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AU-CNS

Association for the Application of Neuroscientific Knowledge to Social Aims (AU-CNS)
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Being instituted in Viareggio in 1994, AU-CNS is as a no-profit association aiming to promote the spreading of scientific knowledge and its application upon issues of mental illness and substance abuse. AU-CNS is involved into research and teaching activities, and the organization of seminars, conferences and public debates with either scientific or popular audience targets. Among these, the most remarkable are the National Conference of Addictive Diseases, taking place in Italy every two years, The European Opiate Addiction Treatment Association Conference taking place in different European towns every two years, and a Europad satellite meeting within the American Opioid Treatment Association Conference (AATOD) in the USA, every 18 months. AU-CNS directly cooperates with national and international associations on the basis of common purposes and fields of interests, and runs an editing activity comprising psychiatry and substance abuse textbooks, and the official magazine of Europad-Wftod "Heroin Addiction and Related Clinical Problems".

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EUROPAD (formerly EUMA) was founded in Geneva (Switzerland) on September 26, 1994. It is, and shall remain, independent of political parties and of any government. EUROPAD exists to improve the lives of opiate misusers and their families and to reduce the impact of illicit drug use on society as a whole. The Association works to develop opiate addiction treatment in Europe but also aims to make a major contribution to the knowledge of, and attitudes to, addiction treatment worldwide. EUROPAD aims to (a) promote the development and acceptance of Agonist Opioid Therapy, (b) encourage collaborative research into effective addiction treatment, (c) provide a forum for the communication of research results and best practice, d) encourage contact between individuals and groups within treatment services, (e) co-operate in the development of effective public policy.

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World Federation for the Treatment of Opiod Dependence (WFTOD)
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The World Federation for the Treatment of Opioid Dependence (WFTOD) officially started during the EUROPAD conference Ljubljana, Slovenia during July 2007. EUROPAD and AATOD have worked together since the AATOD conferences of 1989 in Newport, Rhode Island. EUROPAD conducted a major panel presentation from a number of its member nations for the conference participants. EUROPAD and AATOD have exchanged such collegial presentations at all of the AATOD and EUROPAD meetings since that date, creating the foundation for the working relationship, which led to the development of the WFTOD. EUROPAD and AATOD also worked together in filing an application to the NGO branch of DESA during 2010. The application was accepted on February 18, 2011 during the regular session of the Committee on Non-Governmental Organizations to the U.N. Department of Economic and Social Affairs (DESA). In the regular session held on July 25, 2011, the Economic and Social Council of the United Nations granted Special Consultative Status to the WFTOD.

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Foreword — EQUATOR publication series

Icro Maremmani

Editor in Chief

Opioid dependence is recognised as a chronic disease that affects an estimated 21 million people worldwide. Based on published literature, it is clear that the human and economic cost of opioid dependence to society is substantial. Opioid-dependent individuals have a higher mortality and morbidity rate than their non-dependent counterparts, carry a higher risk of blood–borne viruses, are more likely to take part in criminal activities, and have a lower quality of life and social functioning. Society as a whole is burdened by the high costs of crime, healthcare and lost productivity associated with opioid dependence.

Importantly, opioid dependence is a treatable condition. The negative consequences of opioid dependence can be substantially and cost-effectively reduced by ensuring opioid-dependent individuals have access to high-quality, evidence-based treatment interventions, including opioid maintenance treatment (OMT) in conjunction with psychosocial support. However, success is not guaranteed by simply providing access to treatment, but rather depends heavily on how treatment is delivered. It is important to note that there are significant differences in the structure and process of treatment delivery across national borders. Moreover, some aspects of treatment delivery processes can have significant unintended consequences that impact negatively on patients. If opioid dependence is to be managed optimally, it is vital that the impact of the structure and process of treatment on outcomes is well understood. In this regard, real-world evidence is crucial in helping to understand the current challenges and barriers to achieving optimal outcomes, thereby leading to a more robust discussion of the changes that can be made to overcome these barriers.

In the current issue of Heroin Addiction and Related Clinical Problems, there are five articles reporting findings from the European Quality Audit of Opioid Treatment (EQUATOR), a multinational project involving the combined analysis of survey data from over 3000 participants (including opioid-dependent individuals and treating physicians) across 10 European countries. Authored by some of the leaders in the field of opioid-dependence treatment, these articles provide an overview of the demographic profile of patients, out-of-treatment users and treating physicians involved in OMT in Europe, the quality of care provided, and the current state of public-health-related outcomes. These data will help the treatment community to identify barriers to success that currently exist within our national treatment systems. Detailed information on the methods of EQUATOR

has been published previously (2).

EQUATOR provides a timely snapshot of current treatment practices across Europe from the perspectives of opioid-dependent individuals (both in and out of treatment) and the physicians who treat them. Key findings from EQUATOR highlight important questions, for example:

- Are opioid users staying out of treatment because they find the conditions and control measures of treatment too restrictive on their daily lives?
- Do demographic profiles of patients and users vary across European countries?
- Is there variation in access to treatment and quality of care across European countries, such as access to available medications and/or psychosocial support?
- Across Europe, do models of care differ more substantially for opioid dependence than for other chronic diseases?
- Why do the number of prior treatment episodes vary across Europe?
- To what extent do patients receiving OMT continue to use heroin, other illicit drugs and non-prescribed medications in different countries?
- To what extent do untreated opioid users report regularly using or abusing diverted opioid pharmacotherapies?
- How often are opioid users entering prison for drug-related offences?

Considered in conjunction with existing evidence, the findings of EQUATOR provide grounds on which to question whether current treatment approaches are achieving the desired outcomes. For several of the key markers of treatment success, such as rates of ongoing drug use, misuse or diversion of opioid medications, and levels of reintegration (e.g., employment), the EQUATOR analysis reveals evidence of significant variation across countries and between types of intervention. These observations may provide insight as to whether current treatment systems are successfully achieving the basic harm-reduction goals and/or setting patients up for recovery.

Crucially, this evidence base emerges at a time when the outcomes expected of treatment for opioid dependence are being actively reconsidered by treatment professionals, policymakers, and the EU Commission. In several international settings, policies on treatment of opioid dependence are building on the success of *harm reduction* and moving towards a more ambitious vision of *rehabilitation and recovery*, which, according to the European Monitoring Centre for Drugs and Drug Addiction, encompasses abstinence or stabilisation of drug use, physical and mental health, personal relationships and social reintegration (1). In this context, insights derived from the EQUATOR analysis and similar studies may help to inform policy making around the desired structure, process and outcomes of the treatment system necessary to achieve the desired state of recovery.

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The profile of patients, out-of-treatment users and treating physicians involved in opioid maintenance treatment in Europe

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Summary

Opioid users often cycle in and out of opioid maintenance treatment (OMT), consistent with opioid dependence being a chronic, relapsing condition. Results from the European Quality Audit of Opioid Treatment (EQUATOR), the largest analysis of OMT undertaken in Europe to date, revealed similar demographic profiles for patients in OMT and out-of-treatment opioid users (most of whom have been in OMT previously). Demographic profiles appeared relatively consistent across all 10 participating countries. Overall, EQUATOR data suggest that the healthcare setting for OMT is far more varied than the demographics of the OMT patient population, supporting the idea that variability in treatment outcomes is unlikely to be related to the clinical characteristics of patients but rather to other 'environmental' factors.

Key Words: OMT patient demographics, out-of-treatment opioid user demographics, treating physician demographics

1.   Introduction

1.1. Treatment of opioid dependence in Europe

Opioid dependence is recognised by the major global health organisations, including the World Health Organization (WHO) and United Nations Office on Drugs and Crime (UNODC), as a chronic relapsing brain disorder, for which the most effective intervention is opioid maintenance treatment (OMT) combined with psychosocial therapy (23). Although this treatment approach is generally supported all across Europe, many specific aspects of treatment provision differ across national boundaries. For example, variations exist between countries with respect to the level of access to treatment (both in the community and in prisons), medication options available to patients, whether doses of medications are individualised or standardised, whether psychosocial counselling is mandatory or even available, the use of control measures such as supervised dosing, and the availability of treatment guidelines and physician training. Even the predominant setting of treatment differs between countries, with some (e.g., Greece, Italy, Spain, Portugal, Norway) preferring management in specialist clinics and others (e.g., France) delivering OMT within the normal primary care setting. Other countries, such as Germany and the UK, have a hybrid model combining primary care and a specialised setting.

The implications of such variability in opioid dependence management remain unclear. Previous

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literature suggests that patient populations in different European countries are relatively similar demographically (7) and that treatment variation is therefore probably due to system-level factors such as treatment goals, policy and structure rather than patient variables. How treatment is structured, organised and delivered may be influenced by political objectives, religious and cultural values, financial considerations, available resources, public attitudes and stigma toward addiction (3), all of which vary widely across Europe.

This variability in treatment approaches distinguishes OMT from the treatment of other chronic diseases (e.g., diabetes, hypertension) which typically have a more consistent pattern of treatment delivery (13,15).

1.2. Existing data on OMT patients across Europe

In Europe, comparative data on characteristics of patients receiving OMT in different countries are limited. Large national studies or surveys have only been conducted in a few countries, including Germany (COBRA and PREMOS; (21), Spain (PROTEUS; (18)) and the UK (NTORS and DTORS (9,11)). These are difficult to compare as they were conducted over different periods of time, using different methodologies and research instruments, and had different goals. The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) systematically collects information on substance abuse from local focal points on an annual basis, but does not collect patient-level data (4,7). Therefore, it could prove valuable to collect and assess a snapshot of data from patients on a multinational basis using a common methodology.

1.3. Existing data on out-of-treatment users across Europe

In order to develop strategies that engage as many opioid users in treatment as possible, it is important to understand this challenging population. The chronic relapsing nature of opioid dependence suggests that they are likely to have previously been engaged in treatment. However, data for out-of-treatment opioid users are even more limited than data for patients receiving OMT, and this group are typically under-represented in studies of opioid dependence. A contributing factor may be difficulty in recruitment, as out-of-treatment users are less likely than OMT patients to be in contact with sites of recruitment such

as services providing support to drug-dependent individuals, and/or the difficulty in gathering reliable information from a population that is still actively using drugs.

1.4. The relevance of demographic data in relation to treatment planning and goals

Demographic data may be important for understanding the real-life circumstances and potential clinical needs of the target population for OMT. The new focus on 'recovery' in some national drug policies (e.g., the UK) (10) places great emphasis on helping patients not only to reduce their drug use but also to build and exploit their own social, physical, financial and cultural resources to sustain their recovery and reintegrate into society (1). It is therefore useful to understand the educational, marital, employment status and other demographic characteristics of those who are in or out of treatment in order to assess their ability to achieve these goals. It is also useful to understand the true characteristics of opioid-dependent patients and users in order to challenge common stereotypes and stigma often linked to current and former drug users.

1.5. Characterising the treating physician population

Understanding who treats opioid dependence is critical if we are to identify factors that may influence treatment outcomes. For example, in Germany, the number of actively prescribing physicians has barely increased for nearly a decade (19), while the number of patients increased by 50% between 2002 and 2007 (16). Thus, a situation is arising whereby ageing prescribers are retiring and are not being replaced, leading to potential shortfalls in physicians willing and available to treat opioid dependence. Factors such as cumbersome bureaucracy, low reimbursement or the requirement for additional specialised training may discourage physicians from providing care for opioid-dependent patients. In Germany, physicians wishing to prescribe opioid-dependence treatment must complete a 50-hour course in addiction medicine before being allowed to prescribe, which may be a disincentive for some physicians.

It is informative to consider the setting in which physicians work. Some countries, such as France, have embraced 'office-based' or GP-based prescribing as a strategy for maximising accessibility of treatment. The option of being treated in a primary care

setting, in addition to making use of existing health-care infrastructure, may be particularly favourable for patients who have difficulties accessing specialised clinics for logistical reasons or because of the stigma often associated with these settings. In countries such as Italy and Portugal, pharmacological treatment of opioid dependence has been delivered almost entirely in publicly funded addiction clinics *(Servizi Tossicodipendenze [SerTs], Instituto da Droga e da Toxicodependência [IDT, IP]).* The specialist clinic model can be useful in concentrating resources and expertise (particularly for treating commonly comorbid disorders or more complex cases), but patients' resolve to change their social circles may be tested by the opportunity to interact with other patients. To this extent, the specialist clinic model could contribute to stigmatisation and marginalisation of patients, potentially discouraging opioid users from seeking access to OMT and thereby limiting the total benefit of treatment. Conversely, it can be harder to provide integrated care including psychosocial counselling in the primary care setting, and often primary care physicians have little or no training in addiction medicine.

It is important to evaluate the characteristics of the treating physician population and the settings in which they practice in order to identify patterns of care that may affect treatment outcomes and unmet needs that could potentially be fulfilled.

1.6. EQUATOR Analysis

The European Quality Audit of Opioid Treatment (EQUATOR) analysis was designed to provide an overview of the current state of opioid treatment provision in Europe from the perspective of opioid users not currently receiving OMT, opioid-dependent patients currently receiving OMT, and the physicians who treat opioid-dependent patients. The output from EQUATOR complements existing datasets by providing individual-level data which form a snapshot of who receives and prescribes OMT across 10 European countries. This is the first time that individual-level data from so many different treatment systems have been compared within a single methodological framework.

This article examines the demographic profiles of the patient, user and physician populations associated with opioid use in Europe. Using a common methodology across 10 countries, as described previously (8), the EQUATOR analysis enables us to highlight whether there are demographic differences in the target patient and user populations, whether these populations differ across national borders and whether there are differences in the profile of those physicians responsible for providing treatment.

2. Methods

Detailed methodology of the EQUATOR analysis has been described previously (8). Briefly, questionnaires were compiled comprising a core set of questions specific for three target groups: opioid users not currently in OMT (50 questions per survey), opioid-dependent patients currently in OMT (50 questions per survey), and physicians involved in the treatment of opioid-dependent patients (60 questions per survey).

Data were collected in each country in accordance with the European Pharmaceutical Market Research Association (EphMRA) code of conduct and the Declaration of Helsinki. This article presents data on sample sizes and patient/user/physician demographics (age, sex, marital status, education level, employment and previous OMT episodes for patients and users; age, sex, medical specialty and practice setting for physicians). Additional background information on patients and users is presented in subsequent articles in the EQUATOR series of publications, including information regarding health status and prison history, which is discussed as part of a broader consideration of treatment outcomes and public-health consequences of opioid dependence (see article by Stöver in this issue).

Data are presented as frequencies or means for the purposes of comparisons between patients and users, and across countries. Statistical comparisons were performed on categorical data by Pearson's chi-square, using standardised residuals to identify individual instances of significant variation of proportion. For linear data, analysis of variance (ANOVA) was used for comparisons and post-hoc tests (Tukey's) were performed to identify any significant country interactions. Significance was ascribed for $p \leq 0.05$.

3. Results

3.1. Sample size

A total of 3888 people were recruited and included in the EQUATOR analysis, including 703 physicians, 2298 patients and 887 out-of-treatment opioid users (Table 1).

Table 1. Sample size by country.

Country	Patients (currently in treatment)	Users (currently out of treatment)	Physicians
Austria	228	50	77
Denmark	103	27	32
France	130	33	100
Germany	200	200	101
Greece	601	150	24
Italy	378	0*	100
Norway	98	70	49
Portugal	160	50	60
Sweden	152	111	60
UK	248	196	100
Total	2298	887	703

*In Italy, there was no sample of opioid users out of treatment owing to legal constraints on surveying this population

3.2. OMT patients and out-of-treatment opioid users

Demographic data for OMT patients and out-of-treatment users were compared across a number of parameters, including age, sex, education level and marital status, both across Europe and between individual countries. Owing to the large sample size, statistically significant differences were observed between OMT patients and out-of-treatment users in some of these parameters (see below). However, these differences were generally small in magnitude and OMT patients and out-of-treatment users appeared largely similar with regard to demographics. Specific differences between these populations are highlighted in the following sections.

3.2.1. Age distribution

There were differences in the mean age of OMT patients and out-of-treatment opioid users across Europe. The mean age of patients across Europe was 36.5 years, ranging from an average of 31.9 years in Austria to 43.8 years in Denmark, whereas the mean age of out-of-treatment users was 34.6 years, ranging from 26.1 years in Austria to 43.1 years in Sweden (Figure 1).

Similarly, the mean age of patients entering treatment for opioid dependence in the EMCDDA dataset was 34.1 years; neither mean age of patients entering treatment for opioid dependence in individual countries nor mean age of users were reported separately, preventing comparison with EQUATOR

data (7). The mean age of patients in the EQUATOR analysis is also similar to the mean age reported in the German COBRA study (34.8 years (21)) and in the PREMOS study (35 years (22)). The mean age reported in the PROTEUS study in Spain, a country currently not included in the EQUATOR analysis, was 39 years for patients receiving OMT (18), which is within the range of values reported for the countries participating in EQUATOR.

The age distribution of patients in the EQUATOR analysis is similar to the age distribution reported by the EMCDDA for patients receiving OMT in Europe (Figure 2; (7)). In the UK DTORS study, which used different age-distribution categories to those in EQUATOR or the EMCDDA study, 72% of those seeking OMT treatment were aged between 25 and 44 years (45% were 25–34 years; 27% were 35–44 years, 7% were ≥45 years) (12).

3.2.2. Sex distribution

Across the ten European countries included in the analysis, no difference in sex distribution (i.e. proportion of male participants) was observed between OMT patients and out-of-treatment users (χ^2=0.73, df=1, n=3155, NS). Overall, most participants were male (74.6% of patients and 76.1% of users; Figure 3). This distribution was also seen in individual countries, where there were consistently more men among both the patient (range 66–82%) and user (range 62–88%) samples. However, for the combined patient and user group, there were differences in gender distribution between countries (χ^2=30.19, df=9, n=3155,
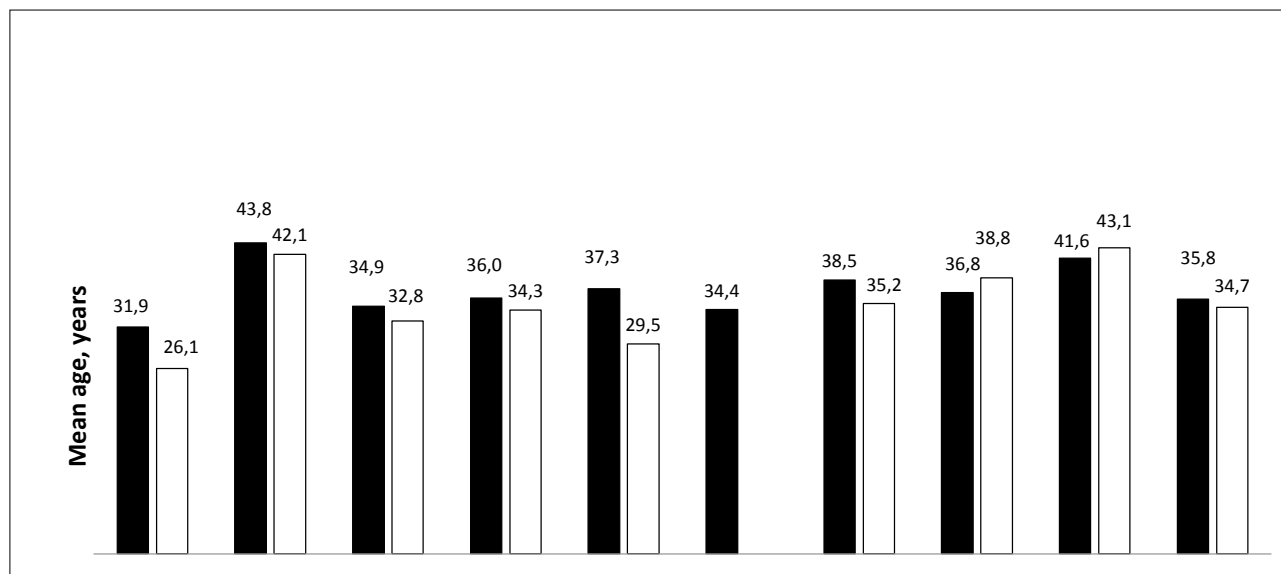
Figure 1. Age distribution of OMT patients and out-of-treatment opioid users in 10 European countries. *Users were not surveyed in Italy

p<0.01); Germany and Austria had proportionally fewer male participants than other countries included in the analysis.

There was no significant statistical interaction between patients/users and country with regard to the gender of participants. With the exception of Denmark, the proportion of patients *versus* users who were male differed by less than 10%. Overall, the most equal proportions of male and female OMT patients were in Austria and Germany, and the most

equal proportions of male and female users were in Denmark and Germany (Figure 3).

The overall sex distribution of patients observed in the EQUATOR study (74.6% male, n=2277) is broadly similar to the sex distribution of opioid-dependent patients observed by the EMCDDA (79% male, based on EMCDDA data from countries taking part in EQUATOR) (7). Similarly, 84% of OMT patients in the PROTEUS study in Spain (18), 73% of OMT treatment seekers in the DTORS study in the
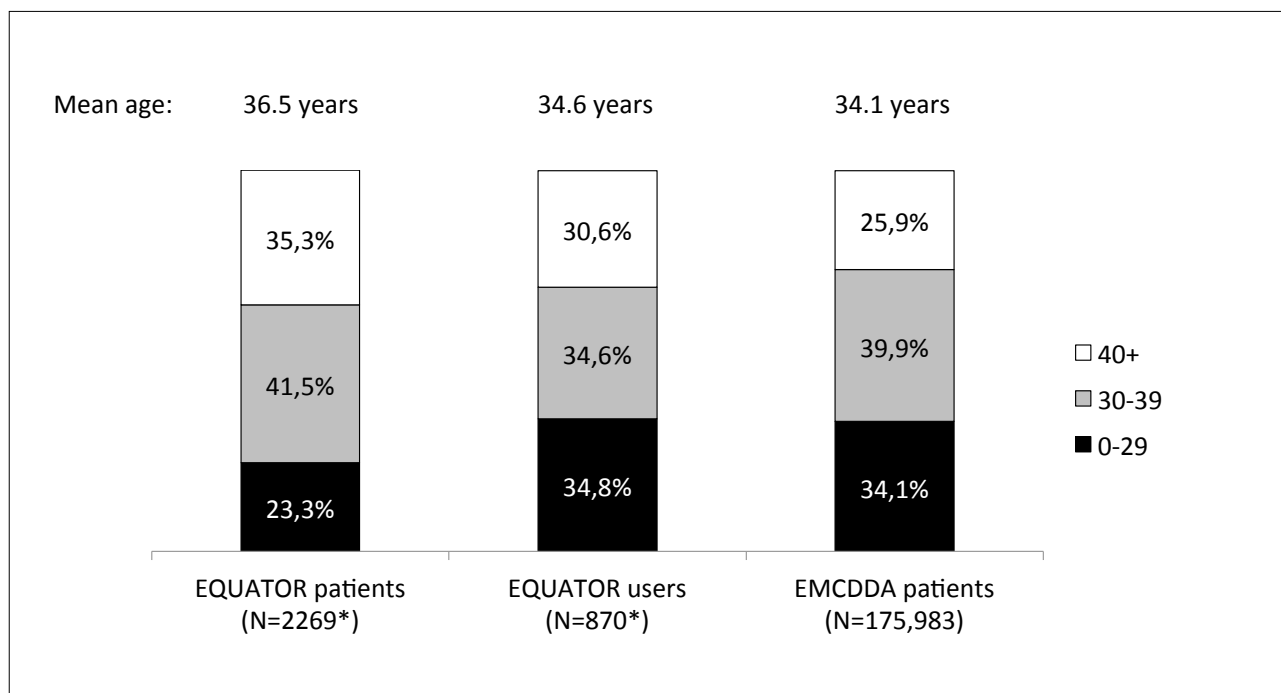
Figure 2. Comparison of age distributions reported in EQUATOR (OMT patients and out-of-treatment opioid users) and EMCDDA (EU patients entering treatment for opioid as primary drug (7)) studies.
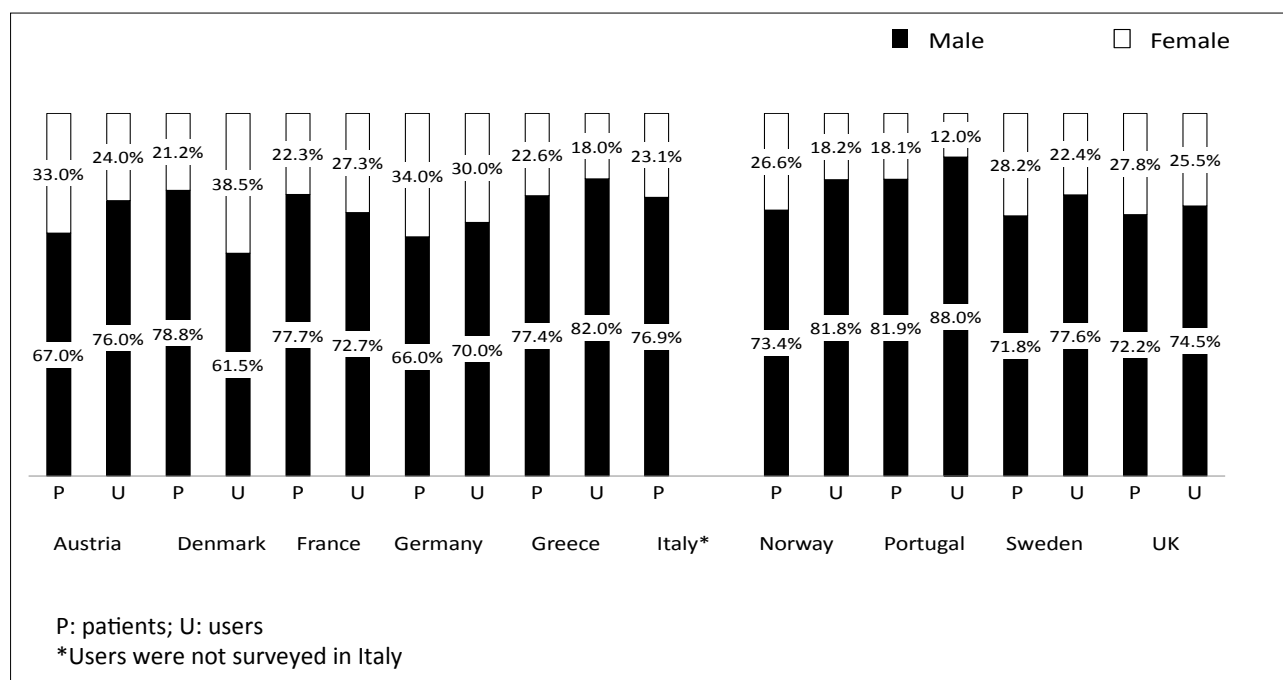
Figure 3. Sex distribution of OMT patients and out-of-treatment opioid users in 10 European countries.

UK (12) and 68% of patients in the German PRE-MOS study were male (22).

3.2.3. Educational level

There were significant differences in reported educational levels between OMT patients and out-of-treatment opioid users as well as between countries (χ^2=7.24, df=1, n=2899, p<0.01) (Table 2). Most patients and users were educated to secondary school level or lower; 42.3% of patients had no secondary school qualifications compared with 33.9% of out-of-treatment users, and approximately 30% of patients and users had secondary school qualifications or equivalent.

There was significant variation between countries in the level of education attained by patients and users (χ^2=581.54, df=9, n=2899, p<0.01). The proportion of patients and users with no secondary school education ranged from 6.6% (patients) and 6.0% (users) in Austria to 87.5% (patients) and 84.0% (users) in Portugal. Only a small percentage of patients and users in the UK (1.2% of patients; 1.5% of users) and Norway (5.1% of patients; 10.0% of users) reported that they had a graduate or professional degree. In Greece, users reported a greater likelihood than patients of having secondary school or equivalent-level education (56.2% of patients *versus* 87.3% of users) and in France, more patients than users reported having some degree of college education (10.8% of patients *versus* 0.0% of users).

Although the data on education level collected

by the EMCDDA are not directly comparable with data from EQUATOR, they are consistent in showing that the majority of outpatients and inpatients entering outpatient treatment for drug use (not only opioid use) had a secondary or lower level of education in Austria, Denmark, France, Germany, Greece, Italy, Portugal and Sweden (7). No equivalent EMCDDA data were available for the UK or Norway.

In Spain, the PROTEUS study also showed that the majority of OMT patients had a secondary school or lower level of education (62.4% had only primary education (18)), and in the UK, the DTORS study reported that 38% of OMT treatment seekers had left school before the age of 16, with 49% having left school at age 16 or 17 (12).

3.2.4. Marital status

There were significant differences in marital status between OMT patients and out-of-treatment users across Europe (χ^2=12.40, df=2, n=3149, p<0.01) (Table 2), although these differences were small in magnitude. The majority of participants (61.0% of users and 54.0% of patients) were single. Of the remainder, 30.3% of patients and 25.9% of users were married or cohabiting, and 14.4% of patients and 12.1% of users were divorced or widowed.

There was more between-country variation in marital status for users than for patients (χ^2=135.93, df=18, n=3149, p<0.01). The proportion of single patients ranged from 48.1% in Portugal to 62.1% in Denmark, whereas the proportion of single users

Table 2. Level of education and marital status of OMT patients and out-of-treatment opioid users in 10 European countries and the European sample

	% of patients (P) and out-of-treatment users (U)																						
	Europe		Austria		Denmark		France		Germany		Greece		Italy			Norway		Portugal		Sweden		UK	
	P	U	P	U	P	U	P	U	P	U	P	U	P	U*		P	U	P	U	P	U	P	U
Sample size	2298	887	228	50	103	27	130	33	200	200	601	150	378	0		98	70	160	50	152	111	248	196
Educational level																							
No high school	42.3	33.9	6.6	6.0	56.3	44.4	29.2	33.3	59.0	61.5	39.8	10.0	54.2			6.1	7.1	87.5	84.0	35.5	23.4	39.5	32.7
High school or equivalent	30.9	29.7	41.7	44.0	5.8	11.1	30.0	42.4	6.5	7.5	56.2	87.3	27.0			32.7	27.1	11.3	14.0	40.1	45.0	2.4	1.0
Vocational	9.5	10.4	46.5	42.0	13.6	14.8	26.2	21.2	0	0	0	0	0			33.7	30.0	0.6	2.0	7.2	7.2	8.1	15.3
Some college	6.7	8.9	0	0	18.4	18.5	10.8	0	29.5	29.5	0	0	12.2			6.1	8.6	0	0	5.9	8.1	0	0
College degree	3.8	2.6	3.1	8.0	1.9	3.7	3.1	3.0	4.0	1.0	4.0	2.7	5.0			12.2	11.4	0.6	0	3.3	0	2.4	1.5
Graduate/ professional degree	0.3	1.1	0	0	0	0	0	0	0	0	0	0	0			5.1	10.0	0	0	0	0	1.2	1.5
Marital status																							
Single	54.0	61.0	54.8	64.0	62.1	51.9	50.0	33.3	52.0	58.5	51.1	78.7	58.7			52.0	60.0	48.1	78.0	52.6	53.2	59.3	55.6
Cohabiting/ married	30.3	25.9	32.0	32.0	23.3	33.3	43.1	51.5	32.0	25.0	21.5	12.0	32.5			34.7	22.9	41.3	6.0	30.9	31.5	32.7	33.7
Divorced/ widowed	14.4	12.1	11.0	4.0	10.7	11.1	6.9	15.2	15.5	16.5	27.5	9.3	7.1			9.2	10.0	10.6	16.0	14.5	13.5	6.5	10.2

*Users were not surveyed in Italy
P= patients; U= users

Table 3. Age and sex distribution of physicians treating opioid-dependent patients in 10 European countries and Europe as a whole.

	Europe	Austria	Denmark	France	Germany	Greece	Italy	Norway	Portugal	Sweden	UK
Sample size	703	77	32	100	101	24	100	49	60	60	100
Mean age (years)	51.4	51.1	54.3	53.2	53.6	46.6	53.6	48.7	51.3	52.6	46.4
% men	69.7	66.2	50.0	82.0	78.2	62.5	69.0	71.4	51.7	70.0	70.0

ranged from 33.3% in France to 78.7% in Greece.

The percentages of patients in the COBRA and PREMOS studies who were single (55.9% and 54.8%, respectively) were comparable to the percentages in the EQUATOR analysis (21). In the DTORS study in the UK, a slightly higher percentage of OMT treatment seekers had a partner (38%) compared with equivalent data from the EQUATOR analysis; whether the remainder were divorced/widowed or single was not reported (12). EMCDDA data on the marital status of OMT patients are not available in a form that can be compared with these data.

3.3. Physicians treating opioid-dependent patients

3.3.1. Age and sex of physicians

The mean age of physicians treating opioid-dependent patients across Europe (mean 51.4 years) was significantly different between countries ($F=10.24$, df=9, 686, $p<0.01$), although the small variation in mean ages between countries suggests that this may not have practical implications. The UK reported the youngest physicians across Europe (mean age 46.4 years, SD=8.25), and these were significantly younger than physicians in all other countries (Tukey HSD post hoc, $p<0.01$ for each country) except Norway and Greece. Physicians treating opioid dependence in Denmark, who were the oldest in Europe (mean age 54.3 years, SD=9.47), were significantly older than equivalent physicians in the UK (Tukey HSD post hoc t=7.99, $p<0.01$) and Greece (Tukey HSD post hoc t=7.76, $p<0.01$) (Table 3). In Europe as a whole, 69.7% of surveyed physicians treating opioid-dependent patients were male. There were some differences between countries ($\chi^2=26.88$, df=1, n=703, $p<0.01$) in sex distribution, with Denmark and Portugal having significantly higher proportions of female physicians than other countries and France having a significantly lower proportion (Table 3).

3.3.2. Medical specialty

In the European sample as a whole, 58.9% of physicians treating opioid-dependent patients were GPs, 27.2% were psychiatrists, 6.4% were hospital house officers (HOs)/senior house officers (SHOs)/internists, 1.7% were neurologists, and 5.7% had other specialties (Table 4). The distribution of medical specialties of physicians in the sample varied between countries ($\chi^2=457.35$, df=36, n=698, $p<0.01$).

Physicians in Germany, UK, Sweden, France, Austria, Norway and Denmark were primarily GPs, but those in Greece and Portugal were primarily psychiatrists. In Italy, there was a mixed pattern of specialties involved in treatment of opioid-dependent patients (37.0% were psychiatrists, 24.0% were hospital HO/SHO/internists, 34.0% had other specialties, and a small minority were GPs or neurologists).

Consistent with the inclusion criteria, all physicians questioned were active prescribers of OMT at the time of the survey. A sample of accredited non-prescribers was included in the original German study (20) as well as a group of patients in Portugal receiving residential non-OMT-based care, but neither population was included in the EQUATOR analysis.

Physicians had been practising in their specialty for a mean of 18.1 years and prescribing OMT for a mean of 12.4 years. The number of years physicians had been practising in their specialty varied between countries (F=16.66, df=9, 702, p<0.001), as did years practising OMT (F=19.46, df=9, 693, p<0.01). Physicians in Italy had the most experience (23.5 years in the specialty and 18.7 years prescribing OMT), followed by physicians in France (22.7 years in the specialty and 13.7 years prescribing OMT), whereas physicians in Greece had the fewest years of experience (11.2 years in the specialty and 7.0 years prescribing OMT) (Figure 4).

3.3.3. *Practice setting*

Across Europe, 49.8% of physicians treating opioid-dependent patients were based in private practices, 31.9% were based in outpatient clinics, 15.5% were based in hospitals and only 1.8% were based in private practices that were specialised in addiction medicine (Table 4).

Across Europe, there were significant differences in practice settings of physicians treating opioid-dependent patients (χ^2 =861.18, df=36, n=703, p<0.01). Whereas the vast majority of physicians treating opioid-dependent patients in Italy, Greece, Portugal and Denmark were based in specialised outpatient clinics, the majority in Germany, the UK, France, Austria and Norway were based in private practices not specialised in addiction medicine. In Sweden, physicians treating opioid-dependent patients were primarily based in hospitals.

