that bind them are so strict that many colleagues feel alienated, and wonder: “Does society want or support what we do?”. It really does not look that way. OAT, which was originally provided by private practitioners, is dying out. It is increasingly taking the form of an offer made by clinics to large numbers of patients. By now, the average number of OAT patients who go regularly to the offices of OAT-providing German colleagues is around 30. Numbers over 100 are common. Patients there are artificially concentrated. OAT

induces densely populated drug scenes. Baden-Wurttemberg, the region where the German delegation comes from, has 10.7 million inhabitants and 460-OAT providing physicians, including 113 who are only allowed to treat up to 3 patients under the supervision of a doctor who has a licence. 9,896 GPs, other family doctors and psychiatrists are working in the same region. Over 95% of them do not provide OAT. 9,211 patients received OAT during the first quarter of 2011, around 9,000 of them from only 347 physicians in less than 250 offices, which means 26.5/physician and about 40 for each OAT-providing centre. In Stuttgart, the capital city of this region, with 500,000 inhabitants, only 10 offices provide OAT for 900 patients. Two offices are scheduled to close in the next two years.

Because of limited treatment places, it is difficult, often impossible to get OAT, or to choose or change a physician. The treatment has the character of providing care for a discharged mass of people in more and more places. The aim of rehabilitation and integration into normal society has been given up in the case of many patients. Treatment is like a prison without future prospects, and some patients suffer more from the treatment than from the disease. Once patients are no longer in OAT, they hesitate to come back, even if they need therapy. Some have had the experience that OAT "was the worst phase in my life". Some have told us that they had the feeling of being a more worthy person after buying buprenorphine for a few weeks on the street than going to a treatment centre daily, where they ended up with the feeling of being treated as a second- or third-class person. Most patients have to come every day for their supervised intake of the substitutes. Take-home prescriptions are strictly limited and last for 7 days at most.

There are also many patients who make good progress, but the number of unhappy patients who continue to return unsuccessfully to the treatment centres for years is alarming, and is still rising. The strict regulation of OAT seems to lead to a dead end. Its effects are reminiscent of the mistakes made in America by applying outright alcohol prohibition.

5. The Contrast with Belgium

Our Belgian colleagues presented a completely different picture: because of the revocation of all the previous regulations, 25% of all Belgian GPs now offer OAT. Wallonia has 3.4 million inhabitants. Approximately 8,000 opiate addicts are in OAT; they are being treated by about 1,240 GPs, with a ratio of 6.5/physician. 63.8% of the OAT-providing GPs have only 1 or 2 OAT patients (data for 2008). Take-home prescription is the usual procedure, and the period covered by each prescription is typically 7-14 days.

It is so easy for patients to get opioids in substitution treatment (methadone and buprenorphine) that it would be absurd to buy it on the street. The consequence of refraining from street sources is to curtail drug scenes and limit the black market. Once a holistic view is adopted, these patients can be considered 'normal' patients. Though they are drug users, they are primarily patients requiring all available therapeutic attention to be directed to their physical and mental well-being. Opiate addicts in the Belgian context have a much more normal and integrated life than in Germany.

6. Discussion

Germany had an unregulated OAT system during the 90s. Society in general was sceptical, and most experts and politicians opposed it. As a result, no constructive treatment system was developed. Many treatments had a partly subversive character. Death cases appeared to be associated with this unpopular, unregulated system. They led to the impression that this kind of treatment would be impossible without the imposition of strict regulations.

Physicians and other professions built a network comprising regular meetings and education, which was actually very similar to the current Belgian system, but in only a few regions, and the effects proved to be the same as in Belgium. There were almost no death cases and a comprehensive system bringing many elements of confidence. But, due to the scepticism about applying OAT that was predominant at that time, these promising experiences were not developed any further. Policies of caution and scepticism became the general rule, and OAT became subject to strict regulation.

The crucial point seems to be that greater investment is needed in networking and permanent education than in controls whose main outcome is demotivation and alienation. Doctors and patients must feel an atmosphere of well-founded trust and support based on a reliable treatment structure. One of the most central aspects is the avoidance of therapeutic scenarios where patients remain excluded outsiders.

The attendants of the conference in Brussels discussed point by point the following issues:

6.1 Do we need a licence for physicians? The answer was: "No!"

Making a licence mandatory is useless, even harmful, because it excludes a majority of physicians and leads to a dangerous concentration of patients - a result that brings various disadvantages to all. The aim of ensuring quality is definitively lost, considering that many physicians have to work in absolute solitude in their region, that they have to provide OAT for too many patients, and that patients are made overdependent on a physician they are not allowed to choose. The best systems share the feature of involving many practitioners in the OAT-providing system. GPs need a good level of cooperation with cooperative psychiatrists. The German group gave a good example. But for family doctors, as well as for psychiatrists, providing OAT should be a normal part of their job. A system which, for whatever reasons, fails to attract over 95% of all potential providers of life-and-death care is a system that desperately calls for re-examination and change.

6.2 Should a special form be required for a doctor to write a prescription? Here too the answer was: "No!"

In the German regions that had a good network, as well as in Belgium, the best experiences were those that did without this expensive system. In summary: control exerted in this way is counterproductive rather than helpful for the patients.

6.3 Do we need mandatory psychosocial counselling/care? In this case too the answer was: "No!"

To sum up the comments made, cooperation and truly interdisciplinary treatment is much more coherent and beneficial for patients if physicians and psychosocial counsellors cooperate voluntarily on the basis of mutual respect.

6.4 Do we need compulsory urine controls? Once again the reply was: "No!"

The Belgian colleagues stressed the need to consider the amount of money wasted on urine analyses! These analyses have a strong influence on care providers' relationship with patients, by showing an attitude of permanent mistrust. It is much better to invest in good contacts and founded trust in patients. They will then tell doctors much more, and the quality of the whole treatment will improve greatly as a result. Addiction diseases are strongly correlated with the central symptoms of underhandedness and mistrust. Urine analyses are a permanent indicator that these symptoms are never surmounted. The general impact is more negative than it is useful. If we cannot see the effects of a disturbing substance - why should we scrutinize the last corner, to determine if there is something there? If the whole development of a patient is unsatisfactory, we can reach the patient in a therapeutically more effective way if he/she experiences our unbroken trust in that patient's motivation to move forward. Newman expressed this by saying: "In most cases, our patients tell us dependably what they consume, if this consumption is not penalized".

6.5 Do we need regulations on dosages, on the substances that can be prescribed, on take-home opportunities, and so on? The unanimous answer was: "No, no, no!"

All these regulations are complicated, and make physicians fearful of breaking laws, so that they react by refusing to become involved in treatment provision altogether. Many of these regulations exclude treatments compatible with the attitudes of normal good care. The development of a good treatment standard, networking, education and a valid support system is much more effective - and is exactly what is needed!

6.6 Do we need strict controls on OAT-providing physicians? The answer given was: "No!"

These controls are counterproductive and alienating. It is much better, and more effective, too, to develop a motivating atmosphere, by investing in networking, education, support and evaluation of a whole system.

Maremmani amended this by saying: "A good approach could be to carry out some initial clinical controls to help achieve the aim of a patient's stabilization, followed by a more friendly attitude towards treatment-responsive patients".

A direct comparison between a widely regulated OAT system and a widely deregulated one showed us that most regulations are useless, even harmful. For the German delegates - all of them experienced OAT-providers - facing confronta-

tion with the widely unregulated Belgian system acted like a wake-up-call by indicating that it is much better to develop a good treatment system free of all these regulations, as long as many physicians are willing to contribute their services. An addiction disease is a chronic disease like every other chronic illness. There is no evidence in favour of getting any better outcome by disregarding the general principles of providing chronically ill patients with good treatment. In fact, many clear, strong hints indicate the opposite. Each and every regulation and/or demand that applies to OAT in a given country must be reviewed with one key question in mind: is there any other field of medical treatment where a similar regulation or demand exists? If the answer is no, the follow-up question must be: is there a compelling reason why a unique exception must be made for OAT? That was exactly the line the Belgians adopted in writing their unobtrusive regulations.

7. Conclusions

It is clearly best to treat addicted patients as normally as possible, without any special regulations laid down by law.

The Germans started a new initiative to change their regulations, and one physician in the German group, who had been providing OAT to 120 patients, decided to give up shortly after the conference. His office is due to close at the end of March 2012 without any linked treatment offer for that whole 120-strong group!

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No conflict of interest.

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Heroin addicts' psychopathological subtypes. Correlations with the natural history of illness

Angelo Giovanni Icro Maremmani [1,2], Luca Rovai [1], Pier Paolo Pani [4] and Icro Maremmani [1,2,3]

1. Vincent P. Dole Dual Diagnosis Unit, Santa Chiara University Hospital, Department of Psychiatry, NPB, University of Pisa, Italy, EU
2. Association for the Application of Neuroscientific Knowledge to Social Aims (AU-CNS), Pietrasanta, Lucca, Italy, EU
3. G. De Lisio Institute of Behavioral Sciences Pisa, Italy, EU
4. Social-Health Services, Health District 8 (ASL 8) Cagliari, Sardinia, Italy, 09127.

Summary

By recently using an exploratory factor analysis of the 90 items in the SCL-90, we identified a five-factor solution for 1055 heroin addicts who answered that questionnaire at treatment entry. On the basis of the highest z-scores obtained on these factors, subjects can be assigned to 5 mutually exclusive groups labelled "worthlessness and being trapped", "somatization", "sensitivity-psychoticism", "panic anxiety", and "violence-suicide". In this study we correlated the distribution within these groups of 455 heroin addicts. The patients belonging to the "worthlessness and being trapped" group had the highest average age and were those who, most frequently, had a white-collar job. Those belonging to the "somatization" group were less frequently at their first treatment, more frequently reported sleep disturbances and less frequently referred to their use of hallucinogens. The leading distinctive feature of those in the "sensitivity-psychoticism" group was that they were the youngest. Patients belonging to the "panic anxiety" group less frequently reported major problems with their love life, sleep disturbances, and more frequently referred to their use of CNS stimulants. The features of being more excitable and violent brought with them the highest likelihood of belonging to the "violence-suicide" group. These differences were independent of the presence of dual diagnosis. These data support the hypothesis that heroin has as its foundation a specific psychopathology.

Key Words: Heroin addiction; psychopathological subtypes; dual diagnosis; natural history of heroin addiction.

1. Introduction

By recently using an exploratory factor analysis of the 90 items in the SCL-90, a five-factor solution was identified for 1055 heroin addicts who answered the SCL-90 questionnaire at treatment entry. We named these factors on the basis of items that showed the highest loadings. "Worthlessness and being trapped", "somatization", "sensitivity-psychoticism", "panic anxiety" and "violence-suicide" were the five dimensions that were extracted. On the basis of the highest z-scores obtained on the 5 SCL-90 factors (allowing identification of a number of dominant SCL-90 factors), subjects can be assigned to 5 mutually exclusive groups. These five groups are sufficiently distinct, and fail to reveal any significant overlap [47].

On the basis of this psychopathological classification, a cohort study was designed with the aim of correlating membership in one of the above groups with the natural history of heroin addiction of patients enrolled in an Opoid Agonist Treatment (OAT).

Study data were obtained from a general database of patients enrolled during the years

Correspondence: Angelo Giovanni Icro Maremmani, MD; Vincent P. Dole Dual Diagnosis Unit, Santa Chiara University Hospital, Department of Psychiatry, University of Pisa, Via Roma, 67 56100 PISA, Italy, EU.
Phone +39 0584 790073 Fax +39 0584 72081, E-Mail: angelogimaremmani@gmail.com

1994-2010 at the Vincent P. Dole Dual Diagnosis Unit, Santa Chiara University Hospital, Department of Psychiatry, University of Pisa, Italy. We selected patients whose group membership (derivable from a baseline SCL-90), together with a complete drug addiction history, was available. This can therefore be classified as a retrospective, observational, cross-sectional study.

2. Methods

2.1 Setting

The research study was implemented using a dataset from previous studies on AOT carried out in Italy and used in previously published articles (Pisa agonist opioid addiction dataset: a database including anonymous individual information originally collected for clinical research purposes) [41, 47, 48].

The treatment programme attended by patients included in this dataset featured: outpatient treatment; easy access to services; treatment and ancillary services oriented towards a prolonged retention of patients in the programme; delivery of different types of interventions for addictive disorders and related problems (methadone, buprenorphine, naltrexone maintenance, general medical care, counselling, rehabilitative services, and psychological-psychiatric care); dosing of methadone or buprenorphine soon after diagnosis of opioid dependence (with physical dependence); participation of patients in the determination of the methadone/buprenorphine dose, and knowledge of the dose dispensed; collection of urine specimens on a weekly basis, followed by analysis for any presence of morphine or cocaine (ensuring the availability of 1-3 results per month).

2.2 Subjects

The sample consisted of 455 heroin-dependent patients (according to DSM III/IIIR/IV/IVR criteria), of which 340 (74.9%) were males and 115 (25.3%) females. The average age was 28 ± 7 years old (range 16-50). Most of the patients were single (N=295; 64.8%), had had less than 8 years of education (N=346; 76.0%), and were unemployed (N=212; 46.6%).

Compared with the females in the group, the males were older (T=2.33; p= 0.021) more often single (chi=11.69; df1; p=<0.001) and blue-collar workers (chi=25.17; df3; p<0.001). No differences were observed regarding education, income, type of housing, place of birth or residence, or as to whether they were receiving public welfare benefits.

According to our classification model [47], the group whose dominant was 'worthlessness and being trapped' comprised 73 subjects (16.0%), the group with 'somatization' as its dominant gathered 107 subjects (23.6%), the group showing 'sensitivity-psychoticism' as its dominant included 94 subjects (20.7%), the group identified by 'panic anxiety' as its dominant numbered 108 subjects (23.7%), and the group whose dominant was 'violence-suicide' group profiled a cluster of 73 subjects (16.4%). These four groups were then compared for demographic, toxicological, psychopathological and treatment-related variables.

2.3 Instruments

2.3.1. Drug Addiction History Questionnaire (DAH-Q)

The DAH-Q [36] is a multi-scale questionnaire comprising the following 8 areas: 1-demographic data, 2-physical health, 3-mental status, 4-social adjustment and environmental factors, 5-substances abused, 6-substance abuse modalities (heroin intake, modality of use, stages of illness, nosography), 7-treatment history and 8-addiction history (age at first contact, age at initiation of continuous use, dependence length, and age at first treatment). The Scale rates 10 presence-absence items: 1-somatic comorbidities, 2-abnormal mental status, 3-work problems, 4-household problems, 5-sexual problems, 6-socialization and leisure time problems, 7-drug related legal problems, 8-polysubstance abuse, 9-previous treatment, 10-combined treatments.

We coded the modality of use as follows: 1-stables, 2-junkies, 3-two worlders, 4-loners. 'Stable' or 'conformists' heroin addicts lead an existence that is apparently acceptable to social conventions. 'Junky' heroin addicts can be called 'destructive' or 'violent'; they are immersed in their drug sub-culture, and live in places and situations that are often at the limits of the law or may even be in open conflict with rules or conventions. 'Two worlder' heroin addicts do not care about their criminal activities or living together with other addicts, but often have a regular job. The 'loner' heroin addicts are not involved in the drug culture, do not have a stable job and in most cases live on State subsidies rather than on the proceeds of criminal activities [29].

The development of addiction may be considered to consist of three stages: (1) acute (immediate) drug effects; (2) transition from recreational use to patterns of use consistent with addiction; and (3) end-stage addiction, which is characterized by an overwhelming desire to obtain the drug, a diminished ability to control drug seeking and entails reduced pleasure from biological rewards [25]. Considering clinical typology, drug addicts can be divided into three types: Type 1 or 'reactive' heroin addicts show psychosocial stressors before using heroin. Type 2 or 'self-therapeutic' heroin addicts report psychiatric stressors before using heroin. Type 3 or 'metabolic' heroin addicts show no psychosocial or psychiatric antecedents [50].

2.3.2 Psychiatric diagnostic evaluation

Psychiatric disorders were investigated on the basis of the DSM-IV Decision Trees for Differential Diagnosis [1]. Each decision tree starts with a set of clinical features. When one of these features is a prominent item within the current clinical picture, the clinician will ask a series of questions to rule in or rule out a number of disorders. The questions are just approximations to the diagnostic criteria and are not meant to replace them. Three decision trees have been used: "Differential Diagnosis of Psychotic Disorders" (initial clinical features: delusions, hallucinations, disorganized speech, or grossly disorganized behaviour); "Differential Diagnosis of Mood Disorders" (initial clinical features: depressed, elevated, expansive or irritable mood; two separate items record the presence of depression and/or any tendency towards the bipolar spectrum as testified by an elevated, expansive or irritable mood); "Differential Diagnosis of Anxiety Disorders" (initial clinical features: symptoms of anxiety, fear, avoidance, or increased arousal).

As to bipolar spectrum diagnoses, histories of previous hypomanic episodes, as well as temperamental characteristics, were explored using the criteria listed in the SID, the Semistructured Interview for Depression [13]. All this information was gathered from the patient and at least one close relative (usually from parents or siblings); in addition, all available clinical records were carefully examined. Inquiries into temperamental attributes were made about the habitual behaviour of the patient - during periods free of affective episodes - by gathering information from the patient and significant others. Although it may seem strange that such figures have been documented for addicted patients, Italian addicts find it hard to become detached from their families, despite the disruption of family relationships. In fact, almost 90% of the patients in our sample were still living with their original or acquired families.

Our operational criteria for affective temperaments have been drawn from the University of Tennessee [2] modification of the Schneiderian descriptions [62]. The SID, developed as part of the Pisa-Memphis (now San Diego) collaborative study on affective disorders, has been used with over 2000 patients at the time of writing: its reliability for diagnostic assessment of patients and their temperaments has been documented elsewhere [58, 59]. The SID was resorted to in order to increase the level of diagnostic accuracy with respect to bipolar disorders. Even accepting the hypothesis that minor bipolar syndromes had been overrated, such a bias would not affect the rate of DD. In fact, the relationship between outcome and specific diagnostic subgroups is beyond the study's terms of reference.

Patients were evaluated while outside the acute phases, for which hospitalization would often be required, so as to reduce the diagnostic ambiguity between intoxication-related symptoms and spontaneous mental disorders. In cases where further information emerged on clinical grounds or from later interviewing, diagnoses were reviewed.

When an independent psychiatric disorder is concomitant with a substance abuse disorder, we consider the patient as being affected by a dual diagnosis condition.

2.4. Data analysis

The 5 groups were compared for demographic and addiction history by means of chi-square test for categorical variables, and one-way analysis of variance for continuous variables, a posteriori contrasts according to the Scheffe procedure.

All analyses were carried out using the statistical package of SPSS (version 4.0). Since this is an exploratory study, statistical tests were considered significant at the $p < 0.05$ level.

3. Results

3.1 Socio-demographic data

Regarding sociodemographic data, no dif-

ferences were observed regarding gender, marital status (single), education (<8 years), income (poor) and living situation (alone). Patients characterized by worthlessness and a feeling of being trapped were older. Sensitivity-psychoticism patients were younger. White-collar patients were more frequently observed in the "worthlessness and being trapped" group (Table 1).

3.2 DAH-Q factors and addiction history

Table 2 shows differences across the 5 dominant-factor SCL90 groups with reference to DAH-Q factors. No significant differences were observed. Somatization patients reported more somatic symptoms and recorded a lower frequency in stating that they were at their first treatment for opioid dependence.

3.3 Mental status at treatment entry

Regarding patients' mental status at treatment entry (Table 3), the absence of insight, the presence of alterations in consciousness

Table 1. Demographic data according to SCL90 dominant groups

	M	GR1 N=73	GR2 N=107	GR3 N=94	GR4 N=108	GR5 N=73	F/ Chi	p
Age	0	30±6 [b]	29±6 [ab]	27±5 [a]	28±6 [ab]	27±5 [ab]	3.13	0.015
Gender (males)	0	51 (69.9)	83 (77.7)	76 (80.0)	75 (69.9)	55 (75.3)	4.84	0.303
Education (>8years)	2	26 (36.1)	20 (18.9)	18 (19.1)	31 (28.7)	14 (19.2)	10.75	0.029
Marital status (single)	9	51 (15.3)	77 (73.3)	74 (80.0)	81 (75.0)	51 (70.8)	2.30	0.680
Occupation								
Student	1	1 (1.4)	7 (6.5)	11 (11.7)	7 (6.5)	2 (2.8)		
White collars		21 (28.8)	13 (12.1)	11 (11.7)	19 (17.6)	10 (13.9)		
Blue collars		22 (30.1)	43 (40.2)	32 (34.0)	36 (33.3)	22 (30.6)		
Unemployed		29 (39.7)	44 (41.1)	40 (42.6)	46 (42.6)	38 (52.8)	22.08	0.037
Income (poor)	12	15 (21.1)	30 (29.1)	20 (21.5)	24 (23.1)	14 (19.4)	2.91	0.572
Welfare benefit (Yes)	14	2 (2.8)	5 (4.9)	5 (5.5)	0 (0.0)	4 (5.6)	6.23	0.183
Living situation (In family)	6	14 (19.4)	17 (16.2)	10 (10.9)	15 (14.0)	7 (9.6)	4.11	0.391

GR1= Worthlessness-being trapped; GR2= Somatization; GR3= Sensitivity-psychoticism; GR4= Panic-anxiety; GR5= Violence-suicide
Letters indicate homogenous subset (p=0.05)

Table 2. DAH-Q factors according to SCL90 dominant groups

	M	GR1 N=73	GR2 N=107	GR3 N=94	GR4 N=108	GR5 N=73	Chi	p
Somatic complications (presence)	0	55 (75.3)	90 (84.1)	64 (68.1)	79 (73.1)	61 (83.6)	9.95	0.041
Altered mental status (presence)	1	63 (86.3)	99 (92.5)	87 (92.6)	99 (91.7)	67 (93.1)	3.00	0.556
Occupation (absence)	6	39 (54.2)	53 (49.5)	44 (47.3)	51 (47.7)	31 (44.3)	1.55	0.818
Household (unsatisfactory)	15	36 (50.0)	45 (43.3)	40 (45.5)	43 (41.0)	29 (40.8)	1.83	0.767
Romantic involvement (unsatisfactory)	21	38 (55.1)	49 (48.0)	43 (47.8)	39 (37.9)	32 (45.7)	5.29	0.258
Social-leisure activity (unsatisfactory)	8	43 (60.6)	56 (52.8)	51 (56.0)	62 (58.5)	31 (42.5)	6.19	0.185
Legal problems (presence)	7	38 (52.8)	57 (53.8)	43 (46.7)	47 (44.8)	34 (46.6)	2.49	0.646
Polyabuse (presence)	3	29 (39.7)	40 (37.4)	37 (39.8)	57 (53.8)	34 (46.6)	7.40	0.116
Previous unsuccessful treatments	0	61 (83.6)	89 (83.2)	63 (67.0)	79 (73.1)	54 (74.0)	10.12	0.038
Current associated treatments	0	49 (67.1)	79 (73.8)	58 (61.7)	59 (63.9)	52 (71.2)	4.50	0.342

GR1= Worthlessness-being trapped; GR2= Somatization; GR3= Sensitivity-psychoticism; GR4= Panic-anxiety; GR5= Violence-suicide

and memory, the presence of anxiety, depressed mood, eating disturbances, suicidality, delusions and hallucinations revealed no differences between the 5 dominant-factor SCL90 groups.