Of those physicians treating opioid-dependent patients in private practice across Europe, 57.7% were in their own practice, 19.1% worked in a joint practice, and 23.1% worked in a group practice (Table 4). The proportions of group, joint and sole practices varied substantially between countries. In the UK, the majority of treating physicians worked in group practices, whereas in Austria, Germany and France the majority had their own practice. In Portugal and Italy, the number of private practice physicians responding to this question was very small, consistent with the
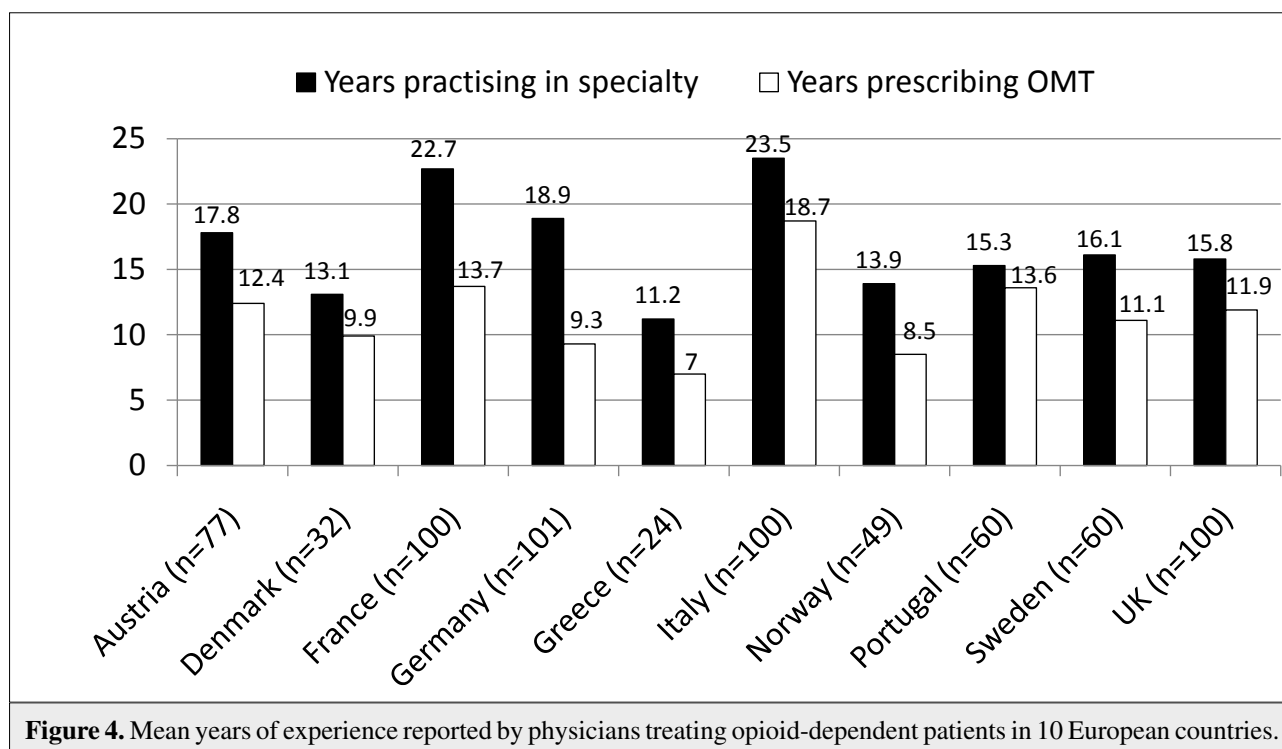
Figure 4. Mean years of experience reported by physicians treating opioid-dependent patients in 10 European countries.

Table 4. Distribution of medical specialties and practice settings of physicians treating opioid-dependent patients in 10 European countries and the European sample.

	Europe	Austria	Denmark	France	Germany	Greece	Italy	Norway	Portugal	Sweden	UK
Sample size	703	77	32	100	101	24	100	49	60	60	100
Medical specialty											
GP (%)	58.9	63.6	69.0	93.0	72.3	0	3.0	81.6	31.7	63.8	77.0
Neurologist (%)	1.7	1.3	0	0	3.0	0	2.0	2.0	0	5.2	2.0
Psychiatrist (%)	27.2	35.1	24.1	7.0	9.9	79.2	37.0	14.3	66.7	25.9	21.0
Hospital HO / SHO/ Internist (%)	6.4	0	6.9	0	8.9	20.8	24.0	2.0	1.7	5.2	0
Other (%)	5.7	0	0	0	5.9	0	34.0	0	0	0	0
Practice setting (Survey question: In what settings do you mainly work?)											
Private practice (%)	49.8	63.6	0	90.0	89.1	0	0	79.6	3.3	10.0	74.0
Private practice specialised in addiction medicine (>50 patients) (%)	1.8	0	0	2.0	5.9	0	3.0	0	0	0	2.0
Outpatient clinic (%)	31.9	16.9	87.5	0	4.0	100.0	97.0	2.0	81.7	1.7	7.0
Hospital (%)	15.5	19.5	12.5	5.0	1.0	0	0	18.4	8.3	88.3	17.0
Other (%)	1.0	0	0	3.0	0	0	0	0	6.7	0	0
For those in private practice (Survey question: Do you work in your own practice, joint practice, or group practice?)											
Private practice sample size	350	49	0	92	96	0	3	39	2	6	76
Own practice (%)	57.7	91.8	Not applic	64.0	75.5	Not applic	0	Not avail	50.0	Not avail	7.9
Joint practice (%)	19.1	8.2	Not applic	32.0	14.9	Not applic	0	Not avail	0	Not avail	15.8
Group practice (%)	23.1	0	Not applic	4.0	9.6	Not applic	100.0	Not avail	50.0	Not avail	76.3
Number of patients treated with OMT (Survey question: How many patients are you currently personally treating with substitution therapy?)											
Mean	56.4	60.9	183.6	19.0	45.8	Not avail	103.1	12.0	125.5	15.0	19.0

HO: House Officer; not applic: not applicable; not avail: not available ; SHO: Senior House Officer

clinic/institution-based model in these countries.

3.3.4. Number of opioid-dependent patients being treated per physician

The mean number of opioid-dependent patients being treated per physician in the European sample was 56.4 (N=703), but this number varied substantially between countries (F=54.53, df=8, 670, p<0.01), with low average numbers of OMT patients per physician in Norway (n=12.0), Sweden (n=15.0), the UK (n=19.0) and France (n=19.0) and high numbers in Denmark (n=183.6) and Portugal (n=125.5) (Table 4).

4. Discussion

4.1. The value of the EQUATOR dataset

The findings from EQUATOR presented in this article help to address important knowledge gaps regarding the profile of the target population of opioid-dependent patients, opioid users and the treating population of physicians involved in OMT across Europe. To our knowledge, EQUATOR is the largest multinational assessment of OMT participants and providers featuring a common methodology and individual-level data. The key strengths and limitations of our methodology have been described in detail previously (8).

The data on demographics of opioid-dependent individuals in EQUATOR are overall very similar to previous data from the EMCDDA (7) and from large national studies such as PROTEUS in Spain (18), DTORS in the UK (12) and PREMOS and CO-BRA in Germany (21,22), thereby suggesting that the EQUATOR sample is likely to be representative of the wider population of opioid-dependent individuals in Europe. Moreover, EQUATOR data are complementary to existing data from the EMCDDA; whereas EMCDDA data are typically collected at a top-down, system level by national focal points, EQUATOR provides a bottom-up perspective by directly assessing the experiences and attitudes of a sample of opioid-dependent individuals and physicians actively involved in treatment provision. Additionally, whereas there are many previous studies looking separately at OMT patients, opioid users or physicians involved in OMT provision, relatively few studies have assessed all three of these groups within a single framework.

4.2. Consistent demographics of patients and users

The demographics of OMT patients and out-of-treatment opioid users appear very similar for most outcomes, with remarkable consistency across 10 countries on some indicators. The large sample size means that significant differences were found that were frequently small in magnitude. Patients had a mean age of 36.5 years (approximately one third of patients were ≥40 years; sampled populations were slightly younger in Austria and older in Sweden and Denmark), most were male, and almost one third were married or cohabiting. The EQUATOR findings are consistent with opioid dependence being a chronic, relapsing condition (14), with dependent opioid users typically cycling through repeated treatment–relapse–treatment episodes. Data from EQUATOR may thus be considered as a snapshot in time, with an individual's category as a patient or a user depending on where they were in the cycle at the time of the survey. The mean number of previous treatment episodes for the countries across Europe was 1.8, (ranging from 0.22 episodes in Greece to 3.67 episodes in Denmark) prior to their current treatment, and patients were thus typically engaged in their third OMT episode on average at the time of the survey [see article by Fischer, Nava & Stöver in this issue]. The large variation in the number of previous treatment episodes between countries is greater than may be expected based on the relatively similar patient demographics in each country. Instead, this variation may be a result of differences between countries in how treatment is delivered, including variations in treatment models and quality of care. In this regard, numerous factors have the potential to impact on treatment–relapse cycling, including whether treatment occurs predominantly in the setting of specialist clinics or in doctors' surgeries, the process for selection of medication (e.g., making use of all the therapeutic options available), patient preference, patient awareness, ease of access to medication, availability of low-threshold programmes and medication prescribing versus integrated care. These topics are discussed in more detail elsewhere in this issue.

4.3. Implications of socio-demographic characteristics for treatment

The mean age of OMT patients (36.5 years) suggests that they are predominantly a population of long-term users, many of whom are approaching or

have reached middle age. Other evidence suggests a trend towards increasing age of OMT patients (4). Data have shown that nearly half of OMT patients reported first using opioids before the age of 20, and 88% first used opioids before the age of 30 (4). The average time lag between first use and entering treatment has been reported as 9 years (4). Age may thus represent an imprecise but relevant marker of how long someone has been opioid dependent and affected by the associated negative consequences (e.g., disease, imprisonment, overdose).

Many patients reported having had previous OMT episodes, suggesting they may be cycling in and out of treatment with consequent re-exposure to the harms of illicit opioid use to their mental health, physical health and social functioning. Notably, EM-CDDA data suggest opioid users entering treatment generally have lower rates of employment, lower levels of educational attainment and higher rates of psychiatric disorders than users of other drugs who enter treatment (4).

The socio-demographic characteristics of OMT patients may have implications in terms of the management of and expectations for treatment. For example, the fact that many patients have potentially experienced the negative consequences of periods of untreated opioid dependence multiple times may motivate them to seek treatment. Conversely, previous unsuccessful treatment episodes may discourage patients from accessing or lower their expectations of further treatment, particularly if the same treatment has been used unsuccessfully on multiple previous occasions. In addition, the psychiatric disorders that occur frequently in this population may make their treatment more of a challenge, as a result of their comorbidities or the limitations on their treatment posed by potential interactions with other medications they may be taking or need to take to treat their comorbid conditions.

4.4. Challenging stereotypes

Policymakers and members of society are sometimes prone to stereotypes of opioid users as being young, single, unemployed, homeless, engaged in criminal behaviour, and on the margins of 'normal' society. As a result, there can be a tendency to judge opioid users as morally flawed, with consequent problems of stigmatisation and marginalisation which often results in a more crime- and punishment-focussed attitude. However, the demographic profile of patients and users in EQUATOR challenges the stereotype of the typical opioid user.

EQUATOR data show that OMT patients and out-of-treatment opioid users were most likely to be long-term users above the age of 30, with a third of patients and a quarter of users married or cohabiting. Data from the DTORS study in the UK showed that 49% of OMT treatment seekers (58% female, 46% male) had children under the age of 16, although 74% of those lived apart from their children (12). As is reported elsewhere (see article by Stöver in this issue), rates of unemployment were high amongst OMT patients, but these rates varied substantially between countries (51.3% of OMT patients surveyed in Portugal, 47.7% in Italy and 35.9% in France reported being unemployed compared with 88.4% in the UK and 88.0% in Denmark). These data indicate that employment is not unrealistic for OMT patients under the right conditions (e.g., with appropriate medical and social support available), but that appropriate treatment systems need to be in place to achieve improvements in employment status. Thus, a strategy focused on recovery and improved employment readiness should be central to drug policy.

4.5. Profile of physicians who treat OMT patients

The EQUATOR analysis has enabled us to profile physician demographics across Europe and the treatment settings for OMT patients. Physicians treating OMT patients were predominantly men in their late forties or early fifties, with Denmark, Germany and Italy reporting the oldest population of physicians. In Germany, many of these physicians are believed to be nearing retirement and there does not appear to be a vast number of younger physicians to take their place. A potential future shortfall in OMT-prescribing physicians and loss of expertise may have negative consequences for access to and quality of care. This has the potential to result in a public health crisis reminiscent of the 1990s HIV epidemic if opioid-dependent individuals cannot access treatment.

Across the European country samples analysed here, more than 50% of surveyed physicians prescribing OMT were GPs and almost 50% were based in private practices. Overall, very few of these physicians classified their practice as private and specialised in addiction treatment. With such dependence on nonspecialist GPs for the routine treatment of opioid dependence across Europe, it is important that appropriate guidelines and training (including continuing medical education (CME)) are provided so that qual-

ity of care can be optimised and the potential benefits of improved availability and access to treatment outside a specialist centre can be reaped. An important consideration is the need to ensure appropriate linkages between different treatment services for patients treated outside specialist centres so that they can still access appropriate psychosocial support and other care, as required.

There was considerable variation in medical specialties of treating physicians and practice settings between countries, reflecting the structure of healthcare systems in each of the countries. In Greece and Portugal, physicians were primarily psychiatrists rather than GPs, while specialties were mixed in Italy. In Italy, Greece, Portugal and Denmark, OMT physicians were largely based in outpatient clinics, whereas in Germany, France, the UK, Austria and Norway the practice setting was primarily private practices not specialised in addiction medicine. In Sweden, most OMT physicians were based in hospitals. For physicians in private practice, the majority in the UK were in a group practice, whereas those in Austria, Germany and France were more likely to have their own practice.

Treatment models (e.g., GP-based vs specialist clinics) may impact on both access to care and quality of care. Specialist clinics may serve to focus expertise and resources appropriate for treatment of drug dependence but can also provide a barrier to access for patients who do not live nearby, or to users who will not access treatment due to stigmatisation (2,17). Whilst not necessarily offering the depth of treatment options and multidisciplinary expertise of specialist clinics, treatment delivery by GPs recognises opioid dependence as a chronic medical condition like diabetes or hypertension which can potentially be managed within the primary care setting if those physicians are given adequate training and support.

The expertise of physicians (GP vs psychiatrist or other specialist) and years of experience may lead to different approaches to treatment or indeed quality of care. Physicians in Italy had the most years of experience in the treatment of opioid dependence, whereas physicians in Greece had the fewest. OMT was introduced in Italy in 1975 (6), which may explain the considerable experience of physicians there; in contrast, OMT was only introduced in Greece in 1993 (5). Experience of physicians may impact on attitudes to OMT and supportive care, relative degree of specialist training and relevant knowledge, selection of available OMT pharmacotherapies, or access to other specialists and support staff.

Overall, EQUATOR data suggests that the healthcare setting for OMT is far more varied than the demographics of the OMT patient population, supporting the idea that variability in treatment outcomes may in part be due to non-clinical factors (e.g., treatment settings and structures) rather than the clinical characteristics of patients.

5. Conclusions

In conclusion, findings from the EQUATOR analysis described here suggest a fairly homogeneous target population for OMT between European countries. Most demographic variables assessed in this analysis were similar for OMT patients and out-of-treatment opioid users, and, as reported elsewhere in the EQUATOR analysis [see article by Fischer, Nava & Stöver in this issue], both groups had typically cycled through previous OMT episodes. The 'revolving door' phenomenon of treatment and relapse is consistent with our understanding of opioid dependence as a chronic relapsing disease, but variation in the rates of previous OMT episodes between countries cannot be explained simply by the nature of the condition and supports the hypothesis that aspects of treatment delivery, rather than variations in patient characteristics, may be major contributors to this pattern. If this is the case, there could be important lessons to learn regarding the strengths and limitations of various treatment systems (e.g., primary care vs specialised centre) across Europe, and their impact on patient outcomes and, consequently, on public health.

The appreciation that aspects of treatment delivery, rather than differences between opioid-dependent individuals themselves, may be contributing to treatment cycling raises several questions that need to be considered in order to establish the most appropriate treatment approaches for opioid dependence. Are current treatment systems delivering the desired outcomes? To what extent do factors related to the treatment setting and quality of care influence patient outcomes? Are there gaps in current models of care and barriers to quality of care? With the average time lag between first use of opioids and entering treatment reported to be 9 years (4), how could opioid-dependent individuals be motivated to enter OMT treatment earlier? Which, if any, aspects of current treatment systems require improvement? Can current systems deliver recovery or does the way treatment is provided need to change fundamentally? The articles that follow within this issue examine these questions in relation to treatment systems in different countries,

and provide an overview of current patterns in the management of opioid dependence across Europe.

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Quality of care provided to patients receiving Opioid Maintenance Treatment in Europe: Results from the EQUATOR analysis

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Summary

Patients receiving treatment for opioid dependence are prone to relapse into illicit drug use, risking significant harms to themselves and to society. The European Quality Audit of Opioid Treatment (EQUATOR) analysis assessed aspects of opioid maintenance treatment (OMT) delivery and the quality of care offered to patients undergoing OMT across 10 European countries. Findings suggest quality of care may be improved by: ensuring patients and physicians discuss the range of available treatment options, achieving the appropriate balance between control and patient flexibility, reducing the likelihood of misuse and diversion, and providing appropriate psychosocial care in conjunction with pharmacotherapy.

Key Words: diversion, misuse, psychosocial counselling, supervision, time on treatment.

1. Introduction

Opioid dependence can be a chronic, relapsing disorder which is associated with long-term changes to brain structure and function. Consequently, individuals with opioid dependence experience cravings which can occur long after their last use of opioids (4). One of the most effective treatment strategies involves opioid maintenance treatment (OMT) delivered in conjunction with psychosocial support (21). These interventions are aimed at reducing patients' use of opioids, with a longer-term goal of abstinence and recovery, although, in many cases patients cycle between treatment compliance and relapse. Heroin users can achieve recovery, however, and there is a growing evidence base and policy drive which recog-

nises this (10). It is critical to understand why treatment 'cycling' occurs if we are to achieve optimal treatment and patient recovery outcomes.

OMT has been shown to reduce opioid use and retain patients in treatment (14) until they can attempt abstinence; enforced withdrawal of OMT may lead to relapse and increase in drug-related harm including overdose (1,5). However, as demonstrated elsewhere in the European Quality Audit of Opioid Treatment (EQUATOR) analysis (see article by Goulão & Stöver in this issue), patients receiving OMT across Europe have similar demographics to opioid users who are out of treatment, and both groups show histories of repeated treatment and relapse. This cycling between treatment and relapse may be a consequence of the chronic, relapsing nature of opioid dependence

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and recovery. A similar 'revolving door' phenomenon has been documented for other long-term health conditions such as diabetes and chronic mental-health disorders (9,20). However, it is also possible that aspects of OMT delivery may contribute to variations in the quality of care, and, ultimately, to how likely it is that patients will repeatedly cycle through treatment (14,15). The EQUATOR analysis reveals indirect support for this hypothesis by demonstrating that the number of previous OMT episodes patients have undertaken shows significant variation between countries (see article by Fischer, Nava & Stöver in this issue).

Other articles in this series document important between-country differences relating to treatment, such as whether OMT occurs predominantly in the setting of specialist clinics or in doctors' surgeries. In addition to the care setting, there are many other important OMT delivery variables that may impact on treatment quality and retention, and several of these have been assessed in the EQUATOR analysis. These include: the role that patients and physicians play in selecting the OMT medication; whether patients are sufficiently aware of and informed about the range of available OMT options; patient satisfaction with their OMT; ease of access to care; and utilisation of psychosocial support in addition to pharmacotherapy.

1.1. Informed choice and access to different OMT options

An important consideration concerns the extent to which patients have information and access to a range of opioid medication and psychotherapeutic interventions, and whether these are used in an evidence-based fashion. The pharmacotherapy options, methadone, mono-buprenorphine, buprenorphine–naloxone and heroin (diacetylmorphine), have all been shown to be effective but have distinct pharmacological profiles with respect to safety and abuse liability (14,15,18,19).

National and international treatment guidance and regulations reinforce the importance of considering all available evidence-based options, taking into account the clinical needs of each patient (3,11,16,21). However, there are known to be major variations in treatment delivery across different countries, including the use of different OMT medications and the extent to which psychosocial and other support is an integral component of treatment. Rather than being due to differences in patient populations, these variations appear to reflect non-clinical factors including histor-

ical practices, national guidance, physician education and cost. Although system-level statistics regarding the relative use of different options are available for many European countries, there remains a need for individual-level data regarding medication awareness levels, preferences and satisfaction among patients and physicians.

1.2. Balancing access to OMT medication with control and supervision

It is important to consider the conditions under which access to available OMT medications is granted as this can impact on patient entry, retention and outcomes during treatment. In particular, a careful balance must be struck between the need for appropriate monitoring and controls, for example, to limit safety risks associated with initiation onto opioid medication (6) and harms related to misuse (injecting or snorting) or diversion (selling, swapping or giving away) of prescribed OMT medications, and the potential negative impact that strategies such as supervised dosing can have on patients. The way in which supervised dosing is managed and implemented, such as requirements for daily attendance at certain times, may present barriers to patients accessing or remaining in treatment, and may also interfere with efforts to reintegrate into society and obtain employment. The EQUATOR analysis has enabled a snapshot to be taken of current levels of daily supervised dosing, in addition to historic rates of misuse and diversion among OMT patients, as a means of informing efforts to achieve this optimal balance.

1.3. The importance of psychosocial support

Evidence demonstrates that better outcomes are generally achieved when pharmacotherapy is combined with psychosocial support; indeed, UK guidelines and German regulations state that treatment for drug misuse should always involve a psychosocial component (3,6). Elsewhere, while best-practice guidelines propose that psychosocial support should not be mandatory, they also state that it should be available to all opioid-dependent patients in association with pharmacological treatments (21). Indeed, given the complex nature of opioid dependence, widespread provision of medications without psychosocial assistance may constitute a lost opportunity to optimise care, maximise recovery and respond to the total needs of the patient (21). However, there are limited data at present to determine the extent to which pa-

tients are willing and able to access psychosocial support throughout Europe.

1.4. EQUATOR

Differences in the above treatment-delivery variables might be expected to have an impact on the acceptability and effectiveness of OMT and thus contribute to rates of cycling between treatment and relapse. If treatment systems fail to attract and retain patients until they gain sustained benefit, they are likely to fail in achieving the desired reductions in drug use, associated crime, injecting and other risk behaviour, and improvements in health and well-being may be limited. The current article presents results from the EQUATOR analysis pertaining to the quality of care and OMT delivery across Europe and addresses the following key questions: *'are patients making informed treatment choices based on the full range of opioid pharmacotherapy options available?'; 'to what extent are opioid pharmacotherapies delivered under supervised versus unsupervised conditions?'; 'how frequently do patients report having diverted or misused their OMT medication?'; 'how satisfied are patients with their OMT medications?';* and *'to what extent are opioid pharmacotherapies being delivered in conjunction with psychosocial support?'*

2. Methods

The methodology for the EQUATOR analysis has been described in detail previously (7). Briefly, questionnaires were compiled comprising a core set of questions specific for three target groups: physicians involved in the treatment of opioid-dependent patients (60 questions per survey), opioid-dependent patients currently in OMT (50 questions per survey), and opioid users not currently in OMT (50 questions per survey).

Outcomes on quality of care in OMT across ten countries in Europe were assessed by collating responses to questions regarding patient requests for, awareness of, use of, and satisfaction with, different OMT medications; levels of dosing supervision; OMT diversion and misuse; and utilisation of psychosocial support. The specific questions around different OMT medications that were posed to patients were as follows:

- *'Did you explicitly ask your substituting doctor for a certain drug?'*
- *'Did the doctor give you what you asked for?'*

- *'In your opinion, how well informed were you prior to beginning the treatment?'*
- *'Which of the following substitution medications had you heard of prior to beginning your therapy?'*
- *'Which substitution medication are you using for your current treatment?'*
- *'All in all, how satisfied are you with this substitution medication?'*

Physicians were asked:
- *'How often do your patients expressly request a specific substitution therapy preparation?'*
- *'And in which percentage of these cases, when a patient requests a specific preparation, do you follow the request?'*

Levels of dosing supervision were assessed by asking patients: *'Which of the following best describes where you take your substitution drug doses? 1) Every dose is under a doctor's supervision; 2) Every dose is under a pharmacist's supervision; 3) I am allowed take-home doses at weekends and/or holidays; or 4) I am allowed take-home doses not only at weekends and/or holidays, but more often'.* OMT diversion was assessed by asking patients: *'Have you ever sold or given your substitution medication to someone else?'* and misuse was assessed by asking patients: *'Have you ever injected or snorted your substitution drug?'.* Patients were asked: *'Are you currently receiving psychosocial counselling of any kind?',* and a definition of psychosocial counselling was provided relevant to each country in order to assess utilisation of psychosocial support.

Data were collected in each country in accordance with the European Pharmaceutical Market Research Association (EphMRA) code of conduct and the Declaration of Helsinki. Data are presented as frequencies or means for the purposes of comparisons between countries and between OMT medications.

Statistical comparisons were performed on categorical data by Pearson's chi-square and using standardised residuals to identify individual instances of significant variation of proportion. For linear data, analysis of variance (ANOVA) was used for comparisons and post-hoc tests (Tukey's) were performed to identify any significant country interactions. Significance was ascribed for $p \leq 0.05$.

Proportion of patients who explicitly asked their doctor for a certain medication

Proportion* of those whose doctor gave them what they asked for

Figure 1: Proportion of patients who explicitly requested and the proportion who were granted requests for individual OMT medications
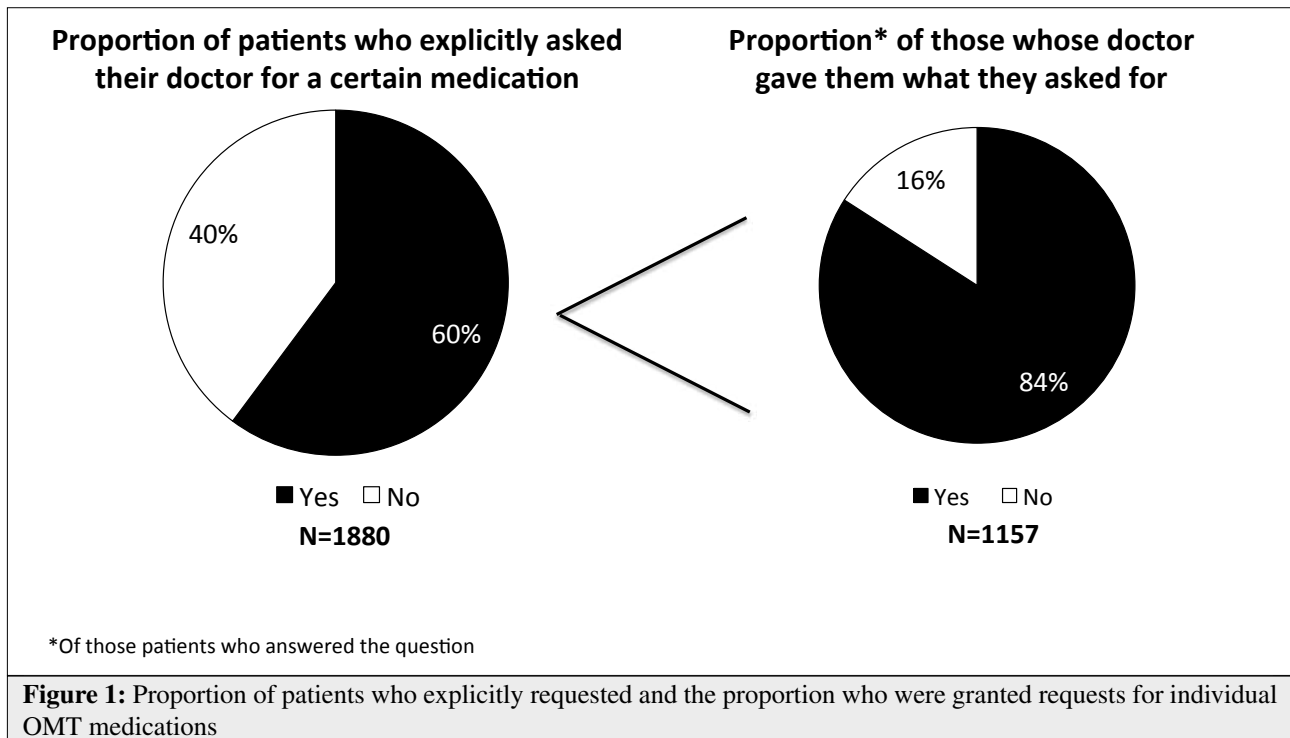
3.   Results

3.1.   Patient requests for, and awareness of, specific opioid pharmacotherapies

Patients frequently reported requesting a specific OMT medication and often being granted this request by their physician. Sixty per cent of patients in the European sample (n=1880) reported explicitly asking their physician for a particular OMT medication (Figure 1). Of those patients who provided additional information in a follow-up question (n=1157), 84% (n=972) reported receiving the medication they had asked for (Figure 1).

The majority of physicians agreed that their patients always (6%) or often (51%) expressly requested a specific OMT preparation (n=698), and physicians reported following through with specific requests on 55% of occasions. Thus, both patient and physician data indicate that patients are playing a significant role in medication selection.

Before starting OMT, patients generally considered themselves to be well informed of OMT medication options, with 73% of patients believing they were well (49%) or very well (24%) informed (n=1657). Only 20% and 7% considered themselves poorly informed or very poorly informed of OMT medications, respectively.

In contrast, data on actual knowledge of OMT medication options indicates that most patients were

not aware of all OMT options available to them. Levels of knowledge regarding OMT medication options varied between countries, with the level of knowledge tending to follow the pattern of prescribing within each country. For example, levels of awareness of methadone liquid were high (ranging from 82–98% of patients) across all countries from which data was collected (Table 1), with the exception of France where only 62% of patients were aware of this formulation. Whereas methadone is the most commonly used OMT medication in most countries, mono-buprenorphine is the most commonly used OMT medication in France. France was the only country in which patients had a higher level of awareness of mono-buprenorphine than methadone (82% of patients had heard of mono-buprenorphine but only 62% had heard of methadone). Levels of awareness of buprenorphine–naloxone were generally low in most countries (Table 1).

Levels of awareness of 'other' medication, which included slow-release oral morphine (SROM), were high in Austria. SROM is the most commonly prescribed OMT option in Austria and the country-level data indicate that 75% of patients surveyed were aware of one formulation of SROM (Substitol® and 47% were aware of another formulation (Compensan®).

Table 1: Patient awareness of OMT options from country samples

Proportion of patients aware of the following options:	Austria N=225	Denmark N=103	France N=130	Germany N=200	Greece N=601	Italy N=378	Norway N=98	Portugal N=160	Sweden N=128	UK N=248
Methadone	81.8%	96.1%	61.5%	97.5%	97.3%	96.6%	88.8%	90.6%	87.5%	94.0%
(Mono)-bupre-norphine	68.4%	51.5%	82.3%	61.5%	83.9%	67.2%	86.7%	80.6%	80.5%	73.0%
Buprenorphine–naloxone	36.0%	35.9%	4,6%	26.0%	53.6%	38.1%	64.3%	50.6%	52.3%	46.0%
Diamorphine	1.3%	48.5%	2.3%	22.5%	42.4%	0.0%	0.0%	0.0%	0.0%	37.9%
Codeine	1.8%	0.0%	30.0%	76.5%	0.2%	14.8%	0.0%	0.0%	0.0%	60.1%
Naltrexone	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	53.1%	0.0%	23.8%
Other	82.2%	6.8%	3.8%	2.5%	0.2%	2.9%	11.2%	0.6%	14.1%	36.3%
I hadn't heard of any such substance	1.8%	1.0%	3.8%	0.0%	2.0%	2.1%	2.0%	3.8%	1.6%	4.0%

Table 2: Proportion of patients receiving different OMT options by country

Proportion of patients receiving the following options:	Europe	Austria N=228	Denmark N=103	France N=130	Germany N=200	Greece N=601	Italy N=378	Norway N=98	Portugal N=160	Sweden N=152	UK N=248
Methadone	59.7%	19.3%	71.8%	32.3%	72.0%	70.4%	66.1%	38.8%	59.4%	48.7%	75.4%
Mono-buprenorphine	21.0%	21.5%	6.8%	69.2%	15.0%	20.8%	10.3%	32.7%	21.3%	25.0%	15.3%
Buprenorphine–naloxone	14.6%	13.6%	12.6%	0	13.0%	8.8%	23.3%	29.6%	18.8%	23.0%	12.1%
SROM	4.6	46.1%	0	0	0	0	0	0	0	0	0
Other	3.0	11.0%	15.5%	0	0.5%	0	0.3	0	0.6%	6.6%	6.0%

Some country data add up to >100% as patients may have indicated they were currently receiving more than one OMT medication
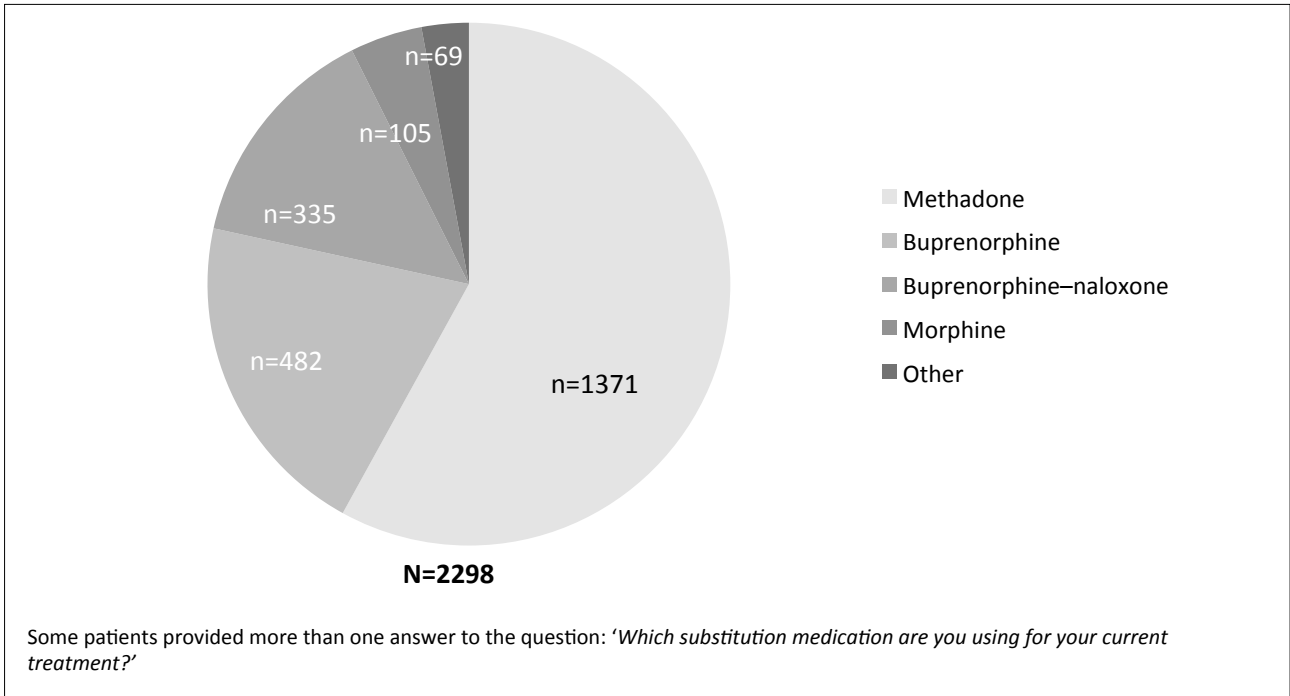
Figure 2A. Number of patients surveyed who received specific OMT medications

3.2. *Use of specific opioid pharmacotherapies*

The majority of patients included in the analysis (60%) were receiving methadone, whereas mono-buprenorphine was the current OMT medication for 21% of patients and buprenorphine–naloxone for 15% of patients (Figure 2A). It is important to note that recruitment strategies required a minimum of 30 patients per major OMT medication to allow for meaningful comparisons, which may have resulted in oversampling for some options. A minority of patients (8%) reported receiving other medications, including SROM, diamorphine, codeine or other non-opioid medications.
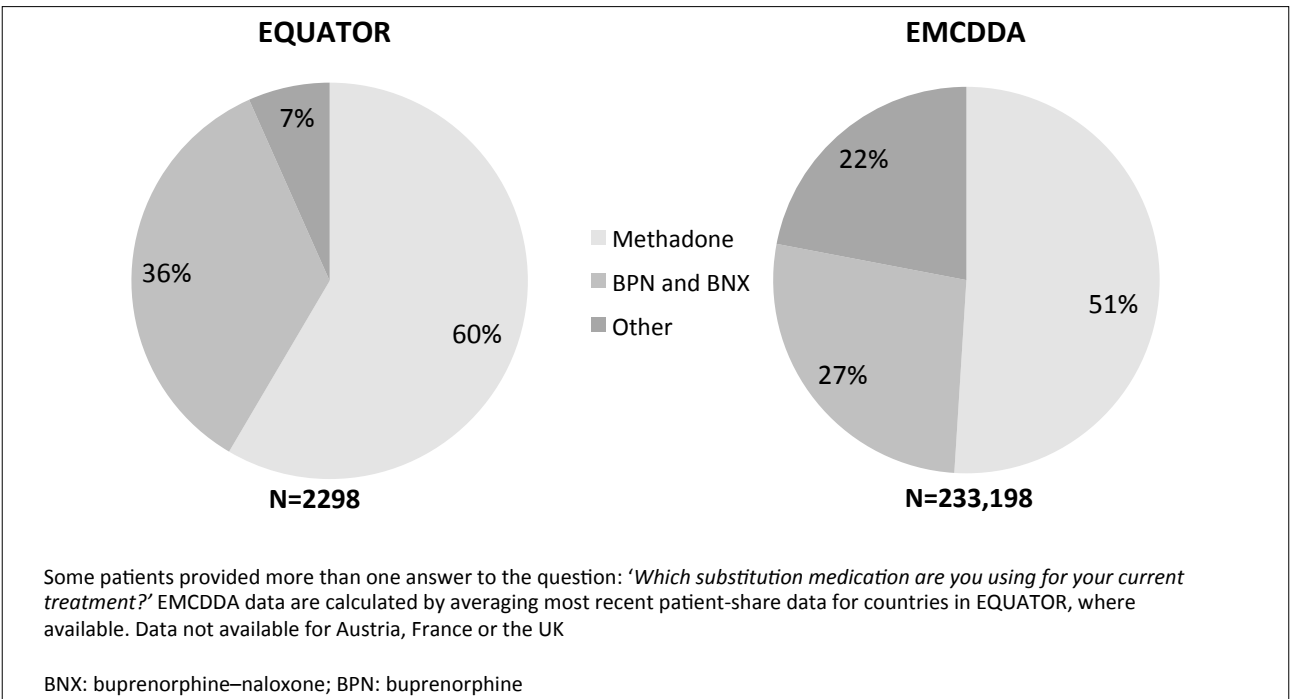
Figure 2B. EQUATOR data and EMCDDA data showing proportion of patients receiving specific OMT medications.