Sleep disturbances were more frequent in the dominant somatization group and less frequent in the panic anxiety dominant group. Excitement and violence proved to be frequent in the violence-suicide dominant group.

3.4 Lifetime concomitant substances of (self-reported) abuse at treatment entry

With respect to lifetime concomitant substance (self-reported) abuse at treatment entry (Table 4), no differences were observed in the frequencies for the concomitant use of alcohol, CNS depressant, cannabinoids, inhalants or illegal methadone.

The patients who featured the panic-anxiety symptomatology reported a more frequent use of CNS stimulants. Patients characterized by somatization symptomatology reported a less frequent

Table 3. Mental status according to SCL90 dominant groups

Altered mental status	M	GR1 N=73	GR2 N=107	GR3 N=94	GR4 N=108	GR5 N=73	Chi	p
No-insight	13	26 (36.6)	53 (50.0)	47 (52.8)	56 (53.3)	30 (42.3)	6.81	0.146
Consciousness	7	3 (4.1)	7 (6.7)	8 (8.8)	11 (10.2)	9 (12.7)	4.27	0.371
Memory	7	12 (16.4)	26 (24.8)	17 (18.3)	24 (22.4)	14 (20.0)	2.40	0.662
Anxiety	3	33 (45.2)	47 (43.9)	44 (47.3)	49 (45.8)	40 (55.6)	2.67	0.613
Depression	3	39 (53.4)	56 (52.8)	50 (53.2)	65 (60.2)	44 (62.0)	2.72	0.606
Sleep	3	31 (42.5)[ab]	65 (61.3)[b]	35 (37.6)[a]	44 (40.7)[a]	30 (41.7)[ab]	14.70	0.005
Eating	3	12 (16.4)	27 (25.5)	26 (28.0)	22 (20.4)	16 (22.2)	3.89	0.421
Excitement	4	16 (21.9)[a]	37 (34.9)[a]	25 (26.9)[a]	39 (36.1)[ab]	40 (56.3)[b]	22.50	0.000
Violence	8	12 (16.4)[a]	31 (29.2)[ab]	25 (28.1)[ab]	38 (35.5)[ab]	33 (45.8)[b]	16.13	0.003
Suicidality	8	6 (8.2)	14 (13.2)	5 (5.6)	18 (16.8)	14 (19.4)	9.93	0.042
Delusions	3	4 (5.5)	12 (11.3)	9 (9.7)	14 (13.0)	8 (11.1)	2.84	0.584
Hallucinations	4	3 (4.1)	4 (3.8)	6 (6.5)	9 (8.3)	7 (9.7)	3.84	0.427

GR1= Worthlessness-being trapped; GR2= Somatization; GR3= Sensitivity-psychoticism;
GR4= Panic-anxiety; GR5= Violence-suicide
Letters indicate homogenous subset (p=0.05)

Table 4. Concomitant substance abuse according to SCL90 dominant groups

Use of	M	GR1 N=73	GR2 N=107	GR3 N=94	GR4 N=108	GR5 N=73	Chi	p
Alcohol	7	21 (29.2)	40 (37.7)	30 (33.0)	47 (44.3)	29 (39.7)	5.20	0.267
Opioids	2	71 (97.3) [a,b]	104 (97.2) [b]	80 (85.1)[a]	96 (90.6)[a,b]	68 (93.2)[a,b]	13.80	0.008
CNS-Depressants (BDZ)	4	28 (38.4)	45 (42.1)	46 (49.5)	44 (41.9)	37 (50.7)	3.71	0.446
CNS-Stimulants (Cocaine)	4	34 (46.6)	62 (57.9)	56 (60.2)	67 (63.8)	48 (65.8)	7.14	0.128
Hallucinogens	5	19 (26.4)	26 (24.3)	32 (34.4)	44 (41.9)	29 (39.7)	10.35	0.035
Cannabinoids	3	46 (63.0)	66 (61.7)	57 (61.3)	75 (70.8)	53 (72.6)	4.54	0.337
Inhalants	6	2 (0.4)	4 (0.9)	3 (0.7)	2 (0.4)	5 (1.1)	3.29	0.509

GR1= Worthlessness-being trapped; GR2= Somatization; GR3= Sensitivity-psychoticism;
GR4= Panic-anxiety; GR5= Violence-suicide
Letters indicate homogenous subset (p=0.05)

Table 5. Clinical characteristics according to SCL90 dominant groups.

	M	GR1 N=73	GR2 N=107	GR3 N=94	GR4 N=108	GR5 N=73	Chi	p
Heroin intake (daily or more)	43	61 (87.1)	82 (80.4)	62 (80.5)	81 (86.2)	58 (84.1)	2.38	0.665
Modality of use (unstable)	48	42 (16.3)	63 (24.5)	48 (18.7)	67 (26.1)	37 (14.4)	4.82	0.306
Periodic self-detox (presence)	83	47 (71.2)	59 (67.0)	46 (65.7)	61 (72.6)	41 (64.1)	1.79	0.774
Stage (late stage)	65	46 (70.8)	64 (68.8)	49 (65.3)	56 (62.2)	44 (65.7)	1.58	0.816
Clinical Typology (biopsychosocial stressor)	75	18 (28.1)	24 (26.1)	26 (36.6)	34 (37.4)	20 (32.3)	3.81	0.432
Age first contact (years)	46	19±4	18±3	18±3	18±3	18±4	1.01	0.402
Age of onset (years)	54	21±4	20±5	20±3	21±5	20±4	1.65	0.155
Dependence length (mounths)	84	97±67	93±72	83±56	77±66	86±66	1.08	0.362
Age first treatment	52	25±4	24±5	24±4	25±6	23±4	1.06	0.372
Latency to dependence (years)	57	2.90±3.2	2.73±3.3	2.25±2.48	2.91±3.5	1.50±1.7	2.88	0.022
Latency to treatment (years)	72	3.82±3.7	3.89±3.7	4.20±3.9	4.40±4.7	4.13±3.5	1.33	0.256

GR1= Worthlessness-being trapped; GR2= Somatization; GR3= Sensitivity-psychoticism; GR4= Panic-anxiety; GR5= Violence-suicide
Letters indicate homogenous subset (p=0.05)

Table 6. Diagnoses according to SCL90 dominant groups

	M	GR1 N=73	GR2 N=107	GR3 N=94	GR4 N=108	GR5 N=73	Chi	p
Dual diagnosis (presence)	0	47 (64.4)	66 (61.7)	60 (63.8)	69 (63.9)	48 (65.8)	0.33	0.987
Diagnosis								
Chronic psychosis		4 (5.5)	11 (10.3)	10 (10.6)	17 (15.7)	10 (13.7)		
Depression recurrent		24 (32.9)	24 (22.4)	31 (33.0)	26 (24.1)	12 (16.4)		
Bipolar spectrum	0	11 (15.1) [a,b]	21 (19.6) [a,b]	9 (9.6) [b]	23 (21.3) [a,b]	22 (30.1) [a]		
Anxiety disorders		8 (11.0)	10 (9.3)	10 (10.6)	3 (2.8)	4 (5.5)		
Without psychiatric comorbidity		26 (35.6)	41 (38.3)	34 (36.2)	39 (36.1)	25 (34.2)	27.56	0.036

GR1= Worthlessness-being trapped; GR2= Somatization; GR3= Sensitivity-psychoticism; GR4= Panic-anxiety; GR5= Violence-suicide
Letters indicate homogenous subset (p=0.05)

use of hallucinogens.

3.5 Abuse modalities and treatment history

With respect to abuse modalities (Table 5) and previous treatments, no differences were found.

3.6 Diagnoses

With respect the presence of dual diagnosis (Table 6) no differences were found. Heroin addicts bipolar patients were more frequent represented in violence-suicide dominant group and less frequent in sensitivity-psychoticism group.

4. Discussion

The present sample shows cluster analysis results that closely resemble those of our previous sample [47].

The five psychopathological subtypes into which heroin addiction can be divided show a low level of differentiation in their demographic data, DAH-Q factors, mental status, and lifetime concomitant substances of abuse at treatment entry.

Patients belonging to the "worthlessness and being trapped" group are those with the highest average age, and are more frequently white-collar workers.

Patients belonging to the "somatization"

group less frequently report being at their first treatment, but more frequently report sleep disturbances; they less frequently refer to the use of hallucinogens.

The most prominent feature of those belonging to the "sensitivity-psychoticism" group is that they have the lowest average age.

Those belonging to the "panic anxiety" group less frequently report major problems in their love life and sleep disturbances, while they more frequently refer to the use of CNS stimulants

The features of being more excited and more violent correspond to the highest probability of belonging to the "violence-suicide" group.

To our knowledge, few studies have investigated the demographic characteristics of heroin users at methadone maintenance treatment entry [19]. Trends over time in patients' age at initiation into heroin use have been investigated, the main conclusion being that Australia is experiencing an increase in the use of heroin, particularly among young people [31]. Fully employed heroin users with respect to their unemployed counterparts, have revealed the following differences: employed users were more likely to possess human capital and social capital, and were less likely to use crack cocaine [27]. It is notable that in our sample white-collar patients are more frequently represented among those in the "worthlessness and being trapped" group. This is consistent with the idea that heroin addiction displays its psychopathological effect regardless of the presence or absence of social adjustment. No study, to date, has explored the correlations between age and psychotic symptomatology in any sample of heroin addicts.

With regard to drug addiction history, recent findings in the literature suggest that the movement from recreational to dependent heroin use increases hospital morbidity, and that morbidity is, by contrast, lower when a methadone maintained treatment is available [65]. No study, to date, has offered a profile of heroin addicts suffering from panic and somatization symptomatology, in terms of their drug addiction history.

Regarding mental status, the level of neurocognitive impairment related to the use of heroin has been inadequately investigated. Sex, ethnicity, age and education seem to influence patients' performance in responding to the Trail Making test, a test often used for screening for the presence of cognitive dysfunctions in heroin abuser populations [60]. In order to identify cognitive correlates specific to heroin addiction, a wide range of mental functions including complex visual pattern recognition, working memory, problem solving, executive decision-making, cognitive flexibility and response shifting have all been measured. Heroin addicts exhibited significantly more disadvantageous decision-making and longer deliberation times while making risky decisions than the control groups [65]. To the best of our knowledge the presence of sleep disturbances has not yet been correlated, in the literature, with any of the symptomatological features presented by heroin-dependent subjects. Conversely, the presence of self-injurious behaviours has turned out to provide useful criteria for dividing heroin addicts into subtypes. The frequency of nine varieties of moderate/superficial self-injurious behaviours during active heroin use has been assessed retrospectively in heroin-dependent patients. Subjects who displayed a low level of self-injurious behaviours also reported fewer episodes of suicide attempts and were less frequently diagnosed with bulimia. Patients who had the feature of a high occurrence of scab-picking behaviours got injured more frequently than those with a high occurrence of hitting and cutting behaviours [57]. These data were not, however, confirmed by our findings, which failed to reveal any correlation between eating disturbances and membership of the violence-suicide dominant group.

As far as the presence or absence of a dual diagnosis is concerned, many authors have pointed out that substance use disorders correlate with bipolar disorders, not only at the clinical level [11, 15, 32, 34, 35, 42, 43, 46, 49], but also at the affective-temperamental one [44, 54]. On the basis of these findings in the literature, the role of bipolarity in the pathogenesis of substance use disorders has been widely stressed; this perspective allows the bipolar spectrum to be viewed as the psychic substrate for the development of a substance-resorting attitude [33, 49, 56]. In our sample of heroin addicts the presence or absence of a dual diagnosis failed to reveal the capacity to predict membership of any psychopathological dominant group. We believe that, despite the fact that progression through a toxicomanic career is favoured by the presence of a bipolar spectrum disorder, heroin use, once it has been established, displays its own pathogenic effects, which appear to be independent of the co-occurrence of any specific affective disease. This conceptualization is in line with our previous papers, which, by

examining the mental status of 1090 heroin addicts at entry into treatment, have provided much evidence that the presence of psychopathological features such as a depressive-anxious symptomatology did not necessarily imply the presence of a dual diagnosis [41]. Even more surprising is the fact that in heroin addicts the presence of a dual diagnosis has been reported to exert no influence on their quality of life as assessed by well-validated instruments [6], and to positively influence the long-term outcome of illness with respect to patients showing no psychiatric comorbidity [38, 39].

Polydrug abuse has been widely studied among heroin addicts. When its association with psychiatric comorbidity was assessed in a sample of heroin injectors, significant positive correlations were observed between the number of lifetime/current drug dependence diagnoses and the number of lifetime/current anxiety and affective disorders [17]. In a comparative study between heroin and heroin-cocaine polyabusers that aimed to fill in the details of the psychopathological profile of heroin-cocaine abuse, cocaine abuse was reported to positively correlate with the presence of psychiatric disorders, but to correlate negatively with the severity of self-rated psychopathology [7]. Our data, in line with previous papers, confirm the theory that cocaine is able to precipitate panic disorder [4, 5, 45, 52, 61]. This well-known property of cocaine might even appear in enhanced form in heroin addicts, who typically present an impaired opioid system. The fact that naltrexone induces panic attacks [37], and that opioid agents display anti-panic effects [23], supports this idea.

Few authors have carried out comparative studies on heroin addicts who present and those who do not present a history of sniffing glue and solvents. Those involved in sniffing practices were more likely to have attempted suicide, they more often fantasized about death, and they acknowledged less fear of the pain/deterioration involved in dying. On average, they had abused more than twice as many different substances as those who had no sniffing history [16]. Clear differences emerged between the two groups with reference to age, sex, social status, socialization conditions, family structure, education, vocational training, drug sequence and criminality, in addition to attitudes and motivation displayed towards withdrawal therapy. On the basis of these findings, polytoxicomanic opiate addicts with an experience of sniffing can be defined as a marginal group who are distinguished by their particularly unfavourable developmental conditions and a specific course of addiction [3]. Present results, in line with the literature, make it clear that a differentiation is imperative within the group of heroin addicts, with respect to polydrug abuse.

Research interest in the concept of abuse modalities and treatment careers has been rising. A new instrument for mapping lifetime drug use history has been introduced in assessing transitions in the initial stages of heroin use careers among illicit drug users. A mean age of only 21 years has been reported for the initiation of heroin use; escalation to daily use typically occurs by the age of 23 [9]. On average, there was a time interval of nearly 8 years before treatment was sought. Three discernible groups have been identified on the basis of use patterns. One group showed consistent escalation in total quantity of heroin used across the first year, the second had an intermittent pattern of use, while the third reported an unchanging monthly heroin use pattern. These groups differed in the time taken to initiate treatment and in the proportion of active use of heroin. Despite these findings, no data are available in the literature about the relationship between abuse modalities and the psychopathological profile of heroin addicts. Although abuse modalities and frequency of use are likely to be considered escalation factors in heroin careers, our view is that they do not appear to correspond to any specific psychopathological profile. One outcome of all these findings is to further strengthen the view that the psychopathological profile of heroin addicts is primarily due to their direct involvement in heroin use.

In the literature, opioid agents have been shown to possess antidepressive, [10, 12, 18, 20-23, 66], antimanic [23, 51, 55], anti-panic [23] and antipsychotic [8, 14, 28, 30, 40, 53, 64, 67] properties - but not only in opioid-dependent subjects. They have been clearly shown to be effective in controlling aggressive behaviour in opiate-addicted patients, as confirmed by the fall in levels of aggressiveness that is an aftermath of adequate methadone treatment [24, 26, 63]. These therapeutic properties are also suggested by the fact that dual diagnosis heroin addicts need higher stabilization dosages than heroin addicts who have no additional psychiatric disorder [51].

5. Conclusions

On the strength of this mass of data, we

propose that the dysregulation of the opioidergic system that is determined by heroin addiction might be responsible for the wide range of psychopathological symptoms presented by heroin addicts at the end of their toxicomanic career, independently of comorbid psychiatric conditions, gender, education, drug addiction history, concomitant drug abuse, abuse modalities and previous treatments. In other words, the results of this study strongly support the hypothesis that heroin addiction does indeed possess its own specific psychopathology.

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Profile of an addict, or, beyond the addiction mask

Jasmina Knezevic Tasic, Rosa Sapic and Masa Valkanou

Lorijen Hospital, Clinic for Addiction and Other Psychiatric Disorders, Belgrade, Serbia

Summary

The main purpose of this study was to examine if there is anything that could be correctly described as the "profile of an addict", and whether certain personality disorders occur with a higher frequency in substance abuse patients in Serbia today. The other question investigated in this study is how the presence of psychopathology can be evaluated in individuals who have developed addiction compared with those who have not. In addition, factors such as emotional relationships and education have been examined. The sample selected for this inquiry included 79 participants - 42 addicts, and 37 individuals making up a control group. Personality disorders were assessed by applying the Millon Multiaxial Clinical Inventory III (MCMI III), together with a specially constructed data sheet. Canonical discriminant analysis was used to present the model best able to generate distinct personality features that strongly predict drug abuse and determine the essence of an addiction personality profile. Canonical discriminant analysis was also used to explore differences in the presence of psychopathological features between the two groups. A chi-squared analysis examined the differences in emotional status and level of education between groups. Significant differences were found between the general population and the substance abuse group in terms of the presence of personality disorders and the level of the pathology presented. Individuals who have developed an Antisocial, a Borderline, a Depressive or a Dependent personal style are those most prone to substance abuse, whereas individuals who have adopted a Histrionic or Compulsive Personality style are those least likely to develop addiction. The study found that addiction is firmly attached to the presence of major Depression, PTSD and Dysthymia. Another significant difference in the levels of pathology between the two groups was documented, in a way that showed that the addiction group had a significantly higher overall level of pathology.

Key Words: drug addiction, drug abuse, substance abuse, personality disorder, personality style, psychopathology level

1. Introduction

The main purpose of this study was to examine if there is a higher frequency of specific personality disorders, and personality disorders in general, in substance abuse patients in Serbia today. In addition, factors such as gender, time of onset and duration of substance use were examined. The crucial importance of personality as a concept, along with personality disorders, was quickly recognized as a major discovery to be incorporated at once into the work of every clinician, and a focus of interest for various research topics (18). The typology of personality traits, ranging from personal style to personality disorders, is of compelling interest as an input for psychotherapeutic work in various different settings, and its criteria need to be efficiently applied in cases where a patient is suffering from neurosis or psychosis, or even when psychologically healthy individuals have to face the problem of 'how to improve the quality of their lives'.

Differentiation between levels of pathology is crucial in diagnostics, and in setting boundaries to therapeutic goals and the work to be done. In theory, there is a limited variety of personal

Correspondence: Masha Valkanou, Lorijen Hospital, Tetovska 45, 11000 Belgrade, Serbia.
E-mail: psyonics@gmail.com. Phone +381616717375

styles; Millon defined 11 clinical personality patterns plus 3 severe personality pathologies (16). The intensity of each cluster of personal characteristics is, however, crucially important in daily medical practice. It has been demonstrated that an individual who has a personality disorder will react more inadequately to stress and to life's milestones than someone else who does not fulfil the criteria of a PD (personality disorder). In clinical work therapists encounter individuals who are to some extent impaired, (including some who are psychotic, or neurotic, or who have behavioural problems, and those who simply find it difficult to adjust to stressful events in their lives) and may even display some of the same personal traits as those who have a PD (18).

This study tended to explore the issue of whether particular personality types are especially prone to drug abuse, and looked into the question of whether there is a higher frequency of personality disorders (viewing these as an intense form of pathology) among substance abuse patients who were compared with a control group in Serbia. This study also explored the question of whether substance abuse is gender-sensitive and how subjects' age at onset of use and the duration of their use actually influence substance abuse in each of several personality styles.

To fully understand the context of this inquiry, the concept of personality disorders should be explained in detail at this point, together with their relationship with various aspects of personal experiences and behaviours, including drug abuse, but, considering the limits of space that must be respected to comply with the article format, it will be assumed that the reader is familiar with those concepts. In any case, for a more fully documented version of this paper, a request may be made to the authors, using the contact details given above.

Beyond 'personal style' and towards a "personal disorder" diagnosis

DSM IV treats personality disorders as a category, which means that a person either has or does not have a particular disorder (10). To be given a PD diagnosis, a person must fulfil a number of predetermined criteria. However, it is important to emphasize the concept of Personality Style as well, moving towards a 'continuum approach' as the approach most appropriate to psychological phenomena. That means that two individuals may possess the same or similar psychological attributes, but, depending on the impairment that those characteristics bring to a particular person's everyday life, one person may be diagnosed as having a personality disorder, whereas another may have no more than a certain personality style. Actually, a new revision of DSM has defined a PD as an "adaptive failure" (10). Here it could be noted that the already announced new DSM V is known to be leaning towards a more continuum-like approach for the future.

In this study the frequency of personality disorders in drug addicts was calculated on the basis that patients who satisfied the criterion of a score of 75 or more on the Millon scale were to be diagnosed with PD, while the range of personality styles was reviewed comparatively in the control and in the experimental group, independently of the intensity of those styles. As suggested by a new DSM, version V, which has been announced for 2013, a person should be diagnosed with PD only if: DSM V shows that he/she has a significant impairment in two functional areas (area of self-identity and area of interpersonal relationships), receives a high rating on the personality trait scales, has a history of presenting problems over a long period, and only if that set of findings could not be explained by any another condition (10).

1.1. Types of personality disorder

Classifications of personality disorders do not fully overlap. DSM and ICD concur in including eight categories: the Paranoid, Schizoid, Antisocial, Borderline, Histrionic, Anankastic (Obsessive-Compulsive), Anxious (Avoidant) and Dependent personality disorders, but DSM includes four more types: Schizotypal, Narcissistic, Depressive and Passive-aggressive personality disorder (24; 2). The present study follows Millon's classification of personality disorders, which itself closely follows DSM IV, but differs in recognizing two further categories: Sadistic and Self-defeating (masochistic personality disorder), which have both been deleted from the latest revision of DSM.

1.2. Personality disorders and psychological health

Psychological health is a topic of interest for every clinician, and a goal of every therapy. It seems that it is hard to catch hold of this natural objective, which proves to be slippery and elusive every time someone thinks that he/she has

approached it. A person who experiences a disturbance, with fluctuating patterns of symptoms (ego dystonic), or suffers undesired tension, anxiety and other forms of illness, will most often seek help, or at least feel a need to receive some help or support. In a way that may appear to run contrary to what has been stated above, a person who has a personality disorder may sometimes feel sure that there is nothing wrong with her/him, and reject any professional help. It must be borne in mind that there are professionals in the area of mental health who would certainly not agree. It is believed that personality traits drive the development and course of clinical disorders and syndromes (9).

There are studies that have shown that individuals diagnosed with a PD usually receive a clinical diagnosis as well. The percentage of psychiatric patients with a PD who also have an Axis I diagnosis has ranged from 66% to 97% (giving approximate percentages), whereas patients with an Axis I diagnosis who meet criteria for an Axis II fall within a range of between 13% and 81% (7). To give just one example, those with an avoidant personality style are more prone to anxiety disorders and are resistant to interpersonal treatments (9).

Any personality disorder could be compared with a fallacy in the immune system of any individual, leading to a weak organism that is prone to 'catch' a virus or develop a disease. The personality structure defines a capacity to function in a way that is beneficial to safe mental health. "Every personality style is also a coping style", as Millon stated in 2004, and as such should be understood as a valuable tool for achieving psychological health.

The MCMI III observes pathology as a continuum, and this study follows the diagnostic guidance that this version of MCMI provides. Millon (18) recommends that BR 75 should indicate the presence of a trait, and BR 85 the presence of a disorder in interpreting the scale of personal disorders. These cut-off points were used more as practical guides than as a strict rule. Personal functionality should always be assessed through personal contact with a client, and life functionality will always carry more weight than a test score. For Severe Personality Pathology Scales, a BR in the 75 to 84 range suggests a moderately severe level of personality functioning, and a BR of over 85 a decompensated personality pattern (11).

1.3. Comorbidity between different personality disorders and substance abuse

Many studies have been dedicated to examining the co-occurrence of personality disorders with clinical syndromes. A link was found between Histrionic, Narcissistic, Antisocial and Borderline PD with substance abuse (7; 20; 21; 23).

A moderate association was found between the emotional traits that contribute to the Passive-Aggressive, Self-Defeating and Borderline types, and symptoms of mood disorder and substance abuse (22).

One study has shown that most often the profile for alcoholics is Passive-Aggressive and Antisocial, for drug addicts is Narcissistic and Antisocial or Aggressive (4, 6). Opiate and Cocaine addicts were shown to be mostly Antisocial (60%), Schizoid (36%), Passive-Aggressive (34%), Depressive (32%), and Avoidant (30%), using the PD scales (5).

Haddy, Strack & Choca, (9) supported the previous finding, linking emotionality with substance abuse. However, their expectations that levels of Alcohol Dependence and Drug Dependence would be elevated in Histrionic, Antisocial, Aggressive, and Borderline patients, proved to be fully valid only in the case of antisocial and aggressive subjects. In their study, however, the borderline group did show a certain degree of elevation in alcohol use, while histrionics showed very low rates of substance use.

1.4. Study aims

The significance of examining the link between personality disorders and substance abuse should be seen in the light of aiming for greater mental health and well-being in clients with both diagnoses. If a mental health practitioner is able to understand the features of a certain personality style that are more liable to find a solution or an escape route from an inner tension in substance use, then he or she could turn to those aspects and use them in therapy and, above all, in mental health prevention.

The key to a solution can be found in the pool of choices that a specific person can resort to in her/his daily struggle. To understand the key variables in the choice that someone makes, in deciding to use a substance and so step into substance addiction, the clinician needs to have a clean picture of the deficiencies that are pushing

that person towards the addiction, but also of the strengths that a practitioner could use to pull her/him out.

Some studies have addressed this question, but they have only given uncertain results, and further research is needed. Success in finding a personal profile of the individual who is most likely to submit to the dangers of drug abuse, will remove obstacles not only to providing addicts with help, but to preventing other individuals from falling into the same trap. Also, by defining certain key points in the profile of the substance user, this kind of research will throw more light on the path of counsellors in advising their clients in everyday practice. The present study has set out to examine the following issues: are there a few typical personality profiles that could be pooled to identify 'a typical addict profile' to be drawn; are there any significant differences in personality profiles between the individuals that abuse drugs and those that are not drug-dependent; do individuals that have developed substance addiction show more psychopathological features than those who are not drug addicts; and are there any differences between addicts and non-addicts in their emotional relationships?

2. Methods

2.1. Participants

In this study a convenient sample was used, consisting of 79 participants, more precisely, 29 female and 50 male participants. All the participants in the sample belong to a Serbian-speaking population; in particular, 86.1% reported Serbian nationality and almost half (43%) of the subjects were residents of Belgrade, while another 39.2% were living in a small town in Serbia. Participants ranged from 17 to over 50 years of age; the average age fell within the 25-35 year range. Most of the subjects in this study had finished high school (46.8%), or taken a university degree (22.8%). Participants could be divided into three approximately equal groups: 31.6% were married, 32.9% were in a committed relationship, and 31.6% had no partner at that moment. Participants were divided into two groups - addicts (the experimental group) and individuals with no developed addiction (the control group). The criteria for group division were decided by the researcher, not exclusively on the basis of the self-reported data provided by participants; they took into account the specific nature of addicts' behaviour, their tendency to self-deceptive beliefs and mechanisms whereby the fact of being an addict is repressed.

In any case, those criteria were the result of practical work with addicts, and were chosen as those most appropriate for this study. Following the criteria just referred to, participants in this research were divided into two groups, where the experimental group contained 42 participants, and the control group 37. All the participants signed a written consent form before taking part in the study.

2.2. Instruments

The basic questionnaire that was used in this study was the MCMI-III questionnaire (17). Participants were also asked to fill the demographic sheet that included biographical information (gender, age, nationality, place of birth and residence, education, relationship status and information about their substance use habits).

2.3. Procedure

The control group mostly consisted of participants who had answered the research advertisement published in the Internet space of the University of Belgrade and Mensa Serbia, and contacted a researcher by using the details provided online. These subjects were offered the study materials in electronic or paper form, allowing them to choose according to personal preference; in fact, they all requested the documents in electronic form. Participants first signed the consent form (Appendix A), where they read relevant information about this particular research project and about the ethical issues involved. The other group of participants was made up of patients who were visiting Lorijen Hospital, a private clinic for addictions that is located in Belgrade, Serbia. The patients were given a paper form of the Millon questionnaire, among other psychological instruments used for their personal psychological profile for diagnostic and therapeutic purposes. The participants gave their personal consent for their data to be used for research purposes, but for no other reason.

As this study contained sensitive data, such as drug use habits, the participants were allowed to sign the consent form with their initials, on request. After giving their consent, participants were given the demographic sheet and the MCMI questionnaires. In order to preserve the privacy and anonymity of the participants, every subject

Table 1. The best personality predictors for developing drug addiction	
	Function
Major Depression	.42
PTSD	.41
Dysthymia	.38
Antisocial Personality disorder	.38
Borderline Personality disorder	.33

had a nickname that was used during data storage; in addition, the consent form and questionnaires were kept separately. Original data were available only to the researcher, who altered any of the personal data that could have made identification of the participant possible when presenting and discussing results with the supervisor. At the end of the study, every participant received feedback through an email, reporting the study results. Any questions posed by the participants were answered to their full satisfaction.

2.4. Data Analysis

In this research canonical discriminant analysis was used to determine which personality features are the best predictors of a disposition towards drug abuse. The results of canonical discriminant analysis present the best model for the generation of distinct personality features with the capability of strongly predicting drug abuse. Canonical discriminant analysis was also used to find the characteristics that best separate the two groups in their psychological profiles, to explore differences between the profiles included in the two groups.

To explore the distribution of psychopathological features between groups, the results of discriminant analysis were used. A chi-squared analysis was performed, too, with a defined cut-off point, on a row score of any scale BR - 85, as defined by Millon (17), as a criterion for Personality Disorder. A chi-squared analysis was also used to examine the differences in emotional status and educational levels, between the two groups.

3. Results

The initial hypothesis of this research was to assume that there is something that could be correctly called the typical personality profile of an individual who develops drug addiction. Canonical discriminant analysis was used to determine which personality features function as the best predictors of a disposition towards drug abuse. Discriminant analysis confirmed the initial hypothesis, as it revealed personality characteristics that make up the profile that is the most likely to be that of someone who is predisposed to develop substance abuse. Table 1 is given to show the results of canonical discriminant analysis, presenting the best model - a model that generated five distinct personality features that strongly predicted drug abuse ($p<0.0001$). These analyses selected as the best personality predictors of drug use: Major Depression, PTSD, Dysthymia, Antisocial Personality disorder and Borderline Personality disorder.

In the present study, Millon's personality test has shown the ability to predict 75% of Addiction behaviours. If the complete MCMI III profile is taken into account, the groups of non-addicts and addicts are separated within three standard deviations, as presented in a table given below. The analysis has shown that 92.9% of addicts would be classified as 'addicts' on the basis of a predicted group membership resulting from the MCMI III test.

As the MCMI test itself comprises 'addiction' scales, the same analyses were performed again after ruling out the scales for drug and alcohol dependence, so allowing the weight of prediction to be moved towards a greater number of personality features. The results obtained show that 90.5% of addicts could be truthfully classified as addicts on the basis of the MCMI test alone, even without addiction scales.

Another form of analysis of great interest was to see what would happen with the same prediction if personality disorders only were taken into account (excluding actual psychological symptomatology). The prediction precision remained very high, as it showed a level of accuracy as high as 85.7%.

When the importance of various predictive factors is calculated for personality disorders only, Antisocial PD, Borderline PD and Schizoid

Table 2. Importance of factors in prediction of addiction predisposition	
Personality Disorders	Function
Antisocial	.701
Borderline	.608
Schizoid	.528
Compulsive	- .493
Depressive	.473
Dependent	.472

PD emerge as those most strongly accountable for the disposition to addiction, followed by Depressive and Dependant PD; these data are presented in Table 2**,** and can also be found in Appendix F. Given in the order of their greatest impact, the leading factors are: Antisocial disorder (0.701), Borderline (0.608), Schizoid (0.528), Depressive (0.473), Dependent (0.472) and Compulsive with negative correlation (- 0.493).

The second hypothesis adopted in this study was to assume that subjects who developed addiction and the others who did not become substance addicts would prove to be significantly different in the typical personality profile. Canonical discriminant analysis was used to find the axes that best separated the two groups in their psychological profiles. Discriminant analysis confirmed this second hypothesis, by finding significant differences between the profiles of the two groups. As shown in Table 3 it appeared that the two groups are significantly different in almost all types of disorder, as follows: Schizoid PD, Depressive

Table 3. Differences in Personality Features between Addicts and Non-addicts

	Addicts (n= 42)	Non-addicts (n= 37)		
Personality disorders	M±sd	M	F	P
Schizoid	60.14±17.6	40.18± 23.1	18.82	.000
Avoidant	47.83± 25.8	34.32± 27.0	5.15	.026
Depressive	61.00± 26.2	35.97± 30.9	15.12	.000
Dependent	65.85± 20.1	46.27± 24.7	15.03	.000
Histrionic	48.19± 18.4	62.13± 20.4	10.15	.002
Narcissistic	73.95± 20.2	68.72± 18.2	1.43	.234
Antisocial	74.04± 14.9	48.70± 23.7	33.17	.000
Sadistic	63.52± 14.5	51.43± 21.8	8.54	.005
Compulsive	40.28± 17.6	57.91± 21.0	16.41	.000
Passive-Aggress.	63.59± 26.3	42.81± 26.5	12.16	.001
Self-Defeating	56.30± 24.8	35.37± 31.1	11.00	.001
Schizotypal	58.33± 21.5	39.86± 28.2	10.81	.002
Borderline	62.28± 21.7	35.05± 26.6	24.96	.000
Paranoid	65.80± 22.8	48.86± 23.2	10.66	.002
Anxiety	77.42± 22.0	53.62± 28.2	17.67	.000
Somatoform	53.97± 25.5	25.32± 28.7	21.94	.000
Bipolar Manic	63.19± 16.4	56.27± 22.8	2.43	.123
Dysthymia	64.90± 29.0	26.67± 28.6	34.42	.000
Alcohol use	69.40± 19.5	44.27± 25.0	24.91	.000
Drug use	77.95± 18.5	47.89± 17.7	53.92	.000
PTSD	57.11± 24.9	22.54± 24.6	38.24	.000
Thought Disorder	65.57± 22.1	43.35± 23.7	18.55	.000
Major Depression	69.80± 30.7	24.81± 31.1	41.64	.000
Delusional Disord.	67.00± 22.9	39.70±28.7	22.01	.000

Table 4. Differences in the numbers of pathology addicts and non-addicts

	Millon's scales		
	Without pathology N=22	Presence of pathology N=57	Total
Non addicts	17 (21.5)	20 (25.3)	37 (46.8)
Addicts	5 (6.3)	37 (46.8)	42 (53.2)
Total	22 (27.8)	57 (72.2)	79 (100.0)
Chi square=4.68 df=1 p=0.001			

PD, Dependent PD, Antisocial PD, Sadistic PD, Passive-Aggressive PD, Masochistic PD, Schizotypal PD, Borderline PD, Paranoid PD, Anxiety, Somatoform, Dysthymia, Alcohol use, Drug use, PTSD, Thought Disorder, Histrionic, Compulsive, Depression Major and Delusional Disorder. Significant differences were also found in two other profiles, but these profiles showed higher scores in the control group: Histrionic and Compulsive.

The mean of the subjects who had developed addiction was significantly higher than the mean score of subjects who had not become addicts in: Schizoid PD, Depressive PD, Dependent PD, Antisocial PD, Sadistic PD, Passive-Aggressive PD, Masochistic, Histrionic, Compulsive, Schizotypal PD, Borderline PD, Paranoid PD Anxiety, Somatoform, Dysthymia, PTSD, Thought Disorder, Depression Major and Delusional Disorder.

As presented in Table 3, considering personality disorders, the highest predictive scores reported for addicts were, in descending order, those for the Schizoid, Depressive, Dependent, Antisocial, Sadistic, Passive-aggressive and Masochistic disorders, while the highest predictive scores reported for individuals who did not become substance addicts were those for the Histrionic and Compulsive disorders. Addicts showed higher scores on the clinical scales, too - the Schizotypal, Borderline and Paranoid scales, and higher scores were again recorded on present psychological symptomatology - Anxiety, Somatoform, Dysthymia and PTSD. Thought disorder, major Depression and Delusional disorder likewise proved to be more frequent in the group of addicts. It is important to note that no significant differences appeared in the Narcissistic PD, Avoidant PD and Bipolar manic features.

The third hypothesis adopted in this study stated that individuals who developed substance addiction showed a greater number of psychopathological features than those who did not become drug addicts. This hypothesis was confirmed by the previously acquired results of discriminant analysis; the means recorded for both groups, together with the significant differences between them, are given in Table 5. In addition, a chi-squared analysis was performed to sum up the previous results. Artificial cut-off points were put on the row score of any scale BR - 85, as defined by Millon in indicating the presence of a personality disorder rather than a question of personality style (16).

Table 4 shows the significant differences between the occurrence of a Personality Disorder versus personality style in the two groups.

The fourth hypothesis adopted in this study was to assume that there are differences in interpersonal relationships between the participants who developed addiction and those who did not become drug addicts. A chi-squared analysis was performed, but failed to confirm this fourth hypothesis, as it showed no significant differences in emotional status between the two groups. The results are, however, interesting from an interpretive standpoint, as the two groups show an equal distribution in terms of "being in a long-term relationship", but non-addicts tend to be found in a

Table 5. Differences in Emotional Relationships between the Groups: Addicts and Non-addicts

	Marriage	Relationship	Single	Total
Non-addicts	16 (20.3)	12 (15.2)	9 (11.4)	37(46.8)
Addicts	9 (11.4)	14 (17.7)	19 (24.1)	42 (53.2)
Total	25 31.6)	26 (32.9)	28 (35.4)	79 (100.0)
Chi square 5.39 df=2 p=0.068				

"marriage" relationship, too, whereas addicts are more frequently found in a "single" group than non-addicts (Table 5).

In addition, an analysis was performed to investigate whether there was a link between level of education and addiction. The statistical results do show statistical significance, but cannot be taken into account, because of the characteristics of the sample. Participants in the control group was mostly selected from the membership of "Mensa" in Serbia - a fact that biased the control group members towards having had a higher level of education. In any case, it is interesting to note that a high proportion (39.2%) of the individuals belonging to the group of addicts had had at least 12 years of education, and had finished high school (Table 6).

To summarize the results of this study, there is a significant difference in characteristic personality style between individuals who are drug addicts, and those who have no addiction problems. Individuals who developed an Antisocial, a Borderline, a Depressive or a Dependent personal style were those most prone to substance use, whereas individuals who had a Histrionic or Compulsive Personality style were those least likely to develop addiction (significant level: $p < .001$).

Also, addiction is firmly attached to a major presence of Depression, to PTSD and Dysthymia, although, considering the need to avoid breaking any causality chain, it cannot be concluded either that those symptomatologies are the consequence of drug abuse or that they are its primal resource.

Also, there is a significant difference between the levels of pathology in the two groups, whereby the addiction group showed a significantly higher level of pathology than the control group (significant level: $p < .001$). These findings are of the greatest importance for the implications of the study and its potential use in clinical practice.

Table 6. Differences in education years between addict and non-addict subjects

	12 yrs	14 yrs	16 yrs	>16 yers	Total
Non addicts	9 (11.4)	7 (8.9)	14 (17.7)	7 (8.8)	37 (46.8)
Addicts	31 (39.2)	4 (5.1)	4 (5.1)	3 (3.8)	42 (53.2)
Total	40 (50.6)	11 (13.9)	18 (22.8)	10 (12.7)	79 (100.0)
Chi square 19.83 df=3 P=0.000					

4. Discussion

The link between personality disorders and clinical symptoms has always been an interesting theme from a research perspective, and it also carries strong implications for clinical practice. From the layman's point of view, the topic of social and psychological phenomena, such as drug addiction, alcohol addiction and the like, were often explained by predetermined personality factors, with the customary attribution of addiction to elements such as "weakness of character", "spoiled children, who have had everything in life and don't know what else to do with themselves" and so on. There are many reasons why someone might feel better if those doing research could find a strong connection between certain personality types and drug addiction phenomena. One likely reason is that it would strengthen the illusion that something like that could never happen to themselves, their children or other people dear to them. But the question arises: what is the truth? Can anyone become an addict, or are there certain personality types that are at greater risk of contracting this form of mental illness?

These study findings support the existence of a positive correlation link between Antisocial and Borderline PD and substance abuse, and a negative correlation between Histrionic and Compulsive PD and substance use. Narcissistic and Avoidant PD turned out to have no significant correlation in either direction. Those findings partly confirm the findings of previous research studies.

The study results on the links between Histrionic, Antisocial and Borderline PD with substance abuse confirm the findings of other researchers (7; 20; 21; 23) in support of a link between Antisocial PD and alcoholism and/or drug addiction (4;6). A link between Antisocial PD and substance abuse was confirmed in the way indicated in the study of Haddy, Strack & Choca (9).

Conversely, the results of our study do not concur with the results to be found in the literature for Narcissistic PD (7; 20; 21;23). Our study

failed to confirm the findings on Passive-aggressive and Self-Defeating personality reported in a previous study (22) and on the Passive-aggressive, Narcissistic and Avoidant profiles for drug addicts found in Craig's study (5).

Differences in study results could be accounted for by differences in methodology, study samples, and so on. In any case, it is important to note that almost all the findings agree that Antisocial and Borderline personality characteristics correlate strongly with a substance addiction. Which characteristics could be responsible for those two personality patterns, linking them both to a high degree of proneness to substance abuse?

Antisocial personality disorder is characterized by refusing to conform to social norms - a definition that could also be applied to drug abuse. Someone who possesses no strong antisocial traits will to some extent be 'protected' from an initial use of drugs by considering drugs to be 'bad' and 'socially unacceptable'. The other typically antisocial traits are impulsivity and inability to think about the consequences of certain types of behaviour. One of the main reasons for a person deciding not to take drugs is her/his ability to think about 'what will happen afterwards' - the fear of the consequences that anyone who takes drugs will have to bear, as well as their responsibilities towards themselves and others. The fact that an Antisocial individual is unable to feel any consideration for personal well-being could also play a major role in the decision to use drugs on a more regular basis. Someone with Antisocial PD inevitably suffers from high tension, strong anger and a great deal of anxiety, and they are unable to think far ahead, as there is one simple way to discharge and relieve those negative feelings in a single act, which is the intake of a substance.

It is also important to note that one of the consequences of prolonged substance abuse is the secondary development of the characteristics of the Antisocial personality disorder. Experience from clinical practice shows that an addicted person displays the same traits and behaviour as someone who has an Antisocial PD. Characteristic behaviour lasts as long as a person is using drugs, and disappears when he/she enters a stable period of abstinence. This feature seems to be related to drug abuse only, and should not be attributed to personal characteristics in themselves. It is safe to conclude that someone who is going through a prolonged period of drug abuse will adopt antisocial personality traits, such as being manipulative, lying, abusing others, behaving recklessly and impulsively, disregarding other people's feelings, and so on. Although personality disorder is a condition which, by definition, develops at an early age, certain characteristics may become personality characteristics as a result of a life event, or of other influences, such as substance use. Neither a person who has an Antisocial PD, nor a drug addict, feels any self-consciousness, or empathy towards others and their needs, or has any sensitivity about what is good or right, besides which they are unable to learn from past experience and its consequences. The only difference between them is that a person who doesn't suffer from an Antisocial PD will not preserve the typical personality features of that disorder if he/she is able to maintain prolonged drug abstinence.

An individual with a Borderline personality is bound to suffer from a strong sense of emptiness and boredom. The use of a substance is a cheap and simple way to overcome those harmful feelings. Whatever may come later as a consequence of drug abuse is less important than the process of 'filling' a deep, unbearable void that they usually feel. Work with drug addicts has shown that the highest risk of a relapse comes in periods of monotony. Boredom is a very interesting phenomenon, defined as an emotional state experienced during periods without activity, or when a person is not interested in their surroundings. Actually the underlying process is the suppression of unpleasant and threatening feelings. That individual will lose control of any selective process of suppression, and the process of removing the existing emotional reactions will spread to all emotions, leaving the person empty and numb. Emotional numbness will then protect that person from its negative emotional content. Even so, it will bring an unpleasant state of meaninglessness and of living a dull life. Chemically induced feelings (even when unpleasant) and sensations offer a simple solution to this complicated psychological phenomenon.