Table 3: Demographic and treatment profile of OMT patients according to OMT medications for the European sample[1]

	Methadone N=1371	Mono-buprenorphine N=482	Buprenorphine–naloxone N=335	SROM N=90	Other N=69	Difference between 5 treatment options
Demographics						
Mean age (SD), years	37.7 (8.3)	35.7 (8.4)	33.9 (8.6)	33.3 (9.4)	42.9 (12.3)	ANOVA: F=18.54, df=4, 1977, p<0.001
Male sex, %	75.2%	74.7%	74.9%	72.5%	66.7%	X^2=4.00, df=4, n=2208; p=0.405
Education, %						X^2=90.03, df=4, n=2082; p<0.001
No high school	50.8%	35.7%	49.8%	3.9%	37.1%	
High school or equivalent	30.5%	41.4%	30.2%	35.3%	25.8%	
Vocational	6.5%	13.1%	8.1%	53.9%	24.2%	
Some college	7.9%	5.7%	7.8%	0.0%	6.5%	
College degree	4.0%	3.5%	3.7%	6.9%	6.5%	
Grad/Prof degree	0.3%	0.7%	0.3%	0.0%	0.0%	
Marital status						X^2=7.87, df=4, n=2202; p=0.097
Single	55.4%	50.8%	55.1%	61.8%	68.4%	
Cohabitating/married	28.2%	36.8%	35.6%	25.5%	5.3%	
Divorced/widowed	16.4%	12.4%	9.3%	12.7%	26.3%	
Employment						X^2=31.09, df=4, n=2189; p<0.001
Full time	14.6%	22.2%	20.9%	10.5%	7.7%	
Part time	11.0%	12.7%	14.9%	11.4%	4.6%	
Self-employed	0.3%	0.4%	0.3%	0.0%	0.0%	
Student	1.6%	3.0%	5.7%	0.0%	3.1%	
Unemployed	72.5%	61.8%	58.2%	78.1%	84.6%	
Number of prior OMT episodes – Mean (SD)	1.4 (2.4)	1.0 (2.1)	1.2 (2.0)	1.3 (1.9)	2.7 (3.0)	ANOVA F=4.54, df=4, n=2060, p=0.001
Supervision levels						X^2=81.67, df=4, n=2201; p<0.001
Every dose supervised	48.2	42.4	22.8	28.6	46.6	
Take-aways on weekends/holidays only	20.2	18.3	12.6	41.9	23.1	
Unlimited take-aways	31.6	39.3	64.6	29.5	32.3	
Receiving psychosocial support	67.3	60.4	59.8	33.3	46.4	X^2=54.40, df=4, n=2075; p<0.001

[1]For each variable, the group's Ns vary slightly. The maximal N is shown in the header for each treatment group. SROM: slow-release oral morphine.

Table 4: Diversion, misuse and levels of supervision reported by patients from each country and the European sample

	Europe N=2298	Austria N=228	Denmark N=96	France N=128	Germany N=200	Greece N=601	Italy N=375	Norway N=98	Portugal N=160	Sweden N=144	UK N=248	Difference between countries
Any diversion*	24.0%	28.1%	37.5%	39.1%	23.0%	16.0%	26.4%	25.8%	15.6%	24.3%	30.2%	χ^2=69.81, df=9, n=2298, p<0.001
Selling	11.1%	11.0%	32.3%	6.3%	8.0%	7.2%	11.5%	10.3%	6.3%	12.5%	21.0%	χ^2=80.55, df=9, n=2298, p<0.001
Swapping ‡	1.4%	0	0	0	0	0	0	0	0	0	12.9%	n/a
Giving away	18.7%	21.9%	32.3%	32.8%	19.5%	10.5%	21.6%	21.6%	10.0%	23.6%	19.4%	χ^2=65.18, df=9, n=2298, p<0.001
Any misuse†	20.8%	48.7%	50.5%	15.3%	26.0%	4.5%	13.3%	37.8%	7.5%	38.8%	22.9%	χ^2=326.25, df=9, n=2298, p<0.001
Injection	14.6%	37.7%	38.8%	7.7%	18.5%	1.5%	11.1%	26.5%	6.3%	25.7%	14.1%	χ^2=276.23, df=9, n=2298, p<0.001
Snorting	9.8%	18.0%	14.6%	6.9%	11.5%	3.2%	3.2%	17.3%	1.9%	26.3%	18.1%	χ^2=155.38, df=9, n=2298, p<0.001
Any supervision	62.0	57.7%	52.0%	41.0%	57.8%	89.9%	44.4%	67.0%	29.5%	44.9%	71.1%	χ^2=474.44, df=9, n=2270, p<0.001
Daily supervised	41.9%	20.4%	15.0%	26.0%	39.7%	77.9%	27.6%	46.4%	20.7%	29.7%	40.2%	χ^2=474.44, df=9, n=2270, p<0.001
Take-aways on weekends/ holidays only	19.4%	37.3%	37.0%	15.0%	18.0%	12.0%	16.8%	20.6%	8.8%	17.2%	30.9%	χ^2=122.60, df=9, n=2270, p<0.001
Unlimited take-aways	37.5%	42.2%	48.0%	59.1%	42.2%	10.1%	55.7%	33.0%	70.6%	53.1%	28.9%	χ^2=374.44, df=9, n=2270, p<0.001
No info	1.2%	1.3%	2.9%	2.3%	0.5%	0	2.1%	1.0%	0	4.6%	0.8%	
Mean length of time on current OMT, years	3.7	5.2	5.9	n/a	4.6	2.2	4.4	2.9	4.7	4.6	2.7	ANOVA: F=29.07, df=8, n=2048, p<0.001

*Selling and/or swapping and/or giving away; †Injecting and/or snorting; ‡only provided as an option in the UK questionnaire
n/a: not available

p<0.01

*Of those who answered the question. P-value denotes between country-difference.
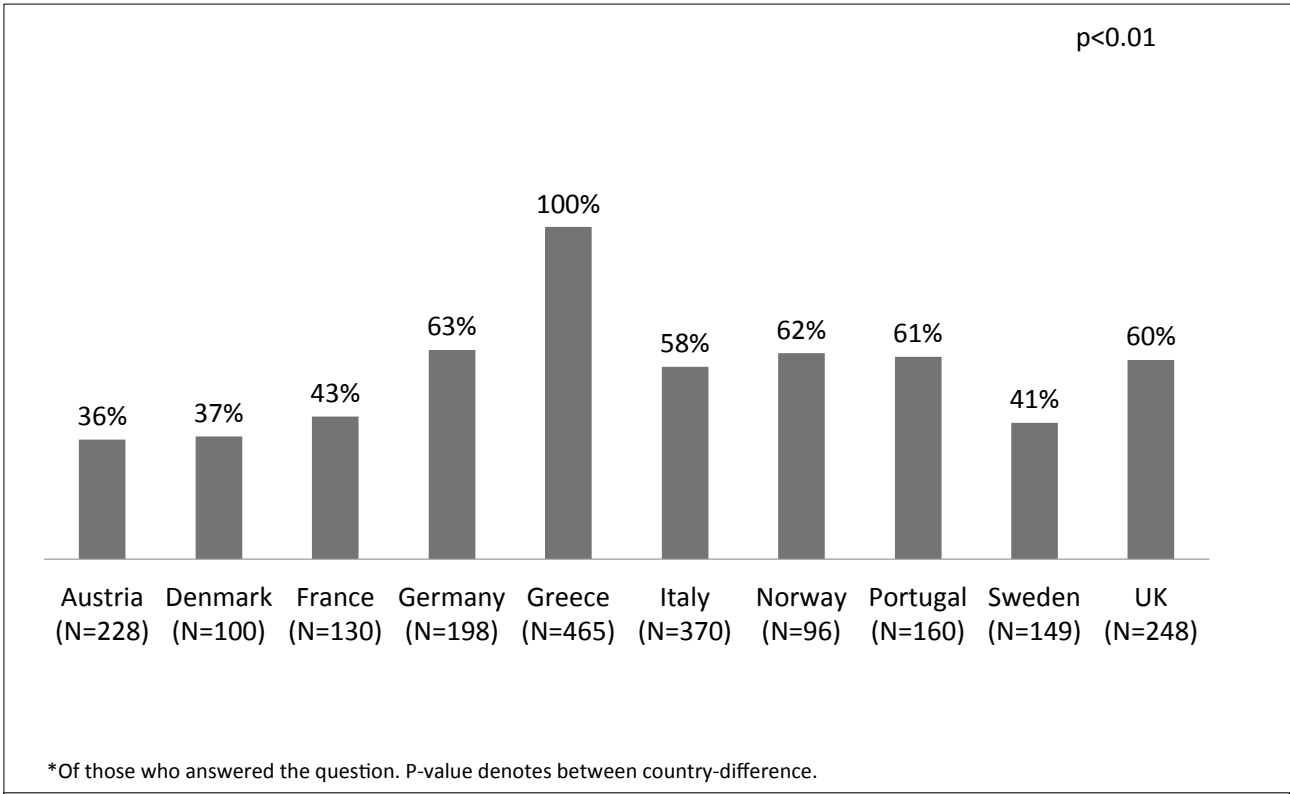
Figure 3: Proportion of patients* reporting they were currently receiving psychosocial counselling

Compared with data available from the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA), there was greater relative use of methadone or buprenorphine (mono- or combination product) and less relative use of other options in the EQUATOR analysis (Figure 2B), although it should be noted that EMCDDA data were unavailable for France (a country with a large population of clients and predominant usage of mono-buprenorphine) and Austria (a country with high usage of SROM).

The proportion of patients receiving specific OMT options varied substantially between countries

N=2279
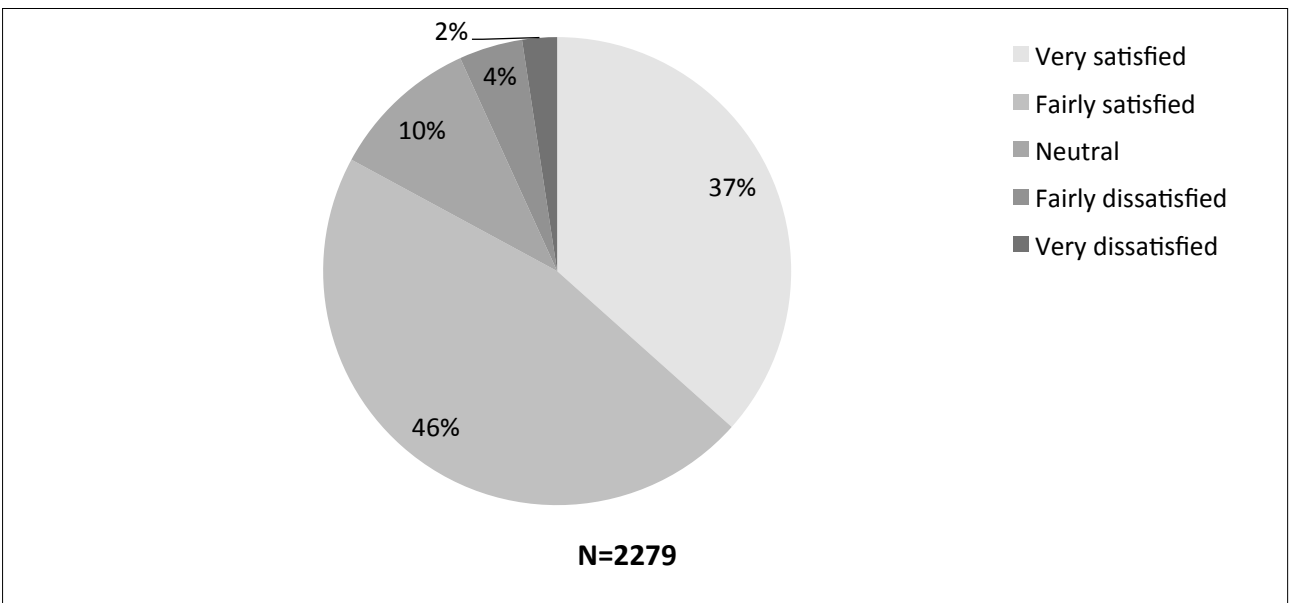
Figure 4: Satisfaction with current OMT among patients in the European sample

(Table 2). The majority of patients in Denmark, Germany, Greece, Portugal and the UK were receiving methadone, whereas almost half of patients in Austria were receiving SROM and almost 70% of patients in France were receiving mono-buprenorphine. In Sweden, nearly half of patients were receiving methadone with the remainder evenly split between mono-buprenorphine and buprenorphine–naloxone, and in Norway there was a roughly even distribution of patients receiving methadone, mono-buprenorphine and buprenorphine–naloxone.

3.3. Profile of patients according to OMT medication received

Patient demographics and treatment variables according to OMT medication received are shown in Table 3. Across all the OMT medications, patients were predominantly male (mean 74.6%); there was no difference in sex ratio between the treatment types (χ^2=4.00, df=4, n=2208, p=0.405). The mean age ($\pm$SD) of patients was 36.6$\pm$8.5 years, ranging between 33.3 and 42.9 years across OMT options. Age of patients varied between OMT medications (F=18.54, df=4,1977, p<0.001). The proportion of patients with at least a high school education varied by OMT medications (χ^2=28.03, df=2, n=1976, p<0.001). Marital status of patients did not vary by OMT medications (χ^2=7.87, df=4, n=2202; p=0.097). Employment status varied by OMT medications (χ^2=31.09, df=4, n=2189, p<0.001); a higher proportion of patients receiving mono-buprenorphine and buprenorphine–naloxone reported that they were in full-time or part-time employment or were self-employed compared with patients receiving methadone, SROM or 'other'.

The number of previous OMT episodes reported by patients before their current OMT episode varied across the OMT options (ANOVA F=4.54, df=4, n=2060, p=0.001). Patients in the 'other' treatment group reported receiving the most previous OMT episodes of any treatment group, having received, on average, 2.7 previous OMT episodes; this may reflect the fact that patients may be treated with less widely used OMT options if they have undertaken multiple, unsuccessful treatment episodes on the more conventional OMT options.

The level of OMT supervision varied by OMT medication (χ^2=81.67, df=4, n=2201, p<0.001). The level of supervision reported by patients receiving methadone was significantly greater than expected (p<0.05). Also, patients in the buprenorphine–

naloxone and SROM groups received significantly less supervision. Patients receiving SROM for their current OMT reported a high level of freedom in their dosing, with the highest proportion (42%) having take-away doses at weekends or during holidays. The majority of buprenorphine–naloxone patients (65%) reported that they had unlimited take-away doses.

3.4. Levels of dosing supervision and medication misuse, diversion and time on current OMT

Table 4 summarises patient-reported past levels of medication misuse and diversion, current levels of dosing supervision and time on OMT. For the European sample as a whole (N=2298), 24% of patients reported ever having sold, swapped or given their OMT medication to someone else.

Rates of diversion differed significantly between countries (χ^2=69.81, df=9, p<0.01). For most countries, 23–30% of patients reported having diverted their medication, with slightly lower levels evident in Portugal and Greece (16%) and higher levels in Denmark (38%) and France (39%).

Levels of OMT supervision varied between countries (χ^2=603.99, df=18, p<0.01). At a country level, there was a significant association between reported levels of supervision in each country and levels of past medication diversion: lower rates of diversion were associated with higher levels of supervision (χ^2=602.18, df=18, p<0.01). Patients from Portugal had the equal lowest rate of diversion within those countries assessed but also one of the lowest levels of dose supervision, whereas Greece had the equal lowest rate of diversion and the highest level of supervision. The situation in Greece may relate to the long waiting list for OMT: patients motivated to endure lengthy waits for treatment may also be motivated to comply with therapy to derive benefit and avoid doing anything that would jeopardise continued treatment access.

For the European sample as a whole, 21% of patients included in the analysis reported ever having misused (i.e., injected or snorted) their OMT. Levels of patient-reported misuse varied substantially between countries (χ^2=326.25, df=9, p<0.01), with less than 10% of patients in Greece (5%) and Portugal (8%) having ever misused their medication compared to approximately half of patients in Austria (49%) and Denmark (51%).

The highest levels of misuse by injection were evident in Austria (38%; possibly reflecting the high

usage of SROM in Austria, and the attractiveness of SROM to those looking to abuse their medication by injection), Denmark (39%), Norway (27%) and Sweden (26%), whilst the lowest levels were reported in Greece (2%) and Portugal (6%) (χ^2=276.23, df=9, p<0.01).

The mean length of time patients had been on their current OMT was 3.7 years, ranging from 2.2 years in Greece to 5.9 years in Denmark.

3.5. Psychosocial support

The proportion of patients receiving psychosocial support was found to deviate between the treatment options (χ^2=54.40, df=4, n=275, p<0.001). Sixty-seven percent of patients receiving methadone reported receiving psychosocial support, while only 33% and 46% of patients receiving SROM or 'other' treatment, respectively, reported receiving psychosocial support.

Patient-reported rates of participation in psychosocial counselling differed significantly across Europe (Figure 3; χ^2=34.54, df=4, p<0.01), with the lowest levels evident in Austria (36%), Denmark (37%), Sweden (41%) and France (43%), and the highest level seen in Greece (100%); it should be noted that these percentages are of those patients who answered the question. For the sample as a whole, 61% were participating in psychosocial counselling.

3.6. Patient satisfaction with OMT medications

The majority of patients reported being satisfied with their current OMT medication (Figure 4), with 83% very or fairly satisfied among the 2279 who answered the question.

4. Discussion

4.1. Variation in opioid treatment delivery practices across Europe

EQUATOR has revealed significant disparities in OMT practices between different countries across Europe. These include: differences in the opioid medications used; how frequently these medications are administered under controlled, supervised conditions; and whether the medications are delivered in the context of adjunctive psychosocial support.

The level of variation in OMT practices is notable, given that the underlying condition of opioid dependence being treated is assumed to be similar ir-respective of geography, and in view of the similar demographic profile of patients receiving OMT in each country (see article by Goulão & Stöver in this issue). Variations in treatment practice may thus reflect a range of non-clinical influences (e.g., history, politics) and also the absence of universally adopted clinical guidelines or evidence-based training across Europe.

4.2. Are patients making informed choices about OMT medication?

Where available, treatment guidelines for OMT commonly emphasise the importance of clinical factors in choosing a treatment strategy, such as the needs of the individual patient and the benefits and risks associated with different treatment options (16,21).

The UK National Institute for Health and Clinical Excellence (NICE) guidelines, for example, recommend that '*the decision about which drug to use should be made on a case-by-case basis, taking into account a number of factors, including the person's history of opioid dependence, their commitment to a particular long-term management strategy, and an estimate of the risks and benefits of each treatment made by the responsible clinician in consultation with the person*' (16). Similarly, the Portuguese National Plan Against Drugs And Addiction recommends that '*a number of diversified treatment and care programmes are made available, covering a wide range of psychosocial and pharmacological approaches, based on ethical standards and scientific evidence*' (11). German regulations state that only registered, 'substitution', drugs should be used and that different profiles of efficacy and side effects should be considered when commencing therapy (3).

Ensuring patients are educated about the range of treatment options available to them in order to make an informed choice is also mandated in the General Medical Council Good Practice in Prescribing Medicines Guidelines (8). However, findings from EQUATOR suggest that many patients remain unaware of the full range of OMT medication options available, despite typically having been in OMT several times. 'Methadone' may, in fact, have become a generic term for medications used to treat opioid dependence due to its long history and universal awareness among patients, and patients may not be as aware of alternative OMT options. Supporting this supposition, most patients (an average of 89% for the countries across Europe) reported being aware of methadone, which has been available for several decades in most coun-

tries, but less than half (an average of 41% for the countries across Europe) were aware of more recently introduced options for OMT such as buprenorphine–naloxone. Patient awareness of OMT is of course likely to be affected by availability of OMT options in their country.

Despite this lack of patient awareness, patients play a significant role in medication selection. Patient-reported data in the current analysis suggest that the selection of medications used in OMT is heavily influenced by patients explicitly requesting a specific medication, and, in the vast majority (84%) of cases, being granted their request. This phenomenon was acknowledged by physicians themselves, albeit to a lesser degree, who reported following patient requests for specific OMT medications 55% of the time. These findings are of concern since patients appear to be influencing the choice of medication whilst having limited knowledge of the available OMT options. Increased dialogue between physicians and patients at the outset of OMT is required to improve patient awareness of treatment options.

4.3. Variation in OMT prescribing practice in the treatment of heroin addiction

EQUATOR has also confirmed that physicians' patterns of prescribing differ markedly between countries, despite the notably similar demographic profile of patients. For example, most countries in Europe predominantly use methadone for OMT, whereas physicians in France appear to prefer mono-buprenorphine and those in Austria prefer SROM. The pattern of medication use observed in this analysis was broadly comparable to that reported by the EMCDDA. Not all OMT options are approved for use in all countries included in EQUATOR, which may explain some of the variation between countries in their use of OMT options. Notwithstanding this fact, it appears that OMT selection is being driven by local and national guidelines (which differ), habit, history and familiarity with specific options. In the case of patients who are returning to treatment following previous failed treatment episodes, the current data do not shed light on whether alternative pharmacological and psychosocial strategies with potentially increased chance of success are actually being offered.

Overall, these findings point to a need for physicians to be empowered to discuss the full range of therapeutic options with their patients in order to ensure that the most appropriate clinical decisions are reached. In this regard, clear national guidelines may

be beneficial or, where these do not exist, European or other international (e.g., World Health Organization) guidelines on OMT should be followed.

4.4. Misuse and diversion occurs by a minority in all countries despite supervision

Another important area of variation in OMT delivery practices concerns the use of supervised dosing. If patients do not take their medication, or do not take it correctly, they are unlikely to derive full therapeutic benefit. Indeed, in other chronic disorders, such as schizophrenia, non-compliance with medication has been associated with the 'revolving door' phenomenon whereby patients enter and exit several rounds of treatment (17).

Supervised dosing is recommended in some OMT guidelines as a means to improve safety (particularly with methadone) and to limit misuse and diversion. However, supervised dosing can also have a negative impact on the acceptability and accessibility of treatment for patients (21), and may potentially interfere with employment opportunities and reintegration.

The findings of the current analysis reveal significant variation between countries (15–78%) in the proportion of patients receiving daily supervised dosing (and in the extent of unsupervised dosing in general), which may have important consequences for patient outcomes. Time on OMT might explain in part these variations, but the correlation between time on OMT and level of supervision was not universal. Since data were not collected on comorbid drug or alcohol dependence and other complexities, it was not possible to determine whether patients with more complex issues or chaotic habits were supervised more closely. Our findings also demonstrate that misuse and diversion of OMT occur in all countries, albeit at different levels, with 16–39% of patients ever having diverted and 5–51% of patients ever having misused their OMT medication. As reported elsewhere in this series, patients reported that they diverted medications primarily to help others to treat themselves, to satisfy their cravings or to achieve a high. For a minority of patients, diversion was used as a source of income.

The highest proportions of patients reporting previous injection misuse were observed in the Austrian and Danish samples. Injection misuse carries particular concerns regarding the potential for injection-related harms (e.g., blood–borne virus transmission). The high rate of injection misuse in Austria may be associated with the widespread use of SROM,

the most frequently used OMT in this country. Morphine has a low oral bioavailability (~30%), which may make it more attractive to individuals seeking to abuse their medication by injection. It is noteworthy that SROM preparations are relegated to second-line treatment in Austria, behind methadone and buprenorphine, but still comprise the majority of prescriptions. Indeed, in many cases patients may be requesting SROM because of the potential for misuse. Although it is important that patients are consulted on their prospective treatment options for opioid dependence, the final choice of treatment should be made by the physician with consideration for the potential of individual patients to misuse their medication. Among alternatives to methadone, buprenorphine has a stronger evidence base than SROM (12,15) and is also available in a formulation that minimises the potential for injection through the addition of naloxone (18).

Whilst supervision undoubtedly can make it more difficult to divert medication, all of the sampled countries showed at least some degree of unsupervised dosing. This analysis failed to show clear evidence that countries investing in supervision derive a substantial benefit with respect to the proportion of patients who engage in diversion of their OMT. In terms of clinical outcomes, a previous randomised controlled trial failed to find significant differences between supervised and unsupervised buprenorphine–naloxone dosing regimens with regard to treatment retention or use of illicit opioids (2).

4.5. Many patients are not accessing psychosocial support

Providing patients with the necessary range and intensity of support also means ensuring that options for psychosocial support and recovery are available. Accumulated evidence suggests that greater benefits are derived from OMT when opioid pharmacotherapy is offered in conjunction with psychosocial support (21). In the present analysis, we found that a significant proportion of patients (37% of those surveyed) were not currently receiving any psychosocial counselling or support of any kind. Although psychosocial support may be beneficial, most treatment experts believe it should be provided on a voluntary basis. Even in Germany, where psychosocial counselling was a mandatory requirement at the time of the survey, a significant proportion of patients was not receiving this support. Based on the current findings, there is insufficient information to determine whether those not receiving psychosocial interventions would

benefit from doing so, or alternatively whether they previously received counselling which was later stopped. The high proportion of patients not receiving psychosocial interventions nonetheless raises the possibility that important opportunities to optimise the benefits of treatment and maximise recovery are being missed.

4.6. Patient dissatisfaction with OMT does not account for cycling phenomenon

Opioid dependence can be a chronic relapsing condition (13). Thus, many patients cycle between treatment and relapse. A key aim in the treatment of opioid dependence is therefore to maximise treatment retention, until a patient is ready to attempt abstinence, thus potentially maximising long-term remission or recovery. Paradoxically, patient satisfaction with their OMT medications was found to be high in this analysis, suggesting that dissatisfaction with treatment is unlikely to be the driver for patients cycling between treatment and relapse. Based on the variable rates of prior OMT per country, a more likely explanation is that entry into, or retention within, treatment is influenced by the different ways in which medications are used and the different treatment structures that apply in each country.

5. Conclusions

Individuals who are trying to overcome or recover from opioid dependence have a difficult journey, often characterised by periods of relapse into illicit drug use, risking significant harms to themselves and to society. A key task for those involved in opioid-dependence treatment, therefore, is to optimise opioid treatment to reduce relapse and promote recovery.

Evidence suggests that the quality of patient care can be improved in a number of ways, such as: by ensuring patients and physicians discuss the range of OMT options; by getting the appropriate balance between control and patient freedom; by reducing the likelihood of misuse and diversion; and by providing appropriate psychosocial interventions in conjunction with pharmacotherapy to maximise recovery outcomes.

This analysis illustrates great variation between European countries in OMT and implies that countries participating in the EQUATOR analysis may not have optimised certain aspects of treatment for opioid dependence. A key step in improving patient outcomes in opioid-dependence treatment is to iden-

tify the impact that differences in treatment approach have on quality of patient care.

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bility for the decision to submit the paper for publication.

Outcomes of opioid-dependence treatment across Europe: identifying opportunities for improvement

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Summary

The European Quality Audit of Opioid Treatment (EQUATOR) analysis suggests that current systems of opioid-dependence treatment in Europe may be failing to achieve optimal outcomes in a substantial subset of patients. In general, opioid-dependent patients report high rates of cycling in and out of opioid maintenance treatment (OMT), past misuse or diversion of their medication, and continued on-top heroin use despite being prescribed OMT. Building on evidence from this analysis of variable treatment delivery across Europe, these findings suggest that greater treatment benefits could be achieved by optimising treatment structures as well as available interventions.

Key Words: diversion, illicit drug use, misuse, treatment cycling

1. Introduction

Opioid maintenance treatment (OMT) has many potential benefits for patients with opioid dependence and for society, including the attainment of a reduction in patients' use of heroin and other illicit opioids, a reduction in crime, a reduced mortality risk and improvements in health and well-being (7,8,10–13). However, the magnitude of gains achieved through OMT can be greatly influenced by how treatment is delivered. We have previously demonstrated that significant disparity exists across Europe on several key treatment-delivery variables (see article by Dale-Perera, Goulão & Stöver in this issue). This is consistent with previous literature regarding the unique history of the treatment structures that exist within differ-

ent countries (5). Importantly, the European Quality Audit of Opioid Treatment (EQUATOR) analysis also highlights concerns regarding the quality of care some patients may be receiving. Many patients appear to be only partially informed about the treatment options available to them, despite having experienced several previous episodes of therapy, and are often not accessing psychosocial support in conjunction with their opioid pharmacotherapy. A significant minority of patients also report having either diverted or misused their opioid medication at some stage, which may have diminished the benefits they have gained from therapy. In view of the disparity in treatment *delivery* practices in the European countries included in the EQUATOR analysis, it is important to assess whether the resulting *outcomes* also vary between

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countries, and whether these outcomes meet the expectations of patients, clinicians, policymakers and other stakeholders.

The goals of treatment with OMT may be different for different stakeholders (e.g., patients and their families, healthcare professionals, government policymakers) and may also change over time (14). At a policy level, there is a growing trend in some countries to consider more ambitious goals of treatment that build on harm reduction and aim towards long-term recovery at the level of individual patients (e.g., improvements in health, well-being and social functioning). In some countries (e.g., Switzerland, Austria and parts of Germany), OMT and psychotherapeutic approaches have been combined within drug rehabilitation programmes (1), amid recognition that psychosocial treatments play a critical role in the overall package of treatment (2). However, more structured interventions do not appear to provide any additional benefit to that afforded by standard psychosocial support (2). While policy priorities and treatment goals may vary somewhat between countries, there are several broad principles regarding outcomes from OMT that remain fairly constant and important in all countries. For example, in order to realise the full benefits of treatment, treatment systems should seek to achieve the following: 1) easy access to treatment without barriers to entering or affording care; 2) minimisation of the frequency of relapse to untreated opioid dependence; 3) significant reductions in illicit (opioid) drug use upon which many other goals of therapy depend (e.g., reductions in blood–borne virus exposure and crime, improvements in health and well-being); and 4) a situation whereby prescribed OMT medications are taken only by the intended recipient via the appropriate route. Conversely, poor public-health outcomes are associated with treatment systems in which patients have difficulty accessing or regularly drop out of treatment, relapse to illicit heroin use, misuse or divert their OMT medication, or continue to use illicit drugs.

The EQUATOR analysis provides an opportunity to assess several markers of treatment success and failure, including how many previous OMT episodes patients and users have had, the consequences of stopping OMT on these previous occasions, whether patients have a history of diverting or misusing their medications, and whether treatment has been effective in reducing patients' use of heroin and other illicit drugs. Whilst these markers each have limitations as indicators of treatment success, they may nonetheless provide useful information to help assess the pattern of treatment outcomes at the pan-European level, between countries and between specific therapeutic options.

2. Methods

Detailed methodology of the EQUATOR analysis has been described previously (6). Briefly, questionnaires were compiled comprising a core set of questions specific for three target groups: opioid users not currently in OMT (50 questions per survey), opioid-dependent patients currently in OMT (50 questions per survey), and physicians involved in the treatment of opioid-dependent patients (60 questions per survey).

Outcomes of opioid-dependence treatment across ten countries in Europe were assessed by collating responses to questions on treatment-related topics such as previous OMT episodes, misuse and diversion of OMT, and illicit drug use during treatment.

To assess previous OMT episodes, patients were asked the following two questions: '*before your current treatment, how many times have you been in a substitution treatment program in the past and on what treatment?*'; '*when did you begin your current substitution treatment?*' and '*after changing or stopping substitution treatment in the past, what consequences did that have on your life and health?*'.

Misuse and diversion were assessed based on responses to the following two questions: '*have you ever injected or snorted your substitution drug?*'; and '*have you ever sold or given your substitution medication to someone else?*', respectively.

To assess illicit drug use, patients were asked the following three questions: '*which drugs or substances are you still currently taking in addition to your prescribed substitution medication?*'; '*which substances have you been taking on a regular basis before you started therapy and how have you been taking each?*'; and '*if you take illegal drugs in addition to or instead of your substitution drug, why do you do this?*'.

Data were collected in each country in accordance with the European Pharmaceutical Market Research Association (EphMRA) code of conduct and the Declaration of Helsinki. Data are presented as frequencies or means for the purposes of comparisons between countries and between OMT medications.

For each of the variables, differences were assessed according to which OMT medication patients are currently prescribed.

Differences in previous OMT episodes, previ-
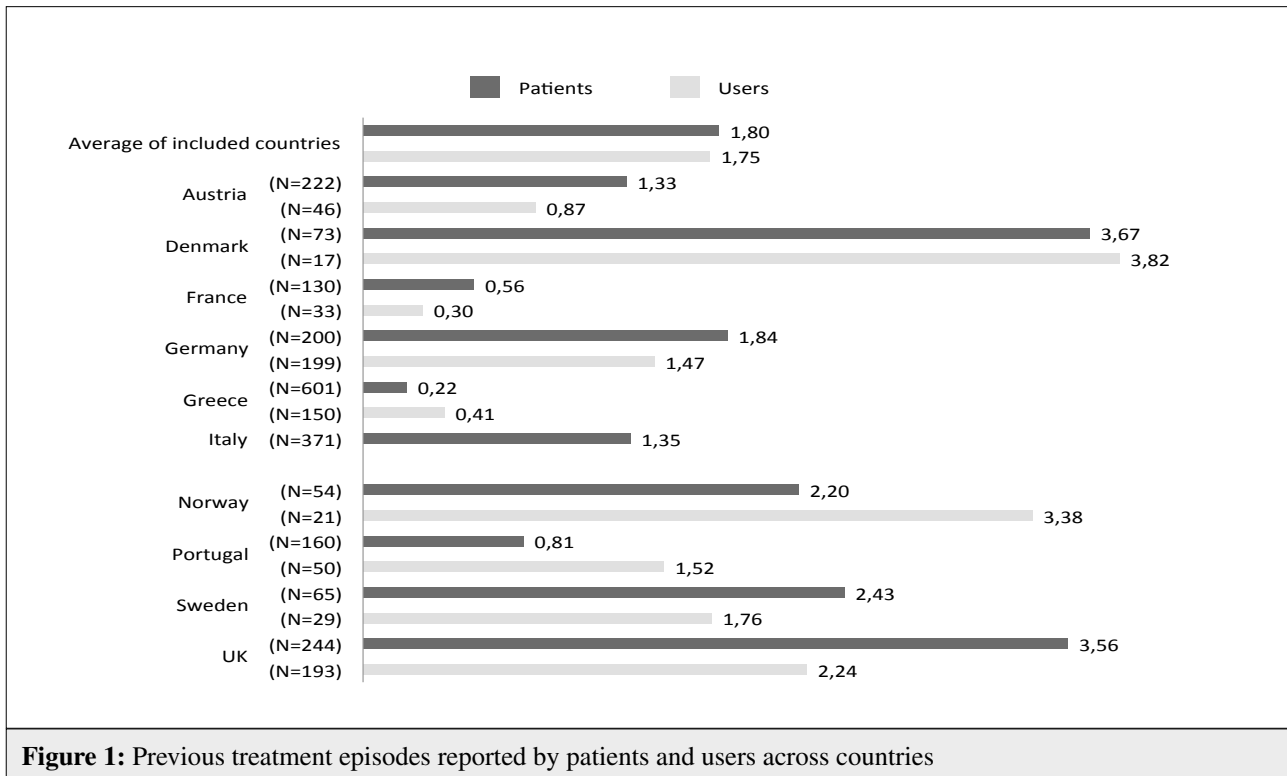
Figure 1: Previous treatment episodes reported by patients and users across countries

ous OMT duration and consequences of changing or stopping OMT between patients and out-of-treatment users and between countries were assessed by analysis of variance (ANOVA) and regression analysis. Pearson Chi-squared (χ^2) analysis was used to assess differences between patients and users with regard to consequences of changing or stopping OMT, and to assess differences between countries with regard to OMT diversion, OMT misuse and on-top heroin use. For tests that were statistically significant, post-hoc tests were performed to identify any significant country interactions. Significance was ascribed for $p \leq 0.05$.