When a person is addicted, the whole spectrum of human experiences is reduced to two extremes - being 'high', or suffering from withdrawal symptoms. The wide spectrum of human emotions has to be narrowed down to suit the needs of someone who is on drugs - someone who is bound to feel sick when abstinent. Splitting as a dominant mechanism for Borderline personality disorder bears a resemblance to this usual behaviour of an addict. One of the features shared by a

Borderline person and an addict is that both lose control over their impulses. In Borderline PD, impulses will usually have aggressive characteristics, and for an addict these will take the form of behaviour induced by craving. Just like drug addicts, Borderline individuals will act impulsively, without thinking about the act or its consequences. Also, it is worth noting that Borderline PD people are prone to act out their behavioural impulses, and the use of substances is an example of this kind of enactment. Pervasive patterns of instability in personal relationships hide a frantic fear of closeness and attachment, so that they not only run away from a significant person, but also from a substance they have become attached to. If they feel their addiction is rising, they are more prone to escape from the 'mother substance', and substitute it with another, usually developing a pattern of polytoxicomania.

Instability of self-image and identity confusion are features that fit in with the work of the drug (making an addict feel on top when taking the drug, and on the bottom when left without it). The substance is used to control the anger that is being felt and the impulses that are hard to control. Self-defeating behaviour and self-negligence are crucial parts of everyday life for Borderlines. Unstable affects may be finally controlled, and predictive and inner pain may be numbed through drug abuse. On the other hand, drug addiction degrades a person and his /her personality structure, to a borderline level of functioning.

Besides Borderline and Antisocial PD, those most prone to develop the addictions seem to be the Depressive and Dependent types. Clinical practice has shown that the greatest difficulty in giving up addiction is experienced by those with a Depressive personality. Once a Depressive individual becomes attached to an opiate, for example, it is very unlikely he/she will ever let go. There are various reasons for that, besides the very nature of opiate addiction itself. A depressive person feels sad and empty most of the time, takes no pleasure in anything, feels physically weak, and usually has little energy or motivation. Most of these subjects state that when they took an opiate for the first time in their life they felt "normal, just as someone should feel". How hard it must be for someone who constantly feels like that to give up the immediate intake of energy and good mood that the substance initially brings! Could the consequences of that drug intake be more frightening than the already grim reality they are experiencing? Feelings of worthlessness and guilt magically disappear, at least for the moment, after taking a drug. This new source of pleasure is hard to break away from. All the above applies to Dysthymia and Major Depression.

Dependent types lack self-esteem and the feeling of personal worth, to the extent that they need others to help them and take responsibility for almost all the areas in their life. They have a disproportionate need for care, love, nurture and support from others, no matter what price they have to pay in return (mostly in giving up their own needs and individuality). They also feel preoccupied by the fear of being left alone. When such a person discovers the beauty of feeling independent and self-sufficient by taking drugs, it is hard for her/him to give up such a treasure. Someone with a Dependent PD reaches the point of treating their chosen substance(s) of abuse as they had previously treated significant others in their lives. A substance becomes a transitory object, a substitute for significant human relationships that are viewed as a source of inner tension and anxiety. These are the main reasons why people with a Dependent PD establish the full cycle of dependency earlier and more firmly than others.

The results of this study have shown the negative correlation between addiction and a Histrionic or Compulsive PD. It might be argued that Histrionics, who are characterized by a pattern of excessive emotionality and attention-seeking, along with an excessive need for approval and admiration, already 'have their drug'. They are 'hooked' on other's people attention, and their mood is often elevated, especially in social situations. It is no wonder that they find no reward in taking drugs, as drugs make people feel isolated and lonely - a condition that is the worst nightmare of a typical Histrionic. Also, they pay a great deal of attention to the picture of the self that is created in other people's eyes, and a drug addict carries a negative stigma. Histrionics may flirt with substance abuse, but it is unlikely that they will decide to get involved; this diffidence is characteristic of their other relationships, too.

An individual with a Compulsive PD will be over-conscious, scrupulous, and inflexible about matters of morality, ethics, or social values; these features are all contraindicative to drug abuse. In fact, such people have a strong need to exercise control; this need protects them from giving up control to the substance. Also, a lifestyle of work preoccupations, and having little time for relaxa-

tion, socializing and fun, makes them less likely to end up in the predicament of having to cope with drug abuse. Even if they find themselves in a situation where drug-taking might be an easy choice to take, their rigidity, stubbornness and attachment to principles will prevent them from trying something new like a drug.

Apart from personality disorders, this study has shown the importance of other factors involved in substance abuse, such as clinical symptoms, dysthymia and posttraumatic stress disorder. It could be expected that addicts will have more psychopathological symptoms than people who have never developed any addiction. It is only hard to say which phenomenon actually comes first. It is like the famous dilemma about which of the two came first - a chicken or an egg? Is one individual who decides to take drugs more disturbed than another who does not suffer from any psychological disturbance? Most probably the answer is 'Yes'. On the other hand, someone who is already using drugs will most certainly develop a psychological disturbance, as a direct consequence of her/his drug abuse. In our case this could be defined as the chicken and the egg appearing at the same time.

Posttraumatic stress disorder (PTSD) seems to be correlated with some form of drug abuse, but it would be interesting to examine other variables that might influence this link. For example, is it more probable that a soldier who is caught up in war will develop drug addiction, as a consequence of the psychological trauma he has suffered, than a girl who was raped as she was walking back home at night? Which of the two? The answer might seem to be very simple, but turn out to be significant for the purposes of drug prevention. It is less likely that a girl with such a trauma will be offered a drug by a pusher as a solution to her problem, whereas it is very common for narcomafia agents to spread their roots behind army lines, counting on the bad psychological state of soldiers who live under constant stress.

In conclusion, there are certain psychological disorders that are especially prone to drug addiction. On the other hand, a variety of factors have to be met for such addiction to develop. In some situations, it is clear that social impact is the factor that is mainly responsible for someone becoming involved with drugs. If the drugs had not been available, that person would have had to find another way of dealing with his/her inner psychological problems. Maybe even by going to a psychotherapist.

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Factors associated with discharge against medical advice from an alcohol and drug inpatient detoxification unit in Barcelona between 1993 and 2006

Gail Gilchrist[1,2], Klaus Langohr[3,4], Francina Fonseca[1,5], Roberto Muga[6,7], and Marta Torrens[1,5,8]

1 Substance Use Disorders Research Group, Institut Municipal d'Investigació Mèdica (IMIM)-Hospital del Mar, Barcelona, Spain, EU
2 Centre for Applied Social Research, School of Health and Social Care, University of Greenwich, London, United Kingdom, EU
3 Human Pharmacology and Clinical Neurosciences, Institut Municipal d'Investigació Mèdica (IMIM)-Hospital del Mar, Barcelona, Spain, EU
4 Department of Statistics and Operational Research, Polytechnical University of Catalunya, Barcelona, Spain, EU
5 Institut de Neuropsiquiatria I Adiccions (INAD); Barcelona, Spain, EU
6 Hospital Universitario Germans Trias i Pujol, Barcelona, Spain, EU
7 Department of Medicine, Universitat Autònoma de Barcelona, Spain, EU
8 Department of Psychiatry and Legal Medicine, Universitat Autònoma de Barcelona, Barcelona, Spain, EU

Summary

Records from 1,228 consecutively admitted patients (74.5% male) to an inpatient detoxification unit in Barcelona between 1993 and 2006 were examined to determine factors associated with discharge against medical advice (AMA). 21.5% of admissions were discharged AMA. In multiple logistic regression and compared with patients who were medically discharged, those discharged AMA were younger, more likely to be dependent on heroin, other opiates, cocaine or psychostimulants, or to be experiencing reduction or elimination methadone maintenance therapy [reference category: alcohol]. The provision of assistance to clinicians in identifying the patients who are most at risk of leaving inpatient detoxification AMA will enhance their ability to motivate such patients to stay in treatment.

Key Words: Discharge against medical advice (AMA), detoxification.

1. Introduction

Inpatient detoxification is a common treatment modality for substance-dependent individuals. Studies report that around 13%-64% leave treatment against medical advice (AMA) or do not complete treatment [1]; more precisely, the range is 13%-33% among alcohol abusers [8,10] and 18%-64% among heroin abusers [1,2,6,9,11,12]. Despite these elevated rates, the reasons for this remain poorly understood [12].

Sociodemographic factors associated with being discharged AMA or failing to complete inpatient detoxification for substance abuse include being younger [1,2,9,10], single [1,6], unemployed [9], having a criminal history [2,4], having a lower level of education [2] and having State health insurance or no health insurance at all [3]. Studies do not report differences in discharge AMA by sex of the patient [1,5,6,10,13]. Results on the ethnicity of the patient are inconclusive [3,8].

Being in inpatient detoxification treatment for drugs rather than alcohol [3,5] predicted discharge AMA. Opiate abusers, especially injectors [2,9], were more likely not to complete detoxifi-

Gail Gilchrist, MD - Centre for Applied Social Research, School of Health and Social Care, University of Greenwich, Avery Hill Road, London, SE9 2UG;
Tel: +44 20 8331 9621, Email: G.Gilchrist@gre.ac.uk

cation than other substance abusers [1,5,8,10,13]. In addition, several studies reported that cocaine or amphetamine use [4,6,10], recent cannabis use, or concurrent benzodiazepine dependence [10], were associated with being discharged AMA. Those that had more severe medical and substance use problems [12], had fewer months of abstinence prior to hospitalization [6], began heavy drinking at an earlier age [10] and believed that drug use did not impair their health [9], were also more likely not to complete detoxification. Antisocial or borderline personality disorder and hepatitis C infection were found to be associated with being discharged AMA in one study on alcohol abusers [10].

Treatment incompletion is a predictor of readmission to inpatient detoxification [12-16]. Thus, patients who leave inpatient detoxification AMA present a significant challenge to detoxification programmes [9], and incur greater health care costs. The preliminary identification of patients at risk of leaving inpatient detoxification, would enhance interventions and strategies to reduce discharges AMA among patients at increased risk [17].

Remarkably, few studies examining the factors associated with being discharged AMA from inpatient detoxification have been carried out. Most have been conducted in the US and Canada, many include small samples of females and none have examined sex differences. Risk factors for discharge AMA were ascertained on the basis of medical records on consecutive admissions from an inpatient drug and alcohol detoxification unit in Barcelona from 1993 to 2006. Sex differences were also examined.

2. Materials and Methods

2.1 Sample

Records from all consecutive admissions to an inpatient alcohol and drug detoxification unit between 1993 and 2006 were included.

2.2 Setting

The mixed sex inpatient detoxification unit was located in the psychiatric department of a general teaching hospital in Barcelona, Spain. This was a six-bed unit providing assessment and medically assisted withdrawal to individuals with drug and alcohol dependence disorders. All patients were admitted on a voluntary and planned basis. Patients were eligible for admission if they were substance-dependent, with a risk of severe or medically complicated withdrawal symptoms (e.g polysubstance abuse), co-morbid general medical conditions that made ambulatory detoxification unsafe, and/or a documented history of not engaging in or benefiting from treatment in outpatient facilities [18]. Inpatient methadone suppression was following methadone maintenance therapy and not where methadone was a substance of abuse. Services were provided free of charge to the patient.

2.3 Variables assessed

Data were collected using a standardized questionnaire on all consecutive admissions including: sociodemographic data, substance abuse history, number of overdoses, treatment history, reason for admission, type of discharge (medical discharge, against medical advice, administrative discharge), dates of admission and discharge for each detoxification, personality disorders, HIV and hepatitis C status, and functioning level was assessed using the Global Assessment of Functioning scale (GAF) (DSM-IV, Axis V) [19]. The GAF is a numeric scale that assesses the social, occupational, and psychological functioning of adults. The scale ranges from 0 to 100. Higher scores related to greater functioning.

2.4 Outcomes

Data are presented for first admission covering the years 1993-2006 for each patient. Length of stay and discharge type were recorded for each admission. Length of stay was patient-specific and depended on patients' needs, as determined by a psychiatrist. "Medical discharge" was the description applied whenever a patient completed his/her detoxification treatment. Patients leaving the detoxification treatment without medical consent prior to treatment completion were classified as "discharged AMA". Patients received an administrative discharge from the unit if they had violated treatment rules (e.g. by resorting to drug trafficking or violence). Patients who were administratively discharged were excluded from the analysis presented in Tables 1-3.

2.5 Statistical Analysis

For the analyses, only data from a patient's first admission were used (n=1,228). Data were

analysed using the "R" software package [20]. Simple descriptive statistics were calculated using frequencies and percentages for categorical data, and means and standard deviations for continuous data. T-tests, ANOVA (for continuous variables) and chi-square tests (for categorical variables) were performed to examine sex differences in baseline patient characteristics (Table 1) and by type of discharge (Table 2).

Multiple logistic regression was carried out to determine factors associated with discharge AMA. For this purpose, the procedure proposed by Hosmer and Lemeshow [21] was used; at a univariate level, all variables with a significance level of less than 0.2 (in Table 2) were included in the multivariate model. Subsequently, step by step, variables were removed from the model if they failed to reach a significance level of 0.05, and as long as the parameter estimates of the remaining variables did not change substantially. This ensured that potential confounders were not excluded from the model. Once the model had been reformulated to include only significant independent variables, it was checked to determine whether previously excluded variables were now significant. In addition, possible interactions of the remaining variables were evaluated. Lastly, the global goodness of fit was checked using the test proposed by le Cessie and van Houwelingen [22]. The model parameters were interpreted in terms of adjusted odds ratios.

Length of stay and GAF scores were omitted from the model, due to the fact that they were assessed on discharge.

3. Results

During 1993-2006, there were a total of 2024 admissions (26.1% by females) by 1511 patients (25.7% female) to the inpatient detoxification unit. The majority of patients had been admitted once (68.1%), however 18.9% had been admitted twice during this time period and 13% three or more times. On average, the mean number of admissions per patient was 1.6 (SD: 1.3).

Of all admissions, 67.8% led to medical discharges, 21.5% were discharged AMA, 8.7% were followed by an administrative discharge, and 34 patients (1.7%) were subsequently transferred to other services. Six cases (0.3%) were listed as "other discharges", but no further information was available. There was no significant difference in the proportion of male and female patients that were discharged "AMA" (23.9% [219/915] versus 20.8% [65/313], p= 0.28), respectively.

3.1 Baseline characteristics by sex of patient

The majority of patients were polydrug users and had never injected (Table 1). The main abused substances for which patients were admitted to the inpatient unit for detoxification were: heroin and other opiates (including methadone); cocaine or other stimulants; and alcohol. Almost a third were HIV-seropositive (30.3%) and 62.8% were hepatitis C-seropositive. Almost 40% had a history of psychopathology and 19.3% had been diagnosed with a personality disorder. Patient characteristics are shown separately for males and females in Table 1. Briefly, males were older than females and a significantly greater proportion of males than females were single. A significantly greater proportion of females than males lived with a drug user, were assessed as having some kind of psychopathology or were HIV-seropositive. The average length of stay in the detoxification unit was 12.5 days (SD 6.2). Females stayed in detoxification significantly longer than males (13.1 days versus 12.3 days, p=0.03).

3.2 Baseline characteristics associated with medical discharge between 1993 and 2006 by sex of patient (Table 2)

Males who were discharged AMA were younger than those who were medically discharged. The length of stay in inpatient detoxification treatment was significantly shorter for patients who were discharged AMA, whether male or female. Among males, a significantly greater proportion of those who were discharged AMA reported that heroin was their principal drug of abuse, were currently injecting and were polydrug users. A significantly greater proportion of males who were medically discharged reported alcohol as their main substance of abuse and were hepatitis C-seropositive. Among females, a significantly greater proportion of those who were discharged AMA reported heroin as their main drug of abuse. A significantly greater proportion of females who were medically discharged reported alcohol or sedatives as their main substance of abuse.

3.3 Multiple logistic regression for discharge against medical advice

Compared with patients who were medically discharged, patients discharged AMA were younger (OR 0.98; 95% CI 0.96-0.995), were more likely to be taking heroin and other opiates (OR 2.94; 95% CI 1.77-4.91), or cocaine or other psychostimulants (OR 1.13; 95% CI 0.54-2.39) as their main substance of abuse, and to be experiencing reduction or elimination of methadone maintenance therapy (OR 1.98; 95% CI 1.13-3.39) (rather than taking alcohol as their main substance of abuse). Having a personality disorder was almost significantly associated with being discharged AMA (OR 1.38; 95% CI 0.98-1.93). The risk of discharge AMA was significantly higher for male polydrug users compared with both male non-polydrug users (OR 1.63; 95% CI 1.14-2.32) and female polydrug users (OR 1.67; 95% CI 1.12-2.50). Compared with female non-polydrug users, no significant difference was detected (OR 1.12; 95% CI 0.67-1.87) (Table 3).

4. Discussion

The current study determined the variables associated with discharge AMA from an inpatient drug and alcohol detoxification unit in Barcelona between 1993 and 2006.

As with other studies, no significant difference was reported in the proportions of male and female patients that were discharged AMA [1,5,6,10,13]. Almost a quarter of patients (21.5%) were discharged AMA. This proportion,

Table 1. Baseline characteristics by sex of patient

	Missing	Total (N=1228)		Males (N=915)		Females (N=313)		
	N	N	%	N	%	N	%	p
Sociodemographics								
Age [mean, (SD)]	12	33.6	(8.4)	34.1	(8.5)	32.2	(7.9)	<0.001
Civil status	19							<0.001
Single		569	47.1	460	51.2	109	35.2	
Married/ partner		395	32.7	257	28.6	138	44.5	
Widowed/ separated/ divorced		245	20.3	182	20.2	63	20.3	
Highest education level attained	52							0.454
Primary studies or less		870	74.0	652	74.6	218	72.2	
Secondary/ tertiary studies		306	26.0	222	25.4	84	27.8	
Employment status	71							0.124
Unemployed		645	55.7	467	54.2	178	60.1	
Receiving pension/ benefits		204	17.6	152	17.7	52	17.6	
Employed/ studying/ military service		308	26.6	242	28.1	66	22.3	
Lives with drug user	49	237	20.1	153	17.3	84	28.3	<0.001
Substance abuse								
Age first drug use [mean, (SD)]	202	20.6	(7.4)	20.4	(7.4)	21.1	(7.4)	0.224
Number drug overdoses [mean, (SD)]	109	1.0	(2.4)	1.0	(2.6)	0.9	(1.8)	0.418
Principal drug of abuse	22							0.15
Heroin & other opiates		481	39.9	370	41.2	111	36.0	
Methadone		174	14.4	124	13.8	50	16.2	
Cocaine & psychostimulants		262	21.7	195	21.7	67	21.8	
Alcohol		197	16.3	149	16.6	48	15.6	
Sedatives		92	7.6	60	6.7	32	10.4	
Polydrug-use	0	811	66.0	603	65.9	208	66.5	0.915
Intravenous drug use								
Ever	0	658	53.6	501	54.8	157	50.2	0.18
Current route of administration	11	476	39.1	369	40.6	107	34.6	0.071

Table 1. Baseline characteristics by sex of patient (cnt)

	Missing	Total (N=1228)		Males (N=915)		Females (N=313		
	N	N	%	N	%	N	%	p
Treatment								
Length of stay in inpatient detoxification unit (days) [mean, (SD)]	0	12.5	(6.2)	12.3	(6.1)	13.1	(6.5)	0.031
Psychological								
Any psychopathology	49	465	39.3	329	37.4	136	44.9	0.038
DSM Personality Disorders	8	235	19.3	166	18.3	69	22.1	0.162
DSM Axis IV Psychosocial and Environmental Problems	41							0.506
Low		454	38.2	346	39.1	108	35.6	
Moderate		537	45.2	392	44.3	145	47.9	
Severe		182	15.3	134	15.2	48	15.8	
Extreme		14	1.2	12	1.4	2	0.7	
Biological								
HIV seropositive	81	347	30.3	244	28.7	103	34.6	0.07
Hepatitis C seropositive	104	706	62.8	519	62.1	187	64.9	0.428

while similar to that indicated in some studies carried out on substance users [1,6,9], proved to be considerably lower [2,11,12] or greater than that found in other studies [8]. These differences could be attributed to the patient mix (i.e. percentages of males and females) and different substances of abuse (e.g. heroin versus alcohol) in each study. We found that 29% of the males and 26% of the females admitted for detoxification for heroin and opiates other than methadone were discharged AMA, compared with 12% and 8% of those admitted for alcohol detoxification, respectively. The proportion of discharges AMA for heroin users was similar to that found in one study on opiate users [4]. However, other studies on heroin users reported far greater proportions of discharge AMA (51-64%) [2,11,12]. The reason for these variations could be due to these studies having a larger proportion of injecting drug users in their samples; to the different definitions attributed to treatment completion in different studies (e.g. transfer from the detoxification unit to prolonged treatment, staying a minimum of 14 days, negative drug-screening urine analysis, absence of withdrawal symptoms and completion of the psychotherapeutic programme [2], or planned discharge [10,11]; or else to the differing length of treatments for each inpatient detoxification, ranging from three [1] to 42 days [10]. In the current study, females stayed around a day longer on average than males, which may be the result of greater psychopathology at admission as studies have reported that planned discharge is associated with depression [10].

Supporting results from other studies, patients who were discharged AMA were younger [1,9,10] compared with those who were medically discharged. Previous studies have not examined sex differences in risk factors for discharge AMA. Interestingly, the current study reported that males discharged AMA were younger than males who were medically discharged. This was not found for females. Substance abuse is a chronic relapsing condition [23], with most users having to go through multiple treatment episodes and modalities before successfully stopping all forms of abuse. The phenomenology of discharge against medical advice among younger patients could be viewed as a reflection of this. It is also possible that some patients may not be sufficiently motivated to stop their substance use, as some studies have reported higher levels of discharge AMA among those who were not in counselling, who did not report plans for entering follow-up treatment following discharge, or who did not believe such treatment would be suitable for them [2,12]. Means et al. [24] suggest that older patients with longer substance abuse careers have had more experience with treatment, and therefore believe there are benefits attached to the

Table 2. Baseline characteristics associated with medical discharge during 1993-2006 by sex of patient

	Males (N=915)			Females (N=313)		
	DAMA N=219	MD N=696		DAMA N=65	MD N=248	
	N (%)	N (%)	p	N (%)	N (%)	p
Sociodemographics						
Age [mean, (SD)]	31.9 (7.7)	34.8 (8.6)	<0.001	30.8 (8.2)	32.5 (7.8)	0.13
Civil status			0.243			0.455
Single	114 (24.8)	346 (75.2)		26 (23.9)	83 (76.1)	
Married/ partner	62 (24.1)	195 (75.9)		24 (17.4)	114 (82.6)	
Widowed/ separated/ divorced	34 (18.7)	148 (81.3)		13 (20.6)	50 (79.4)	
Highest education level attained			0.275			0.595
Primary studies or less	145 (22.2)	507 (77.8)		44 (20.2)	174 (79.8)	
Secondary/ tertiary studies	41 (18.5)	181 (81.5)		14 (16.7)	70 (83.3)	
Employment status			0.673			0.962
Unemployed	99 (21.2)	368 (78.8)		37 (20.8)	141 (79.2)	
Receiving pension/ benefits	37 (24.3)	115 (75.7)		10 (19.2)	42 (80.8)	
Employed/ studying/ military service	56 (23.1)	186 (76.9)		13 (19.7)	53 (80.3)	
Lives with drug user			0.432			0.81
No	177 (24.3)	552 (75.7)		45 (21.1)	168 (78.9)	
Yes	32 (20.9)	121 (79.1)		16 (19.0)	68 (81.0)	
Substance abuse						
Number drug overdoses [mean, (SD)]	1.1 (1.9)	1.0 (2.8)	0.609	0.6 (1.4)	0.9 (1.9)	0.313
Principal drug of abuse			<0.001			0.021
Heroin & other opiates	118 (31.9)	252 (68.1)		32 (28.8)	79 (71.2)	
Methadone	28 (22.6)	96 (77.4)		10 (20.0)	40 (80.0)	
Cocaine & psychostimulants	41 (21.0)	154 (79.0)		14 (20.9)	53 (79.1)	
Alcohol	18 (12.1)	131 (87.9)		4 (8.3)	44 (91.7)	
Sedatives	11 (18.3)	49 (81.7)		3 (9.4)	29 (90.6)	
Polydrug-use	163 (27.0)	440 (73.0)	0.003	39 (18.8)	169 (81.2)	0.276
Intravenous drug use						
Ever	129 (25.7)	372 (74.3)	0.181	34 (21.7)	123 (78.3)	0.803
Current route of administration	101 (27.4)	268 (72.6)	0.044	26 (24.3)	81 (75.7)	0.274

DAMA= Discharge against medical advice MD= Medical discharge

completion of treatment.

For both males and females, a significantly greater proportion of those who were discharged AMA reported heroin as their principal drug of abuse [where alcohol was the reference category]. For males only, injecting and polydrug use were additional factors associated with being discharged AMA. This could be accounted for by the profile of alcohol and opiate patients, as the former tend to be older, while the latter present a higher likelihood of axis II comorbidity (data not shown).

In multiple logistic regression, patients discharged AMA turned out to be younger, were almost three times as likely to have heroin and other opiates as their principal substance of abuse, or twice as likely to have cocaine as their principal substance of abuse, or to be experiencing the reduction or elimination of methadone maintenance therapy. Poorer treatment outcomes and craving have been associated with higher levels of impulsivity among cocaine users [25,26].

Table 2. Baseline characteristics associated with medical discharge during 1993-2006 by sex of patient (cnt)

	DAMA N=219	MD N=696		DAMA N=65	MD N=248	
	N (%)	N (%)	p	N (%)	N (%)	p
Treatment						
Length of stay in inpatient detoxification unit (days) [mean, (SD)]	6.3 (4.5)	14.2 (5.2)	<0.001	6.7 (4.8)	14.8 (5.8)	<0.001
Psychological						
Any psychopathology	72 (21.9)	257 (78.1)	0.617	31 (22.8)	105 (77.2)	0.444
DSM Personality Disorders	48 (28.9)	118 (71.1)	0.115	17 (24.6)	52 (75.4)	0.475
DSM Axis IV Psychosocial and Environmental Problems			0.694			0.105
Low	74 (21.4)	272 (78.6)		15 (13.9)	93 (86.1)	
Moderate	97 (24.7)	295 (75.3)		36 (24.8)	109 (75.2)	
Severe	31 (23.1)	103 (76.9)		8 (16.7)	40 (83.3)	
Extreme	2 (16.7)	10 (83.3)		1 (50)	1 (50)	
Biological						
HIV seropositive	59 (24.2)	185 (75.8)	0.252	27 (26.2)	76 (73.8)	0.102
Hepatitis C seropositive	119 (22.9)	400 (77.1)	0.039	38 (20.3)	149 (79.7)	0.879

DAMA= Discharge against medical advice MD= Medical discharge

Very few studies have investigated the role of psychopathology or the completion of inpatient detoxification treatment. In line with others [10], we found that personality disorders were closely associated with leaving treatment AMA.

Contrary to Martínez-Raga et al. [10], no association was found between hepatitis C infection and discharge AMA for all patients, although an association was found for males. One reason could be the lower proportion of hepatitis C-infected patients in that study compared with ours.

Although the topic was not considered in the current study, a previous study reported that being treated by a specific doctor was associated with being discharged AMA [3]. Negative attitudes towards substance users in treatment set-

Table 3. Logistic regression for discharge against medical advice

	OR	95% CI
Age	0.98	0.96 – 0.99
Principal drug of abuse (ref.: alcohol)		
Heroin and other opiates	2.94	1.77 – 4.91
Methadone	1.98	1.10 – 3.58
Cocaine and Psychostimulants	1.96	1.13 – 3.39
Sedatives	1.13	0.54 – 2.39
Any personality disorder	1.38	0.98 – 1.93
Males vs. females		
Among polydrug user	1.67	1.12 – 2.50
Among non-polydrug user	0.69	0.30 – 1.20
Polydrug user		
Among males	1.63	1.14 – 2.32
Among females	0.67	0.37 – 1.21

tings [27] have a potential impact on the quality of the care provided [28] and on patients' decisions on whether to stay in treatment [29,30]. Priority should be given to ensuring that the staff recruited for inpatient detoxification programmes have the competence and the motivation required for working with substance-abusing patients.

5. Study limitations

The variables included in the model were restricted to the questions included in the routine questionnaire completed for all consecutive admissions.

6 Implications for treatment

Patients discharged AMA are more likely to be readmitted to inpatient detoxification. Thus, patients who discharge themselves AMA accrue to significant financial health and social care expenditures. Understanding the reasons for AMA discharge is vital to assist clinicians identify those patients most at risk for leaving inpatient detoxification AMA and enhance their ability to motivate such patients to remain in treatment [31]. Further qualitative research is required with patients who have discharged themselves from inpatient detoxification units to inform the development of strategies to reduce the risks of discharge AMA. The provision of adequate information would insure that patients had realistic expectations of what to expect from inpatient detoxification treatment, and motivational sessions prior to being admitted could reduce discharge AMA.

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Conflict of Interest

None.

Contributors

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Barcelona 2012 Faculty

Hannu Alho, Helsinky, Finland
Natalia Baranok, Murmansk, Russia
Amine Benyamina, Paris, France
Rik Bes, Hilversum, The Netherlands
David Best, Melbourne, Australia
Marcel Buster, Amsterdam, The Netherlands
Duncan Cairns, London, UK
Miguel Casas, Barcelona, Spain
Pietro Casella, Roma, Italy
Thomas Clausen, Oslo, Norway
Joan Colom Ferran, Barcelona, Spain
Pascal Courty, Clermont Ferrand, France
Annette Dale-Perera, London, UK
Isabelle Demaret, Liege, Belgium
Chin,Eap, Prilly-Lausanne, Switzerland
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A compartmental model for the pharmacokinetics of heroin and its metabolites in man

Renato Urso[1], Giuseppe Montefrancesco[1] and Mario Rigato[2]

1 Centre for the Study of Pathological Addiction, Department of Neurological Sciences, Neurosurgery and Behavioural Sciences, "Giorgio Segre" Pharmacology Section, University of Siena, Italy, EU
2 Medical Physics Section, Department of Physics, University of Siena, Italy, EU

Summary

A compartmental model was used to describe the pharmacokinetics of heroin, 6-monoacetylmorphine, morphine and glucuronides. The parameters of the model were estimated by pooling the observations collected and published in various studies, and were used to predict the effect of a reduced rate of glucuronidation and renal excretion on the plasma profile of morphine and its glucuronides after single and multiple administrations of morphine. Simulations were performed by assuming that some rate constants were representative of the rates of morphine glucuronidation and renal excretion. The results showed that renal impairment may produce more extensive drug accumulation during multiple dose treatments than an impaired morphine metabolism (leading to as much as a tenfold increase in the plasma levels of morphine after a 90% reduction of renal clearance). This happens because enterohepatic recycling takes place fast enough to allow morphine to stay in equilibrium with its glucuronides in blood, while the pool of morphine and morphine-glucuronides is only slowly cleared by the kidneys.

Key Words: Pharmacokinetics, morphine, enterohepatic recycling, renal impairment

1. Introduction

Heroin (diacetylmorphine, diamorphine or Diagesil) is a semi-synthetic morphine derivative and a powerful opioid analgesic. The medical prescription of pharmaceutically prepared heroin is applied even in the treatment of chronic heroin addicts who do not respond to conventional interventions such as methadone and buprenorphine [14, 15].

The starting heroin dose is based on the estimated tolerance level of the individual patient, and is adjusted in the course of the treatment, taking the clinical effects and the personal response of the patients as the main dose-defining indicators. The prescription of heroin lasts for several months, and unexpected changes in concentrations of heroin and its active metabolites in plasma may occur, so inducing withdrawal symptoms or toxic adverse events. Furthermore, heroin can be administered in various different ways, and during treatment alternative routes of administration may be needed.

Hepatic impairment and renal damage are common diseases in this special population, and both liver and kidneys are involved in the elimi-

Correspondence: Giuseppe Montefrancesco, MD - U.O. "Prevenzione Dipendenze Patologiche" ASL/7, Sezione di Farmacologia "G. Segre", Università degli Studi di Siena, Strada delle Scotte 6, 53100
E-mail: montefrance2@unisi.it

nation of heroin and its metabolites.

In man, heroin is rapidly hydrolysed to 6-monoacetylmorphine and finally into morphine. Thereafter, glucuronides are conjugated to the 3- and 6-positions of morphine, morphine-3-gluronide (M3G) being the major metabolite (see Figure 1) [7]. Morphine-glucuronides are mainly excreted in urine and in minor quantities in bile. After intravenous administration, about 70% of the total heroin dose is recovered in urine, mainly as conjugated morphine (55%). Other metabolites were found in minor quantities in human urine (normorphine-glucuronide, codeine, morphine-3-6-diglucuronide and morphine-3-ether-sulphate). The hydrolysis of heroin and 6-monoacetylmorphine is catalysed by various types of esterases that are abundantly present in the circulatory system and in tissues. Glucuronidation is catalysed by uridine 5'-diphosphate-glucuronosyl-transferases (UGT). Primarily, the UGT2B7 and, in minor quantities, the UGT1A1 subtypes are involved in the morphine metabolism. The glucuronidation of morphine mainly occurs in the liver. Results of pharmacokinetic studies following intramuscular, intravenous, intranasal and snorting administration or by inhalation of vapours of heated heroin have been reported [3, 4, 5, 6, 7, 8, 9, 12].

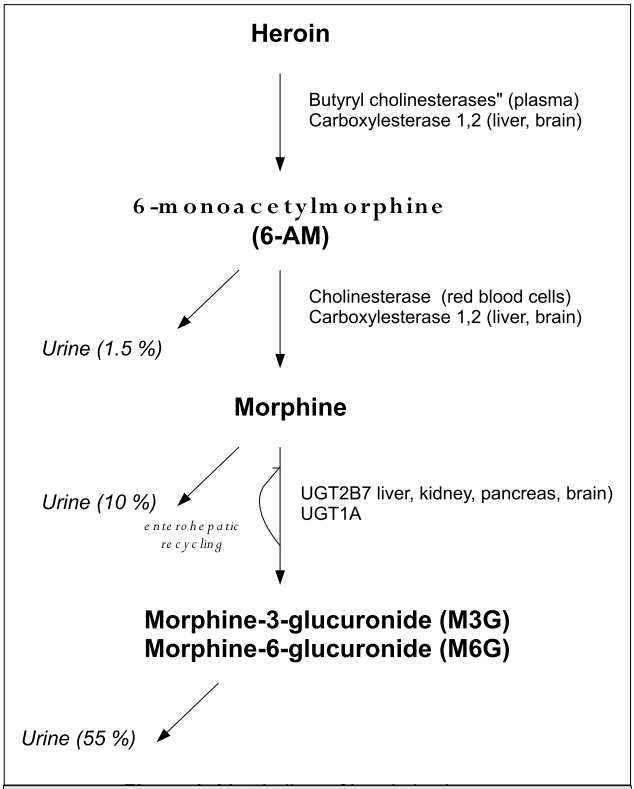

Figure 1. Metabolism of heroin in vivo

Heroin blood levels declined very rapidly after intravenous drug administration, and became undetectable after 10-40 min when measured with a lower limit of quantification of the analytical methods between 5-50 ng/mL. Estimates of the volume of the distribution of heroin varied between 60-100 L and the half-life averaged 1.3-7.8 min. The estimates of the mean heroin clearances far exceeded the hepatic and renal blood flow, so indicating that heroin may be metabolized primarily in peripheral tissues and in the circulatory system.

Heroin was not recovered in urine; this finding implies that heroin is almost entirely converted into its metabolites.

6-monoacetylmorphine (6AM) is the first hydrolysis product of heroin. It is considered to be responsible for almost all the acute effects that follow heroin administration.

The maximum concentrations of 6AM were reached 0.7-2.7 min after intravenous heroin administration, then the metabolite levels declined somewhat more slowly than heroin levels. Estimates of half-life ranged from 5.4 to 52 min and, after heroin injection, 6-monoacetylmorphine was detected in plasma for 1-3 hours. The metabolite was detectable for 1.2-4.3 hours in urine after the intravenous injection or inhalation of 2.6-20 mg heroin, and about 1.3% of the total intravenous heroin dose was recovered in urine as 6AM.

The formation of morphine after heroin administration occurs very rapidly, and peak concentrations can be detected between 3.6 and 8.0 min after heroin administration. The half-life of morphine after heroin administration was 100-280 min - a range comparable with the data obtained after morphine administration.

The terminal half-lives of morphine-glucuronides (M3G/M6G) ranged from 2.0 to 6.4 h and did not depend on the method of heroin administration. Tmax varied from 0.7 to 5.1 h.

M6G is a powerful opioid, whereas M3G does not act intrinsically as an opioid.

The long-lasting presence of morphine and glucuronides in plasma is the outcome of enterohepatic cycling. After excretion in bile, morphine-glucuronides are hydrolysed into morphine in the digestive tract by the beta-glucuronidase enzymes of the colon flora and the regained morphine molecules become available for reabsorption into the circulation. Animal studies showed that the contribution of enterohepatic cycling to

the total bioavailability of morphine is probably considerable. For example, in rodents the bioavailability of oral M6G declined by 65% when the enterohepatic cycle was interfered with by blocking the beta-glucuronidase activity of the colon flora.

The pharmacokinetics of heroin and morphine have been extensively studied in man, and the aim of this paper is to propose a pharmacokinetic model that may prove to be useful in predicting the effects of hepatic and renal impairment on the plasma levels of the main heroin metabolites.

2. Material and Methods

2.1. The data

The data published so far on the pharmacokinetics of heroin and its metabolites have shown that the inter-study and inter-subject variability of plasma concentrations is very high. Despite this problem, an attempt to provide a graphic rendering of the typical profile of the drug and its metabolites after heroin or morphine iv administrations is shown by the plots appearing in Figures 2, 3 and 4.

These profiles have been generated by drawing on data and figures published in a number of different articles [4, 6, 9, 12] and do not correspond to the results of any single study; they also include urine data extrapolated from the percentages of doses recovered in the urine samples that were collected during various experiments.

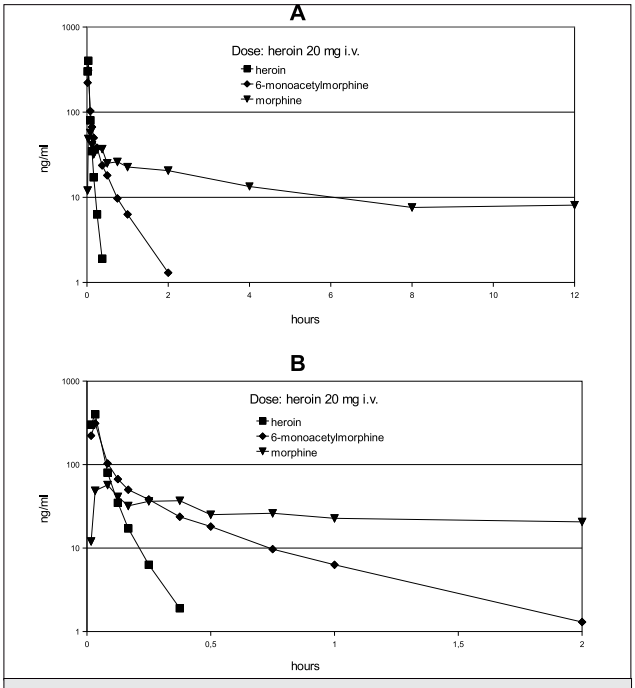

Figure 2. Plasma profile of heroin, 6-monoacetylmorphine and morphine after intravenous administrations of 20 mg of heroin. A: plasma concentrations up to 12 hours; B: plasma concentrations up to 2 hours

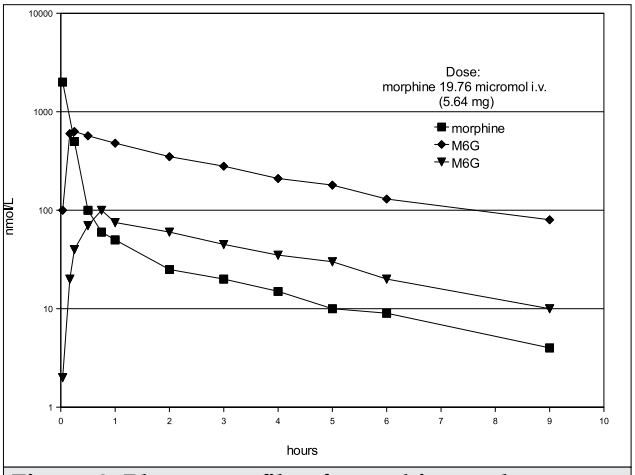

Figure 3. Plasma profile of morphine and glucuronides after intravenous administration of 5.64 mg of morphine

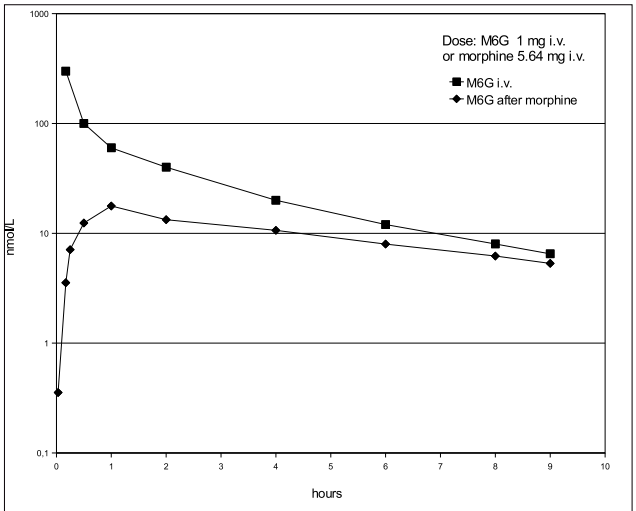

Figure 4. Plasma profile of M6G after morphine administration and after intravenous M6G administration (the concentrations were normalized to the same molar doses).

When a full set of observations has not been made available on a single subject, the only way forward is to hypothesize that various data gathered from different populations may provide a reasonable approximation to the drug kinetics in a typical individual. This assumption may be questionable, and may even produce unpredictable errors in estimating the model parameters. In any case, we have worked on the assumption that

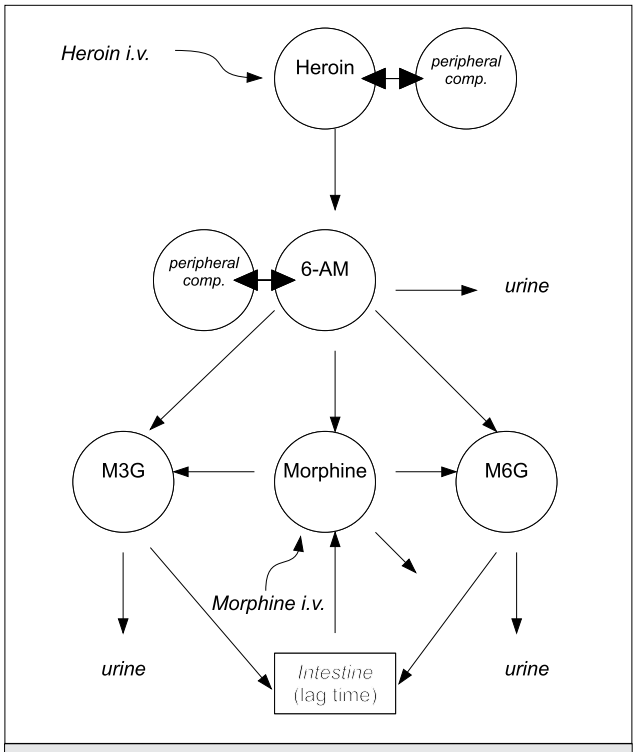

Figure 5. Graph of a compartmental model for the kinetics of heroin and metabolites: 6-monoacetylmorphine (6-AM), morphine and morphine-glucuronides (MG6, MG3)

these data may be turn out to be useful in defining a reasonable compartmental model that is able to predict the pharmacokinetics of heroin and metabolites in a variety of experimental conditions.

2.2. *The compartmental model*

Compartmental models have been introduced in pharmacokinetics as tools in synthesizing and describing the main pertinent features of the systems under study [10, 11]. The parameters of these models are the rate constants between compartments and volumes of distribution. These parameters do not represent a single physiological variable, but a combination of variables that are often hard to distinguish from the commonly used experimental design [13]. On the other hand, compartmental models could be used to describe the profile of morphine in plasma and discrete areas of the rat brain [15] and provide linkage between drug kinetics and analgesia [1] through a single pharmacokinetic-pharmacodynamic model.