3. Results

3.1. *Number of previous OMT episodes*

The average number of previous OMT programmes undertaken by opioid-dependent patients varied from 0.2 in the Greek sample to 3.7 in the Danish sample (Figure 1). The mean number of previous treatment episodes for the countries across Europe was 1.8. In other words, the average European patient had been in treatment nearly three times, including their current treatment episode. The average number of previous OMT programmes undertaken by users for the countries across Europe was 1.8, ranging from 0.3 in France to 3.8 in Denmark.

3.2. *Consequences of stopping previous OMT episodes*

In response to the question *'after changing or stopping substitution treatment in the past, what consequences did that have on your life and health?'*, the most frequent response from patients was that they relapsed or took illegal drugs again (27% of responders; Table 1). Other effects were reported to be stress with family and friends (17%), increased use of illegal drugs (15%), having no or little money (15%) and committing crimes (13%).

3.3. *Compliance outcomes: diversion and misuse of OMT medications*

Across the European sample, 24% of patients reported ever having diverted (i.e., sold, swapped, or given away) their OMT. Within Europe, the percentages of patients reporting diversion varied from 16% in Portugal to 39% in France (country-level data are reported in article by Dale-Perera, Goulão & Stöver in this issue). Among the responses given (n=550) to the question *'if you have ever sold, swapped or given your opiate substitution medication to someone else, please indicate your reason or reasons for doing this'*, the most frequently cited reason for diversion from the three options provided was to help others to treat themselves (52% of responses). Incidental earnings/

Table 1: Patient-reported consequences of changing or stopping opioid maintenance treatment

	Europe N=2274	Austria N=228	Denmark N=103	France N=130	Germany N=200	Greece N=601	Italy N=378	Norway N=98	Portugal N=160	Sweden N=128	UK N=248
Relapsed/took illegal drugs again	26.8%	30.7%	46.6%	16.2%	0.0%	11.5%	30.2%	39.8%	18.8%	32.9%	70.2%
Increased my usage of illegal drugs	15.4%	19.7%	34.0%	7.7%	0.0%	5.2%	10.1%	23.5%	8.8%	24.3%	48.8%
Overdosed	2.4%	0.0%	0.0%	0.0%	1.0%	0.0%	0.0%	0.0%	0.0%	0.0%	21.8%
Improvement of health	0.7%	0.0%	0.0%	0.8%	2.0%	0.0%	0.0%	0.0%	0.0%	0.0%	4.8%
Strong negative impact on health	5.0%	0.0%	0.0%	0.0%	6.5%	4.7%	15.9%	0.0%	9.4%	0.0%	0.0%
Committed crimes	13.0%	16.7%	28.2%	3.1%	0.0%	4.5%	6.9%	25.5%	6.3%	23.7%	41.9%
Imprisonment	9.4%	14.0%	24.3%	1.5%	0.0%	1.8%	6.9%	6.1%	2.5%	17.1%	33.5%
Job loss	7.0%	14.5%	12.6%	3.1%	0.0%	0.5%	9.3%	5.1%	9.4%	9.2%	15.3%
No/little money	14.5%	18.9%	26.2%	6.9%	0.0%	2.8%	10.6%	25.5%	13.1%	16.4%	51.2%
Homeless	7.5%	9.2%	21.4%	3.1%	0.0%	0.3%	2.4%	14.3%	4.4%	15.8%	28.2%
Stress with family/friends	16.8%	25.0%	19.4%	6.2%	2.0%	5.2%	18.5%	24.5%	11.9%	21.7%	48.8%
Social isolation/negative impact on social status	11.5%	0.0%	24.3%	6.9%	2.5%	3.3%	12.2%	24.5%	8.8%	15.8%	39.1%
Difficulty getting back into treatment	9.3%	7.5%	18.4%	5.4%	0.0%	2.5%	3.2%	25.5%	7.5%	14.5%	34.3%

source of money made up 40% of responses. Helping others to satisfy their cravings/get high constituted 39% of responses.

Of the European sample, 21% of patients reported that they had ever misused their medication while 15% of patients reported that they had misused their medication by injecting it. Patients in Austria reported the highest level of misuse by injection (38% of patients), whereas only 2% of patients surveyed in Greece reported misuse by injection (country-level data are reported in the article by Dale-Perera, Goulão & Stöver in this issue). Specifically, 54% of patients in Austria currently receiving SROM reported past OMT medication misuse by injection. Among the responses given (n=312) to the question *'if you injected or snorted your substitution drug at any time in the past, please indicate your reason or reasons for doing this?'*, the most frequent in the European sample of those who gave a reason was 'I want to get high occasionally' (64%); this was significantly more frequent than all other responses (p<0.01). The second most frequent response was 'My drug treatment doesn't control my cravings' (25%); this was significantly (p<0.05) more frequent than all the other less frequent responses.

3.4. Use of illicit opioids and other drugs by patients

In response to the question *'how often do you take illegal drugs in addition to or instead of your opiate substitution medication?'*, 60% of patients reported that they continued to use illicit drugs. It was encouraging that 31% of patients reported that they used illicit drugs only 1–2 times per month or less frequently, but 28% of patients reported that they took illegal drugs in addition to or instead of their OMT at least once per week (Figure 2). Fewer patients reported heroin use while in treatment (27% of patients) compared with before they started treatment (92% of patients) (p<0.01).

Rates of reported on-top heroin use varied substantially across the European countries in the analysis: 56% of patients in the Danish sample reported that they 'sometimes' (46%) or 'regularly' (10%) used heroin on top of their OMT compared with 13% of patients in Portugal who reported that they 'sometimes' (11%) or 'regularly' (3%) used heroin on top of their OMT. The proportion reporting they 'regularly' use heroin on top was highest in the UK (20%), compared with between 2% and 10% elsewhere in Europe (Figure 3). There were significant differences

in the reported rates of on-top heroin use depending on which OMT medication patients were receiving (χ^2=90.89, df=4, n=1823, p<0.001); the highest rate of on-top heroin use was among methadone-treated patients, of whom 42% reported they were sometimes or regularly using heroin, and the lowest rate was among patients treated with buprenorphine–naloxone (20%) (Figure 4).

Of the 1620 participants who answered the question *'if you take illegal drugs in addition to or instead of your substitution drug, why do you do this?'*, the most frequent reason selected by patients was the desire to get high occasionally (50%). Of the other options provided to respondents, 'drug treatment not controlling cravings very well' was the second most frequent choice (17% of respondents), and 'missed appointments' was cited by 15% of respondents.

Further detail on patterns of drug use (including drugs other than heroin) by patients and users is presented in the article by Stöver in this issue.

4.   Discussion

OMT is proven to have many benefits for individuals and the wider community, including reducing mortality, illicit drug use, comorbidities and crime, while improving physical well-being, quality of life and psychosocial functioning (7,8,10–13). However, successfully realising the benefits of OMT is dependent on how treatment is delivered and the quality of care patients receive. We have previously shown in this series that key aspects of treatment delivery, including which OMT options are used, how they are supervised, and whether pharmacotherapy is combined with psychosocial support [see other EQUATOR articles in this issue], differ between European countries in ways that may be more indicative of policy and historical factors than of differing clinical needs of patients. Building on these findings, the results presented in this article indicate that current treatment systems may be failing to achieve several key desired outcomes for many patients.

4.1. Treatment cycling

An important goal of OMT is to provide patients with a prolonged period of stability during which the multiple challenges and comorbidities arising from their drug use can be addressed. Whilst there is no single optimum treatment duration for all patients, evidence indicates that a sustained period of treatment is often necessary and that efforts to expedite
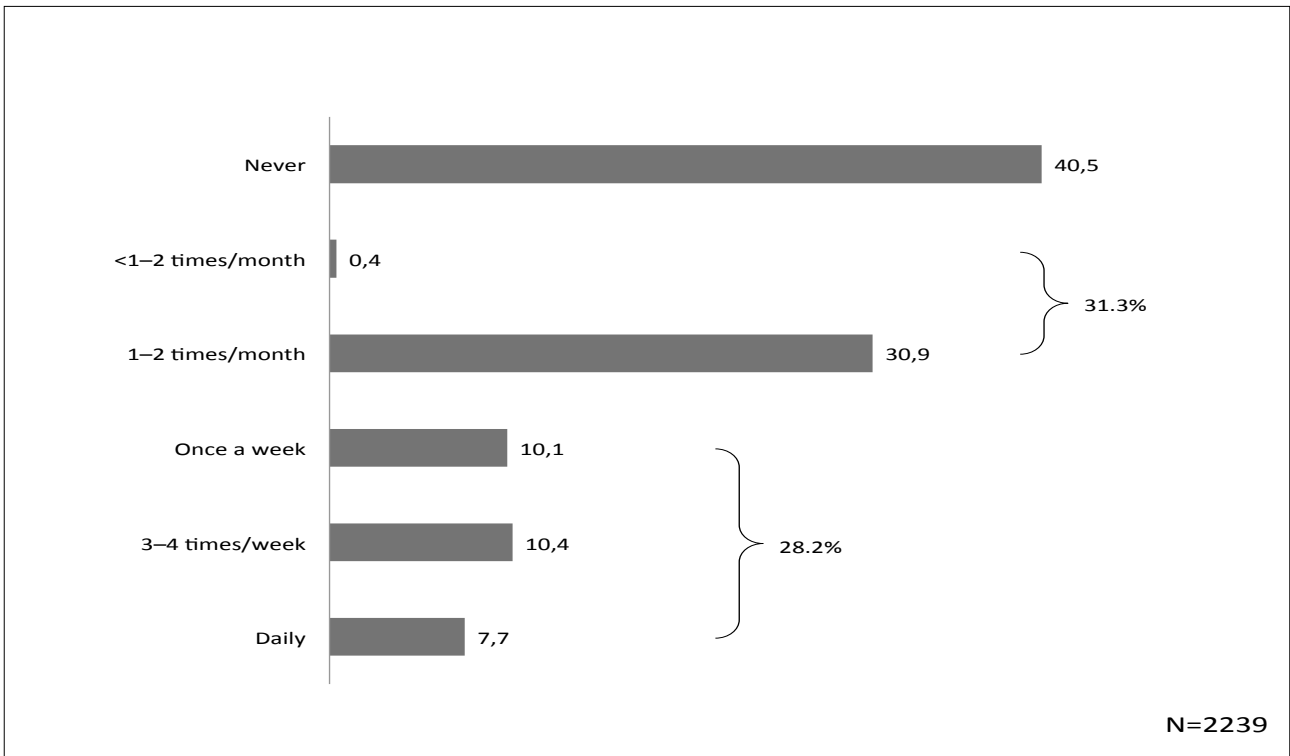
Figure 2: Frequency of on-top illicit drug use ('regularly' or 'sometimes') reported by patients

tapering from OMT to achieve a complete drug-free state (free of both medication and illicit opioids) are often associated with high rates of relapse (17).

Patients were found, on average, to have re-

ceived OMT on 1.8 (range: 0.2–3.7) previous occasions, and were thus often engaged in their third episode of OMT at the time of the survey. Based on these data, in view of the chronic relapsing nature of opioid
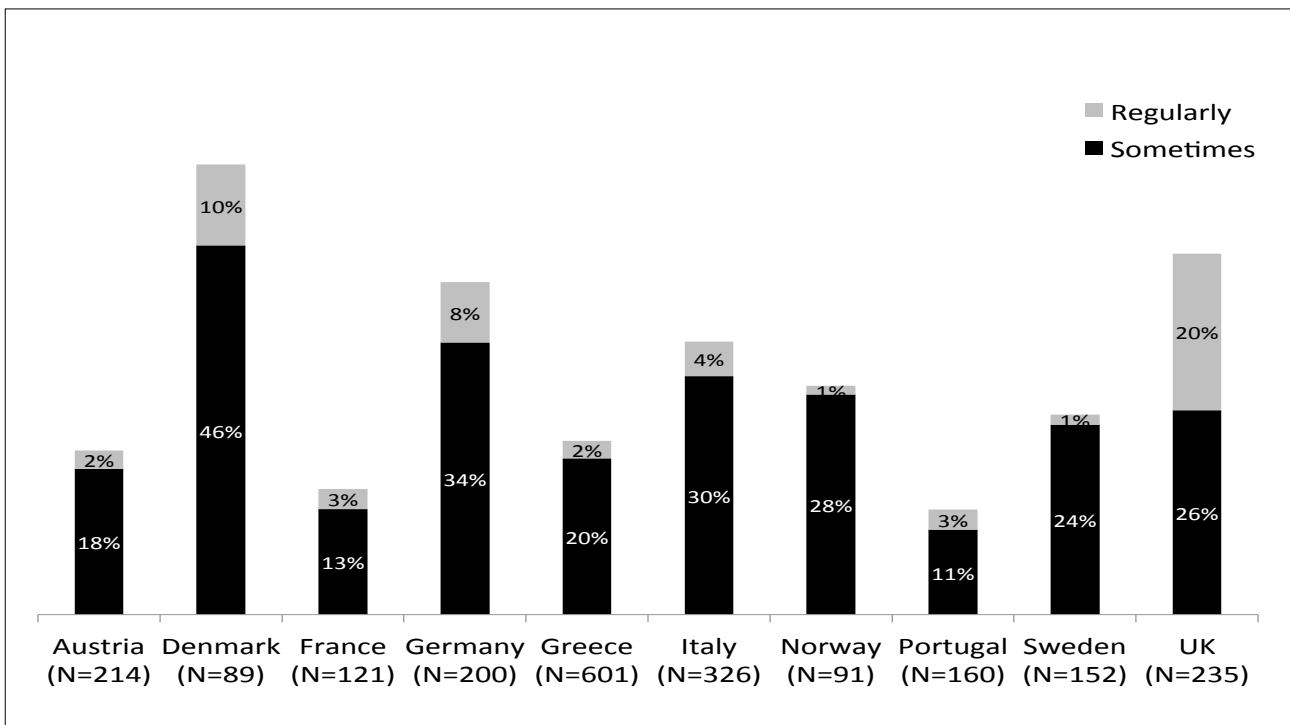
Figure 3: On-top heroin use reported by patients from each country sample

Figure 4: Heroin use reported by patients in the pan-European sample before and while receiving different OMT options
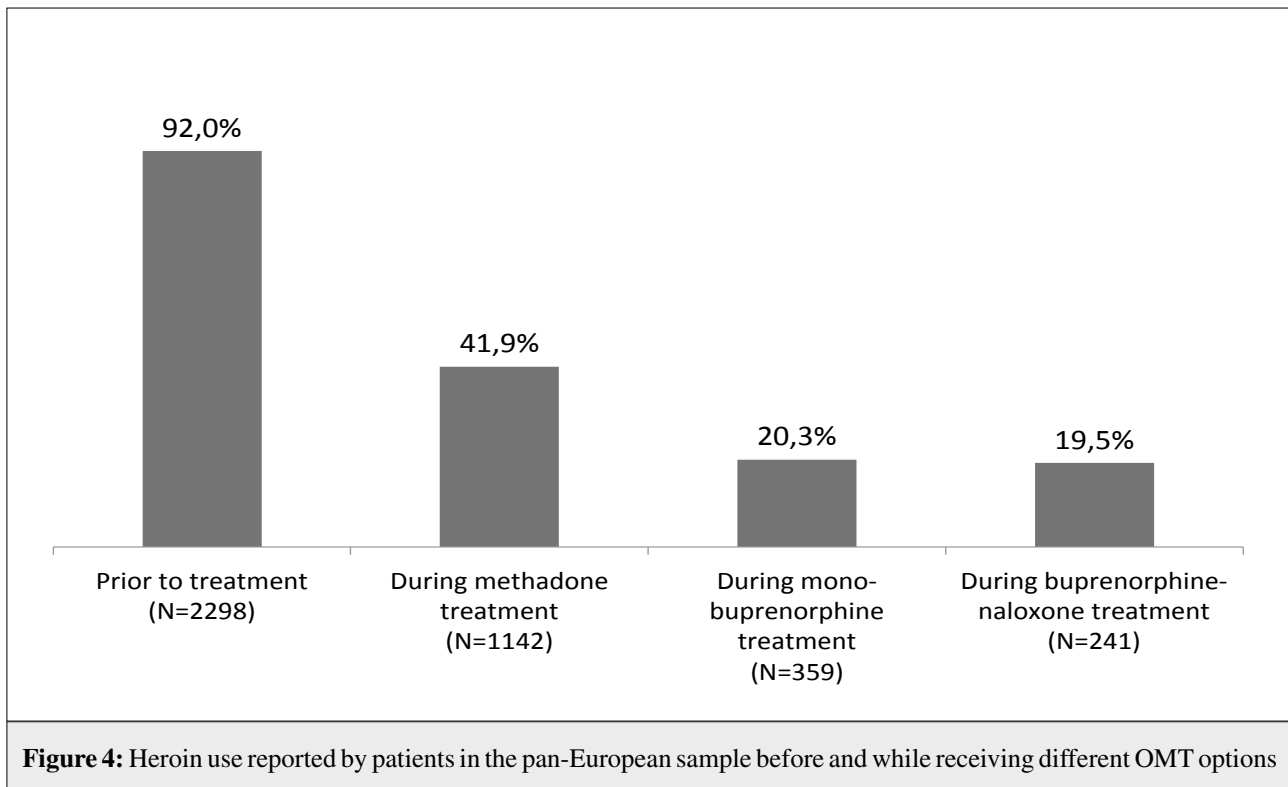
dependence, and in light of the fact that medication adherence and relapse rates are generally poor for chronic conditions (type 2 diabetes mellitus, hypertension, and asthma) (15), it is unrealistic to expect a single OMT episode to be effective in enabling complete recovery for the majority of patients, and therefore further intervention is likely to be necessary. However, it is also clear from our findings that great variations exist across countries in the frequency of cycling through periods of OMT and untreated opioid dependence. Patients surveyed in the UK and Denmark, for example, had previously been in treatment 3.6 and 3.7 times on average, respectively, suggesting that many patients in these countries cycle in and out of treatment more than four or five times. In contrast, patients in Greece and France had just 0.2 and 0.6 previous OMT episodes on average, respectively, suggesting many were engaged in their first episode of treatment. The current methodology does not allow us to ascertain definitively the reasons for this variation, and our results must be interpreted in light of the limited sample sizes within each country. However, it is possible that the structure of treatment may be contributing to how frequently patients cycle in and out of treatment. Notably, France, with the second lowest average number of previous treatment episodes, has adopted a different model of treatment access compared with many countries, which includes predomi-

nant delivery of treatment in primary-care settings rather than in specialist addiction clinics. The use of primary-care settings to deliver OMT may encourage those opioid users to enter treatment more easily (e.g., owing to accessibility, lower stigma) and to stay in contact with treatment at higher rates due to the normalised treatment setting, in contrast to countries such as the UK and Denmark which utilise specialist clinics. It should be noted, however, that psychiatric comorbidity, which occurs frequently in opioid-dependent patients (9), may require the support of psychiatrists and specialised clinics for diagnosis and treatment.

The low number of prior treatment episodes in Greece, despite the specialist clinic treatment model, is likely due to long waiting lists (often up to 7 years or more), causing patients to stay in treatment at high rates once they are finally able to access it. However, other explanations for these findings cannot be excluded.

Irrespective of the reasons why patients cycle in and out of OMT, these results support the link between treatment cessation and the likelihood of negative consequences in a substantial proportion of individuals. The primary consequences of stopping OMT, as reported by patients and users, included relapse to use of illegal drugs, increased use of illegal drugs and increased involvement in criminal activity. There is,

therefore, a clear need to assess both the opportunities that exist for reducing the number of treatment–relapse cycles each patient experiences and the barriers that may make it difficult to access or remain in treatment (see article by Benyamina & Stöver in this issue).

4.2. Non-compliance: misuse and diversion

If OMT medications are not taken by the intended recipient, by the intended route of administration, or at the correct dose, the likelihood of positive outcomes may be reduced and there may also be an increase in the potential for harm. These harms include opioid toxicity, overdose and transmission of infectious diseases due to injecting, and may affect either the patients themselves or third parties (e.g., out-of-treatment users, children). As reported in the article by Dale-Perera, Goulão & Stöver in this issue, a significant minority of patients in EQUATOR have reported either misusing or diverting their medication at some point. The most common reasons for misuse resembled the reasons separately stated for continuing use of illicit heroin or other drugs; namely: to get high occasionally. This raises the question as to whether patients are receiving adequate therapeutic doses of their medications to control cravings, or indeed adequate additional support (e.g., psychosocial counselling).

The results presented in this article also extend our knowledge by examining how reported misuse and diversion (viewed as clinical compliance outcomes) vary according to groups of patients receiving different OMT medications. It is important to note that we have assessed the proportion of patients who have ever diverted/misused their medication, but not the frequency with which they have done so. Past misuse by injection was more frequently reported by patients currently receiving SROM (54%). The pharmacology of SROM may make it more attractive to those who wish to misuse their OMT medication by injecting it: firstly, morphine is the major product of heroin metabolism (20), and secondly, the oral bioavailability of morphine is approximately 30% meaning that if the slow-release feature is disabled by crushing the tablets, intravenously injected doses could deliver several times the oral dose equivalent (16). The levels of supervision applied to each medication should also be taken into account when considering the differences between reported diversion across countries as observed dosing is primarily deployed to limit diversion (and ensure compliance). For example, some medication options are more likely to be administered in an observed setting whereas buprenorphine–naloxone was far more likely to be administered unsupervised (see article by Dale-Perera, Goulão & Stöver in this issue).

The consequences of misuse and diversion may differ according to the OMT in question. For example, as a partial μ opioid receptor agonist, buprenorphine is associated with a ceiling effect such that, beyond this dose, larger doses of buprenorphine are not associated with any greater effect (22). As a result, there is a greater margin of safety from overdose-related death by respiratory depression when increased doses of buprenorphine are used, compared with increased doses of full opioid agonists such as methadone. In the case of buprenorphine–naloxone, if injected by a dependent opioid user, the naloxone component is likely to deter subsequent misuse as it inhibits the effects of opioids and may precipitate withdrawal (18). Attempts have been made to limit misuse or diversion of methadone by the widespread use of less concentrated, highly viscous and/or less injectable liquid forms. Conversely, for buprenorphine, the more easily abused mono-buprenorphine formulation remains widely used even though the buprenorphine–naloxone formulation predominates in many countries (e.g., Italy, Greece, Spain, Netherlands, the US, Canada, Australia, Finland).

Diversion also indicates the bottlenecks of OMT provision in several European countries, and may be regarded as a mutual support system in which users help each other in facilitating self-treatment and managing craving (4) under situations where access to OMT might be restricted or too high-threshold.

4.3. On-top heroin use

One of the primary goals of OMT is to achieve reductions in heroin use. According to the data presented here, OMT is associated with a significant reduction in the proportion of patients self-reporting heroin use. This reduction was evident for each of the three main medication options, with significantly different (p<0.001) proportions of patients reporting on-top heroin use across the medications; patients receiving buprenorphine–naloxone reported the lowest rate, patients receiving methadone reported the highest rate. This may reflect the different pharmacological properties of methadone and buprenorphine and specifically the blockading effects of the latter (21). Alternatively, due to the non-randomised nature of this comparison, these findings could also be influ-

enced by pre-selection bias; for example, physicians may prescribe buprenorphine to patients who they consider to be more stable or more motivated to cease illicit heroin use.

Despite the reduction in the proportion of OMT patients self-reporting heroin use, our results show that a high proportion of patients in EQUATOR continued to use illicit drugs, and a substantial proportion reported doing so frequently. Data from the Treatment systems Research on European Addiction Treatment (TREAT) project indicate even higher levels of on-top heroin use across Europe: approximately 30% of patients reported that they consumed heroin on more than 25 days in the past month and another 30% on 5–24 days (19). Therefore, for many patients, current treatment systems are failing to achieve one of the primary desired outcomes of OMT. We also observed significant between-country variations in the proportions of patients using heroin in addition to their OMT, with the highest rates evident in Denmark, the UK and Germany, and the lowest rates evident in Portugal and France. These between-country comparisons are subject to limitations, including variable sample sizes across countries, but are nonetheless informative in identifying countries for which continuing on-top heroin use is a particular problem. Patients who fail to derive adequate benefit from OMT based on their continued use of heroin may be more liable to drop out of treatment. Consistent with this hypothesis, the UK and Denmark had both the highest levels of on-top heroin use and the highest number of prior OMT episodes. When patients were asked why they use, the most common responses were to get high or that their OMT did not control cravings. Both of these answers may be consistent with a failure to adequately suppress cravings, which in turn may be due to subtherapeutic dosing. Indeed, previous surveys have shown that it is common in the major countries of Europe for lower-than-recommended doses of both methadone and buprenorphine to be used (3). It is important to note that many patients were not accessing psychosocial support, as reported elsewhere (see article by Dale-Perera, Goulão & Stöver in this issue), and evidence suggests better outcomes are achieved when pharmacotherapy is combined with other support (23). It should be noted that our analyses are not stratified by duration of treatment; heroin use on top of OMT might be expected in unstable patients newer to treatment but it is not possible to determine whether this assumption is supported by our analysis.

5. Conclusions

In summary, our findings suggest that current systems of treatment for opioid dependence may be failing to achieve basic optimal outcomes in a substantial proportion of patients. This is evident by patients who report high rates of cycling in and out of OMT, past misuse or diversion of their medication, and continuing on-top heroin use despite being in OMT. Wanting to get high and failure of the OMT medication to adequately suppress cravings were identified by patients as reasons underlying both continued illicit drug use and misuse of their OMT medication. Collectively, building on the results presented in the other articles in this series, these findings raise concerns about whether current interventions are being optimised to deliver on harm-reduction goals, and to achieve recovery. Many patients in EQUATOR had not been exposed to the full range of treatment options available to them, despite repeated past treatment episodes, indicating repeated attempts with failed interventions. Continuing to offer patients the same treatment options each time they cycle in and out of OMT, or failure to achieve a dose that adequately suppresses cravings, constitutes a significant missed opportunity to optimise individual treatment and to capitalise on the significant benefits of OMT to the individual and society.

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Contributors

GF analysed and interpreted the data, critically reviewed the manuscript and had final responsibility for the decision to submit the paper for publication. FN critically reviewed the manuscript and had final responsibility for the decision to submit the paper for publication. HS designed the original Project IMPROVE questionnaires, participated in the survey, analysed and interpreted the data, critically reviewed the manuscript and had final responsibility for the decision to submit the paper for publication.

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Assessing the current state of public-health-related outcomes in opioid dependence across Europe: data from the EQUATOR analysis

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Summary

Many opioid users across Europe remain outside treatment, and not all of those in treatment derive optimal benefit. The European Quality Audit of Opioid Treatment (EQUATOR) analysis shows that opioid-dependent people report high levels of polydrug use, high rates of unemployment and past imprisonment, and significant physical and mental health comorbidities regardless of whether they are currently in or out of treatment. Improved strategies are required to deliver the benefits of treatment while managing the risks of non-compliance (e.g., misuse/diversion/drug use). Treatment systems should be judged by their ability to effectively reduce harm and promote individual recovery and social reintegration.

Key Words: comorbidities, diversion, employment, illicit drug use, prison

1. Introduction

Opioid dependence is a complex, chronic condition that causes substantial harm to individuals and to wider society. Opioid users are at risk of overdose, increased mortality and comorbidities (e.g., infectious diseases (30)). The high economic burden associated with opioid dependence predominantly comprises crime-related, healthcare and social-welfare costs (30). In assessing the overall success of treatment for opioid dependence, it is therefore important to consider both clinical and the wider societal and public-health outcomes. Moreover, these outcomes should be considered for the opioid-dependent population as a whole, taking into account the outcomes of both patients in treatment and opioid users who remain outside of treatment, the latter being particularly burdensome on the system.

Recently, there has been significant evolution in drug-related policy goals across many countries. Harm reduction, which has been the standard for over 20 years, has remained an important goal, supported by evidence that harm-reduction strategies, such as needle exchanges and drug consumption rooms coupled with opioid-maintenance treatment (OMT), cost-effectively reduce the spread of blood–borne viral (BBV) infections and drug-related deaths (18,29).

However, there is a growing trend in many countries to build on the success of harm-reduction strategies by adding more ambitious 'recovery-oriented' goals focused on reintegration into society and improvement in patients' quality of life. Countries that

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emphasise recovery in their drug treatment strategies include England, Scotland, Ireland, Australia, Germany and the US (2,5,13,17). Recovery-orientated approaches recognise the need to ensure individuals have access to a broad range of support, delivered with an individual focus, with the goal of improving the individual's quality of life and capacity to reintegrate fully into society (e.g., through enhanced relationships and employment). The increasing emphasis on recovery stems from the recognition that reducing drug-related harms is only the first step in successful treatment of opioid dependence. Indeed, at a patient level, desired outcomes from treatment are typically not limited to a reduction in drug use and related risks, but also encompass improvements in health, well-being and social functioning, and rebuilding relationships, stopping criminal activities and finding employment. These targets represent important steps in an individual's recovery journey towards a more 'normal' life.

Given the high cost of untreated opioid dependence, it is vital to consider the wider consequences of the current, variable approaches to opioid-dependence treatment across Europe. This is particularly important given the current economic climate in Europe, which necessitates a continuous assessment of the cost-effectiveness of treatments in all areas.

The European Quality Audit of Opioid Treatment (EQUATOR) analysis is designed to characterise the current state of treatment provision in Europe from the perspective of opioid users not currently in OMT, opioid-dependent patients currently in OMT, and the physicians who treat opioid-dependent patients. The current article examines a broad range of outcome variables that reflect whether current treatment systems are effectively reducing the societal burden of opioid dependence, such as by improving health and wellness, reducing prison episodes and enabling employment. Exploring the impact of different treatment systems and approaches on the ability to achieve the desired public-health-related outcomes can provide useful insights to guide drug treatment policy changes in the future.

2. Methods

Detailed methodology for the EQUATOR analysis has been described previously (14). Briefly, questionnaires were compiled comprising a core set of questions specific for three target groups: opioid users not currently in OMT (50 questions per survey),

opioid-dependent patients currently in OMT (50 questions per survey), and physicians involved in the treatment of opioid-dependent patients (60 questions per survey).

Survey data were collected in each country in accordance with the European Pharmaceutical Market Research Association (EphMRA) code of conduct and the Declaration of Helsinki. Information on sample sizes and demographics of patients, users and physicians in the survey is described elsewhere in this series of articles (see article by Goulão & Stöver in this issue).

This article presents data from the analysis that has particular relevance to public health, including the level of illicit drug use (both illegal drugs and diverted OMT medications not originally prescribed to the individual), mental and physical health, experience of prison, and participation in employment. Data are presented as frequencies or means for the purpose of making comparisons between patients and users or between countries. All categorical comparisons were performed using Pearson's Chi-squared (χ^2) with standardised residuals being used for post-hoc comparisons. Linear variables were analysed by either using student's t-test or analysis of variance (ANOVA) with Tukey's for post-hoc comparisons. Imprisonment data from patients and users were combined to assess prior incarceration history independent of current treatment status. Data on multiple aspects of physical and mental health were collected from participants; however, only some of the most noteworthy are presented here. Significance was ascribed for $p \leq 0.05$.

3. Results

3.1. Illicit drug use by OMT patients and out-of-treatment users

As expected, the analysis showed that patients in OMT were less likely than out-of-treatment users to take heroin ($p < 0.01$; Table 1). However, 60% of patients in the pan-European sample reported that they continued to use illicit drugs while in treatment and 28% of patients reported that they took illegal drugs at least once a week. The reported concomitant use of illicit benzodiazepines was significantly higher in patients than in out-of-treatment users (36% of patients reported that they were currently using benzodiazepines not prescribed to them whereas 24% of users reported they were currently using benzodi-

Table 1. Current use of illicit drugs by patients and users across the European sample

	Patients N=2298	Users N=887	Difference
Alcohol only, %	9.9	2.0	χ^2=55.52, df=1, n=3054, p<0.01
Heroin, %	28.9	66.7	χ^2=373.73, df=1, n=3054, p<0.01
Cocaine, %	14.9	19.7	χ^2=10.84, df=1, n=3185, p<0.01
Crack, %	7.3	14.0	χ^2=34.74, df=1, n=3185, p<0.01
Benzodiazepines not prescribed to me, %	36.2	24.3	χ^2=39.02, df=1, n=2693, p<0.01
Methadone not prescribed to me, %	8.9	18.8	χ^2=47.48, df=1, n=2257, p<0.001
(Mono) buprenorphine not prescribed to me, %	4.5	15.9	χ^2=88.63, df=1, n=2304, p<0.001
Buprenorphine–naloxone not prescribed to me, %	2.5	6.0	χ^2=17.27, df=1, n=2182, p<0.01

Percentages given here are of those individuals who answered the question.
Questions posed to patients and users were not identical. The following questions were judged to be the most accurate assessments of current drug use: *'Which drugs or substances are you still currently taking in addition to your prescribed substitution medication? Please tick for each substance in the table how often you are currently using it'* (patients; 'regularly' and 'sometimes' responses were counted) and *'Please indicate for each drug you are currently using on a regular base whether you inject, sniff, smoke or swallow it. For drugs you don't currently use on a regular base, just leave the line blank'* (users; all responses were counted).

azepines; p<0.01). Patients also reported higher use of alcohol only (p<0.01), compared with users. Fewer patients than users reported using all other drug categories (e.g., cocaine: p<0.01; crack: p<0.01).

Patterns of illicit drug use for patients and users showed variation across country samples (see article by Fischer, Nava & Stöver in this issue for detailed consideration of heroin use by country among patients). Illicit benzodiazepine use also differed by country for both patients and users (p<0.01 for both; Table 2). The highest level of benzodiazepine use was reported by patients in Denmark (73% of sampled patients), and benzodiazepine use was reported by more than 25% of sampled patients and users in Denmark, Norway, Sweden and the UK. In comparison, fewer patients used benzodiazepines in Portugal and Italy. Crack use by patients and users varied between countries (Table 2; p<0.01 for both patients and users), and was reported by more than 30% of patients and users in the UK, 10% of patients and 34% of users in Portugal, 10% of patients and 18% of users in France, and 13% of users in Germany; crack use was rare in all other countries sampled. Powder cocaine use by patients and users varied by country as well (p<0.01 for both patients and users). Cocaine use was reported by approximately 30% of patients and users in Austria, 14% of patients and 18% of users in France, nearly 50% of users in Denmark, and nearly 70% of users in Portugal (Table 2).

3.2. Use of diverted OMT medications

Both patients and out-of-treatment users in the pan-European sample reported current use of OMT medications not prescribed to them (Table 1). Users were more likely than patients to report use of each of the three OMT options (methadone: p<0.001; mono-buprenorphine: p<0.001; buprenorphine–naloxone: p<0.01). Methadone was the diverted OMT medication used by the highest percentage of patients and users; mono-buprenorphine and buprenorphine–naloxone were used less frequently.

Current use of diverted OMT medications differed across Europe (Table 2). Diverted methadone was used most frequently in the Nordic regions. In Denmark, 57% of patients reported using diverted methadone, while more than 50% of users reported using diverted methadone. In Norway, 40% of users reported using diverted methadone and 15% of patients; 26% of users and 21% of patients did so in Sweden. Current use of diverted mono-buprenorphine was reported by 51% of users in Norway, 32% in Sweden and 29% in Greece. In comparison, 29% of users and 14% of patients in Norway and 22% of users in Sweden reported using diverted buprenorphine–naloxone, and this figure was much lower (between 0–8%) in all other countries sampled (between-country difference for both patients and users: p<0.01).