A reasonable and simple compartmental model that is put forward by us to describe the kinetics of heroin and metabolites in man is shown in Figure 5.

The circles display the compartments whose function is to represent the concentrations or amounts of substances in blood or tissues (or pools of tissues). The arrows define the connections between compartments; when the task is to model the drug amounts, they may show the passage of substances between compartments. Each arrow defines a transfer rate constant which is the ratio between the rate of transfer (i.e. amount per unit of time) and the amount present in the starting compartment. According to the model, this ratio is assumed to be constant over time. Both the compartments and the arrows have the function of visually displaying the underlying system of a linear differential equation and defining a mathematical model for the drug kinetics involved.

The definition of the compartments is part of the model and in this case we assume that they represent the amount of substance in particular districts of the body. As a result, the solution to the model provides the drug amount time profile in each compartment.

For example, in the model shown in Figure 5 the compartments are the amounts of heroin, 6-monoacetylmorphine (6-AM), morphine and morphine-glucuronides (MG6, MG3) in blood and fast-equilibrating tissues. The arrows show that heroin can be converted into monoacetylmorphine, which, in turn, can be transformed into morphine and morphine-glucuronides (MG6, MG3). These transformations are irreversible. On the other hand, morphine can be converted into MG6 and MG3, which, in their turn, are eliminated into the intestine, where they can be transformed back into morphine and reabsorbed in blood (so implementing enterohepatic recycling). The intestine compartment has been given a different shape to indicate the presence of a time lag between glucuronides and morphine in blood due to discontinuous gallbladder swelling. The arrow that connects monoacetylmorphine with morphine-glucuronides means that glucuronidation in the liver may take place so fast that they appear in blood at the same time as the intermediary product (morphine), as in the case of hepatic first-pass effect after oral drug administration.

Monoacetylmorphine, morphine and morphine-glucuronides (MG6, MG3) are, likewise, eliminated into the urine, where these compounds may be recovered and quantified. The presence of other minor metabolites in urine was excluded, because these metabolites have no significant influence on the performance of the model and are therefore of no interest in this context.

Heroin and monoacetylmorphine were reversibly connected with a peripheral compartment to improve the precision of the fit, and the central and the peripheral compartment may be thought of as a group of fast and slowly equilibrating tissues, respectively.

The model shows two possible drug inputs, too: an intravenous bolus of heroin and an intravenous bolus of morphine. This means that the model can be used to predict the amounts of drugs in all the compartments by setting the initial condition equal to the dose administered in the input compartment and equal to zero in the remaining compartments.

As drug concentrations are available, but not drug amounts, it is necessary to define one additional parameter for every sampled compartment in order to make the model fit the experimental data. These parameters are the volumes of distribution of the compartments and are defined as the ratio between the drug amount and the drug concentration in any given compartment. According to the model, these parameters are assumed to be constant over time.

To represent all the particular experimental conditions, it may be useful to use the SAAM II graphical representation of the compartmental models (SAAM, Copyright 2006-07, University of Washington), as shown in Figures 6 and 7.

The compartments are named qi, the measured concentrations are named si and are represented by filled circles (each filled circle defines the volume of the sampled compartment). The transfer constant from compartment j to i has been labelled K(i,j) and the injection site has been labelled exi and is represented by a syringe. The models shown in Figures 6 and 7 have been adapted to three different experimental conditions where morphine or M6G or heroin are administered.

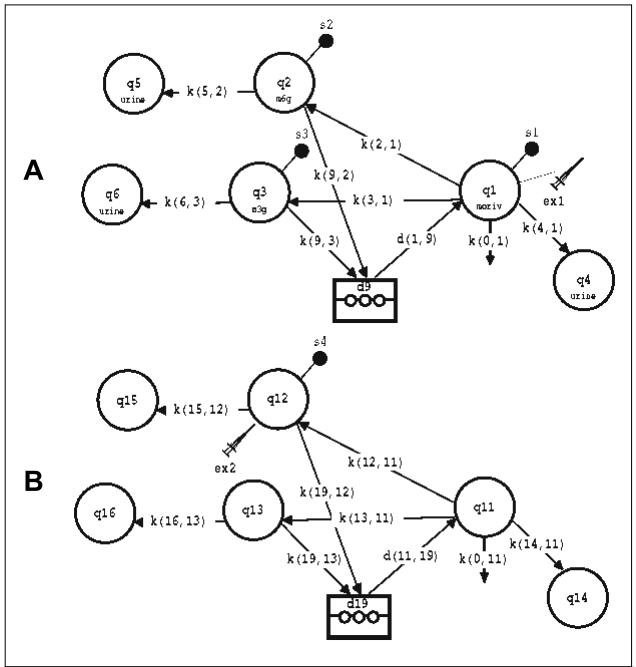

Figure 6. Graphical representation of the compartmental model used to describe the kinetics of morphine and metabolites. A: after intravenous administration of morphine; B after intravenous administration of the metabolite M6G.

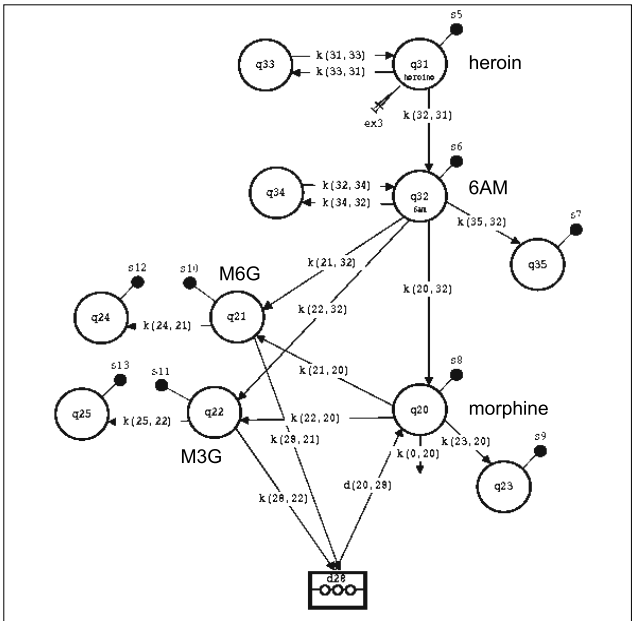

Figure 7. Graphical representation of the compartmental model used to describe the kinetics of heroin and metabolites.

In Table 1 the parameters of the full model are listed, together with a short description.

3. Results

3.1. Estimating the pharmacokinetic parameters of heroin and metabolites

The parameters of the compartmental model were estimated after fitting the experimental data in three stages: after intravenous administration of morphine, after intravenous administration of M6G and after intravenous administration of heroin. The data were rescaled to take into account the differences in the molecular weights of heroin and its metabolites, as well as the differ-

Table 1: List of the parameters of the compartmental models shown in Figure 6 and 7

Parameter		Description
V6AM		Volume of 6AM associated to s6
V heroin		Volume of heroin associated to s5
V M3G		Volume of M3G associated to s3, s11
V M6G		Volume of M6G associated to s2, s4, s10
V morphine		Volume of morphine associated to s1, s8
k(0,1)	= k(0,11) = k(0,20)	rate of metabolism of morphine to other metabolites
k(2,1)	= k(12,11) = k(21,20)	rate of metabolism of morphine to M6G
k(20,32)		rate of metabolism of 6AM to morphine
k(21,32)		rate of metabolism of 6AM to M3G (in the liver)
k(22,32)		rate of metabolism of 6AM to M6G (in the liver)
k(3,1)	= k(13,11) = k(22,20)	rate of metabolism of morphine to M3G
k(31,33)		transfer rate of heroin from the peripheral to the central compartment
k(32,31)		rate of metabolism of heroin to 6AM
k(32,34)		transfer rate of 6AM from the peripheral to the central compartment
k(33,31)		transfer rate of heroin from the peripheral to the central compartment
k(34,32)		transfer rate of 6AM from the peripheral to the central compartment
k(35,32)		elimination rate of 6AM into the urine
k(4,1)	= k(14,11) = k(23,20)	elimination rate of morphine into the urine
k(5,2)	= k(15,12) = k(24,21)	elimination rate of M6G into the urine
k(6,3)	= k(16,13) = k(25,22)	elimination rate of M3G into the urine
k(9,2)	= k(19,12) = k(28,21)	transfer rate of M6G to the intestine through bile
k(9,3)	= k(19,13) = k(28,22)	transfer rate of M3G to the intestine through bile

ences between doses.

In the fitting procedure the weighted (1_y2) sum of squared criteria was used by the computer programme SAAM II.

Table 2 shows the list of the estimated pharmacokinetic parameters.

Figure 8 shows the plot of the observed and predicted concentrations of morphine and glucuronides after the intravenous administration of 5.64 mg of morphine. In Figures 9 and 10 the blood profiles of heroin, 6AM, morphine and glucuronides after 20 mg heroin i.v. are plotted.

Visual inspection of these plots shows that the plasma concentrations were well interpolated by the model; in addition, a good degree of agreement between predicted and observed data was achieved in fitting the data for urinalysis recovery (data not shown).

On the basis of the model and its parameters, it becomes possible to predict the blood profile of heroin and its metabolites in a variety of experimental conditions. For example, the model makes it possible to quantify the effects of impaired metabolism or renal excretion on systemic drug concentrations or to simulate the drug and metabolite kinetics after multiple dose administration [2].

3.2. Predicting the effects of reduced rates of glucuronidation on the plasma profile of morphine and its metabolites

Holding all the other parameters in the model constant, morphine, M6G and M3G blood profiles were simulated after intravenous morphine administration (5.64 mg) for different values of k(2,1) and k(3,1) . The results are shown in Figures 11, 12 and 13 and were obtained by setting [k(2,1), k(3,1)] to: [0.0167 , 0.071] = 100% of the estimated values in normal subjects and to [0.00167, 0.0071] = 10% of the estimated values in normal subjects.

Figure 11 shows that major increase in morphine concentrations is likely to occur only

Table 2: Pharmacokinetic parameters of heroin and metabolites

Parameter		Value
V6AM		17.2 l
V heroin		16.5 l
V M3G		90.7 l
V M6G		56.1 l
V morphine		8.0 l
K(0,1)	= k(0,11) = k(0,20)	1E-10 l/min
k(2,1)	= k(12,11) = k(21,20)	0.0167 l/min
k(20,32)		0.0319 l/min
k(21,32)		0.0391 l/min
k(22,32)		0.7510 l/min
k(3,1)	= k(13,11) = k(22,20)	0.0710 l/min
k(31,33)		0.3159 l/min
k(32,31)		0.8090 l/min
k(32,34)		0.0622 l/min
k(33,31)		0.1708 l/min
k(34,32)		1.0000 l/min
k(35,32)		0.0056 l/min
k(4,1)	= k(14,11) = k(23,20)	0.0180 l/min
k(5,2)	= k(15,12) = k(24,21)	0.0023 l/min
k(6,3)	= k(16,13) = k(25,22)	0.0026 l/min
k(9,2)	= k(19,12) = k(28,21)	0.0015 l/min
k(9,3)	= k(19,13) = k(28,22)	0.0008 l/min

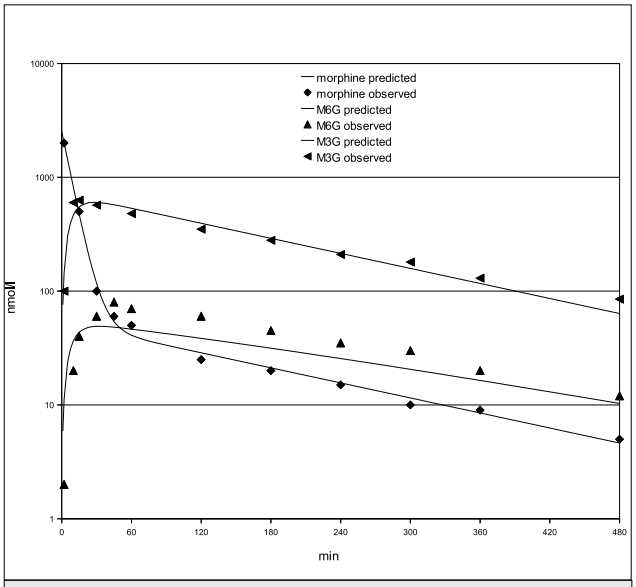

Figure 8. Morphine, M6G and M3G profiles in plasma after 5.64 mg i.v. of morphine.

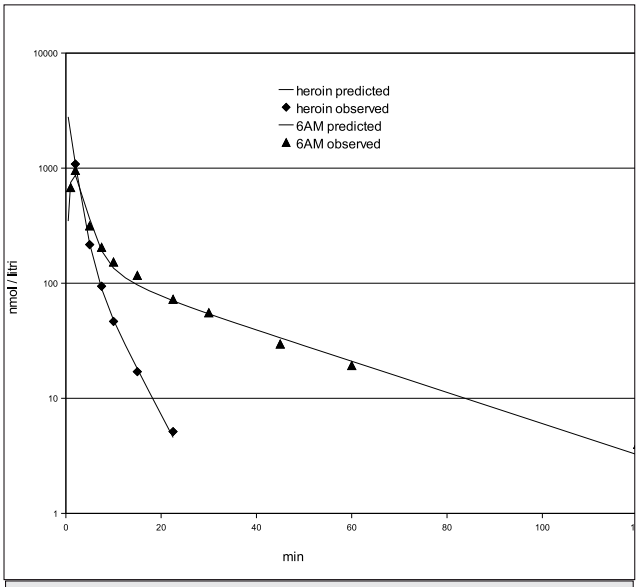

Figure 9. Heroin and 6AM profiles in plasma after 20 mg i.v of heroin.

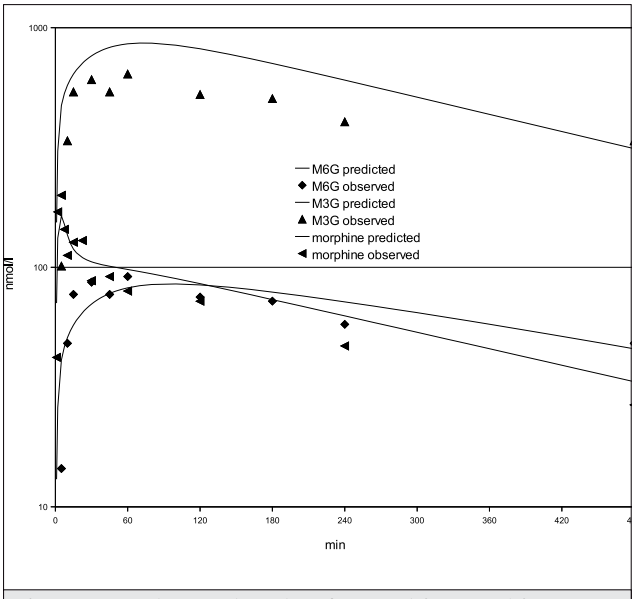

Figure 10. Plasma levels of morphine and its glucuronides M6G e M3G after 20 mg iv of heroine

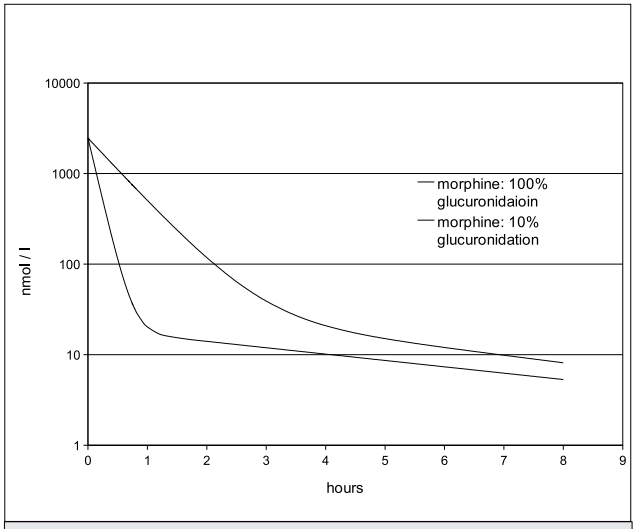

Figure 11. Impaired glucuronidation: plasma levels of morphine after 5.64 mg morphine i.v. for different values of k(2,1) and k(3,1): 100% and 10% of normal values.

during the first 2-3 hours after administration, whereas at a later stage the effects of metabolism reduction (up to 90% reduction) produced only minor variations in morphine concentrations (under 30%). The extent of the increase in morphine levels after a 25% or even a 50% reduction of glucuronidation fell within the range of the natural inter- and intra-subject variability of morphine kinetics (data not shown); as a result, this effect cannot be considered clinically significant.

On the other hand, Figure 12 shows that the reduction of glucuronidation produces lower circulating levels of M6G, which may partly balance the pharmacodynamic effect of higher morphine concentrations. The predicted effect on the metabolite kinetics is relatively small up to a 50% reduction in glucuronidation.

The kinetic behaviour of M3G shows a pattern similar to that of M6G (see Figure 13). Moreover, it may be observed that in all these simulations the apparent terminal half-life of morphine, M6G and M3G appears to be unchanged.

In conclusion, even a strong reduction in the rate of glucuronidation of morphine cannot be expected to produce clinically relevant effects on drug pharmacodynamics, because of its relatively small influence on drug levels in blood.

3.3. Predicting the effects of renal impairment on the plasma profile of morphine and its metabolites

The effects of renal impairment were predicted by tuning the parameters k(4,1), k(5,2) and k(6,3), which are the rate constants associated with the renal elimination of morphine, M6G and M3G, respectively. The results are shown in Figures 14, 15 and 16 and were obtained by setting [k(4,1), k(5,2), k(6,3)] to [0.018, 0.0023, 0.0026] = 100% of the estimated values in normal sub-

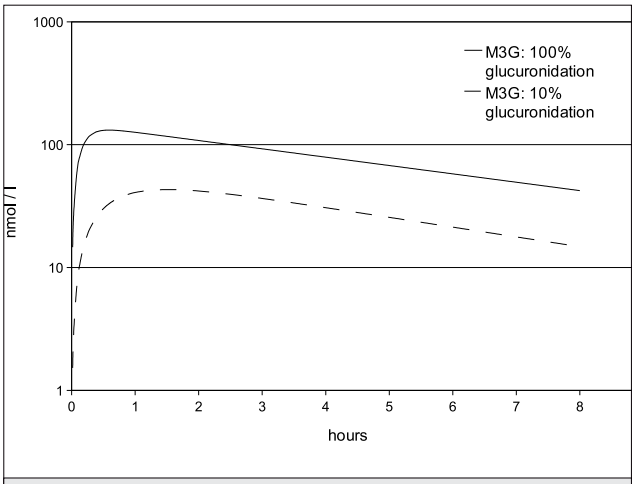

Figure 12. Impaired glucuronidation: plasma levels of M6G after 5.64 mg morphine i.v. for different values of k(2,1) and k(3,1): 100% and 10% of normal values.

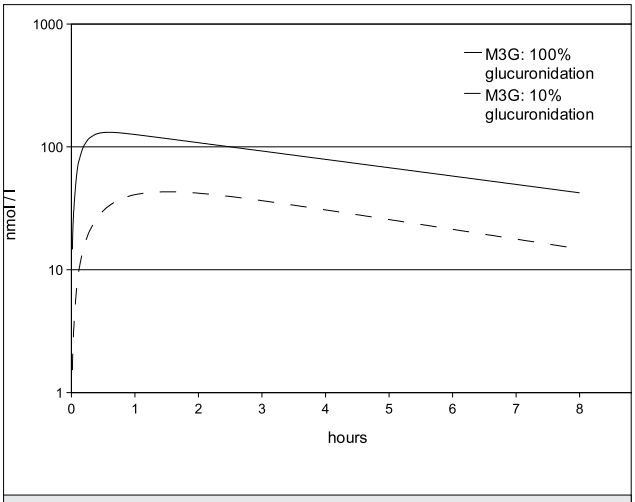

Figure 13. Impaired glucuronidation: plasma levels of M3G after 5.64 mg morphine i.v. for different values of k(2,1) and k(3,1): 100% and 10% of normal values.

jects and to [0.0018, 0.00023, 0.00026] = 10% of the estimated values in normal subjects.

These simulations show that the effects of renal impairment are qualitatively different from those of lowered glucuronidation. By examining the plots, it becomes clear that the apparent terminal half-lives increase as a result of the decreased rate of renal elimination. This trend is often found in the profiles for morphine, M6G and M3G; consequently, the persistence of morphine and its metabolites in the circulatory system appears to be enhanced by renal impairment.

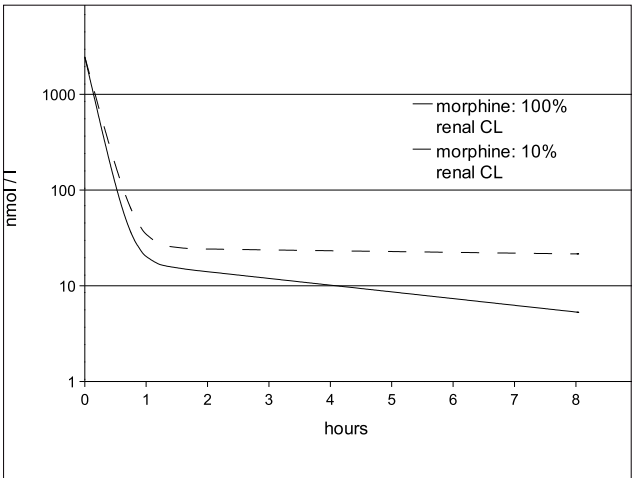

Figure 14. Impaired renal clearance: plasma levels of morphine after 5.64 mg morphine i.v. for different values of k(4,1), k(5,2) and k(6,3): 100% and 10% of normal values.

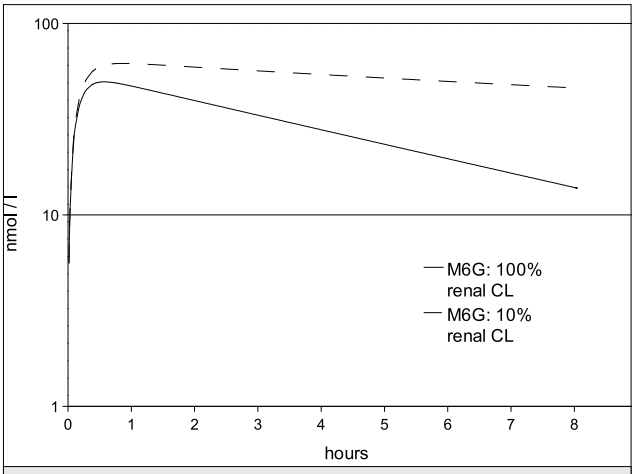

Figure 15. Impaired renal clearance: plasma levels of M6G after 5.64 mg morphine i.v. for different values of k(4,1), k(5,2) and k(6,3): 100% and 10% of normal values.