3.3. Health and comorbidities

Patients and users were asked to rate both their physical and mental health on a 5-point Likert scale (1= very good; 5= very poor). Patients generally rated both their physical and mental health statistically bet-

Table 2. Current use of illicit drugs by patients and users across the country samples

	Austria Pts N=228	Austria Users N=50	Denmark Pts N=103	Denmark Users N=27	France Pts N=130	France Users N=33	Germany Pts N=200	Germany Users N=200	Greece Pts N=601	Greece Users N=150	Italy Pts N=378	Norway Pts N=98	Norway Users N=70	Portugal Pts N=160	Portugal Users N=50	Sweden Pts N=152	Sweden Users N=111	UK Pts N=248	UK Users N=196	Difference between countries
Alcohol only, %	8.9	4.0	3.4	7.4	18.2	3.4	8.0	2.0	5.2	0	14.1	5.5	2.9	13.8	0	14.2	2.7	14.0	2.0	Patients: $\chi^2=47.94$, df=9, n=2171, p<0.01 Users: $\chi^2=9.79$, df=8, n=883, p=0.280
Heroin, %	20.6	40.0	56.2	48.1	15.7	48.3	41.5	89.0	21.6	91.3	34.0	28.6	62.9	13.1	100.0	28.4	23.4	45.1	54.6	Patients: $\chi^2=134.21$, df=9, n=2171, p<0.01 Users: $\chi^2=242.40$, df=8, n=883, p<0.01
Cocaine, %	29.4	30.0	24.3	48.1	13.8	18.2	18.5	16.5	5.8	22.7	20.1	5.1	12.9	17.5	68.0	7.2	14.4	16.5	7.7	Patients: $\chi^2=109.82$, df=9, n=2298, p<0.01 Users: $\chi^2=114.96$, df=8, n=887, p<0.01
Crack, %	4.8	2.0	1.9	0	10.0	18.2	5.5	13.0	0.2	0	3.2	4.1	5.7	10.0	34.0	2.0	6.3	37.9	32.1	$\chi^2=418.05$, df=9, n=2298, p<0.01 Users: $\chi^2=115.22$, df=8, n=887, p<0.01
Benzodiazepines not prescribed to me, %	36.0	24.0	73.2	25.9	25.0	12.1	29.5	22.0	63.3	13.3	7.9	67.1	45.7	10.0	6.0	54.4	39.6	29.0	25.0	Patients: $\chi^2=360.20$, df=9, n=1806, p<0.01 Users: $\chi^2=53.98$, df=8, n=887, p<0.01
Methadone not prescribed to me, %	5.7	10.0	56.9	51.9	7.1	3.0	9.5	11.5	2.9	21.3	2.6	15.1	40.0	5.3	4.0	21.3	26.1	6.9	16.8	Patients: $\chi^2=188.67$, df=9, n=1370, p<0.01 Users: $\chi^2=66.95$, df=8, n=887, p<0.01
(Mono-) buprenorphine not prescribed to me, %	9.6	16.0	5.0	11.1	8.2	6.1	2.5	3.5	4.1	29.3	0	15.7	51.4	6.7	2.0	11.6	31.5	2.0	2.6	Patients: $\chi^2=65.64$, df=9, n=1417, p<0.01 Users: $\chi^2=165.83$, df=8, n=887, p<0.01

Table 2. Current use of illicit drugs by patients and users across the country samples

	Austria Pts N=228	Austria Users N=50	Denmark Pts N=103	Denmark Users N=27	France Pts N=130	France Users N=33	Germany Pts N=200	Germany Users N=200	Greece Pts N=601	Greece Users N=150	Italy Pts N=378	Norway Pts N=98	Norway Users N=70	Portugal Pts N=160	Portugal Users N=50	Sweden Pts N=152	Sweden Users N=111	UK Pts N=248	UK Users N=196	Difference between countries
Buprenorphine–naloxone not prescribed to me, %	7.5	6.0	0	7.4	0	0	0	1.5	NA	0	0	14.0	28.6	0	2.0	6.6	21.6	1.2	0	Patients: χ^2=76.08, df=8, n=1295, p<0.01 Users: χ^2=144.71, df=8, n=887, p<0.01

NA: not applicable; Pts: patients
Percentages here are of those participants who answered the question
Questions posed to patients and users were not identical. The following questions were judged to be the most accurate assessments of current drug use: 'Which drugs or substances are you still **currently** taking in addition to your prescribed substitution medication? Please tick for each substance in the table how often you are currently using it' (patients; 'regularly' and 'sometimes' responses were counted) and 'Please indicate for each drug you are currently using on a regular base whether you inject, sniff, smoke or swallow it. For drugs you don't currently use on a regular base, just leave the line blank' (users; all responses were counted).

ter than users (p<0.01 for physical health; p<0.01 for mental health).

Patients' and users' self-reported levels of physical and mental health differed among countries (Tables 3 and 4). The most marked overall difference in patients' and users' ratings of physical and mental health were in Greece, where users rated their health substantially worse than patients (physical health: mean score 3.18 *vs* 2.83, t=–4.78, df=749, p<0.01; mental health: mean score 3.77 *vs* 3.13, t=–7.75, df=749, p<0.01, respectively). Notably lower health ratings among users versus patients were also found in France (physical health: mean scores 2.85 *vs* 2.34, respectively, t=–3.38, df=159, p<0.01; mental health: mean scores 3.06 *vs* 2.53, respectively, t=–3.37, df=158, p<0.01).

Rates of self-reported HIV infection were generally low across Europe; however, variation in rates differed by country for patients (p<0.01) and for users (p<0.01) as there were significantly higher rates in Portugal (22% of patients and 34% of users) compared with other countries, e.g., the UK and Greece, where self-reported rates were less than 2% in both subgroups. The rate of self-reported hepatitis C virus (HCV) infection was high in most countries but still differed between them in both patients (p<0.01) and users (p<0.001). More than 60% of patients in Germany, Sweden, Norway, and Greece self-reported HCV while less than 30% did so in the UK and France. For users, self-reported rates of HCV were particularly high in Sweden (61%) while rates in the UK and Austria were lower (28% and 14%, respectively). In most countries, HCV infection was more commonly reported by patients than by users while only in Portugal and France were rates of self-reported HCV infection substantially higher among users than patients (Tables 3 and 4).

The rate of self-reported hepatitis B virus (HBV) infection also varied substantially between users and patients (χ^2=123.31, df=9, n=3185, p<0.01), and also varied between countries (patients: p<0.01; users: p<0.01). Among patients, 5% in France reported being HBV positive compared with 28% in Sweden. Among users, the self-reported incidence of HBV infection ranged from 0% in France to 23% in Sweden. In most countries, HBV infection was more commonly reported by patients than by users, with the exception of Greece, Norway and Portugal where the reported HBV infection rates were higher in users than in patients (Tables 3 and 4).

Self-reported history of depression was generally high across Europe, differing across countries

Table 3. Health comorbidities self-reported by patients from across Europe
Data based on the question *'Which of the following health problems have you been experiencing since you have been taking drugs?'*

	Austria N=228	Denmark N=103	France N=130	Germany N=200	Greece N=601	Italy N=378	Norway N=98	Portugal N=160	Sweden N=152	UK N=248	Difference between countries
Physical health rating											
Mean (SD) Likert rating (1= very good; 5= very poor)	2.55 (0.96)	2.90 (0.98)	2.34 (0.76)	2.73 (0.86)	2.83 (0.83)	2.35 (0.84)	2.41 (1.20)	2.39 (0.83)	2.48 (0.97)	ND	$F=13.96$, df=8, 2017, $p<0.01$
Infectious disease status											
Self-reported HIV status, %	2.6	1.0	4.6	5.0	1.7	3.2	2.0	21.9	3.3	1.2	$\chi^2=155.85$, df=9, n=2298, $p<0.01$
Self-reported HCV status, %	42.1	47.6	23.1	63.0	63.7	43.4	65.3	43.8	77.6	27.0	$\chi^2=219.05$, df=8, n=2298, $p<0.01$
Self-reported HBV status	11.8	25.2	4.6	18.0	4.7	10.1	16.3	13.8	27.6	9.3	$\chi^2=105.12$, df=9, n=2298, $p<0.01$
Self-reported overdose, %	18.4	19.4	2.3	31.0	31.8	7.4	50.0	5.6	27.0	21.4	$\chi^2=195.32$, df=9, n=2298, $p<0.01$
Mental health rating											
Mean (SD) Likert rating (1= very good; 5= very poor)	2.76 (1.18)	3.00 (1.17)	2.53 (0.81)	2.93 (0.92)	3.13 (0.94)	2.34 (0.85)	2.70 (1.13)	2.26 (0.76)	2.50 (1.02)	2.86 (1.07)	$F=25.77$, df=9, 2208, $p<0.01$
Self-reported depression, %	60.5	55.3	36.9	65.5	73.5	45.5	73.5	40.6	55.3	76.2	$\chi^2=172.96$, df=9, n=2298, $p<0.01$
Self-reported anxiety, %	41.2	48.5	54.6	44.0	69.4	51.3	69.4	63.1	53.3	72.6	$\chi^2=115.84$, df=9, n=2298, $p<0.01$

ND: no data available

Table 4. Health comorbidities self-reported by users from across Europe
Data based on the question *'Which of the following health problems have you been experiencing since you have been taking drugs?'*

	Austria N=50	Denmark N=27	France N=33	Germany N=200	Greece N=150	Norway N=70	Portugal N=50	Sweden N=111	UK N=196	Difference between countries
Physical health rating										
Mean (SD) Likert rating (1= very good; 5= very poor)	2.56 (1.03)	2.96 (1.22)	2.85 (0.80)	3.01 (0.91)	3.18 (0.67)	2.80 (1.14)	2.70 (0.89)	2.55 (1.10)	ND	F=5.63, df=7, 674, p<0.01
Infectious disease status										
Self-reported HIV status, %	2.0	0	9.1	3.5	1.3	1.4	34.0	8.1	1.5	$\chi2$=109.47, df=8, n=887, p<0.01
Self-reported HCV status, %	14.0	25.9	30.3	51.5	52.7	41.4	56.0	61.3	27.6	$\chi2$=71.64, df=8, n=887, p<0.01
Self-reported HBV status, %	2.0	18.5	0	12.0	8.0	17.1	18.0	22.5	8.2	χ^2=30.97, df=8, n=887, p<0.01)
Self-reported overdose, %	26.0	25.9	3.0	34.0	54.0	42.9	10.0	19.8	31.1	χ^2= 69.67, df=8, n=887, p<0.01
Mental health rating										
Mean (SD) Likert rating (1= very good; 5= very poor)	2.85 (1.11)	2.92 (1.16)	3.06 (0.83)	3.21 (1.03)	3.77 (0.77)	2.79 (1.22)	2.30 (0.76)	2.73 (1.19)	2.93 (1.02)	F=15.98, df=8, 851, p<0.01
Self-reported depression, %	60.0	44.4	33.3	61.0	78.7	77.1	38.0	38.7	75.0	χ^2=91.97, df=8, n=887, p<0.01
Self-reported anxiety, %	46.0	22.2	45.5	33.0	74.0	70.0	68.0	51.4	67.9	χ^2=99.15, df=8, n=887, p<0.01

ND: no data available

Table 5: Prison episodes experienced by patients and users in the pan-European sample

		Patients and users (N=3161)
Ever in prison		45.4% (n=1431)
Mean no. of prison episodes		3.40
Total time in prison	≤1 year 2–5 years 6–9 years 10+ years	47.0% (n=619) 34.2% (n=451) 12.5% (n=164) 6.3% (n=83)
Mean no. of prison episodes for drug-related offences		3.27 (n=863)
In OMT before prison		35.8% (n=504)
OMT continuation upon prison entry	Continued Stopped completely Changed OMT drug Received counselling	62.6% (n=256) 27.4% (n=112) 7.8% (n=32) 2.2% (n=9)

(p<0.01) and between patients and users (χ^2=254.24, df=9, n=,3185, p<0.01). The highest rates were evident in the UK (76% of patients and 75% of users), Greece (74% of patients and 79% of users), Norway (74% of patients and 77% of users), and Germany (66% of patients and 61% of users). A similar profile was observed for self-reported history of anxiety (Tables 3 and 4) (patients vs users: χ^2=202.69, df=9, n=3185, p<0.01).

Across Europe, significantly fewer patients (22%) reported previous overdose compared with us-

ers (33%) (χ^2=257.68, df=9, n=3185, p<0.01). For patients, the percentage of patients reporting previous overdose varied between 50% in Norway and 2% in France; the percentage of users reporting previous overdose varied between 54% in Greece and only 3% of users in France (Tables 3 and 4).

3.4. Prison episodes

No surveys were conducted in prisons; therefore, user and patient data on prison episodes were

Figure 1: Proportion of patients and users stating they were currently employed. Combined data for those patients and users stating they were in full-time or part-time employment. Italy had no user sample.
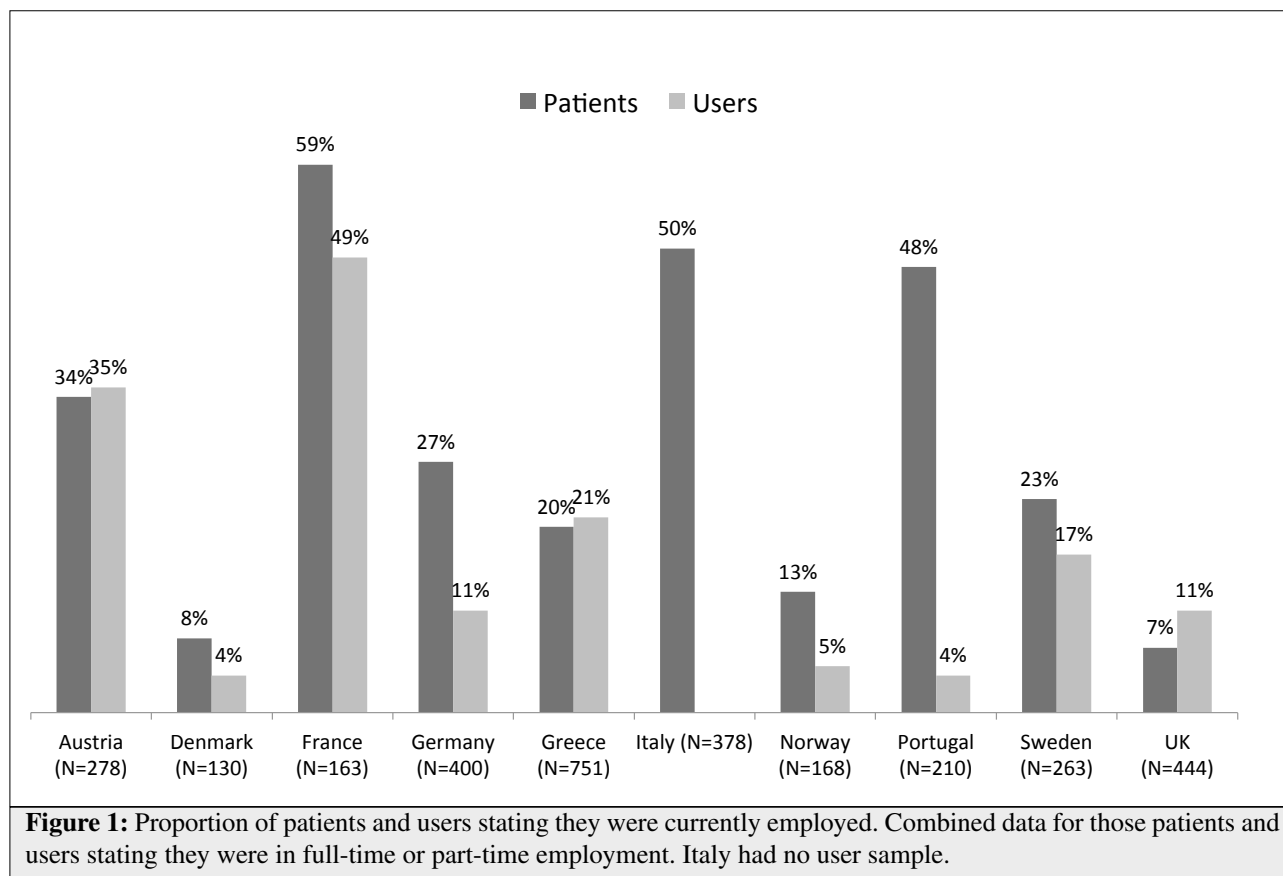
retrospective. These data were considered together to assess incarceration history independent of current treatment status (Table 5).

Almost half of opioid-dependent individuals (45%) in the pan-European sample reported having been in prison, and on average they had been in prison more than three times (mean 3.4 times). Among those who had been in prison, almost half (47%) had been there for less than 1 year and more than one-third (34%) for between 2 and 5 years. For the entire sample, the mean number of times in prison for drug-related offences was 3.27. Approximately one-third of opioid-dependent individuals (36%) were in OMT before entering prison, and of these, only 63% continued their OMT in prison.

3.5. Employment

The proportion of individuals reporting full- or part-time employment varied across the countries (patients: χ^2=281.82, df=9, n=2256, p<0.01; users: χ^2=66.66, df=8, n=859, p<0.01). Notably, more than half of patients in France were employed (Figure 1), the highest among the participating countries. The UK and Denmark had the lowest reported employment rates among patients, with just 7% and 8% of patients employed, respectively. With the exception of the UK, Greece and Austria, which had similar proportions of patients and users in employment, there was generally a lower percentage of users compared with patients in employment across the countries surveyed (χ^2=357.29, df=9, n=3115, p<0.01). Significantly more patients receiving mono-buprenorphine or buprenorphine–naloxone were in employment (36.1% and 36.4%) compared with patients receiving methadone or slow-release oral morphine (26.4% and 20.0%; χ^2: 26.81, df=3, n=2173, p<0.01).

4. Discussion

The findings of the EQUATOR analysis confirm the significant and far-reaching consequences of opioid dependence for both the individual and society. Despite the proven benefits of OMT in reducing illicit opioid use, treatment systems face a number of broader challenges, including: high rates of ongoing polydrug use; wasted resources and potential harms due to diversion and misuse of OMT medication; high rates of infectious and psychiatric comorbidities; lost productivity and associated social-welfare costs resulting from low rates of employment; and missed opportunities for engaging patients and users in treat-

ment while in prison.

4.1. Illicit drug use

While patients reported lower levels of heroin use compared to pre-treatment levels and in comparison to users, the extent of this reduction is disappointing. Patients continued to use a variety of illicit drugs, including heroin, at high rates, and thus continue to be exposed to the risks and consequences of illicit drug use. The extent of polydrug use is also cause for concern as it increases the complexity of treatment, reduces the likelihood of success and increases the potential for adverse reactions (7). Current use of crack cocaine and powder cocaine was high in many countries, while substantial proportions of patients and users reported using diverted benzodiazepines (i.e., not prescribed to them). The levels of illicit drug consumption reported by users in EQUATOR are broadly comparable to those reported in the TREAT project: 27% of opioid-dependent individuals entering treatment from six European cities in Germany, Greece, Italy, Sweden, Switzerland and the UK reported using benzodiazepines on more than 5 days per month and 19% reported using cocaine on more than 5 days per month (24). Benzodiazepines can interact with opioids to produce greater sedation and drug effects, and increase the potential for overdose and opioid-related fatalities (20). Beyond safety considerations, benzodiazepine–opioid interactions also have implications for recovery including potential impaired cognitive ability, which could preclude driving or manual work and limit employability (20). Collectively, these findings suggest that current treatment systems are failing to eliminate or even reduce illicit drug use, which is one of the primary desired outcomes of treatment.

4.2. Use of diverted OMT medications

The results of EQUATOR confirm that OMT medication diversion occurs across all the participating European countries. As discussed in an earlier article (see article by Dale-Perera, Goulão & Stöver in this issue), almost one-quarter of patients reported that they had diverted their OMT. The primary reasons for this were to help others to treat themselves, to help others satisfy their cravings or get high, or as a source of income. Findings reported here extend our knowledge by highlighting that up to one-sixth of opioid users are choosing to remain outside the treatment system but to consume diverted OMT medi-

cations. Notably, use of diverted OMT medications by out-of-treatment users was more widespread in Greece (21% and 29% of users reported using methadone and mono-buprenorphine, respectively), where access to OMT is poor, than in France, which has good access to OMT.

4.3. Implications of use of diverted OMT medications for treatment provision

Medication diversion occurred across all the participating countries. However, there was little evidence to demonstrate that countries with higher levels of control and supervision (e.g., Greece, Italy, Portugal) are achieving a significant reduction in misuse/diversion versus countries with fewer controls (e.g., France). Use of diverted OMT appears to be more widespread in countries where access to OMT is poor (e.g., Greece, Sweden). In addition, supervised dosing is unpopular with patients (4) and may impact negatively on treatment entry and retention, supported by the current analysis (see article by Benyamina & Stöver in this issue).

The EQUATOR analysis also showed that use of diverted methadone and mono-buprenorphine was more common than use of buprenorphine–naloxone, consistent with evidence that mono-buprenorphine is more desirable for abuse than the buprenorphine–naloxone combination (1). The different rates of diversion may in part reflect the different prescribing volumes for each medication, but may also reflect their different pharmacological profiles (23). Despite the evidence that different OMT medications carry different levels of risk with regard to misuse, few of the European countries sampled in EQUATOR currently have systems of treatment provision that differentiate based on the different safety and abuse profiles of these OMT options. For example, in Austria, slow-release morphine is associated with a high level of injection misuse, and may therefore warrant a higher level of control (as suggested by Austrian treatment guidelines) than is actually applied in practice. Conversely, preparations that may be less readily divertible and abusable (such as buprenorphine–naloxone rather than mono-buprenorphine and diluted oral methadone solution rather than methadone tablets) may require a lower level of control.

Beyond the clinical consequences, diversion of controlled OMT medications is illegal and potentially has serious legal implications for the individuals involved. Diversion also has societal implications in terms of the wasted cost of the medication not being

taken by the intended recipient, the impact of diversion and trafficking on criminal justice resources, and the potential harms (e.g., spread of BBV infection) that could result from non-medical use of opioids. It is clear that consumption of diverted OMT is a complex, substantial problem with health, legal and economic implications for both the individual and society. Diversion of OMT medication may be a symptom indicating that OMT services are not adequately adjusted to the needs of patients, resulting in underprescribing, disempowerment and disengagement with treatment (6). Improving treatment access and encouraging the use of medication options that are abuse-deterrent are two ways to discourage diversion and limit the associated negative public-health consequences.

4.4. Health status of opioid-dependent individuals

The majority of patients surveyed reported being infected with HCV (mean 51% across all countries, n=2325) with wide variation between the countries. This is consistent with European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) data showing that HCV antibody prevalence varied from 22 to 83% in national samples of injecting drug users (IDUs) across Europe in 2008–09, and was more than 40% in eight of 12 countries (8) and with data from the TREAT study in which 57% of opioid-dependent individuals entering treatment reported an HCV infection (24). The fact that users in the EQUATOR analysis were less likely to report being HCV-positive compared with patients may also reflect differences in exposure to screening and diagnosis, as many patients are screened upon entry and thus more likely to be aware of their HBV/HCV status.

The self-reported HIV infection rate was relatively low in all countries except Portugal. This is consistent with data from EMCDDA suggesting that the rate of new HIV infections in IDUs in Portugal remains relatively high (13.4 per million population) (8). In contrast, the incidence rate of HIV in this population is declining in most European countries, and the prevalence of HIV has declined among IDUs since 2004 in France, Austria, Italy and Portugal.

These findings have important implications. Firstly, differences among countries in the prevalence of BBV infections may reflect differences in coverage of screening, the propensity to inject versus snort opioids, and/or the presence of harm-reduction strategies. For example, policies for screening on prison entry may influence awareness of HCV infection. EM-

CDDA data show that HCV testing on prison entry is extensive in Sweden, Portugal, Austria, Spain and Greece, limited in Germany, and rare in the UK and France (there are no data for Norway, Italy or Denmark)(11). Where the EMCDDA reports HCV testing is rare, EQUATOR data showed a low level of self-reported HCV infection, indicating that viral infection rates may be underestimated in some countries and cannot therefore be assumed to be an indicator of systems with reduced risk. Secondly, when selecting appropriate OMT options for this population, it is necessary to give special consideration to co-morbid conditions and potential drug–drug interactions to ensure that anti-viral treatments do not compromise the efficacy or safety of OMT or vice versa. Notably, buprenorphine has fewer interactions with HIV antiretroviral therapies than methadone (3,15). Thirdly, patterns of HCV/HIV infection reinforce the need to invest in OMT. For example, OMT has been shown to reduce the risk and spread of HIV through reductions in risk behaviours and improved compliance with HIV medications (21,27). Finally, physical and mental health was generally rated better by patients in EQUATOR than by out-of-treatment users, consistent with previous evidence regarding the benefits of OMT. However, these differences in health ratings were typically of a small magnitude and not consistent across all countries. Moreover, many patients and users self-reported a history of anxiety or depression. These findings highlight the complex health needs of opioid-dependent patients and suggest there may be opportunities for improving how physical and mental health problems are addressed in conjunction with OMT.

4.5. *Prison history of opioid-dependent individuals*

Nearly half of patients and out-of-treatment users reported having been in prison at some point, on average 3.4 times, with most prison episodes being drug related. This confirms that many patients and users have repeated contact with the criminal-justice system as a result of the inter-relationship between drug dependence and crime (22). The costs of imprisonment are substantial compared with the costs of OMT, and it is interesting to note that the mean number of drug-related prison episodes experienced by patients and users exceeded the mean number of prior OMT episodes. This indicates that countries may be missing the opportunity to divert drug offenders into treatment or other alternatives to prison and/

or to engage users in treatment while in prison. Once in treatment, optimising the quality of care and outcomes patients experience is critical in maximising the likelihood that further drug-related offences can be avoided. The results of EQUATOR demonstrate that a significant proportion of both patients and users continue to use illicit drugs regularly. In the context of low employment rates reported by patients and users in most countries, and the fact that many patients report being in OMT when they entered prison, there is a possibility that in some cases their continued drug use may be financed by acquisitive crime or other illegal activities.

In the current framework, OMT in prison provides treatment continuity for patients receiving OMT before imprisonment while also providing a good opportunity to recruit opioid-dependent individuals into treatment (16). However, despite the benefits of OMT in prison (26), OMT is not available in the prison setting in several countries in Europe, Greece being among them (9). Among opioid-dependent individuals who were in OMT before their most recent prison episode, a quarter of individuals had to stop their OMT completely upon prison entry and 8% were required to switch treatments, indicating that the same treatment options that patients receive outside prison are not available to them once they entered the prison system.

Opioid-dependent inmates who discontinue OMT in prison carry a higher risk of overdose (26), higher mortality and a higher risk of reoffending after leaving prison than patients who continue their treatment (19). In some countries (e.g., the UK), denial of access to appropriate care in prison has been successfully challenged in the courts on the basis that it represents a breach of human rights. The unintended consequences of not providing treatment in prison should be evaluated from an economic point of view as well as from a basic human rights perspective.

4.6. *Employment*

Findings from EQUATOR demonstrate that employment levels are generally low for patients and users across Europe, and significantly lower than for people of a similar age in the general population across Europe (12). Notably, employment rates among patients showed significant variation across countries, with the highest levels being 50% or greater in France and Italy and the lowest levels (<10%) seen in the UK and Denmark. EMCDDA data show a similar pattern of low employment rates among outpatients entering

treatment for drug use (not only opioid use), with the lowest rates in the UK (15%) and Denmark (15%) and the highest rate in Italy (51%) (11). However, the data differ for France, with only 27% of outpatients being reported as employed in the EMCDDA dataset. Notably, there were differences in levels of employment between the OMT options: significantly more patients receiving buprenorphine–naloxone were employed (36%) compared with patients receiving methadone or morphine (26% and 20%; p<0.01). It is not possible to determine whether some treatment options make employment more feasible or if some treatment options are more suitable for those already in employment. What is clear is that employment is less likely to be a realistic option for patients requiring daily clinic appointments or those who have transportation difficulties (e.g., patients who live far from the clinic, in areas without good public-transport provision, or those who cannot drive).

The methodology of this analysis carries limitations, described in detail previously (14). However, it is unlikely that these limitations could account for the significant variations observed across countries. These data are important as engagement in meaningful activities (e.g., employment, education, volunteering) is a key goal of recovery in most countries. According to UK Drug Strategy (17), sustained employment is one of the best-practice outcomes that is key to successful delivery in a recovery-orientated system, and drug treatment services should be commissioned with this in mind. Similarly, Scotland's Drug Strategy (25) suggests that an individual care plan 'should cover both treatment and rehabilitation services, as well as addressing issues such as training or employment needs', and Wales's Drug Strategy states that employment and training are essential for assisting and sustaining recovery (28). The US National Drug Control Strategy (13) highlights 'recovery support services that assist with employment, housing, medical care, and other support' as important factors in the successful reintroduction of ex-prisoners back into the community. Clearly, employment could also differ across countries for economic or social reasons. Nevertheless, the reasons for the different rates of employment across Europe should be examined more closely to determine whether different treatment approaches could make achieving employment a more realistic outcome of treatment.

5. Conclusion

In summary, the EQUATOR analysis suggests

there is a considerable way to go in achieving the desired public-health-related outcomes from the current opioid-dependence treatment system. A significant proportion of problematic opioid users remain out of the treatment system and in our analysis, these individuals had high levels of polydrug use (including use of diverted OMT medications), high rates of unemployment and past imprisonment, significant physical and mental health comorbidities and have often cycled through both OMT and prison on several previous occasions.

The economic costs associated with these public-health outcomes are likely to be substantial (e.g., costs of crime, imprisonment and associated impact on the criminal-justice system, and costs on the healthcare and social-welfare systems). It is therefore essential that different stakeholders (e.g., policy makers, criminal-justice systems, the treatment community) review current treatment structures and processes to identify ways to further engage patients in treatment, improve outcomes and promote reintegration (10). This includes the need to consider the balance between the need for control and the need for flexibility, access to normalised treatment, perhaps using different pharmacotherapeutic strategies involving flexible dosing, take home and/or primary-care delivery. Additionally, BBV infection rates vary between countries, reinforcing the need for continued investment to optimise screening and treatment. Optimising treatment – including therapeutic dosing, providing access to quality treatment in community settings, in prison and upon release – is also critical for preventing patients from continuing illicit drug use and associated criminal activities.

In conclusion, there is a clear need for strategies that deliver the benefits of open access (improved patient participation, satisfaction and outcomes) without the risk of misuse or diversion. More broadly, there is a need for treatment systems that more effectively achieve both the goals of harm reduction (e.g., reduced drug use and infection) and the goals of recovery (improved well-being, employment and social reintegration). The achievement of all of these goals must be considered when assessing the effectiveness of the current treatment system and evaluating alternatives for improving outcomes.

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Barriers to treatment access and informed patient choice in the treatment of opioid dependence in Europe

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Summary

According to the European Quality Audit of Opioid Treatment (EQUATOR) analysis, there is large variation across Europe in the conditions attached to treatment of opioid dependence. Treatment conditions, such as supervised dosing and the need to attend regular appointments, may constitute important barriers to treatment that may impact on successful outcomes for opioid-dependent individuals. Greater flexibility in the provision of treatment and improved education for patients, users and physicians with regards to therapy options may help to improve recruitment and retention of opioid users in treatment, and consequently improve patient outcomes.

Key Words: access, barriers, informed choice, treatment rules

1. Introduction

1.1. Management of opioid dependence in Europe

Opioid dependence is a chronic condition (9) for which opioid-maintenance treatment (OMT) in combination with psychosocial counselling is recognised as the most effective intervention (17). To yield maximum benefit, treatment systems need to be effective in recruiting and retaining individuals in therapy for a period of time sufficient to aid recovery. Thus, any barriers to patients entering or continuing treatment have the potential to limit the benefits of therapy and therefore increase the cost of opioid dependence to both the individual and society.

As with other chronic conditions, such as schizophrenia (16), a common feature of opioid dependence is the cycling of individuals between periods in and out of treatment, and many patients re-present for treatment several times. However, many opioid-dependent individuals are able to break this cycle and take meaningful steps towards recovery, such as improved health and well-being, improved social functioning, and social reintegration.

Despite different rates of re-presentation for OMT across Europe among individuals with opioid dependence [see article by Fischer, Nava & Stöver in this issue], data from the European Quality Audit of Opioid Treatment (EQUATOR) analysis indicate that patients and out-of-treatment users share similar demographics across European countries [see article by

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Goulão & Stöver in this issue]. This suggests that re-presentation rates in different countries may be more closely linked to other factors, such as differing treatment goals between countries and/or system-level differences in how treatment is provided, rather than to different patient types. It is important to explore how the structure of treatment systems across Europe may be differentially affecting patient outcomes and retention in treatment to understand more fully how we can optimise the treatment delivery system.

In the other articles within this series, data from the EQUATOR analysis have shown how treatment systems vary across European countries on a number of levels [see articles by Goulão & Stöver; Dale-Perera, Goulão & Stöver; Fischer, Nava & Stöver; and Stöver in this issue], including medication options available, the role of psychosocial care, access to treatment, levels of control (e.g., use of supervised dosing, urine drug screens), treatment settings, and availability of treatment guidelines.

1.2. Barriers to treatment of opioid dependence

Within the total population of individuals with opioid dependence, a large proportion are currently out of treatment at any given time; according to the EMCDDA, only around half of the 1.3 million opioid users across Europe are receiving any form of OMT (4,5). The proportion of opioid users receiving OMT varies across European countries, ranging from only 7% of users in Poland and 14% in Slovakia to at least 60% in The Netherlands, Luxembourg and Malta (5).

While some opioid users may not be ready to access treatment, many experience barriers that prevent them either from initiating OMT, causing them to withdraw from treatment, or making them unwilling to return to treatment; indeed, the existence of barriers to treatment remains a topic of concern among thought leaders in the treatment of opioid dependence (8, 15). Barriers to treatment may take several forms. For example, opioid-dependent individuals may be unaware of treatment options available to them either because they have not sought information on OMT options or because they have accessed information from uninformed sources. Physicians may be discouraged by obstacles to providing OMT, such as bureaucracy, prerequisites (e.g., training courses) and reimbursement issues (10), which may lead to issues of accessibility and availability of OMT. In countries where individuals have to bear some or all of the cost of treatment (e.g., Spain and Portugal), expense may constitute a significant barrier to treatment.

Stigma associated with OMT is also recognised as a barrier that may deter some opioid-dependent individuals from accessing treatment (8). This may be influenced by treatment setting (e.g., GP-based *vs* specialist clinics): while specialist clinics focus expertise and resources on the treatment of addiction, they can be stigmatising for patients when compared with a primary care or hospital setting, and may provide an additional barrier to access when their location is difficult to reach or is a long distance from the patient's home.

Finally, rules for beginning or continuing treatment, such as regular attendance at appointments, supervision of dosing, and urine testing, may deter users from initiating or remaining in treatment. Patients who have previously had negative experiences or perceptions of a specific treatment may also be deterred from (re-)entering treatment. For example, among individuals in a patient-preference study who had chosen to receive buprenorphine, 28% stated that they would not have entered treatment if methadone were the only treatment option available (13).

1.3. The importance of understanding patients' and users' attitudes to treatment

If we are to understand how to improve the access and provision of treatment for opioid-dependent individuals, it is necessary to understand why some people seek treatment, why some drop out, and why others choose not to seek treatment at all.

Patients are often required to meet specific conditions to enter or remain in treatment. For example, they may need to be compliant with supervised dosing, be attending appointments consistently, have been opioid dependent for a certain length of time, and/or fall within a certain age range (e.g., in Sweden, patients must be established as opioid dependent for at least a year before entering treatment and must be at least 20 years old (6)).

Similarly, understanding additional reasons why users remain out of treatment may help to identify ways in which the benefits of treatment could be expanded to more opioid-dependent individuals.

1.4. EQUATOR

The current article presents the results from the EQUATOR analysis that pertain to barriers to treatment access and informed patient choice in the treatment of opioid dependence. Using a common methodology across 10 countries (7), the analysis assessed

sources of information accessed by patients/users and treatment barriers reported by patients/users in Europe that are perceived to be the most significant in limiting treatment entry and retention.