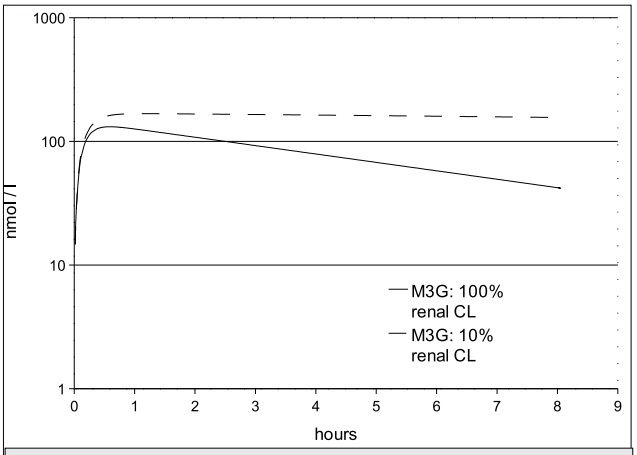

Figure 16. Impaired renal clearance: plasma levels of M3G after 5.64 mg morphine i.v. for different values of k(4,1), k(5,2) and k(6,3): 100% and 10% of normal values.

3.4. Predicting the effects of glucuronidation and renal impairment after multiple dose administration

The simulations after multiple dose administration were performed after assuming that morphine had been injected intravenously at 12-hour intervals for about a week in order to reach an approximartely steady state plateau ("s.s.", i.e. when no further drug accumulation is expected to occur in the body). In Figures 17, 18 and 19 the plasma levels of morphine, M6G and M3G after 5.64 mg multiple dose administration are compared after assuming a 90% reduction in glucuronidation: [k(2,1), k(1,2)]=(0.0167 , 0.071)

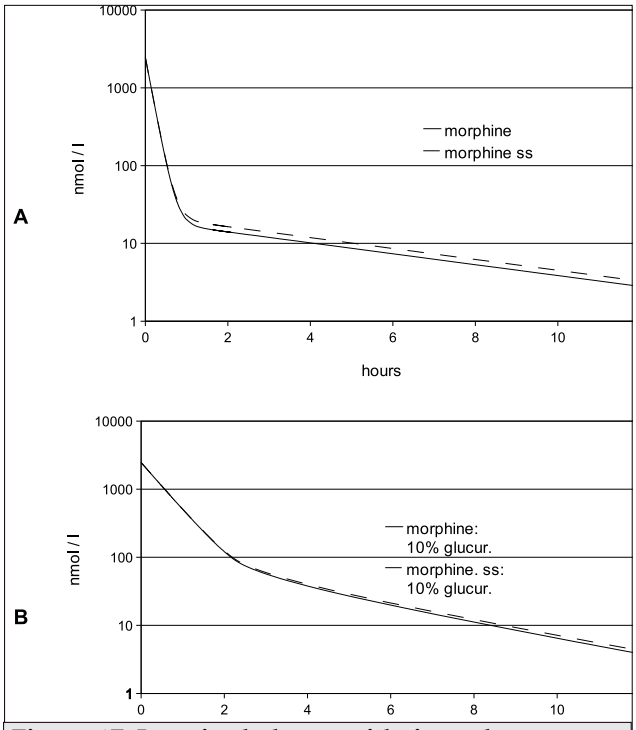

Figure 17. Impaired glucuronidation: plasma levels of morphine after 5.64 mg morphine i.v. every 12 hours for different values of k(2,1) and k(3,1):100% (A) and 10% (B) of normal values (first and last dose).

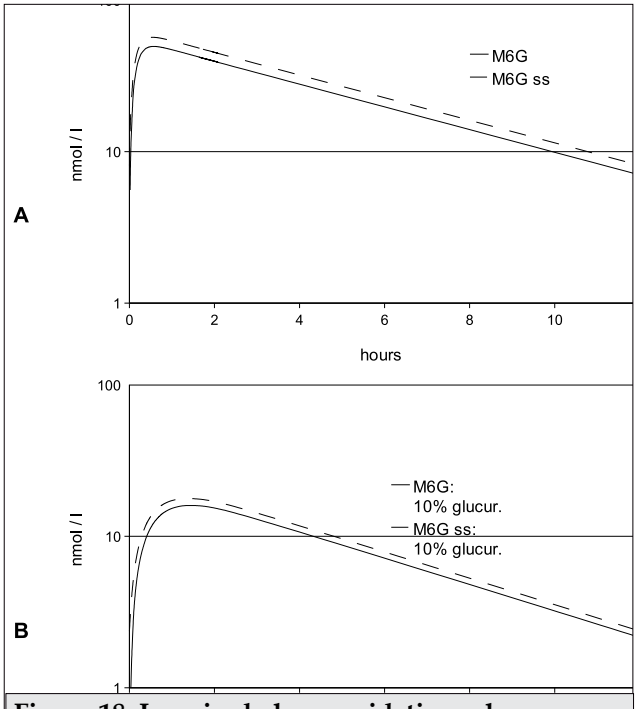

Figure 18. Impaired glucuronidation: plasma levels of M6G after 5.64 mg morphine i.v. every 12 hours for different values of k(2,1) and k(3,1): 100%. (A) and 10% (B) of normal values (first and last dose).

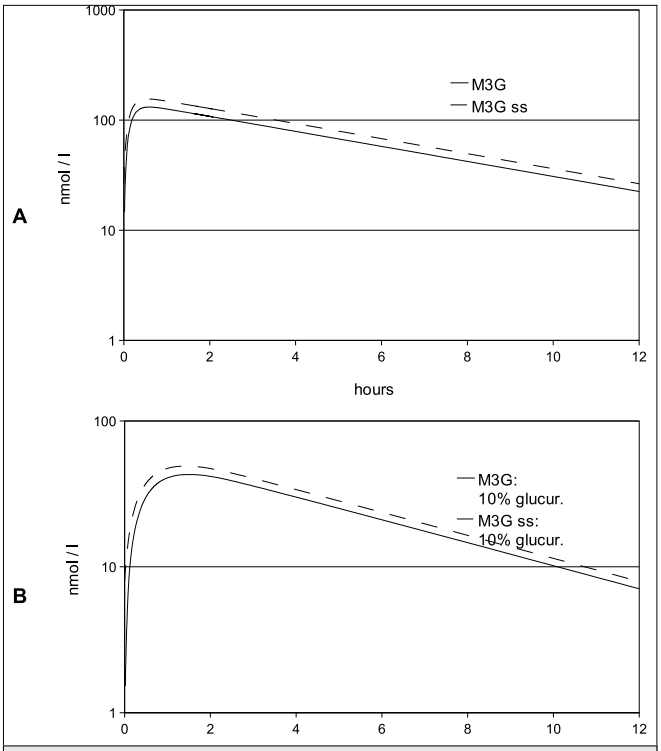

Figure 19. Impaired glucuronidation: plasma levels of M3G after 5.64 mg morphine i.v. every 12 hours for different values of k(2,1) and k(3,1): 100% (A) and 10% (B) of normal values (first and last dose).

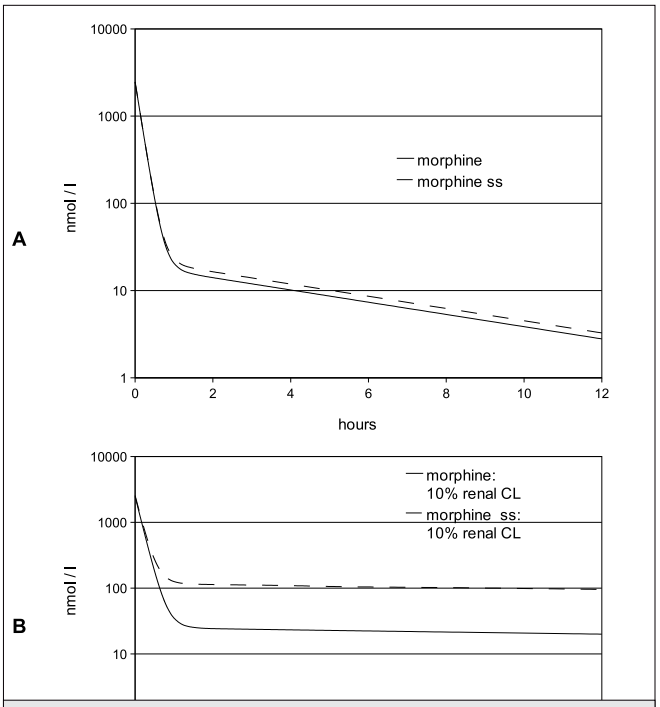

Figure 20. Impaired renal clearance: plasma levels of morphine after 5.64 mg morphine i.v. every 12 hours for different values of k(4,1), k(5,2), k(6,3): 100% (A) and 10% (B) of normal values (first and last dose).

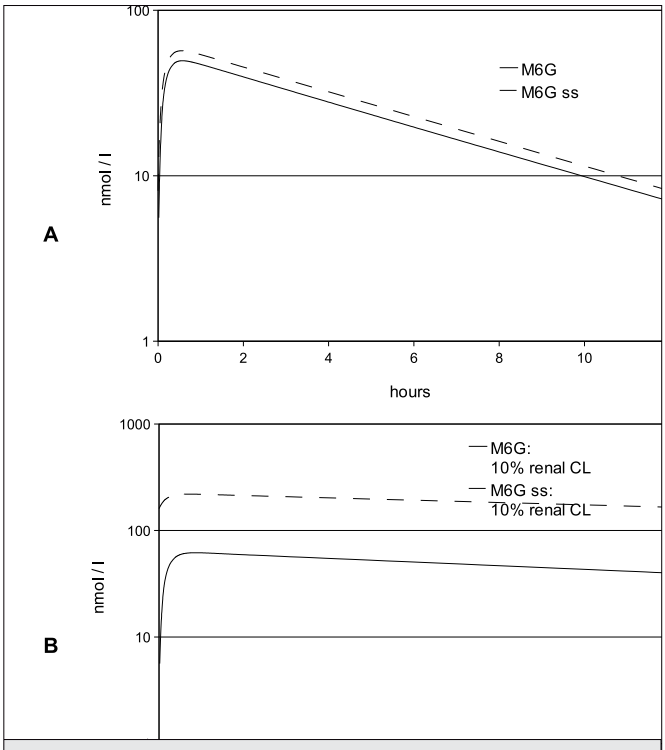

Figure 21. Impaired renal clearance: plasma levels of M6G after 5.64 mg morphine i.v. every 12 hours for different values of k(4,1), k(5,2), k(6,3): 100% (A) and 10% (B) of normal values (first and last dose).

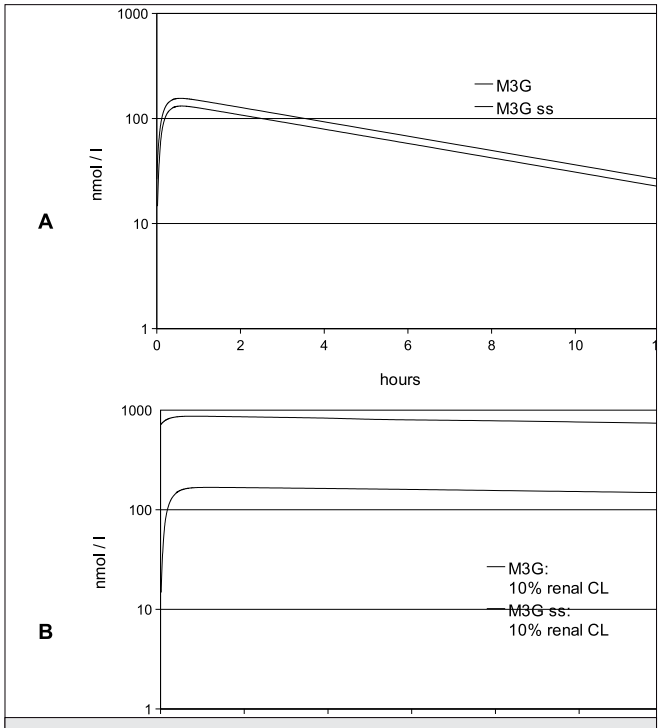

Figure 22. Impaired renal clearance: plasma levels of M3G after 5.64 mg morphine i.v. every 12 hours for different values of k(4,1), k(5,2), k(6,3): 100% (A) and 10% (B) of normal values (first and last dose).

normal values vs [k(2,1), k(1,2)]=[0.00167, 0.0071] reduced values.

The plots show that a strong reduction in glucuronidation does not significantly affect the accumulation of morphine and glucuronides, and, given that all the other metabolic pathways of morphine play a minor role, it may be concluded that drug accumulation and the pharmacodynamics should not be very sensitive to changes in the metabolic activity of morphine.

In Figures 20, 21 and 22 the plasma levels of morphine, M6G and M3G after multiple dose administration are compared after assuming a 90% reduction in renal clearance: [k(4,1), k(5,2), k(6,3)]=(0.018, 0.0023, 0.0026) normal values vs [k(4,1), k(5,2), k(6,3)]=(0.0018, 0.00023, 0.00026) reduced values.

The plots show that renal impairment may have a strong influence on morphine and glucuronide accumulation after multiple dose treatment. This accumulation may be the outcome of the prolonged apparent terminal half-life predicted in subjects with renal impairment, as could be expected, because the morphine and glucuronide equilibrium in blood made possible by enterohepatic recycling is considerably faster than the excretion rate into urine.

4. Conclusions

Knowledge of human pharmacokinetics and pharmacodynamics is necessary for the optimal use of drugs in therapy and in choosing the best route of administration, along with the best dose regimen, while allowing for dose individualization.

Mathematical models are essential tools in these studies, because only through the models is it possible to define a set of pharmacokinetic parameters that are able to provide a synthetic description of the drug disposition and to link the drug disposition with the underlying biological processes.

Model building is a complex multi-step process where, experiment by experiment, and simulation by simulation, new hypotheses can be proven or disproven through a continuous interaction between the experimenter and the computer.

In the present study a compartmental model was used to describe the plasma profile of heroin, 6-monoacetylmorphine, morphine and glucuronides in various different experimental settings.

The parameters of the model were estimat-

ed by pooling the observations collected and published in a variety of experiments. This questionable procedure can be justified by the task to be implemented, which was to highlight some of the kinetic properties of heroin and its metabolites and some of their possible clinical consequences, without putting forward any claim to be defining the pharmacokinetics and pharmacodynamics of any real population.

The model was used to predict the effect of reduced rates of glucuronidation and renal impairment on the kinetics of morphine and glucuronides after single and multiple administrations of morphine. Simulation could be performed by giving a physiological significance to some of the model parameters, i.e., by assuming that some rate constants were representative of the rate of morphine glucuronidation and renal excretion. The results show that renal impairment may produce more extensive drug accumulation during multiple dose treatments than an impaired morphine metabolism.

This finding could have been expected, because enterohepatic recycling seems to take place fast enough to allow morphine to be in equilibrium with its glucuronides in blood, while the morphine-glucuronide pool can only be cleared by the kidneys much more slowly.

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Letter to the Editor

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HEROIN ADDICTION & RELATED CLINICAL PROBLEMS

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The state of the art regarding heroin addicts in prisons in Slovenia during the period from 1990 to 2008

Mercedes Lovrecic and Barbara Lovrecic

National Institute of Public Health, Ljubljana, Slovenia

TO THE EDITOR: We report the data on heroin addicts in prisons in Slovenia during the period from 1990 to 2008 and some of the features of the drug-related treatment system. In spite of some improvements in the use of agonist treatment in the justice system, more evidence-based medical practice should be implemented.

In Slovenia, according to Article 33 of the Production of and Trade in Illicit Drugs Act (9), drug-related use/possession is an offence (Note 1), rather than a criminal act, and drug-related dealing/trafficking is defined in Article 196 (Note 2) of the Penal Code (10), while drug-related use and trafficking is defined in Article 197 (Note 3) of the Penal Code (10).

There are 13 prison units in Slovenia: Dob, Slovenska vas, Ig (female unit; open unit), Celje, Koper, Nova Gorica, Ljubljana, Novo Mesto, Maribor, Rogoza, Murska Sobota, Radece (juveniles) (1,8). Data from the Prison Administration of the Republic of Slovenia reveal that in the period from 1990 to 2008 in Slovenia the number of illicit drug users (mostly taking heroin) among prisoners increased steadily, whereas the total number of prisoners showed continual variation (2-8). The available data show that the total number of prisoners was approximately stable in the 1995-1997 period, then rose over the next three years; from 2000 it fell rapidly until 2005, after which the total number of prisoners in Slovenia rose again between 2005 and 2008 (Table 1).

The percentage of illicit drug users among prisoners in Slovenia in the period from 1995 to 2008 rose, globally and steadily, from a minimum in 1995 (3.3%) to a maximum in 2005 (28%). The data show that from the mid-1990s to 2001 the proportion of illicit drug users (mostly taking heroin) increased from 3.3% to nearly 10.8% of all prisoners, but then rapidly increased again, reaching a maximum of 28% in 2005, whereas, in the last three years reviewed, it has been around one-quarter of all prisoners (Figure 1). In 2008 there were 1210 recognized illicit drug users (mostly taking heroin) out of a total of 4383 prisoners. Using 2007 as a basis for comparison, the number of illicit drug users in Slovenian prisons increased in 2008 by 11% (Table 1). In 2008 in Slovenia 27.6% of all prisoners had illicit drug use problems, the proportion was up by 2.3% with respect to 2007, rising to the second-highest level after the peak figure of 28% recorded in

Correspondence: Mercedes Lovrecic, MD, National Institute of Public Health, Trubarjeva 2, 1000 Ljubljana, Slovenia, EU - Email: mercedes.lovrecic@ivz-rs.si

Table 1. Number and portion (%) of recognized illicit drug users in prisons, 1990-2008, Slovenia

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999
No. of prisoners	na	na	na	na	na	4046	3767	3882	5113	6348
No. of illicit drug users	16	47	68	91	111	133	156	268	306	471
% illicit drug users	na	na	na	na	na	3.3%	4.1%	6.9%	6.0%	7.4%
	2000	2001	2002	2003	2004	2005	2006	2007	2008	
No. of prisoners	6703	6302	5219	4725	4344	3097	3572	4311	4383	
No. of illicit drug users	512	682	703	727	944	868	948	1090	1210	
% illicit drug users	7.6%	10.8%	13.5%	15.4%	21.7%	28.0%	26.5%	25.3%	27.6%	

Source: Prison Administration of the RS. Legend: "na" indicates 'data not available'

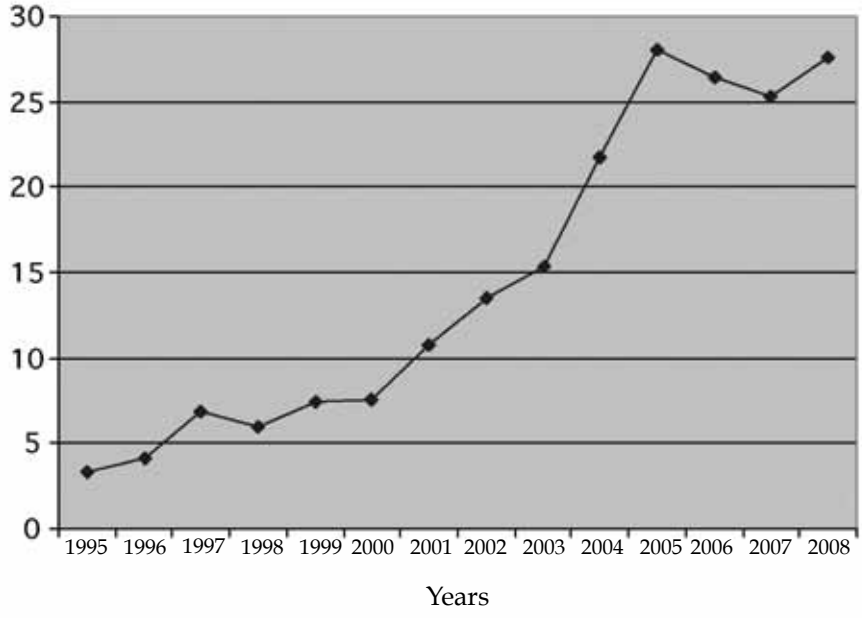

Figure 1. Percentage of illicit drug users among prisoners, 1995-2008, Slovenia (Source: Prison Administration of the RS)

2005 (28%) (see Figure 1, Table 1) (1-8).

A similar situation was observed for the percentage of compulsorily treated subjects under Article 66 of the Penal Code (10) (Note 4) (considering alcohol and illicit drugs together) in the 1995-2008 period in Slovenian prisons. The number of people compulsorily treated under Article 66 of the Penal Code in Slovenia from 2000 to 2008 increased over time, while the proportion of compulsorily treated addicts stayed quite low (with a maximum in 1997 and a minimum in 2000). Most of them were adult males, followed by females and minors. The category that most frequently underwent compulsory treatment was that of adult males in all periods, while some minors were treated according to Article 66 between 2000 and 2004 (Table 2) (1, 2, 8).

In 2008, 790 illicit drug users (65.3% of all the 1210 illicit drug users then in prison) had already had an experience with illicit drugs prior to imprisonment, which is in line with the fact that a relatively high proportion of the prison population start their use of illicit drugs while they are in prison (8). On the other hand, the availability of illicit drugs in Slovenian prisons rose between 2001 and 2006; in 2007 a negative trend began, which was followed by a further fall in the number of cases in which illicit drugs were found. In 2008 there were 131 of findings of illicit drugs in all Slovenian prisons, but in 228 of all cases tablets, alcohol, and/or equipment to be used for injections were found too. The largest

Table 2. The number of people compulsorily treated under Article 66 of the Penal Code, 1995-2007, Slovenia

	1995	1996	1997	1998	1999	2000	2001
Persons who were compulsorily treated under Article 66 of the Penal Code (together)	8	19	19	23	18	14	24
Males	na	na	17	22	15	11	19
Females	na	na	2	1	3	1	3
Minors	na	na	0	0	0	2	2
% compulsorily treated	6.01	5.77	7.09	7.52	3.82	2.73	3.52
	2002	2003	2004	2005	2006	2007	2008
Persons who were compulsorily treated under Article 66 of the Penal Code (together)	39	26	40	44	55	55	67
Males	33	21	36	40	52	50	60
Females	3	2	3	4	3	5	7
Minors	3	3	1	-	-	-	-
% compulsorily treated	5.55	3.58	4.24	5.07	5.8	5.05	5.54

Source: Prison Administration of the RS. Legend: "na" indicates 'data not available'

Table 3. Number of prisoners with illicit drug-related problems out of the total prison population divided into categories, Slovenia, 2008

Prison population divided into categories	Total number present in each category	Number of prisoners with illicit drug-related problems	Percentage in each category with such problems
Condemned inmates	2005	735	37.0
Misdemeanants	1107	124	11.2
Prisoners on remand	1228	326	26.5
Juvenile offenders	43	25	58.1
Total	4383	1210	27.6

Source: Prison Administration of the RS

quantities of illicit drugs were those found in Koper (55 g of heroin) and in Celje (45 g of cannabis and 150 tablets of ecstasy) (2, 8).