2. Methods

Detailed methodology for the EQUATOR analysis has been described previously (8). Briefly, questionnaires were compiled comprising a core set of questions specific for three target groups: opioid users not currently in OMT (50 questions per survey), opioid-dependent patients currently in OMT (50 questions per survey), and physicians involved in the treatment of opioid-dependent patients (60 questions per survey). Survey data were collected in each country in accordance with the European Pharmaceutical Market Research Association (EphMRA) code of conduct and the Declaration of Helsinki.

This article presents results of the analysis regarding the following aspects of treatment provision: sources of information used by patients and out-of-treatment users to inform themselves of OMT (patient question: 'If you informed yourself about substitution treatment [before you came to treatment], where did you obtain this information?' and user question: 'Where did you obtain your information about treatment options?'); reasons given by patients for seeking treatment ('If beginning substitution treatment was your decision, what were your reasons for beginning it?'); reasons given by out-of-treatment opioid users for staying out of treatment ('What are the reasons for you staying out of treatment?'); conditions patients had to meet to start treatment ('What conditions or rules did you have to meet to start therapy?') and to stay in treatment ('What conditions or rules do you have to follow to stay in therapy?'); conditions for staying in treatment that had the greatest impact on patients' daily lives ('And which ONE of these has MOST impact on your daily life?'); factors that would have encouraged patients to start treatment earlier ('What would have encouraged you to start substitution treatment earlier?'); and factors that would have made it easier for patients to stay in treatment ('What would make it easier for you to stay in treatment?').

Data are presented as frequencies or means for the purposes of comparisons between patients and users, and across countries. Pearson Chi-squared (χ^2) analysis was used to assess differences between parameters across countries. For tests that were statistically significant, standardised residuals were used as post-hoc tests performed to identify specific countries

with significantly high or low proportions. Significance was ascribed for $p \leq 0.05$.

3. Results

3.1. Sources of information for patients and users regarding treatment options for opioid dependence

Patients and out-of-treatment opioid users reported using similar sources to inform themselves of treatment options before entering treatment. The most commonly accessed sources of information across all countries were counselling/drug support centres, other drug users, and friends and acquaintances (Figure 1). In most countries surveyed, less than half of the patients and users reported using physicians/pharmacies as a source of information on treatment options (Figure 2). This may help to explain patients' lack of awareness of some OMT options, as reported previously [see article by Dale-Perera, Goulão & Stöver in this issue].

The proportion of patients who reported using physicians/pharmacies as a source of treatment information differed markedly across countries ($\chi^2=167.87$, df=9, n=1935, p<0.001) (60% in Germany, more than 40% in Austria, France and the UK, but less than 20% in Denmark and Greece) (Figure 2). The proportion of users who reported using physicians/pharmacies as a source of treatment information also differed markedly across countries ($\chi^2=37.75$, df=7, n=691, p<0.001) (42% in Germany and Portugal, but less than 15% in Sweden) (Figure 2). Thus, there is a clear divide in the use of professional advice on treatment options by patients and users across Europe.

3.2. Reasons for patients seeking treatment and for users staying out of treatment

When asked why they were seeking treatment for opioid dependence, patients gave reasons that reflected an ambition to recover from drug dependence: 62% of patients across Europe reported seeking treatment to improve their health, and 59% of patients said they were looking to end their dependence on opioids permanently. Substantial proportions of patients reported wanting to change social circles (35%), take care of family (29%), be able to work (28%) or avoid imprisonment (22%; Figure 3).

Common reasons cited by users for staying out of treatment included concerns over whether they would be able to follow the rules governing therapy
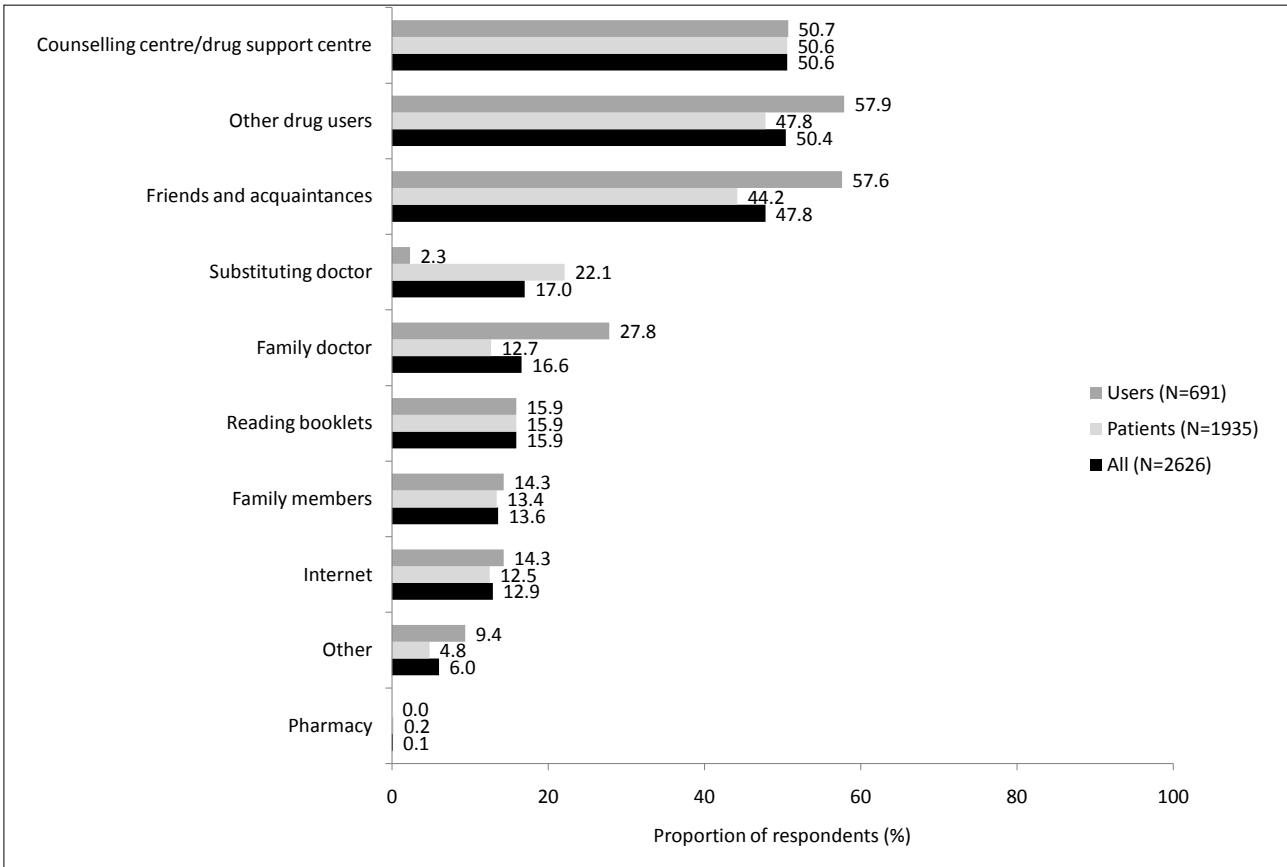
Figure 1: Sources of information regarding treatment used by patients and users for Europe as a whole. Patients were asked to tick all that applied
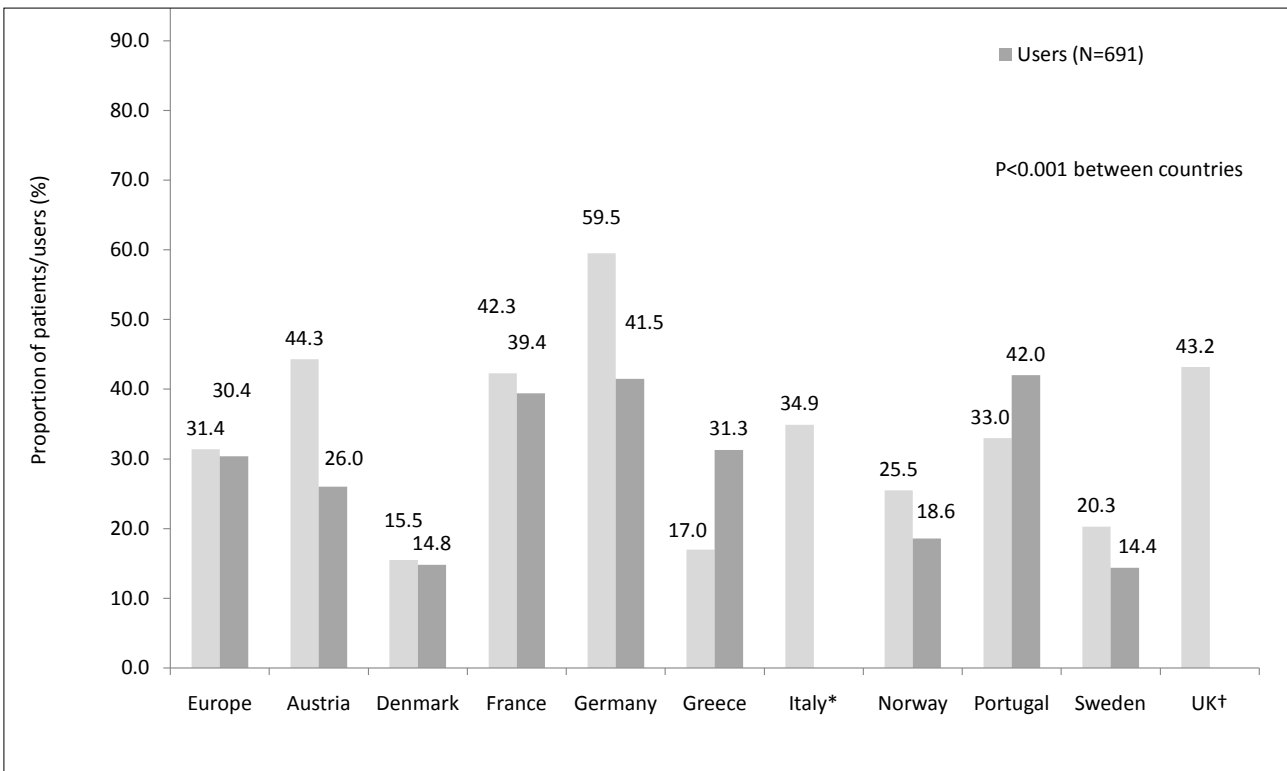
Figure 2: Proportion of patients and users seeking information from physicians or pharmacists across Europe. *Users were not surveyed in Italy; †User data not available for the UK
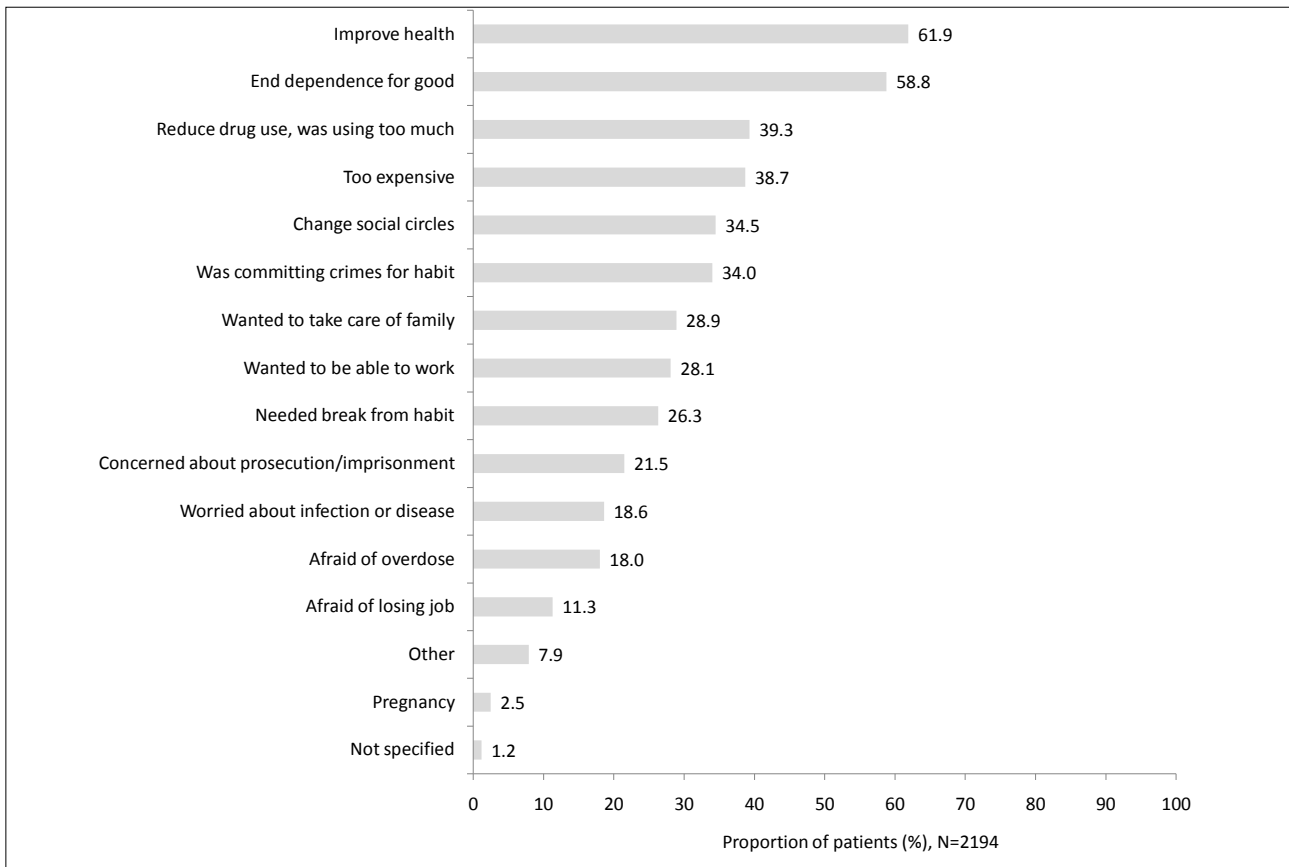
Figure 3: Reasons given by patients for seeking treatment. Patients were asked to tick all that applied
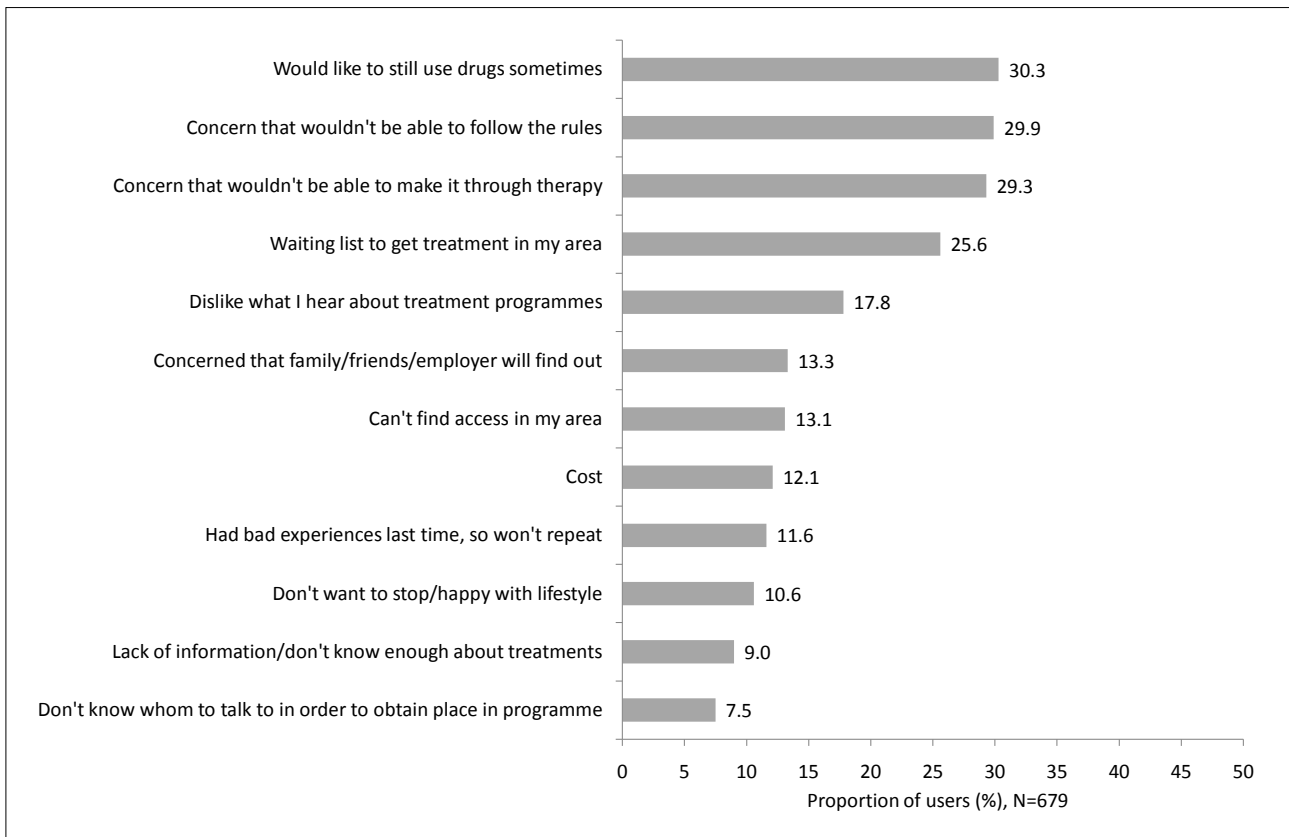
Figure 4: Reasons given by opioid users for staying out of treatment. Patients were asked to tick all that applied

Table 1: Patient-reported conditions/rules patients had to meet before starting treatment based on country

% patients	Europe N=2274	Austria N=228	Denmark N=103	France N=130	Germany N=200	Greece N=601	Italy N=378	Norway N=98	Portugal N=160	Sweden N=128	UK N=248	Difference between countries
Having dose supervised every day	76.3	75.4	67.0	49.2	89.5	87.2	65.1	82.7	57.5	62.5	91.5	χ^2=221.15, df=9, n=2274, p<0.001
Having to attend all appointments	69.7	64.5	46.6	54.6	82.0	82.5	59.8	27.6	88.1	54.7	78.6	χ^2=252.91, df=9, n=2274, p<0.001
Having to completely stop illegal drug use	64.3	64.9	19.4	62.3	80.5	89.2	56.1	31.6	50.6	65.6	44.0	χ^2=390.36, df=9, n=2274, p<0.001
Having to go to key working/group work/ counselling	52.6	37.3	36.9	31.5	83.5	75.0	26.5	9.2	86.9	15.6	59.3	χ^2=580.55, df=9, n=2274 p<0.001
Long-term aim of drug-free state	52.3	39.9	27.2	52.3	58.5	60.6	47.1	39.8	61.3	55.5	54.8	χ^2=76.16, df=9, n=2274, p<0.001
Reducing daily dose over time	35.5	32.9	10.7	40.8	18.5	63.2	19.3	6.1	50.0	3.1	35.5	χ^2=410.55, df=9, n=2274, p<0.001
Having to do urine testing	17.3	1.8	0	3.1	3.0	ND	7.9	5.1	0.6	ND	80.6	χ^2=844.05, df=6, n=1442, p<0.001

ND: No data available

(30% of users) or be able to complete therapy (29% of users). Although only 11% of users were happy with their lifestyle or did not want to stop taking opioids, more than 30% reported staying out of treatment partly because they still wanted to use drugs occasionally (Figure 4).

3.3. Conditions for patients entering and remaining in treatment

Across Europe as a whole, patients reported a requirement to have their dose supervised daily as the most frequent condition they had to meet at the start of therapy (76% of patients). In addition, 70% of patients reported the requirement to attend all their appointments, and 64% reported being required to stop illegal drug use completely (Figure 5; Table 1). The preconditions for treatment entry reported by patients varied across countries (Table 1) (e.g., for mandatory psychosocial counselling, χ^2=580.55, df=9, n=2274, p<0.001). In Germany, for example, 84% of patients reported mandatory psychosocial counselling as a prerequisite of entering treatment (although, according to recent regulations, this is no longer explicitly a prerequisite for commencing OMT), whereas only 9% of patients in Norway and 16% of patients in Sweden reported the same condition (Table 1). The requirement for daily supervised dosing also differed across countries (χ^2=221.15, df=9, n=2274, p<0.001). This prerequisite was most frequently cited as a requirement for treatment entry in the UK (92%) and Germany (90%), whereas in France only 49% of patients reported this condition (Table 1). Similarly, the requirement for urine testing differed across countries (χ^2=844.05, df=6, n=1442, p<0.001). Urine testing was cited as a frequent requirement for entering treatment in the UK (81% of patients) but was not widely reported as a requirement across other European countries (<8% of patients for all other countries surveyed) (Table 1). Preconditions for entering therapy as reported by physicians also differed across countries (Table 2). In Greece, 96% of physicians cited urine testing as a prerequisite for treatment entry compared with 17% in France and 18% in Germany (χ^2=252.26, df=9, n=703, p<0.001) and 83% cited daily supervised dosing compared with 8% in Austria and 7% in the UK.

Most patients surveyed across Europe also reported being required to adhere to specific conditions to stay in treatment (Figure 6). Across Europe as a whole, patients reported urine testing as the most frequently applied condition for staying in treatment

(84% of patients). Other commonly reported conditions included attending all appointments (64%), stopping illegal drug use (61%), and being supervised during daily dosing (57%). The conditions required of patients to stay in treatment also varied across countries (Table 3). For example, the requirement to completely stop illegal drug use was reported by more than 75% of patients in Greece and Germany, but less than 15% of patients in Denmark. There were also wide variations in the proportions of patients reporting a requirement to go to key working/counselling (ranging from 84% of patients in Portugal to 9% in Norway) or have their dose supervised every day (ranging from 84% of patients in Greece to 22% in France) as conditions for remaining in treatment.

3.4. Factors most affecting access and retention in treatment, as reported by patients

Patients reported that the inconvenience of having their daily dose supervised, having to attend all appointments, and, to a lesser extent, having to undergo urine testing had a substantial impact on their daily lives (Figure 7). For each of these factors, there were significant differences across countries (having daily dose supervised: χ^2=216.46, df=8, n=1673, p<0.001; attending all appointments: χ^2=36.37, df=8, n=1673, p<0.001; urine testing: χ^2=176.29, df=7, n=1543, p<0.001). Daily dose supervision was reported as having a substantial impact on daily life by 51% of patients in Norway and 44% in the UK, but by only 2% in France. In Portugal, nearly one-third (33%) of patients cited the requirement to attend all appointments as having a substantial impact on daily life (compared with 11% in Austria), but only 2% cited urine testing (compared with 39% in Sweden).

More than 40% of patients regarded better availability of treatment as a factor that could have encouraged them to start treatment earlier (Figure 8), with the figure varying significantly across countries (e.g., 84% of patients in Greece but only 9% of patients in Italy; χ^2=701.78, df=9, n=2274, p<0.001). More than 25% of patients thought fewer preconditions or more information about treatment options could have encouraged them to start treatment earlier (Figure 8). Although these responses differed significantly across countries (fewer preconditions: χ^2=133.16, df=9, n=2274, p<0.001; more information about treatment options: χ^2=183.42, df=9, n=2274, p<0.001), the magnitude of these differences was generally small. Notably, in Greece, only 7% of patients felt that more information about treatment options would have en-

Table 2: Physician-reported conditions/rules patients had to meet before starting treatment based on country

% physicians	Europe N=703	Austria N=77	Denmark N=32	France N=100	Germany N=101	Greece N=24	Italy N=100	Norway N=49	Portugal N=60	Sweden N=60	UK N=100	Difference between countries
Having dose supervised every day	31.6	7.8	50.0	10.0	10.9	83.3	49.0	57.1	75.0	50.0	7.0	χ^2=215.11, df=9, n=703, p<0.001
Having to attend all appointments	51.2	58.4	43.8	60.0	44.6	58.3	40.0	53.1	61.7	51.7	48.0	χ^2=15.84, df=9, n=703, p=0.070
Having to completely stop illegal drug use	39.3	1.3	43.8	60.0	27.7	62.5	53.0	73.5	73.3	38.3	2.0	χ^2=195.33, df=9, n=703, p<0.001
Having to go to key working/group work/counselling	33.1	7.8	71.9	27.0	33.7	58.3	13.0	63.3	76.7	35.0	18.0	χ^2=152.70, df=9, n=703, p<0.001
Long-term aim of drug-free state	31.0	0.0	9.4	48.0	22.8	58.3	31.0	40.8	80.0	48.3	2.0	χ^2=183.95, df=9, n=703, p<0.001
Reducing daily dose over time	20.5	0.0	12.5	39.0	9.9	58.3	12.0	34.7	38.3	30.0	7.0	χ^2=106.92, df=9, n=703, p<0.001
Having to do urine testing	53.1	54.5	53.1	17.0	17.8	95.8	93.0	93.9	83.3	53.3	35.0	χ^2=252.26, df=9, n=703, p<0.001
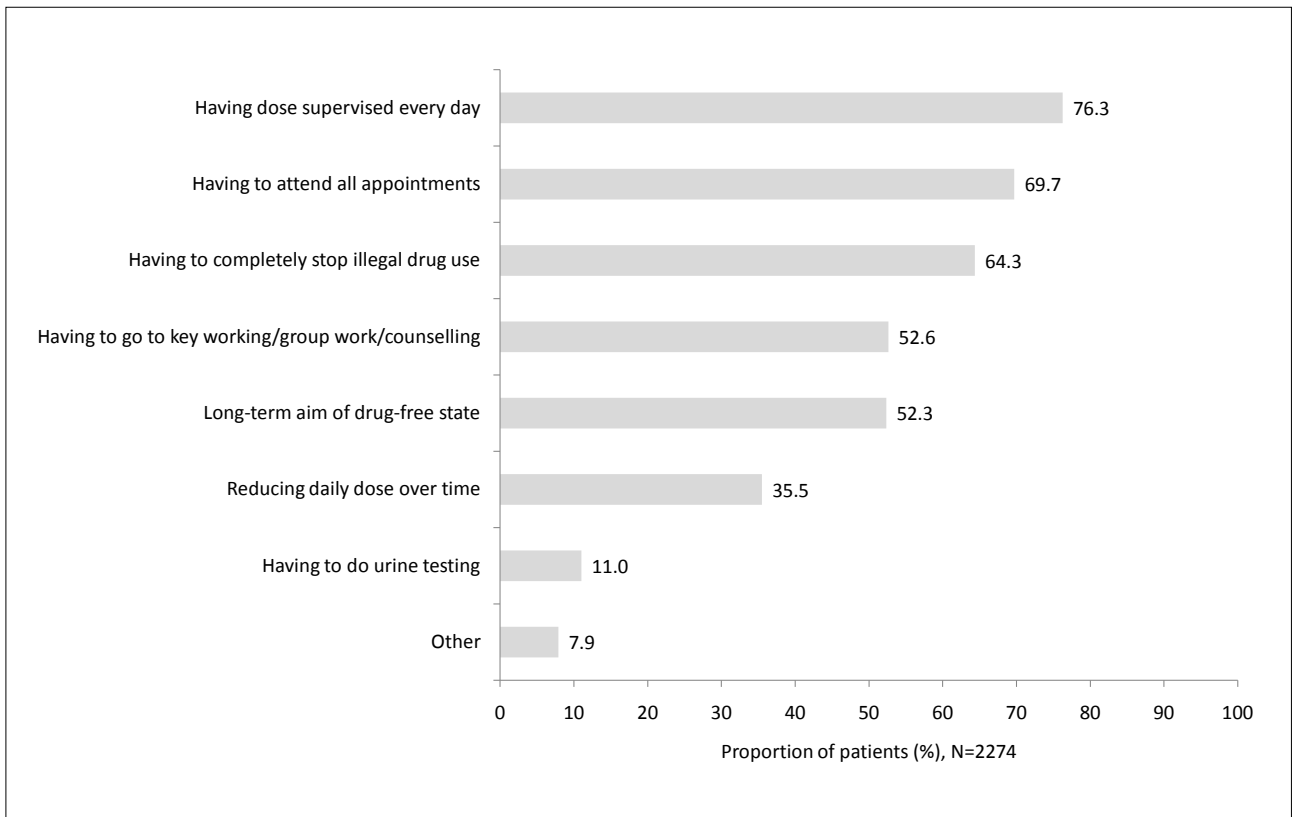
Figure 5: Patient-reported conditions/rules patients had to meet before starting treatment
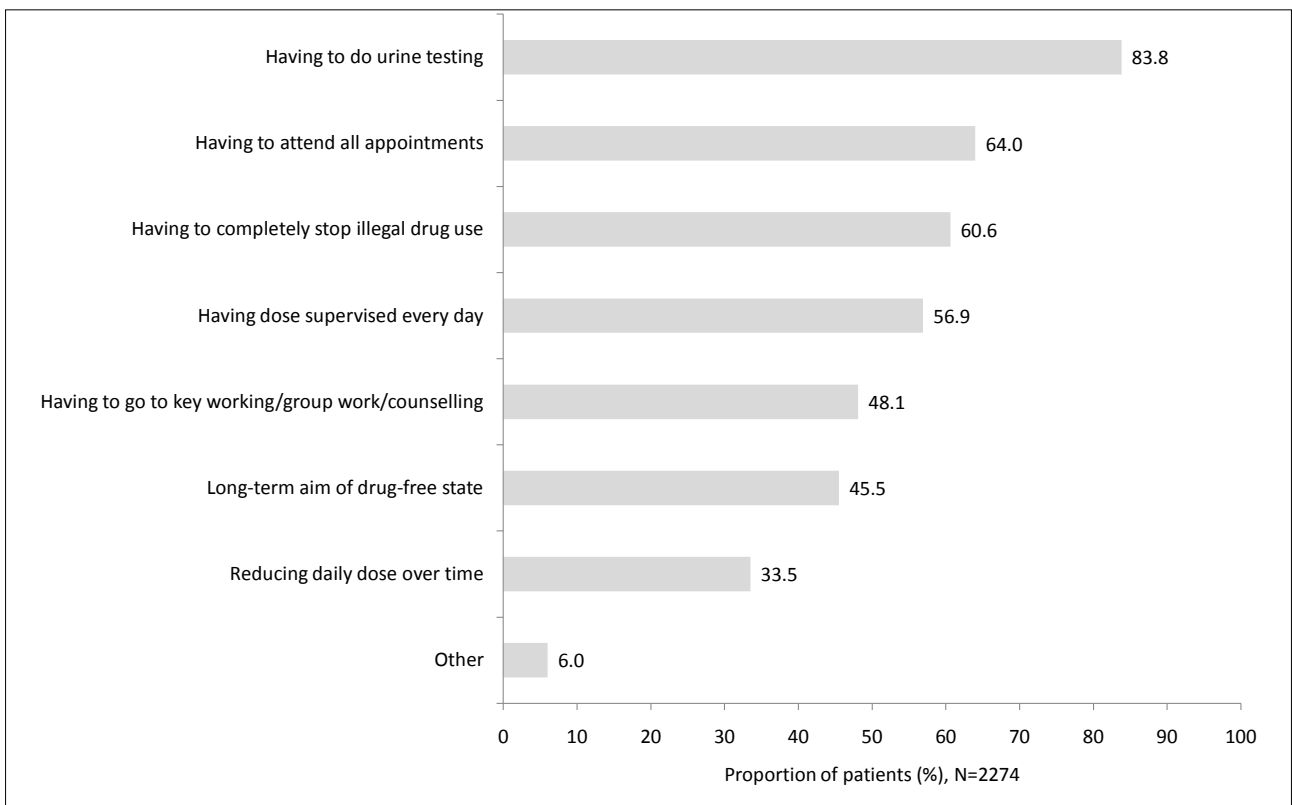
Figure 6: Conditions/rules patients reported they had to meet to stay in treatment

Table 3: Patient-reported conditions/rules patients had to follow to stay in treatment based on country