Taking closer look, the data for 2008 showed that whole group of imprisoned juveniles made up the largest category of inmates with illicit drug-related problems (58.1%) compared with the other categories of prisoners (Table 3) (8).

The available data show that the percentage of illicit drug users out of all prisoners increased steadily in Slovenia in the 1995-2005 period. On the other hand, the percentage of subjects in methadone treatment from 2000 to 2008 showed continual variations in both directions, with a minimum of 31.6% in 2002 and a maximum of 56.1% in 2006 (Figure 2) (1, 8).

According to the Prison Administration, methadone-maintained heroin addicts, active drug users and heroin addicts with withdrawal are sent to prison either because they are on remand or to start a prison sentence. They are first dealt with by the health service (6). On the advice of a doctor a withdrawal condition may be alleviated by the use of methadone or another medication. Methadone therapy is carried out in prisons on the principle of a gradual reduction through to withdrawal. Only as an exception, and on the advice of a doctor specializing in treating drug addiction, can an individual receive methadone maintenance therapy. Medical assistance in prisons is provided by health workers employed full-time, by doctors in the public health care system and by psychiatrists from the Centre for the Prevention and Treatment of Drug Addiction (CPTDA) network. The aim of the medical treatment of heroin addict prisoners is to detoxify them and strengthen their psychophysical abilities. All inmates included in illicit drug treatment programmes or in methadone therapy were regularly tested for drug use. For the purpose of determining whether opiates, cannabis or benzodiazepines were present in the human body, an immunoassay on a urine sample was performed. Whenever a

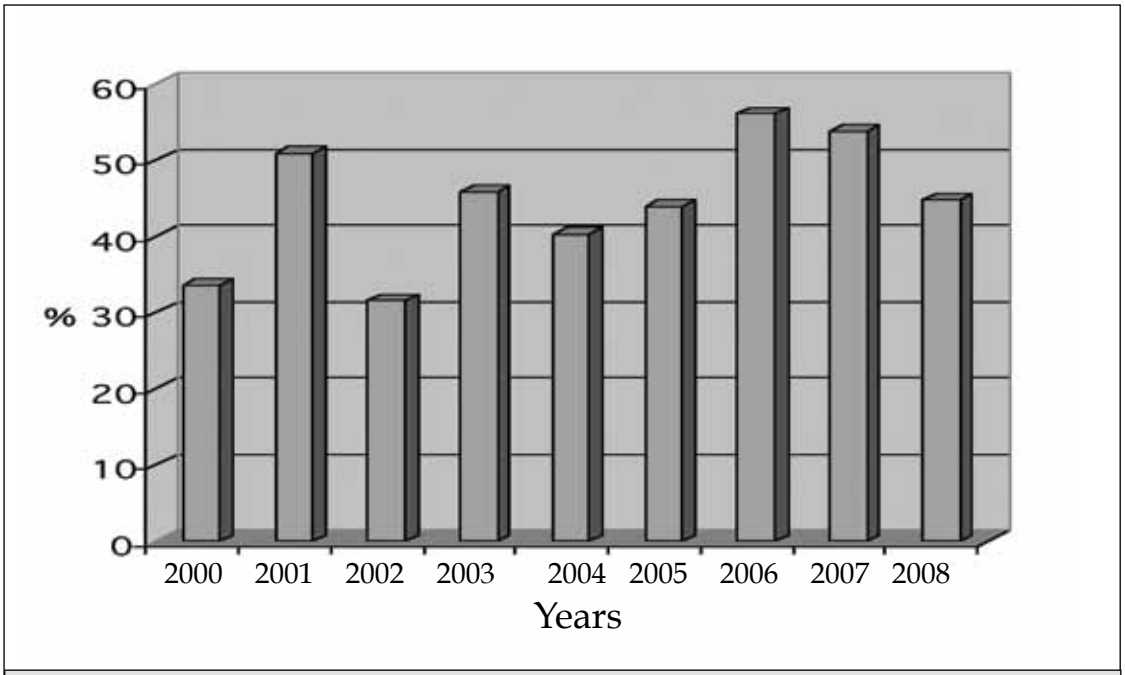

Figure 2. Percentage of methadone-treated illicit drug users out of all illicit drug users in prison, 2000-2008, Slovenia (Source: Prison Administration of the RS)

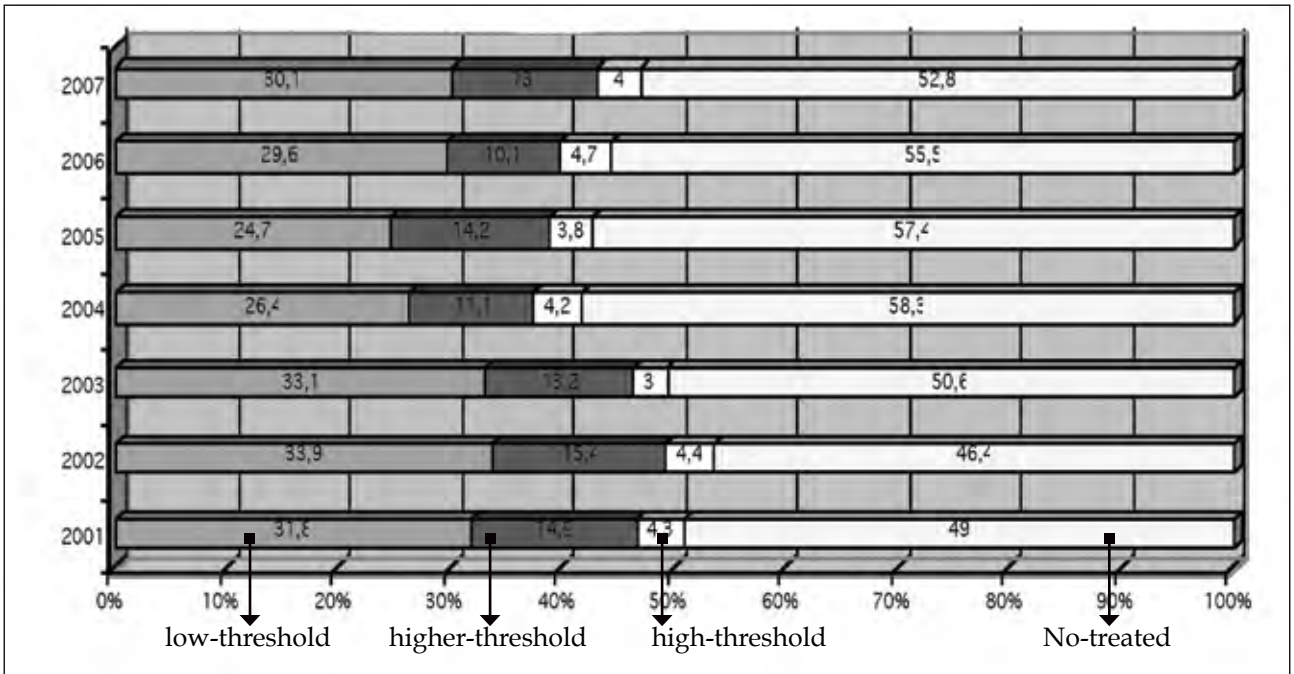

Figure 3. The proportion of different treatments (low-threshold, higher-threshold, high-threshold) among subjects in treatment for illicit drug users and the proportion of non-treated subjects, 2001-2007, Slovenia (Source: Prison Administration of the RS)

test proved to be positive, the methadone therapy was gradually suppressed (6). Those who were abstinent from drugs during their time in prison and were interested in taking part in outdoor treatment programmes offered by the health institutions and NGOs were allowed to do so. In 2008, 35 inmates decided in favour of this kind of treatment. After their imprisonment 48 people

went on with their treatment.

In 2008, methadone substitution treatment continued to be performed by the health services that were operative in prison, in co-operation with medical doctors from regional CPTDAs; 44.8% of heroin addicts in jail were treated with methadone. In addition, 46.8% (N=370) of heroin addicts out of all 790 newly imprisoned individuals had had methadone treatment prescribed before their imprisonment (8).

Data from the Prison Administration of the Republic of Slovenia reveal that interventions in prisons can (according to that Administration) be divided into low-threshold (including substitution treatment with methadone), higher-threshold (therapeutic groups and work with individuals) and high-threshold (drug-free) cases. In the 2001-2007 period, the percentage of subjects without treatment was always higher than that of those treated, except for 2002. Among all the subjects who were treated, the approach most frequently used was the low-threshold one, followed by the higher-threshold one, whereas every year the high-threshold approach was the one showing the lowest percentage (Figure 3).

In the last few years, there has been a growing diversification of treatment in Slovenia, and the chances of finding proper pharmacological treatment for individual patients have improved significantly. It is well known that all the drugs prescribed are effective, but their tolerability differs. The official data issued by the Agency for Medical Products and Medical Devices in the Republic of Slovenia allow us to state that on March 1st, 2008, in the Slovenian drug market the following registered drugs for the medically assisted treatment of heroin addiction were available: methadone, buprenorphine, slow-release morphine, combination buprenorphine/naloxone and naltrexone. In spite of the diversities in pharmacological treatment, there are no data on the use of other opioid agonists in the jail system.

The number and the proportion of heroin addicts in prisons in Slovenia is rising, but it seems that requests for, and offers of, substitution treatment are failing to keep pace with the real need for treatment.. Heroin addiction is a specific conditions which should be treated as soon as possible, but that is not enough; it needs to be treated in the appropriate way. Treatment should be adapted to the patient's changing needs but without prejudice, certainly not in a punitive way.

Note 1

Individuals are liable to a monetary fine of between SIT 50,000 and SIT 150,000 or a prison sentence of up to 30 days for committing the offence of possessing illicit drugs in contravention of the provisions of this Act; Individuals are liable to a monetary fine of between SIT 10,000 and SIT 50,000 or a prison sentence of up to 5 days for committing the offence of possessing a smaller quantity of illicit drugs for one-off personal use. In accordance with the provisions of the Misdemeanours Act, people who commit the offence specified in the first paragraph of this article and who possess a smaller quantity of illicit drugs for one-off personal use and people who commit the offence specified in the preceding paragraph may be subject to more lenient punishment if they voluntarily enter the programme of treatment for illicit drug users or social security programmes approved by the Health Council or Council for Drugs.

Note 2

(1) Whoever unlawfully manufactures, processes, sells or offers for sale, or for the purpose of sale purchases, keeps or transports, or whoever serves as an agent in the sale or purchase of, or in any other way unlawfully places on the market, substances and preparations recognised to be narcotic drugs, shall be sentenced to imprisonment of not less than one and not more than ten years; (2) If the offence referred to in the preceding paragraph has been committed by several people who colluded with the intention of committing such offences, or if the perpetrator has established a network of dealers and middlemen, the perpetrator shall be sentenced to imprisonment of not less than three years; (3) Whoever without authorisation manufactures, purchases, possesses or furnishes other people with the equipment, material or substances which are, to his knowledge, intended for the manufacture of narcotics shall be sentenced to imprisonment of not less than six months and not more than five years.; (4) Narcotics and the means of their manufacture shall be seized

Note 3

(1) Whoever solicits another person to use narcotics or provides a person with such drugs to be used by him or by a third person, or whoever

provides a person with premises for the use of narcotics or in some other way enables another person to use narcotics shall be sentenced to imprisonment of not less than three months and not more than five years; (2) If the offence referred to in the preceding paragraph is committed against a minor or against several people, the perpetrator shall be sentenced to imprisonment of not less than one and not more than ten years; (3) Narcotics and the tools for their consumption shall be seized.

Note 4

Article 66 of the Penal Code of the Republic of Slovenia defines compulsory treatment for alcohol- and drug-addicted people. According to this law, the Court may order the provision of obligatory medical treatment. This provision can be provided in the institution where the sentence is being served (uninterruptedly, in prison) or in a health institution, while in the case of a suspended sentence medical treatment can be given while a patient's movements are unrestricted. For alcohol-related problems, under Article 66 of the Penal Code of the RS compulsory treatment is performed in a formally specified health institution, while for illicit drug-related problems the competent institution has not yet been formally defined. Instead of this, people requiring compulsory treatment for an illicit drug addiction can be treated.

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Clinical assessment of opiate induction: The Opiate Dosage Adequacy Scale Induction Form (O.D.A.S.-IF)

Francisco González-Saiz[1] and Mª Dolores Velo Camacho[2]

1 Psiquiatra. Unidad de Salud Mental Comunitaria (USMC). UGC Salud Mental Hospital de Jerez. Servicio Andaluz de Salud. Spain, EU
2 Médico Especialista en Adicciones. Centro Provincial de Drogodependencias. Sevilla. Spain, EU

TO THE EDITOR: The Opiate Dosage Adequacy Scale (ODAS) [5,4] is a brief semi-structured clinical interview comprising 10 items whose purpose is to clinically assess how adequate the methadone dose prescribed in the context of the patient's methadone maintenance program is to his or her individual needs. This instrument attempts to come close to the construct that we have called "methadone dose adequacy". Operationally, we interpret a methadone dose as being 'adequate' when the patient: a) uses no heroin or uses it only occasionally; b) does not experience continuous opiate withdrawal symptoms (OWS) or, if any, very mild ones; c) does not experience frequent episodes of craving for heroin, or any craving is very mild, d) in the event of heroin use, the patient does not experience its subjective effect, or any such effects are very mild ('narcotic blockade', opioid blockade or crossed tolerance); and e) he/she does not experience continuous symptoms of overmedication, or, if any, they are very mild. The ODAS has been designed to assess the degree of adequacy of the dose taken by the patient during the previous seven days or so. As a minimum, therefore, the patient has to continue on the same dose during this period to ensure that he has reached a steady state for that dose. The ODAS was originally developed to measure the adequacy of the methadone doses, but our experience also supports its application in treatment based on buprenorphine.

Although the scale was designed from the outset to assess the "adequacy" of a methadone dose, as referring to the last seven days, some clinicians and researchers might be interested to assess the degree of adjustment of the methadone dose administered during the early days of the induction process of this drug (proceeding day by day). With this goal in mind and, following the same theoretical construct as the original ODAS, we have introduced some changes in this clinical tool.

In particular, the new Opiate Dosage Adequacy Scale-Induction Form (ODAS-IF) consists of 6 items that assess the same symptoms as the original ODAS (i.e. "Consumption of heroin", "Narcotic blockade or crossed tolerance", "Objective Opiate Withdrawal Syndrome-OWS", "Subjective OWS", "Craving for heroin" and "Overmedication"), but the following changes have been made: a) the evaluation time for each item is now limited to the previous 24 hours, b)

Correspondence:Francisco González-Saiz, Avda. Libertad 48. Pinar Hondo. 11500-Puerto de Santa María. Cádiz, Spain, EU
E-mail: pacogonzalez@comcadiz.com; pacogonzalez62@hotmail.com

for obvious reasons, we have removed the items that assess the frequency of objective and subjective withdrawal symptoms, the craving and the overmedication (thus the items removed are 3a, 4a, 5a and 6a of the original ODAS), whereas c) the items that assess the intensity of those same four symptoms in the last 24 hours have been retained. Item 1, which measures the frequency of heroin use in the last 24 hours has been coded by applying a Likert-type score from 1 to 5, and items 2-6, which measure the severity of symptoms follow an analogic-visual scale that has the same range of scores. Card 1 is used to rate item 2, while Card 2 is used to rate items 3 to 6. ODAS-IF scores may be interpreted both quantitatively (dimensional model) and qualitatively (categorical model). First, they provide a total score which is the sum of the scores of each of the 6 items over a range of 6 to 30 points. The higher the total score, the more "adequate" the dose is. Second, a patient is considered to be taking the "adequate dose" when the 6 items in the ODAS-IF (scored following the procedure defined in "Dimensional scoring") get a score of 4 or 5. Those who fail to meet this condition are excluded from being classified as patients who are taking an "adequate dose".

We must stress the idea that the ODAS-IF is not a shortened version of the original ODAS. We continue to maintain the concept that the adequacy of a given dose of methadone should only be assessed once the steady-state has been reached for this dose, as measured by the original ODAS. However, as mentioned above, in some cases we need a daily measurement of the degree of adjustment of the methadone dose (ODAS-IF) that is conceptually consistent with the weekly measurement (ODAS). For example, we are currently interested in the temporal evolution of each of the elements included in the "adequacy" criterion during the first weeks of induction. This can be assessed by comparing the phases of induction of buprenorphine and methadone; the studies we have reviewed so far are not conclusive in this respect [1-3]. The first point that interests us is to know whether control over the craving was achieved before or after the opioid blockade (or 'narcotic blockade') during the series of successive increases of opioid doses, as well as knowing the relationship between both the mean doses on one hand, and the doses that came nearest to overmedication, on the other. It is probable that by increasing the doses of methadone, the therapeutic range is minor, and is possible that this range is not the same for methadone as it is for buprenorphine. Another issue, which is closely related to this one, is the desirability of achieving doses that are capable of bringing about an opioid blockade as early as possible during the induction phase. This intervention would both reduce the length of time during which the patient is taking doses below the therapeutic level and reduce the chances of the subsequent development of benzodiazepine abuse. Lastly, the ODAS-IF can be used for very specific purposes during the maintenance phase, i.e., after the induction period has begun. For example, in the UK a study is being carried out whose objective is to assess the impact of acute pharmacokinetic changes on the degree of adjustment of the dose of methadone. To find the best answers to some of these issues, it may be useful to combine the ODAS with the ODAS-IF clinical assessments.

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OPIATE DOSAGE ADEQUACY SCALE
INDUCTION FORM

(O.D.A.S. – I.F.)

Francisco González Saiz, M.D.
Psychiatrist

Unidad de Salud Mental Comunitaria Villamartín,
UGC Salud Mental Hospital de Jerez,
Servicio Andaluz de Salud,
Spain, EU.

1. ***Consumption of heroin***

During the last 24 hours, how often have you used heroin?

- *Have you used heroin on any occasion during the last 24 hours?*
- *If you have, how many times a day, on average, have you been using it?*

- No times during the last 24 hours: score of 5.
- Once during the last 24 hours: score of 4.
- Twice during the last 24 hours: score of 3.
- Three times during the last 24 hours: score of 2.
- Four or more times during the last 24 hours: score of 1.

>>> **Cut-off Point:** If the patient has not used heroin at any time during the last 24 hours, pass directly to question 3 (score 5 in questions 1 and 2).

2. ***Narcotic blockade or crossed tolerance***

How intense was the effect you felt from the dose or doses of heroin that you used during the last 24 hours days?

- *Your methadone dose during the last 24 hours was X milligrams per day. Have you felt the effect of the dose or doses of heroin that you used during the last 24 hours?*
- *How intense was its effect?*

- *Was the effect different from what you felt when you were not being treated with methadone?*
- *Was the effect different from when you were taking a bigger or smaller dose of methadone?*

Show Patient Card 1.

Score: __/ (The score for this item is obtained by inverting the figure selected by the patient on the analogue-visual scale of Card 1: e.g. when the value of 1 is selected on the Card, this is equivalent to a score of 5 for this item, and so on, for each of the other items).

3. ***Intensity of objective opiate withdrawal syndrome (OWS)***

Some people taking doses of methadone experience withdrawal symptoms such as: cramps and muscular pains, feeling your hair standing on end, a runny nose, wanting to cry, yawning, stomach cramps or diarrhoea, palpitations, sweating, and generally feeling bad. These are symptoms that other people you are with can generally see.

During the last 24 hours, how intense, on average, were the withdrawal symptoms you say you felt?

- *On the occasions when you felt these symptoms, how intense were they, on average?*

Show Patient Card 2.

Score: __/ (The score for this item is obtained by inverting the figure selected by the patient on the analogue-visual scale of Card 2: e.g. when the value of 2 is selected on the Card, this is equivalent to a score of 4 for this item, and so on, for each of the other items).

4. ***Intensity of subjective OWS***

Some people taking doses of methadone experience withdrawal symptoms such as anxiety, restlessness, irritability, difficulty in sleeping, tiredness, shivering, muscular aches, lack of appetite. These are symptoms that other people you are with generally cannot see.

During the last 24 hours, how intense, on average, were the withdrawal symptoms you say you felt?

- *On the occasions when you felt these symptoms, how intense were they, on average?*

Show Patient Card 2.

Score: __/ (The score for this item is obtained by inverting the figure selected by the patient on the analog-visual scale of Card 2: e.g. when the value of 5 is selected on the Card, this is equivalent to a score of 1 for this item, and so on, for each of the other items).

5. ***Intensity of craving for heroin***

During the last 24 hours, how intensely did you feel the need to use heroin, on average?

- *On those occasions when you wanted to take heroin, how intensely did you feel this need, on average?*

Show Patient Card 2.

Score: __/ (The score for this item is obtained by inverting the figure selected by the patient on the analogue-visual scale of Card 2: e.g. when the value of 4 is selected on the Card, this is equivalent to a score of 2 for this item, and so on, for each of the other items).

6. ***Intensity of overmedication***

Some people who take doses of methadone experience symptoms such as feeling sleepy or sedated, difficulty in speaking, being unusually active or, alternatively, the sensation of "being drugged".

(Ask the patient specifically if they felt they had these symptoms about 3 hours or more after having taken their dose of methadone)

During the last 24 hours, how intense, on average, were the symptoms you say you had, in answer to the last question?

- *On the occasions when you had those symptoms, how intense were they, on average?*

Show Patient Card 2.

Score: __/ (The score for this item is obtained by inverting the figure selected by the patient on the analogue-visual scale of Card 2: e.g. when the value of 1 is selected on the Card, this is equivalent to a score of 5 for this item, and so on, for each of the other items).

ODAS-IF ANNEXES

CARD 1:
On this scale from 1 to 5, indicate how you perceived or felt the effect of that dose of heroin
(or: those doses of heroin).

It had no effect at all on me — The effect was extremely intense

1 2 3 4 5

CARD 2:
On this scale from 1 to 5, indicate the degree of intensity you felt.

Nothing at all — Extremely intense

1 2 3 4 5

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