% patients	Europe N=2274	Austria N=228	Denmark N=103	France N=130	Germany N=200	Greece N=601	Italy N=378	Norway N=98	Portugal N=160	Sweden N=128	UK N=248	Difference between countries
Having to do urine testing	83.8	85.5	19.4	20.8	97.5	98.8	91.8	67.3	97.5	90.1	76.2	$\chi^2=898.20$ df=9, n=2298, p<0.001
Having to attend all appointments	63.9	55.3	42.7	40.0	82.5	81.0	47.6	14.3	85.0	52.0	74.6	$\chi^2=366.54$ df=9, n=2298, p<0.001
Having to completely stop illegal drug use	60.7	58.3	13.6	46.2	78.0	88.0	45.0	30.6	65.0	67.1	39.1	$\chi^2=449.72$ df=9, n=2298, p<0.001
Having dose supervised every day	56.5	61.4	31.1	21.5	64.0	83.7	30.7	76.5	31.9	26.3	74.6	$\chi^2=526.69$ df=9, n=2298, p<0.001
Having to go to key working/group work/ counselling	47.6	28.5	32.0	22.3	81.0	73.7	17.2	9.2	83.8	10.5	55.6	$\chi^2=702.48$ df=9, n=2298, p<0.001
Long-term aim of drug-free state	45.4	36.0	10.7	46.2	53.5	56.6	36.5	21.4	66.3	43.4	45.6	$\chi^2=156.92$ df=9, n=2298, p<0.001
Reducing daily dose over time	33.2	27.2	1.0	38.5	22.5	63.7	12.4	8.2	47.5	6.6	32.3	$\chi^2=481.36$ df=9, n=2298, p<0.001
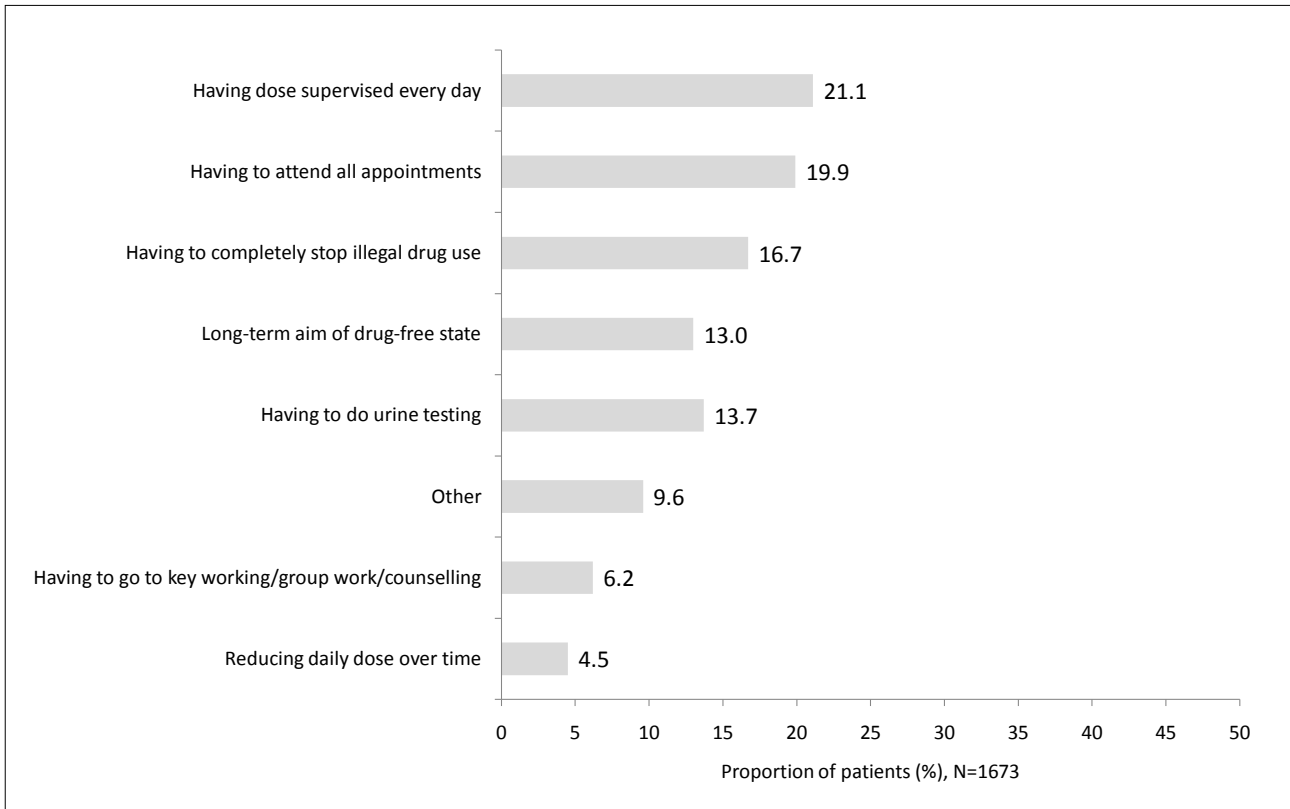
Figure 7: Conditions for staying in treatment reported by patients to have the greatest impact on daily life. Patients were asked to tick all that applied
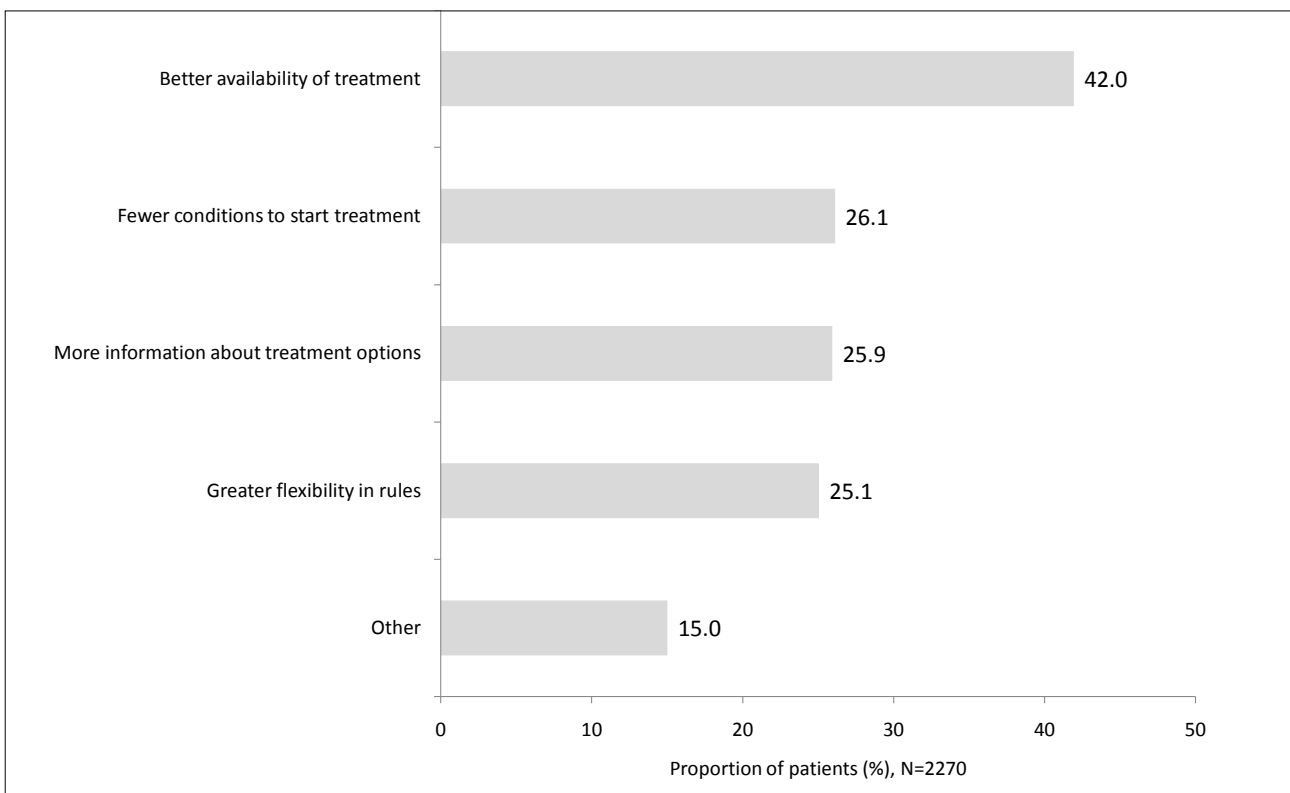
Figure 8: Factors that would have encouraged patients to start treatment earlier. Patients were asked to tick all that applied
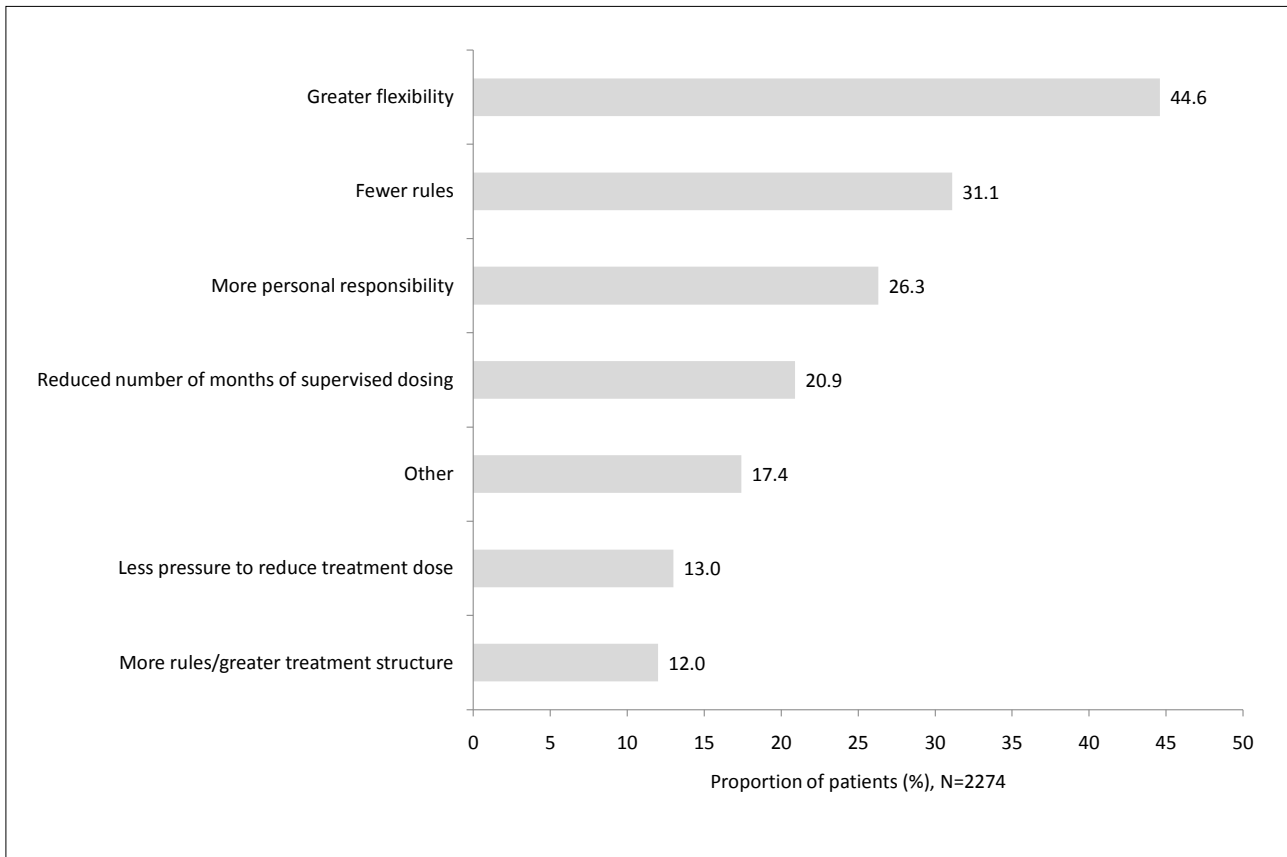
Figure 9: Patient-reported factors that would make it easier to stay in treatment

couraged them to start treatment earlier, whereas more than 40% of patients could have been encouraged by fewer preconditions.

Greater flexibility and fewer rules were the most commonly cited factors that patients believed would make it easier to stay in treatment (Figure 9); these varied significantly across countries (greater flexibility: $\chi^2=191.58$, df=9, n=2274, p<0.001; fewer rules: $\chi^2=179.46$, df=9, n=2274, p<0.001). Greater flexibility was cited by more than 50% of patients in Germany, Greece and Sweden, but less than 30% of patients in Italy and Portugal, and fewer rules were cited by 50% of patients in Sweden and less than 20% of patients in Germany, Italy and Portugal.

4. Discussion

An important step in the treatment of opioid dependence lies in the ability and willingness of opioid users to enter and remain in treatment. Understanding the reasons that underlie this is important if the treatment community and policymakers are to optimise participation in treatment and deliver better public health outcomes. This article provides a unique insight into the reasons why opioid users engage with treatment or choose to remain outside the treatment

system altogether. The EQUATOR analysis of data from 10 European countries has helped to identify several factors associated with the conditions of treatment delivery that may contribute to negative outcomes, with patients and users reporting difficulty in meeting treatment conditions and consequently dropping out or choosing not to enter treatment at all.

4.1. Sources of information for patients and users regarding treatment options for opioid dependence

The EQUATOR analysis shows that patients are not aware of all OMT options available to them [see article by Dale-Perera, Goulão & Stöver in this issue], despite their belief that they are well informed, and despite having been in treatment several times on average. This lack of awareness is particularly significant given that patients appear to play a central role in driving treatment choices.

The sources of information accessed by patients receiving OMT and out-of-treatment opioid users were similar, but in many cases were of questionable credibility and were not linked

to any professional treatment bodies or medical professionals. Many patients and users reported using friends and acquaintances or other drug users as major sources of information on treatment options, and in most countries surveyed, less than half of patients and users reported using physicians or pharmacies as an information source. Across European countries, there are clear differences in how information on opioid treatment is obtained, with more than twice as many patients (>40%) in Austria, Germany and France reporting using credible sources of treatment information such as physicians or pharmacies than in Norway, Denmark and Greece (<20%).

Several factors may contribute to these findings. It is likely that patients seek information from friends, acquaintances and support centres in the first instance. Once they have made the decision to seek treatment, a doctor or other healthcare professional would be expected to ensure that they are fully informed of their treatment options; however, there seem to be barriers that prevent this communication from happening. There may be a reluctance among patients to engage with healthcare professionals for fear of being stigmatised, or they may assume that there is nothing to discuss. In some cases, healthcare professionals themselves may offer limited options to patients due to a lack of experience or confidence with the full range of therapeutic options, and both physicians and patients may prefer to continue with the medication they initially used/prescribed, or medications that they are most familiar with. Methadone has become a generic term for opioid-dependence treatment, based on a 40-year history and a high level of awareness of the drug among patients before they enter OMT (91.4% of patients in the EQUATOR analysis were aware of liquid methadone [see article by Dale-Perera, Goulão & Stöver in this issue]). As such, methadone is often prescribed to patients who have used the drug unsuccessfully on one or more previous occasions, sometimes without regard to clinical appropriateness. Thus, physicians as well as patients and users may benefit from education about the treatment options for opioid dependence so that they can make informed choices about appropriate treatment.

Overall, there is a clear need to improve access to reliable treatment information for opioid-dependent individuals before they access treatment, potentially by improving dialogue between patients and healthcare professionals at the early stages of treatment. This is particularly important for patients who re-present with opioid dependence having previously received OMT, and who may consider themselves already aware of all their treatment options. Patient-oriented education programmes to improve physician–patient communication and to better inform patients about their OMT options may be advantageous.

4.2. Reasons for patients seeking treatment and for users staying out of treatment

A large proportion of patients reported seeking treatment to improve their health or to end their dependence on opioids. Thus, patients embarking on a course of OMT typically have treatment goals that stretch beyond minimisation of drug-related harms (e.g., overdose, disease) and are associated with recovery, including outcomes such as stable housing, improvements in personal relationships, cessation of criminal behaviour and improved ability to work. Unfortunately, these outcomes are often not realised, which may in part be due to high dropout rates in the early stages of the recovery process; a study of opioid-dependent patients receiving methadone or buprenorphine observed a 45–52% drop-out rate over 6 months (14).

It is also important to note any mismatch between patients' treatment goals and the focus of national policies and guidelines. In some countries, harm-reduction approaches remain the predominant focus without the additional support necessary to achieve recovery. One of the most basic goals that treatment systems try to achieve is a significant reduction or complete cessation of opioid use; however, many patients report continuing to use illicit drugs on top of their OMT [see article by Fischer, Nava & Stöver in this issue], often risking exclusion from treatment. For these patients, it is important that exclusion from treatment is avoided in order to optimise treatment outcomes and provide them with a chance of recovery.

In the current analysis, relatively few users (11%) who were out of treatment at the time of the survey were happy with their lifestyle, but concerns regarding their ability to follow the rules governing therapy or to be able to complete therapy, and a desire to still use drugs occasionally, appear to have contributed to their decision to remain as out-of-treatment users. Psychosocial interventions play a crucial role in instilling in patients the motivation to progress towards stages of change that are compatible with the treatment (2). The failure to recruit out-of-treatment users into therapy, and the sometimes limited progress towards recovery made by patients in treatment, may be associated in part with how treatment is delivered

and the conditions that patients must meet to enter and remain in treatment. Owing to the high human and public cost of untreated opioid dependence, it is imperative that policymakers understand the factors that keep users out of treatment, and design strategies to engage with these individuals, even if it requires changes to the current treatment system.

4.3. Conditions for patients entering and remaining in treatment

Patients reported a number of conditions they had to meet to enter and remain in treatment, including having their dose supervised daily, attending all of their appointments and stopping all illegal drug use completely. The need to attend psychosocial counselling to stay in treatment differed across countries, with most patients in Portugal (84%), Germany (81%), Greece (74%) and the UK (56%), but fewer than 10% of patients in Norway, reporting this as a requirement. Patients in Germany, Greece and the UK were also particularly likely to report being required to attend all appointments and receive supervised daily dosing. The situation in Germany with regard to treatment of opioid dependence is somewhat different from other European countries as specific aspects of treatment, such as the provision of psychosocial therapy, have formerly been mandated by law rather than being merely recommendations in clinical guidelines (although recent regulations permit OMT even if psychosocial care is unavailable). This may be a significant contributing factor to the strict conditions reported by German patients. Many physicians in Germany also require patients to avoid alcohol (requiring zero readings on breath tests) and specific medications (e.g., benzodiazepines).

Of the conditions cited by European patients for staying in treatment, daily supervised dosing, attendance at all appointments and the need to cease illegal drug use permanently were considered to be those that most impacted on daily life. In addition, more than one-quarter of patients thought fewer preconditions and more information about treatment options could prompt them to begin treatment at an earlier stage, and greater flexibility and fewer rules were most often cited by patients as factors that could make it easier to stay in treatment. There is therefore a clear indication from patients surveyed that preconditions to treatment for opioid dependence represent a potential barrier for entering and remaining in treatment. Based on these findings, treatments that do not require supervision might be expected to attract patients who are unwilling to take part in supervised dosing.

4.4. Improving treatment access and retention

Understanding the reasons for users remaining outside treatment, and potentially changing the conditions that patients are required to meet to enter or remain in treatment, is important if we are to find ways of making treatment more acceptable to patients and users. Factors that could improve patients' willingness to enter or remain in treatment include reducing the preconditions of treatment (e.g., relaxing dose supervision or urine-testing requirements). It is important to note that supervised dosing can play a role in ensuring the safety of treatment, especially during the early stages of therapy (17). However, once feasible, unsupervised dosing is likely to maximise the chances of recovery, since individuals who need to attend fewer clinic appointments may be able to return to a more normal life and potentially be able to work. Unsupervised dosing is also less costly than supervised dosing (1), which may be important in those countries suffering budgetary pressures. Thus, strategies are needed that correctly balance the need for supervision without overly restricting patient access and retention. Where available, abuse-deterrent formulations of OMT medications can be used to minimise the likelihood of misuse and minimise the need for supervision. For example, in the case of methadone, most practitioners consider that, to limit abuse, it is best to use diluted liquid solutions rather than methadone tablets because the former are less readily abused. In the case of buprenorphine, using the abuse-deterrent formulation containing naloxone can reduce the likelihood of parenteral misuse (12). Even though the buprenorphine–naloxone combination is the preferred formulation in some clinical guidelines, for example in Denmark (11) and the US (3), many countries continue to favour the use of mono-buprenorphine, most probably because it is available as a lower-cost generic. Providing the safest treatment options in a GP-based setting may offer a better balance between an open-access, less stigmatised environment, while managing concerns about diversion and misuse, thus potentially improving patients' willingness to enter and remain in treatment. What is certain is that delivering all treatments in exactly the same way, in exactly the same settings, does not take advantage of the inherent advantages of certain medication formulations over others; neither does it take into account that some treatment options may be

more suitable than others for particular patients or patients at particular stages of their recovery.

5. Conclusions

The aspirations of patients entering treatment are to stop their drug use and to enter a path towards a 'normal' life. Although treatment can offer this potential, many patients are failing to achieve some of the most basic goals of treatment. For example, a substantial proportion of patients continue to use illicit drugs on top of, divert, and/or misuse, their OMT medication [see article by Fischer, Nava & Stöver in this issue]. As shown in the current analysis, patients appear to be uninformed of their OMT options, which may reduce the likelihood of success of each new treatment episode. Patients seem to be consulting their uninformed peers rather than healthcare professionals for information on OMT options, and communication between patients and physicians about treatment choices may be suboptimal. In addition, aspects of treatment delivery, such as the level of supervised dosing and the stigma of regularly attending a specialist clinic, may be a barrier to entering or remaining in treatment. These findings suggest that healthcare professionals and policymakers should review whether their current treatment system is delivering the desired outcomes for patients and public health.

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Aggressive behaviour and heroin addiction

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Summary

In this review we discuss the correlations between aggressiveness, defined according to a behaviourist model, and heroin dependence according to DSM-IV-R criteria. Criminality appears to be only an indirect, partial index of aggressive behaviour in heroin addicts. The aggressive behaviour of heroin addicts is probably different from that of other kinds of mentally ill patients, non-opiate substance abusers and the general population, and seems to be specifically related to the degree of chronic intoxication. Gender differences, aggressive habits before heroin use, and modulation during intoxication and/or withdrawal states have been documented. The association between cerebral opioidergic abnormalities and psychiatric disorders characterized by affective instability, feelings of anger and hostility, perception abnormalities and sexual dysfunction, could explain highly aggressive behaviours of heroin addicts which are not directly related to drug supply. Knowledge about the anti-aggressive property of non-opioid drugs is limited. On the other hand, opioid agonists are promising agents for the treatment of aggressive behaviours in non-addicted patients, too.

Key Words: Aggressive behaviour; heroin dependence; agonist opioid treatment.

1. Background

In this review we deal with the correlation between aggressive behaviour and heroin dependence, according to the behaviourist model of aggressiveness and the DSM-IV diagnosis of heroin dependence [1, 8, 11, 39].

The term "aggression" can be used to describe either active, creative adaptation to the environment or negative, destructive behaviour. According to the 'behaviourist model', aggressiveness is not a constitutional trait, but an acquired one. According to the 'Yale school' definition, aggression is always secondary to frustration [39]. However, the "frustration-aggression theory" postulates that frustration is just one of the many factors that can stimulate aggression,

another factor being instigation. Many types of acquired latent aggression can be manifested too, often in response to appropriate stimuli, not necessarily eliciting frustration [11]: aggression could be evoked, beyond its original meaning, by specific stimuli, but only in people who have learned aggressive behaviours [8]. According to Buss we should distinguish between aggression and feelings of anger or hostile attitudes. He defines aggression as the production of a noxious stimulus in an interpersonal context, directed from one person against another, whether it is physical or verbal, direct or indirect. On the other hand, anger is defined as an emotional reaction, and hostility as a negative attitude towards a person, not necessarily preliminary to aggression and not always required to underlie aggression. Each of these aspects

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can be displayed either separately or together with the others, independently or in a sequence leading from feelings to action. Aggression is more likely to be unleashed as a way of reaching goals, rather than of taking pleasure in victimizing someone [23-25]. Impulsivity and aggressiveness (a tendency towards aggression) are not the same, either. According to the "behaviourist theory", an impulse is triggered by an environmental or inner stimulus; it stems from an alteration to homeostatic balance, and action is the direct consequence of that. Aggressiveness is a planned, premeditated act, whereas impulsive 'acting-outs' are unplanned, overwhelming and inadequate outbursts of rage and anger, which do not help anyone to reach any actual goal. Impulse control disorders were first described in 1838 by Esquirol, who suggested the definition "monomanies instinctives" to describe states of behavioural excitement characterized by recurrent, irresistible urges of a single kind, leading someone to approach the environment or other people in an appetitive or destructive way, going beyond his/her intention or attempt to control themselves.

Buss and Durke described seven different types of hostile-aggressive behaviours, which are sometimes expressed in people who have no psychiatric history: assault; indirect hostility; irritability; negativism; resentment; suspicion; verbal hostility. "Assault" is the tendency to carry out actions that aim to harm and injure people without that occurring in an impulsive way. "Indirect hostility" is aggression perpetrated without any physical contact, for example by denigrating someone in an unpleasant way or slamming doors; "irritability" is characterized by a low threshold for verbal quarrelling and arguing, with a subjective urge to prevail or fight back as a means of achieving one's goals. "Negativism" consists in a strong and persistent opposition in an interactive relationship, with the refusal to perform any task, ranging from simple movements to verbal answers and emotional rejection; "resentment" corresponds to feelings of envy or retaliation that derive from underlying dissatisfaction arising from one's personal condition, which is often blamed on others; "suspicion" is the belief that one is victimized, disliked or even hated by others; "verbal hostility" is the tendency to explicitly disapprove of the actions of others and the tendency to cause controversy, or an inability to avoid it, by overreacting verbally. Lastly, to determine the level of aggression inhibition, there are 7 different grades, from assault down to guilt. People who feel guilty are frequently characterized by a strong ethical or moral rigidity, or a prick of conscience, and they are often worried about their deeds or even thoughts [26].

2. Heroin Addiction and Criminality

Criminality appears to be an indirect, partial correlate of aggressiveness displayed by heroin addicts, since the intersection between the two merely reflects acts of violent assaultive behaviour. In fact, offences perpetrated by heroin addicts can be divided into 3 major categories: crimes against 1) property, 2) people (assaultive violence) and 3) oneself (suicidality).

Although drug users have always been regarded as a single violent social group [103, 135] and their involvement in crime is commonly reported [3, 7, 65, 103]; their commitment to the criminal world is often related to the fact that heroin is expensive and illegal [65, 103]. In any case, many of the crimes committed by heroin addicts do not consist merely in drug selling or trafficking, but also involve other fields of criminal behaviour such as violent assaults; in particular, heroin addiction seems to be closely connected with offences against property [101] of which shoplifting, burglary and robbery, are the most common [10, 78, 87, 123]. In a longitudinal perspective (addiction history), the predominant type of illegal activity varies according to the recurrence of drug-related crime. At the same time, the incidence of violent crime and acts of hooliganism invariably decreases, while the number of people who have committed property crimes shows only a slightly falling trend [80].

Compared with the general population, offenders report higher rates of drug use, and drug users are more frequently found to be offenders. One study reported that 79% of heroin-dependent individuals had been arrested and 60% had been convicted for a criminal offence [81]. Criminal trends assessed by drug of abuse for 2010 confirmed the transition from a downward to an upward trend, starting in 2009, for heroin-related offences; before that, the EU average for such offences had fallen by 39% during the 2003-2008 period. The number of heroin-related offences increased in 16 reporting countries, while a fall was reported in Bulgaria, Germany, Italy and Austria over the same period [43]. A few studies have aimed to investigate the relationship between crime and heroin abuse/dependence [101].

Among heroin addicts entering methadone treatment, a majority (55%) had been criminally active in the month before the interview [117], and over 90% had been convicted at least once of property or drug offences [65].

Homicide perpetrated by heroin addicts is rare,

but lifetime opioid use by serial murderers was related to a preference for female victims, with a disorganized pattern of behaviour [105]. Heroin addiction was also significantly associated with non-homicidal, but severe, intimate partner violence [41].

3. Heroin Addiction and Suicidality

A positive history of attempted or accomplished suicide is common in heroin-dependent people [89]. Studies have reported a 7-fold relative risk of suicide among heroin addicts with respect to the general population [68, 107, 112] and a 14-fold risk rate with respect to age-matched peers [20]. Between 10% and 35% of deaths in heroin-dependent individuals are due to suicide, with about 40% of heroin abusers reporting at least one attempt to commit suicide [20]. Independent variables associated with suicidal ideation in this population are receiving welfare benefits, a bipolar spectrum disorder, unemployment, early onset of addiction, living alone, as well as experiencing social life and leisure time impairment [94]. Also, the number of overdoses can increase the risk of suicide attempts [17]. Attempters were younger and more likely to be female; they more often reported childhood trauma, a family history of suicidal behaviour, a history of aggressive behaviour, treatment with antidepressant medications, alcohol and cocaine addiction [118]. Another study identifies a personal history of suicide attempts and the early onset of heroin addiction, but without any gender difference, as correlates of suicidal risk in heroin addicts [138]. As far as the relationship between suicide and the psychopathology of heroin addicts is concerned, mood disorders, in particular, depression, prove to be major correlates of suicide. Approximately 90% of heroin addicts who attempt suicide have a history of depressive disorder with a higher prevalence of atypical depression. In bipolar I patients without mixed states there is a higher risk of substance abuse, but a lower risk of suicide; on the other hand, the risk of suicide is high in patients who display depressive symptoms and go through mixed states [89].

4. Heroin addicts' aggressive behaviour

4.1. Aggressive behaviour and psychiatric illness

Correlations between psychiatric illnesses and aggressive behaviour have been well summarized in many manuals of psychiatry [50]. It should be noted that those with depressive or anxiety symptoms, and those with traits of sensitivity and shyness traits tend to be less aggressive. Borderline personality disorder (BDP) and antisocial personality disorder (APD) feature impulsive violence and feelings of rage as a main psychopathological component. Patients with BPD are unstable and impulsive, have precarious social relationships, family conflicts that can result in outbursts of rage, peak anxiety, negativism, suspiciousness, destructive reactions and suicidal acts. These subjects are likely to beat people, engage in fights, offend people, and break objects. Antisocial patients too show impaired impulse control: they are extremely irritable, will often produce gratuitous aggressive behaviours towards animals and people; they may steal or destroy things, and often run away from their homes. In mood disorders, the presence of aggressiveness takes different forms during the depressive and the maniac phase: in depressed patients hostility is expressed as irritability, impatience, non-cooperation with others, criticism and blame directed at oneself or others, with reference to past, present and future events. These features can culminate in self-directed aggressive behaviours such as suicide. In the maniac phase, on the basis of unstable mood and psychomotor excitement, physical offence can easily take place. In catatonic schizophrenia, psychomotor arrest alternates with extreme violence and restlessness. In some cases, auditory hallucinations may induce patients to take violent actions. Violence is unlikely in pure anxiety disorders, where emotion often springs from self-frustration towards one's own disorder, and is usually expressed by verbal rage rather than assaults.

There is general agreement on the higher risk of violence among people with severe mental illness (SMI) that is worsened by concomitant substance abuse, medication non-compliance, or lack of insight [133, 134]. Nevertheless, a recent report claimed that SMI alone was not statistically related to future violence behaviours [42, 139]. More precisely, the incidence of violence was only higher for people with SMI who had co-occurring substance abuse and/or dependence [9, 42, 130]. As regards the relationship between specific diagnoses and violence in the absence of concomitant substance use, the strongest association was that found with the bipolar disorder, followed by schizophrenia and major depression. Since the rates of violence seem to show no correlation with the severity of bipolar disease or with the various episodes of disease, the association between bipolar disorder and violent crime (including suicide) was largely mediated by substance abuse comorbidity

[48]. However, if we consider the association between SMI and concurrent substance abuse, schizophrenia showed the greatest risk of violence. Substance abusers were associated with increased odds of current and future violent behaviours in the schizophrenia spectrum disorder [18, 34, 46, 137].

Moreover, the trait impulsivity of bipolar subjects appears to show a positive correlation with substance abuse. Likewise, the episodic impulsivity of bipolar subjects increases during periods of symptom remission only for those with a history of substance abuse. This enhanced disposition to impulsivity even in the absence of full-blown mania, may be the reason for the increased risk of suicide and aggressive behaviours in bipolar substance abusers [132].

4.2. Aggressive behaviour of non-opiate substance abusers

Substance use elicits aggressiveness and impulsivity, especially in those who have a biologically violent" disposition [70]. Certain individuals only become hyperactive, violent and dangerous under the influence of psychoactive substances, whether recreational (alcohol and drugs) or therapeutic (antidepressants), a phenomenon that has been described and classified as Bipolar Disorder type III [5]: that condition looms as an atypical variant of bipolar disorder, rather than an expected reaction to psychoactive substances [105]. In drug addiction, the risk of violence also depends on the type of substance that is being abused; for example, heroin abusers are hardly ever violent under the influence of narcotics, but they can be aggressive during withdrawal, while those who use stimulants are likely to be violent under the effects of those drugs, even in cases of episodic exposure. Actually, violent crime is less frequent in heroin-dependent people than in alcohol an/or stimulant abusers [20, 41, 101].

People who consume alcohol often turn violent during intoxication, but alcohol withdrawal can also feature restlessness, agitation and irritability, especially as a result of hallucinations [40]. Alcohol consumption is associated with various types of violence, including but not limited to sexual aggression, family and marital violence, child abuse and suicide. Reports suggest a close link between acute alcohol intoxication and aggressive behaviour, whereby larger quantities of alcohol are associated with more severe aggressiveness [64, 111].

As regards benzodiazepines, the intake of high doses in non-tolerant individuals can lead to violent outbursts, or escalations of anger, while chronic intoxication may cause an increase in hostile and aggressive tendencies [50].

Data gathered in psychiatric hospitals have proved that cannabis-positive acute bipolar psychoses display a characteristically violent clinical pattern [90]. Recent data showed that this trend also applies to ecstasy users undergoing acute psychotic episodes [119].

In comparing the rate of violent offences among heroin users and methamphetamine abusers, no differences emerged for life-time violence, whereas subjects on methamphetamine were significantly more likely to have committed violence in the past 12 months, so prompting the conclusion that regular methamphetamine use appears to be associated with an increased frequency of violent offences, probably with an earlier onset of violent behaviour within the history of substance use [37].

4.3. Are heroin addicts more violent than the general population?

To our knowledge, few studies have focused on comparisons between the aggressiveness of heroin addicts and that displayed by the general population. Gerra and co-workers demonstrated that the enhancement of aggressive response in heroin-dependent patients on agonist treatment when faced by a laboratory task (Point Subtraction Aggression Paradigm) was higher than in the control group, independently of agonist treatment [59]. Also, heroin addicts who had undergone long-term opioid tapering regimens showed a higher degree of outwardly directed aggressiveness than healthy subjects [57]. Moreover, as long as we consider suicide to be a form of aggressive behaviour, heroin users are 14 times more likely than the general population to commit suicide, and the prevalence of attempted suicide too is far higher than it is among community samples [36].

4.3.1. Gender differences

Male and female opioid-dependent patients differ in their antisocial attitudes and criminal history. In particular, females were significantly more hostile than males [109]. A positive criminal record was much less likely among females than among males, and the recurrence of criminal acts was higher for males. Also, the pattern of criminality was different: in women, the onset of criminal behaviour occurred at a higher age, and their commitment was to drug deal-

ing rather than the violent crime frequently recorded for men [27, 98]. Nevertheless, women reported involvement in illegal activity more often during the year prior to treatment entry [144] and the incidence of incarceration had risen faster than that of men, by an average rate of 4.6% a year, from 1995 to 2005 [69]. Gender differences in hostile attitude seem to influence treatment dropout, as women, who have greater levels of hostility at baseline, are more likely to drop out. On the other hand, men's endurance in treatment did not vary according to their level of hostility [109].

4.4. Aggressive attitude before heroin use

Common people are afraid of drug addicts, because of their violent and antisocial behaviour and their generally aggressive attitude, whether primary, or else induced by drug intoxication or withdrawal [76]. Aggressiveness and violence in heroin addicts before the onset of heroin use, is a poorly investigated issue; but at least one study identified marked premorbid traits of irritability [52]. Few studies shed light on the possible mechanism by which subjects choose between drugs and become attached to specific ones. On one hypothesis, drugs are not chosen randomly; on the other, the choice is the result of an interaction between psychopharmacological action and the dominant painful feelings, which were buffered as a result of drug self-administration. In line with this interpretation, addicts-to-be are likely to different substances for self-medication on the basis of their personality flaws [77]. As a result, narcotic addicts may prefer opiates because of their positive effects in suppressing rage and aggressiveness. Hence, heroin addiction appears to result from the self-medication dynamics by which the substance helps to manage pre-existing aggressive distress. [4]. There is some evidence that the aggressiveness and violence of heroin addicts are frequently associated with the presence of an antisocial personality [33, 35, 51]. Antisocial traits seem to be more important than drug effects in determining outward aggressiveness among heroin addicts [57]. An association has been documented between premorbid personality terms and the clinical features of heroin addiction, and the severity of the withdrawal syndrome [2]. In the light of this evidence, it may be the case that individuals who become opiate users are more likely to show aggressiveness not because of the drug itself, but because of a pre-existing premorbid aggressive disposition, leading them to form ties selectively with narcotics [70].

4.5. Aggressive behaviour during intoxication and/or withdrawal states

The simplest way to explain the co-presence of heroin addiction and violent behaviour is that chronic heroin intoxication can enhance aggressive behaviour. The evidence of a causal relationship between narcotic drug use and crime is derived from longitudinal studies in which the frequency and seriousness of crimes committed during periods of active addiction far exceed what is reported during non symptomatic periods [7, 78, 103, 127]. It was ascertained that, as addiction history evolves, the intensity of illegal activities does increase, but only slightly. On the other hand, the proportion of addicts involved in any criminal activity rises significantly through time, starting from as early as the first two years of addiction. After that the rate of increase declines noticeably [80]. The association between drug use and impulsivity, out of intoxication, is well documented [55]. More precisely, stimulants can induce an elevation of aggressiveness during intoxication [70], and levels of aggressiveness fall as an acute effect of opiate administration [60], while enduring exposure to the same narcotics can lead to a lowered threshold for aggressiveness [84]. A four-year trial of methadone treatment (at a narcotic blocking dosage) in 750 criminal addicts showed that a majority of patients stopped heroin use completely after starting methadone treatment, with high rates of social productivity as defined by stable employment and responsible behaviour, and with no evidence of on-going illicit drug use or further criminal convictions, which indicated that criminal and disruptive behaviours dwindle concomitantly with the extinction of drug related urges [38]. Opiate withdrawal is often associated with crime (64.4%), intoxication by alcohol (13.68%) or other psychoactive substances (4.27%); three-quarters of all property crimes (76.19%) and over a third of all personal crimes (35.48%) were committed by patients showing signs of opiate withdrawal [80].

5. Neurobiological correlates of aggressive behaviour in heroin addicts

The hypothesis of an association between cerebral opioidergic abnormalities and psychiatric disorders characterized by affective instability, feelings of anger and hostility, sensory abnormalities and sexual dysfunction, could explain some of the behaviours of heroin addicts, especially in connection with women [105]. There has been widespread agreement on the

existence of a direct relationship between heroin use and crime, but no consensus as to its nature. It seems not to be a straightforward or direct cause-effect relationship, as other factors (such as psychiatric comorbidity, age and ethnicity) show their influence on criminal activity [101]. Most probably, the need for opiates does not simply lead to crime: rather, opiate use and certain types of criminal activity tend to influence each other via an aggressive link [66]. Back in the eighties, authors explained the increase in crime rates among narcotic addicts on the basis of pre-addictive characteristics, especially criminal habits and drug use prior to narcotic addiction. Early family influences such as parental crime, the use of drugs and alcohol by other family members, and a lack of religious upbringing also appear to play an important role [124]. It is true that illegal activities could be detected as result of chronic intoxication attributable to drug abuse; it is the mental attitudes that had already been developing in the premorbid period that contribute most to an understanding of individual behaviours and the nature of addicts' illegal activities [38, 80]. Antisocial personality disorder (ASPD) is a commonly diagnosed, serious health mental disorder in substance users, with approximately 16-27% meeting DSM-IV for ASPD [6]. Psychopathological symptoms such as impulsive-aggressive behaviour, irresponsibility, egocentricity, lack of conscience, and social maladjustment are diagnostic features of ASPD [99]. Antisocial personality traits, in addition to a finding of lifetime antisocial behaviour, do increase the risk both of violent and non-violent offences [16]. A study on aggressive responses in abstinent heroin addicts showed no correlation between the degree of exposure to heroin (substance abuse history duration) and levels of aggressiveness, but heroin-dependent patients seemed to have higher outwardly directed aggressiveness than healthy subjects, possibly as a result of monoamine hyper-reactivity after long-term opiate discontinuation. Authors have concluded that aggressiveness seems to be related more to premorbid personalities than to addiction itself [58]. High levels of aggressiveness have also been found in heroin-dependent patients treated with methadone, suggesting that the level of aggressiveness demonstrated by methadone patients seemed to be related to personality factors rather than pharmacological ones [56, 70]. On the other hand, heroin-dependent patients with severe psychopathological features need a higher dosage of methadone to become stabilized. Contrary to expectations, when behavioural stabilization is pursued with no dose threshold, treatment-resistant patients with severe mental illness showed a better long-term outcome than treatment-resistant patients without psychiatric comorbidity [93]. In order to better understand the dynamics of violence among heroin addicts, we have looked into the correlation with drug abuse history variables: those for whom crime preceded heroin use (primary criminals) were younger and more likely to be male than those for whom heroin use preceded crime (secondary criminals). Primary criminals were also more likely to have committed violent crime and to qualify for a diagnosis of antisocial personality disorder (ASPD). The criminal behaviour of the secondary antisocials, especially females, may be brought on by heroin addiction rather than being an expression of the underlying antisocial personality [75]. A large body of literature on the effects of opiates on aggressive behaviour in animals suggests that morphine and other opiates temporarily reduce aggressive behaviour [67], although this effect is subject to tolerance [116]. Conversely, controlled studies in humans have demonstrated heightened aggressive behaviour by carrying out laboratory measurements of aggressive behaviour after the administration either of codeine [128] or morphine [12].

From a neuropsychological point of view, heroin use has implies short- and long-term consequences. In particular, impulse control dysfunction and negative affective states have been reported [82, 131]. The continuous intake of this substance increases levels of impulsivity that return to baseline (pre-heroin) levels throughout abstinence: in heroin-dependent subjects, impulsivity therefore becomes more intense as a result of chronic heroin exposure, rather than being a vulnerability trait [120]. Aggressiveness and self-injurious behaviour usually run parallel, as both are supported by impulsiveness, and usually mirror the severity of opiate intoxication [94]. The most common form of impulsiveness in addicts is connected with their extreme proneness to react to drug-related stimuli [19, 142, 143, 145], but a more general reduction of inhibitory control over impulsiveness can be observed in behavioural patterns not directly linked with drug use. The performance of habitual smokers, alcoholics, cocaine users and opiate addicts in carrying out behavioural tasks designed to measure impulsiveness, such as the Iowa Gambling Task Stroop test, indicates a general increase in the level of impulsiveness [49, 83, 110, 115]. The altered response to these tests may also depend on an underlying, previously active mental disorder or condition [30, 79, 100, 102, 136]. Data consistent with the direct pro-impulsive action of drugs have been reported for nicotine, al-

cohol, heroin and cocaine [15, 108, 113, 114, 140]. Subjects with impulsive personality structures and earlier involvement in drug use are those who seem to develop the most severe withdrawal syndromes, suggesting that opiate balance and control over aggressiveness share some brain areas. Before the onset of addiction, impulsive subjects display proneness to aggressive behaviour, together with a disposition towards risk taking, drug use included. In the context of drug use, these subjects experience a quicker transition to regular drug use and tolerance. Once addiction has developed, the two kinds of functional damage run in parallel, and mirror the severity of addiction itself, together with the disruptive behaviour associated with drug seeking. It therefore appears awkward to disentangle earlier mental conditions from those that follow the onset of addiction, since they have common neurobiological roots, and influence each other through a reverberating brain pathway [95].

6. Pharmacological treatment of aggressive behaviour and violence

6.1. Non-opioid medications

Several drugs are currently employed in the treatment of aggressive behaviours, but at the moment the US Food and Drug Administration has not approved any specific drug for aggressiveness [32, 86]. In recent years, antiepileptic drugs have become increasingly popular for the management of aggressive behaviour, and strong evidence exists for most of them, such as phenytoin, carbamazepine, lamotrigine, valproate/divalproex sodium, topiramate [129]. The role of antipsychotics is well established, both for typical and atypical drugs, and they are recommended in cases of acute aggressive behaviour [22, 121, 141], while clozapine should be considered when aggressive behaviour persists or recurs despite treatment [21, 29]. Benzodiazepines have a role in controlling acute agitation, but their long-term use for persistent aggressive behaviour is not recommended [141]. Beta-blockers have been reported as useful in the management of aggressive behaviour in elderly demented patients [126] and they are also effective in treating impulsive aggression in patients with other kinds of brain damage [74]. Aggressive behaviour is associated with reduced central serotoninergic functioning in some areas, so there seems to be an inverse relationship between platelet 5-HTT and aggressive behaviour [31]; in addition, selective serotonin reuptake inhibitors (SSRI) are believed to have a potential role in the treatment of aggressive behaviours [14].

Two studies evaluated the role of anti-aggressive drugs as adjunctive agents in the treatment of heroin addicts on methadone maintenance therapy, indicating that the antipsychotic olanzapine [54] and the SSRI sertraline [72], respectively, could be helpful in reducing aggressive and hostile behaviours.

6.2. Agonist opioid treatment of aggressive behaviour

The body of data available on the impact of different treatments for aggressive phenomena related to heroin addiction is far from being exhaustive. Despite this, some of the data acquired so far allow us to comment on the role of the pharmacological profiles of methadone, buprenorphine and naltrexone within maintenance treatment regimens.

There is general agreement that effective treatment reduces violence and rates of incarceration among opiate addicts [28, 61], and patients who stop using heroin regularly after treatment are also likely to stop offending, or to reduce their levels of offending behaviour [59, 62, 63, 67, 71, 125]. Adopting a prospective view, those who were enrolled in methadone treatment at the 4- or 10-month follow-up assessment had fewer arrests at their 12- and 24-month post-baseline follow-ups [122].

Aggressiveness seems to influence methadone stabilization dosage, which is higher for addicts with high-aggression baseline scores [96, 109].

Therapeutic effects on mental disorders can be expected from buprenorphine, in line with its distinctive receptorial profile. Buprenorphine combines μ-agonism, which is closely linked to its anticraving properties and is shared with methadone, with a k-antagonist activity [104]. This particular combination makes it easier to assess the psychotropic effects of k-antagonism, since retention rates are higher than those made possible by pure antagonists, such as naltrexone, which are poorly tolerated by heroin addicts, in general, and mentally ill ones, in particular [91, 92]. The buprenorphine-naltrexone combination (versus naltrexone only) produced a higher retention rate, with a better psychopathological adjustment (dysphoria, depression, irritability, depression, anxiety, asthenia, nausea, sickness or stomach ache) than the same patients had experienced before dropping out of previous naltrexone maintenance [53].

The highest retention rates and long-term results in buprenorphine treatment are obtained at dosages

that provide a combination of k-antagonism with pre-plateau levels of μ-mediated stimulation [104]. Other studies have stressed that buprenorphine seems to be more effective in opioid-dependent patients affected by depression, probably due to the action of kappa opioid-receptor antagonists in counteracting dysphoria, negativism and anxiety [54]. As previously mentioned, in reviewing the SCL-90 five factor solution, buprenorphine seemed to produce better results than methadone in patients with prominently violent-suicidal behaviours [88].

The idea that the impact of opioid agonist treatment is influenced by the psychopathological profile of heroin addicts has been rarely investigated: we have tried to assess the differential impact of opioid agonist treatment (methadone and buprenorphine) on the psychopathological dimensions found by a factorial analysis of the SCL-90 as administered to a sample of 1,055 patients under agonist treatment. Patients were sub-grouped into five categories according to which of the five following dominant factors were shown: (1) depressive symptomatology with prominent feelings of worthlessness-being trapped or caught, (2) somatization symptoms, (3) interpersonal sensitivity and psychotic symptoms, (4) panic symptomatology, and (5) violence and self-injurious behaviour. The groups did not differ on the basis of sex or duration of dependence. The fifth factor group (violence-suicide) features impulsive acting-outs and self-directed aggressiveness. These patients may cry out loud or throw objects with the aim of smashing them into pieces, or suffer from outbursts of rage. They often argue and feel the urge to push, hurt or beat up others. At the same time, they also report suicidal thoughts, or longings for death, are upset, excited or restless, and find it hard to stay seated or lie down, even for a while. Younger patients with heroin addiction were more strongly represented in the dominant violence-suicide group [95].

No statistically significant differences were observed for subjects belonging to the 'worthlessness-being trapped', 'somatization' and 'panic-anxiety' dominant groups by type of agonist treatment (i.e. whether they were taking buprenorphine or methadone). Methadone treatment was correlated with belonging to the 'sensitivity-psychoticism' dominant group, whereas buprenorphine was associated with belonging to the 'violence-suicide' dominant symptomatology [88]. On the whole, no difference in assault emerged between treatment groups, either in the early or the maintenance stage of treatment. However, any agonist treatment was related to lower levels of suicidality and violent behaviour than with naltrexone treatment, during both the early and the later phases of treatment [89, 97]; highly aggressive patients at treatment entrance are likely to drop out during long-term naltrexone maintenance, like those with mood disorders or psychotic disorders [92]. Despite the reborn interest in sustained-release naltrexone for the treatment of narcotic addiction, the available data indicate that, with this type of naltrexone, retention rates and outreach are the poorest among potentially effective treatments: in particular, aggressive addicts are one of those categories which achieve the worst results when they enter naltrexone maintenance. The employment of naltrexone in rapid detoxification regimens, or as a trail to detoxification as a means to prevent short-term relapse into use, although somewhat popular, cannot be discussed here, as that topic pertains to the issue of addiction treatment.

No data are available on the specific effects of slow-release morphine on the aggressiveness of treated subjects [73], whereas some data indicate the advantages of methadone maintenance over heroin maintenance, in terms of a reduction in levels of newly recorded crimes [85].

7. Points of interest and future research outlines

According to the behaviourist model, most behaviours originate in learning processes. In this way, aggressiveness could be explained in terms of a learning reaction to frustrating and aversive experiences, which can later be evoked more and more readily. The 'addiction world' could represent an environmental substrate on which abusers learn aggressive dynamics, and at the same time a context in which the practice of aggression may turn out to be useful or necessary in maintaining support for the habit. Heroin addicts seem to be best characterized by a non-impulsive aggressive attitude, underlying a habitual antisocial behaviour, rather than an impulsive, explosive aggressiveness that is matched with affective instability and disinhibition, but not necessarily linked to habitual antisocial behaviour.

The crimes perpetrated by heroin addicts appear to have the aim of supplying oneself with the substance, whereas the effects of heroin intrinsically tend to favour control over aggressiveness. Rising aggressiveness as the course of heroin addiction goes forward may stem from a progressive imbalance of the opioid function, due to high tolerance levels. Alcohol and psychostimulants, on the other hand, ap-

pear to raise rates of aggressiveness, so leading to the perpetration of violent crimes such as homicide and physical assault, with a weaker link with the need to support regular use.

According to Khantzian's self-medication hypothesis, narcotic addicts prefer opiates because of their powerful buffering action on the disorganizing and threatening affects of pre-existent rage and aggressive behaviours. In the light of our review, however, that hypothesis has received hardly any support from statistical analyses. Most aggressive behaviours appear in non-compensated heroin addicts, so that it could be counter-hypothesized that it is substance-related damage that causes an increase in levels of aggression, whereas the brain substrate corresponds to premorbid personality traits. Consequently, we could consider the standard aggressiveness displayed by heroin addicts as a symptom of heroin addiction itself, worsening as the loss of opioid balance increases, and becoming exacerbated by repeated learning cycles of violent behaviour that aim to ensure self-supplying of the substance. If that is so, not only do treatments provide aggression control along with their action on core addictive symptoms, but it also follows that aggressiveness itself may be seen as a useful parameter for monitoring the effectiveness of addiction treatment, together with urinalyses and improvements in social functioning.

Lastly, given the effectiveness of opioids as anti-aggressive drugs in heroin addicts and the involvement of the opioid system in modulating aggressiveness, we may also regard them as candidates for future use in violent non-addicted psychiatric patients, at least for slow-acting opiates involving no addiction risk, such as oral methadone, slow release morphine and sublingual buprenorphine. In addition, the possible antidepressant [13, 45, 47], mood-stabilizing [44, 106] anti-psychotic [84] effects of opioids could support their employment as a core psychotropic treatment in a wide range of psychiatric disorders. Buprenorphine may be the optimal drug for this new form of use, because of its kinetics and potency. Unlike methadone, buprenorphine has a longer half-life, it is safer for the induction of non-tolerant subjects, and its abuse liability is limited to injective misuse by heroin addicts.

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Post traumatic stress spectrum and maladaptive behaviours (drug abuse included) after catastrophic events: L'Aquila 2009 earthquake as case study.

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Summary

PTSD is one of the most frequently occurring sequelae in earthquake survivors and increasing literature has been focused on its potential risk factors. More recently increasing evidence has highlighted the onset of maladaptive behaviours in the same populations. The aim of the present study was to explore: 1) the role of degree of exposure ("direct" vs "indirect"), gender and age (> o ≤40) as potential risk factors for PTSD in a sample of L'Aquila 2009 earthquake survivors; 2) the role of these same variables and of PTSD as potential risk factors for maladaptive behaviours in the same sample. A group of 444 subjects was evaluated by the Trauma and Loss-Self Report (TALS-SR) 10 months after exposure. Results showed significantly higher PTSD prevalence rates in: exposed with respect to not exposed subjects; women with respect to men (in the whole sample and in all subgroups, with the only exception of the older subjects not exposed); not exposed younger women with respect to the older ones. PTSD and "direct" exposure represented a major risk factor for the presence of at least one maladaptive behaviour, with female gender playing a role only among no-PTSD subjects. For the TALS-SR item n.99 ("Use alcohol or drugs or over-the-counter medications to calm yourself …?") only PTSD and "direct" exposure emerged as risk factors. Our results confirm the pervasive effects of earthquakes for mental health in the general population, and highlight the role of gender and proximity as primary correlates of PTSD, and of PTSD and degree of exposure for maladaptive behaviours, particularly alcohol and substance use.

Key Words: PTSD; earthquake; gender; age; exposure; L'Aquila; substance abuse

1. Introduction

Several studies have investigated the onset of Post-Traumatic Stress Disorder (PTSD) among victims of earthquakes, as it represents the most frequently reported psychiatric sequelae of traumatic exposure (33, 32, 28, 22, 52) and is often associated with chronic course and high risk for suicide (36,3 26,16,8,18,19).

Italy is one of the most seismically active countries in Europe but it is unusual for the Country to experience deadly earthquakes. On April 6th 2009, an earthquake (Richter Magnitude 6.3) struck L'Aquila, Italy, leading to the collapse of many buildings, to the death of 309 people, to the injury of more than 1600 individuals and to the displacement of about 66,000 individuals.

In two previous studies we explored the prevalence rates of PTSD among adolescents who survived the L'Aquila 2009 earthquake. All subjects were students attending the last year of high school in L'Aquila investigated either 10 (18) or 21 months (19) after exposure. In agreement with previous studies (33, 3, 26), our results showed PTSD rates as high as 37.5% after 10 months (18) and 30.7% after 21 months (19). Further, significantly higher post-trau-

matic stress symptoms rates were reported among survivors who reported the loss of a significant other in the framework of the earthquake (19) corroborating the need to accurately investigate bereavement-related symptomatology (35, 20) .

Increasing effort has been devoted exploring the role of risk factors, such as degree of exposure, gender and age in the development of PTSD following an earthquake.

The degree of earthquake exposure, defined as the distance from the epicenter, has been related to the onset of PTSD (2,9 6, 5). Armenian et al. (2), reported higher PTSD rates among 1785 survivors from areas with the worst destruction in the immediate aftermath of the 1988 Armenia earthquake. Cao et al. (9), found significant differences in PTSD prevalence rates between three different groups of subjects exposed to the 1988 Yun Nan (China) earthquake, examined according to their distance from the epicentre. Results showed the highest PTSD rates in the closest group to the epicenter. These findings as a whole seem to suggest a relationship between the proximity to the epicenter of an earthquake and the increasing levels of PTSD rates in the general population.

There is agreement in the literature on the higher vulnerability of women to the impact of traumatic events, including earthquakes. Women, in fact frequently report higher rates of PTSD than men (44, 38, 27, 33, 24, 3, 12, 13, 26, 41, 53, 54, 19, 55, 21). Priebe et al. (42) in a sample of 2.148 survivors to an earthquake in 2002, in a rural region of Italy, reported PTSD prevalence rates of 14,5%, with higher rates among women, subjects over 55 years of age and people with lower school education.

Conversely inconsistent data have been reported on age. More recently, Zhang et al. (56) found almost a 20% prevalence of PTSD in a sample of elderly subjects exposed to Wenchuan earthquake 1 year after the event, showing also the role of loss of livelihood, bereavement, injury and initial fear during the event. More systematic data is required to understand age and gender differences in PTSD following earthquakes.

Increasing data have highlighted the onset of maladaptive behaviours, defined as volitional behaviours whose outcome is uncertain and which entail negative consequences that impact everyday activities (29, 39, 20) in populations exposed to trauma (48, 30, 31, 23), but data on earthquake survivors are still scarce (18).

The aim of the present study was to explore, in a sample of L'Aquila 2009 earthquake survivors, the role of degree of exposure ("direct" vs "indirect"), gender and age (> o <40) as possible risk factors for PTSD. Secondary aim was to explore these same variables and PTSD as potential risk factors for maladaptive behaviours in the same sample.

2. Methods

2.1. Study Participants

The target population included a total sample of 444 subjects (mean age 34.26±14.23 years): 219 women and 225 men. Within the whole sample, 234 subjects (mean age 33.09±14.44 years; 122 women and 112 men) were residents of the town of L'Aquila who had experienced the April 6th 2009 earthquake 10 months earlier ("exposed"), while 210 subjects (mean age 35.57±13.91 years; 97 women and 113 men) had been "indirectly" exposed to the same earthquake ("not-exposed") as they were recruited among subjects living more than 150 Km far from the town of L'Aquila and had not been affected by the earthquake. The "exposed" population included people living in the town of L'Aquila who had received assistance in the emergency conditions that prevailed. All residents of the town of L'Aquila had been displaced in locations within a 150 km area from the town or in tents located in the urban area due to the distruction of large parts of the town. Even 10 months after the earthquake, only 25% of the inhabitants were able to return to their homes.

On the basis of the assumption that younger and older subjects might report different levels of symptomatology, the age was coded into two categories: ≤40 and >40 years, both for "exposed" and "not exposed" subjects.

Post-traumatic stress symptoms related to the L'Aquila 2009 earthquake were self-rated on the Trauma and Loss Spectrum-Self Report (TALS-SR) (17) .

The Ethics Committee of the University of L'Aquila approved all recruitment and assessment procedures. Eligible subjects provided written informed consent after receiving a complete description of the study and having an opportunity to ask questions.

2.2. Instruments and assessments

The TALS-SR is an instrument developed and validated by clinicians and researchers who comprise an international (Italy-U.S.A) collaborative research

group named "Spectrum-Project". Using the term "Spectrum", these researchers refer to a broad array of manifestations of a mental disorder, including its core and most severe range of symptoms, as well as its subthreshold manifestations. The latter may be either temperamental traits, or prodromal or residual symptoms following or preceding a fully developed episode (25,10). The TALS-SR is the last developed instrument (15), with the first ones being those for the assessments of the panic-.agoraphobic (10) and mood (14) spectra and the most recent those for assessing substance use disorder spectra (46, 4). The TALS-SR includes 116 items exploring the lifetime experience of a range of loss and/or traumatic events and lifetime symptoms, behaviors and personal characteristics that might represent manifestations and/or risk factors for the development of a stress response syndrome. The TALS-SR also addresses symptoms of loss related symptomatology, accordingly to the recent concepts of traumatic or complicated grief (43, 7). Items responses are coded in a dichotomous way (yes/no). The instrument is organized into 9 domains and domain scores are obtained by counting the number of positive answers. According to the aims of the present study subjects were asked to fulfill domains IV and over, referring symptoms occurred after the earthquake exposure. Domain IV ("Reactions to losses or upsetting events") includes a range of emotional, physical and cognitive symptoms occurring as acute response to the event. Domain V ("Re-experiencing"), domain VI ("Avoidance and numbing") and domain VIII ("Arousal") include re-experiencing, avoidance and numbing, and arousal symptoms respectively. Domain VII ("Maladaptive copying") targets maladaptive coping and behaviours. This domain explores whether the subject stopped taking care of him/herself, stopped taking prescribed medications or failed to follow-up medical recommendations, used alcohol or drugs or over-the-counter medications to calm him/herself or to relieve emotional or physical pain, engaged in risk-taking behaviours (e.g. driving fast, promiscuous sex, hanging out in dangerous neighbourhoods), suicidal ideations (wishing he/she hadn't survived; thinking about ending his/her life; intentionally scratching, cutting, burning, or hurting him/herself; attempting suicide).

The presence of PTSD was assessed by means of the items of the TALS-SR corresponding to DSM-IV-TR criteria for PTSD diagnosis.

2.3. Statistical Analyses

The effects of degree of exposure, gender and age on PTSD were measured by the χ^2 tests. A classification method, based on decision tree, was also utilized to locate the independent variables with the strongest interactions with PTSD. Finally, we performed a multiple logistic regression analysis to estimate the relationship between the predictive variables and PTSD prevalence. The effects of degree of exposure, gender, age and PTSD on the presence of at least one maladaptive behaviour, and of each one of these behaviours assessed by the TALS-SR Domain VII items, were explored by means of the same analyses.

All statistical analyses were carried out using the IBM Statistical Package for Social Science, version 20.0.

3. Results

Details on the PTSD prevalence rates compared for degree of exposure, gender and age are reported in Tables 1,2,3. In particular, significantly higher PTSD rates were reported among 'exposed' with respect to 'not exposed' subjects both in the whole sample and in all subgroups. We also found significantly higher PTSD prevalence rates in women with respect to men, in the whole sample and in all subgroups, with the only exception of the older subjects 'not exposed'. Significant age differences in the PTSD prevalence rates were found among women, with younger women being more affected than older ones (50.8% vs 35.2%). Nevertheless, this effect seems quite due to the 'not exposed' women subgroup: note that a significant difference was present in this subgroup (30.8% vs 13.3%, p=.041) while it was not present in the 'exposed' women subgroup (64.1% vs 58.1%) .

A classification decision tree, based on the Chi-Squared Automatic Interaction Detection (CHAID) method, confirmed that the strongest effects on PTSD prevalence rates were due to both exposure and gender, with women and exposed subjects being most affected, and that age had an impact on PTSD prevalence among 'not exposed' women only (see node 7 and node 8 in figure1).

A multiple logistic regression model showed an increased likelihood of PTSD being associated with degree of earthquake exposure (OR=5.87, CI95%: 3.52-9.77) and female gender (OR=5.29, CI95%: 3.27-8.64) only.

With regard to the presence of at least one maladaptive behaviour, the following risk factors emerged:

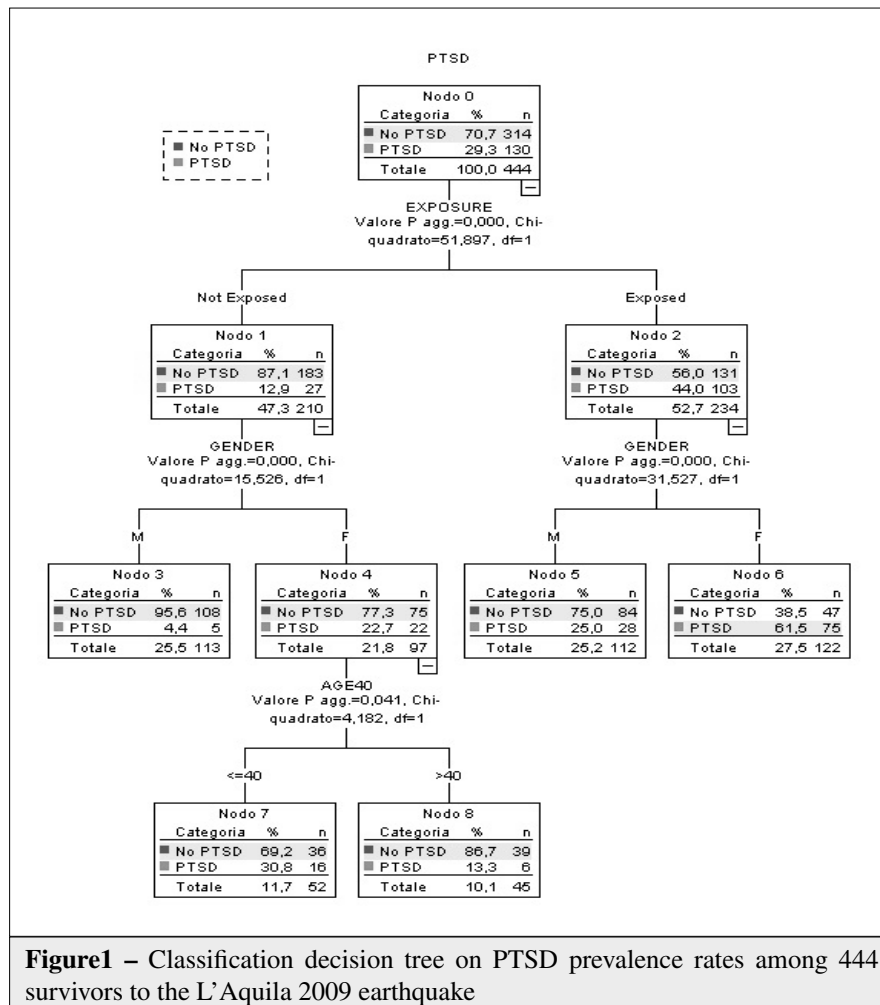**Table 1.** Gender differences in PTSD prevalence rates in the total sample and within Age*Exposure subgroups

		Exposition to earthquake		Total
		Not Exposed	Exposed	
Age categories	≤40 years old	16 (30.8%) vs 4 (5.7%) χ²=13.67, p< .001	50 (64.1%) vs 17(23.9%) χ²=24.22, p< .001	66 (50.8%) vs 21 (14.9%) χ²=39.94, p< .001
	>40 years old	6 (13.3%) vs 1 (2.3%) Fisher, p= .111	25 (58.1%) vs 11 (26.8%) χ²=8.40, p= .004	31 (35.21%) vs 12 (14.3%) χ²=10.05, p= .002
	Total	22 (22.7%) vs 5 (4.4%) χ²=15.27, p< .001	75 (62.0%) vs 28 (25.0%) χ²=32.26, p< .001	97 (44.5%) vs 33 (14.7%) χ²=47.51, p< .001

Table 2. Differences in earthquake degree of exposure ("direct" vs "indirect") in PTSD prevalence rates in the total sample and within Age*Gender subgroups

		Gender		Total
		Males	Females	
Age categories	≤40 years old	17 (23.9%) vs 4 (5.7%) χ²=9.24, p= .002	50 (64.1%) vs 16(30.8%) χ²=13.87, p< .001	67(45.0%) vs 20 (16.4%) χ²=25.12, p< .001
	>40 years old	11 (26.8%) vs 1 (2.3%) χ²=10.29, p= .001	25 (58.1%) vs 6 (13.3%) χ²=19.35, p< .001	36 (42.9%) vs 7 (8.0%) χ²=27.92, p< .001
	Total	28 (25.0%) vs 5 (4.4%) χ²=19.03, p< .001	75 (62.0%) vs 22 (22.7%) χ²=33.68, p< .001	103 (44.2%) vs 27 (12.9%) χ²=52.35, p< .001

Table 3. Age differences ("≤40" vs ">40") in PTSD prevalence rates in the total sample and within Gender*Exposure subgroups

		Exposition to earthquake		Total
		Not Exposed	Exposed	
Gender	Males	4 (5.7%) vs 1 (2.3%) Fisher, p= .648	17 (23.9%) vs 11(26.8%) χ²=0.12, p= .734	21 (14.9%) vs 12 (14.3%) χ²=0.02, p= .901
	Females	16 (30.8%) vs 6 (13.3%) χ²=4.18, p=.041	50 (64.1%) vs 25 (58.1%) χ²=0.418, p= .518	66 (50.8%) vs 31 (35.2%) χ²=5.13, p= .023
	Total	20 (16.4%) vs 7 (8%) χ²=3.25, p= .071	67 (45.0%) vs 36 (42.9%) vs χ²=0.10, p= .756	87 (32.1%) vs 43 (25.0%) χ²=2.56, p= .110

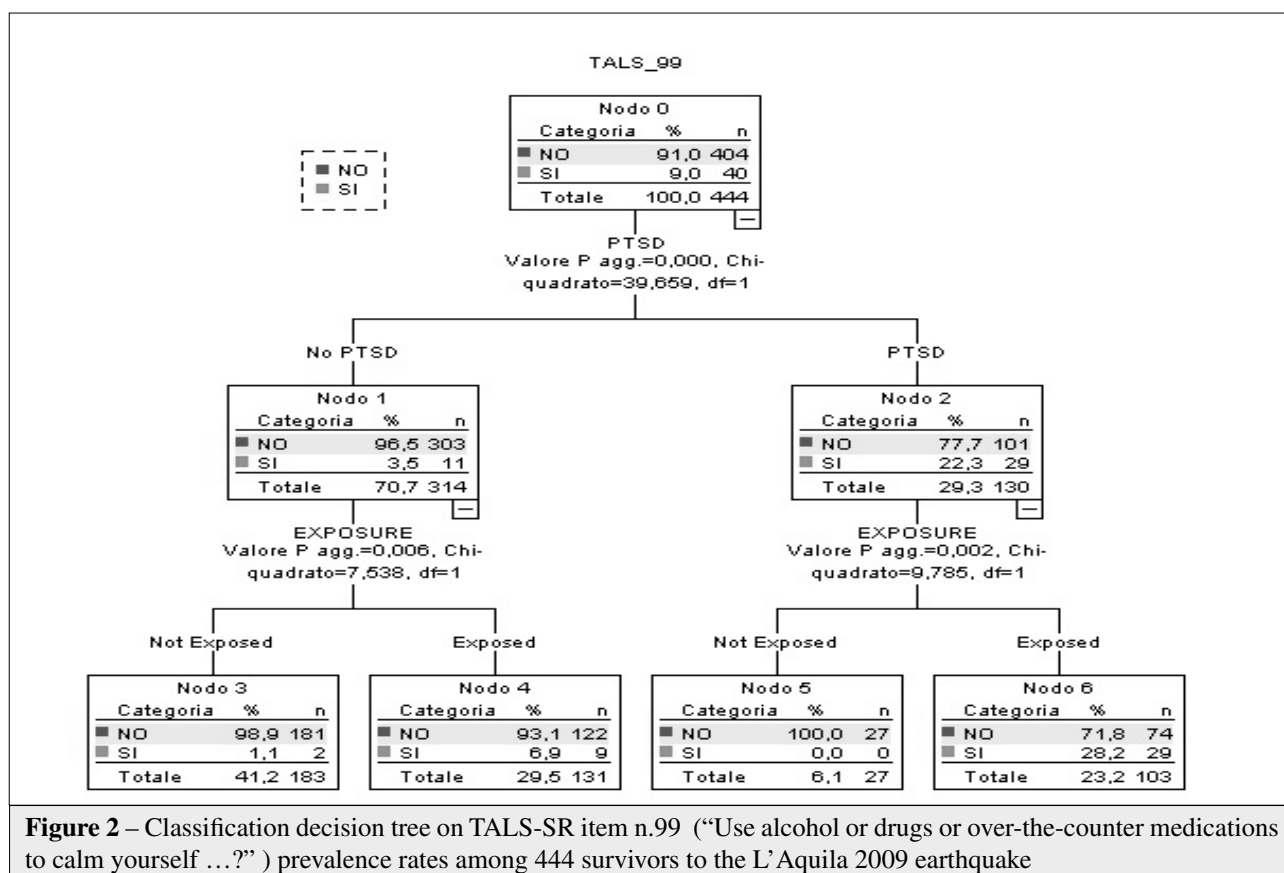**Figure1 –** Classification decision tree on PTSD prevalence rates among 444 survivors to the L'Aquila 2009 earthquake

PTSD vs no PTSD (48.5% vs 13.7%, p<.001); 'exposed' vs 'not exposed' both among PTSD patients (57.3% vs 14.8%, p<.001) and no-PTSD subjects (21.4% vs 8.2%, p=.001); women vs men among no-PTSD only (23% vs 7.8%, p<.001). Exploring each item of the TALS-SR Domain VII independently, PTSD resulted the major risk factor for all of them. PTSD and "direct" exposure (see Fig.2) emerged as risk factors for item n.99 ("Use alcohol or drugs or over-the-counter medications to calm yourself …?"). Further, with regard to the items n. 97 ("Stop taking care of yourself, for example, not getting enough rest or not eating right?") and n. 98 ("Stop taking prescribed medications or fail to follow-up with medical recommendations ...?"), female gender resulted a risk factor among no-PTSD subjects only (18% vs 3.6%, p<.001 and 5.7% vs 1.0%, p=.015 respectively) and in the former "direct" exposure resulted a risk factor both among subjects with PTSD and women without PTSD (46.6% vs 14.8%, p=.003 and 29.8% vs 10.7%, p=.008, respectively).

4.   Discussion

The results of the present study are in line with previous studies on earthquake survivors (6, 33, 5, 34, 42, 50, 51, 18, 19) showing high rates of PTSD among survivors to the L'Aquila 2009 earthquake in Italy. In particular, PTSD rates as high as 44.0% were reported among subjects who had been directly exposed to this event, with women being the most affected. Gender differences also emerged in PTSD rates among subjects who had not been directly exposed to the L'Aquila earthquake who showed significantly lower (16.6%) PTSD rates with respect to the subjects who had been directly exposed.

Our data corroborate previous literature on earthquake-exposed populations investigated at different distances from the epicenter, suggesting the highest impact of these events on individuals located in the closest areas to the epicentre (9, 49, 1, 11, 37). In a previous report (33) female gender was reported to be associated with significantly higher PTSD in earthquake-exposed populations.

Figure 2 – Classification decision tree on TALS-SR item n.99 ("Use alcohol or drugs or over-the-counter medications to calm yourself …?") prevalence rates among 444 survivors to the L'Aquila 2009 earthquake

More recently, Priebe et al. (42) in another earthquake-exposed Italian population, reported female gender to predict higher PTSD rates. Nevertheless, despite these authors having reported older subjects to be also more affected, no age difference emerged in our sample, with the only exception of non-exposed women among which younger females showed higher PTSD rates than older ones. In particular, in our sample low PTSD levels emerged among indirectly exposed subjects, with the exception only of younger women who reported the highest rates. Among directly exposed subjects, younger men reported the lowest rates. These data are in line with authors suggesting women and younger subjects to be more vulnerable to traumatic events and more prone developing post-traumatic stress symptoms when exposed to trauma. Interestingly, our data showed an impact of age among less affected females only (11, 53, 54).

Our results indicate high rates of self-reported maladaptive behaviours in a sample of L'Aquila earthquake survivors 10 months after the event occurred, with significantly higher rates among victims reporting PTSD compared to those without. A further relevant risk factor for such behaviours resulted to be the degree of exposure, with directly exposed subjects reporting significantly higher rates of each one

of the maladaptive behaviours explored compared to not directly exposed ones. Interestingly, gender seemed to play a role only as far as item n.97 and 98 were concerned, respectively ("Stop taking care of yourself, for example, not getting enough rest or not eating right?") and ("Stop taking prescribed medications or fail to follow-up with medical recommendations ...?"), where women were significantly more affected than men despite among no PTSD subjects only. With regard to the risk of alcohol or drug use in order to calm him/herself, only PTSD and "direct" exposure to the earthquake seemed to have an impact on survivors. Despite our results showing only 9% of the sample satisfying this item, Pollice et al. (40) reported a marked increase in levels of substance abuse among young people exposed to the same event compared to prior to the trauma. Similarly, Rossi et al. (45) showed a 37% increase of new psychopharmacological prescriptions for antidepressants and a 129% increase for antipsychotic prescriptions 6 months after exposure to this same event. Our results seem to be in line with these data, but further investigations in larger samples are needed.

Interpretation of our results should keep in mind some important limitations of the study. The most important is the limited number of subjects and for this

reason we consider this study a preliminary report and further investigations on a larger sample are warranted. Another limitation of the present study is the use of self-report instruments, instead of the rating of the clinician, in order to detect PTSD symptoms and even diagnosis. A self-report of PTSD symptoms may be, in fact, considered less accurate. A third limitation is represented by the lack of information on the presence of Axis I psychiatric comorbidities that may particularly affect the results on maladaptive behaviours.

Despite these limitations, our results confirm the pervasive effects of a disaster, such as an earthquake, for mental health in the general population exposed and demonstrate the relevance of mental health as a key component of public health response to mass traumas. Further, our results highlight the relevance of gender differences and the proximity to the earthquake in the response to earthquake exposure, which should be taken into account when facing such events, and suggest possible differences in such reactions among younger and older victims. In order to corroborate our results, further studies on a randomly matched subsample that would avoid significant differences in age and gender distribution between exposed and non-exposed subjects should be performed.

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